Lipoblastoma in one adult and 35 pediatric patients: Retrospective analysis of 36 cases

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Abstract. Lipoblastoma is a rare benign mesenchymal neoplasm that typically occurs at various sites in infants and children but may also occur in adults. Thus, differential diagnoses are often performed. To understand this tumor type, the present study described clinicopathological features, diagnosis and differential diagnosis of different morphological lipoblastomas. A single-institution retrospective review of 36 lipoblastoma cases diagnosed between 2015 and 2021 was performed. Formalin-fixed paraffin-embedded tissue was used for S-100, CD34, P16 and desmin immunohistochemistry analysis, along with rapid fluorescence in situ hybridization (FISH) detection with pleomorphic adenoma gene 1 (PLAG1). The 36 cases included 14 females and 22 males [age range, 7 days to 33 years (median, 16.5 years); 28 patients were aged ≤3 years] and the tumors were located in the trunk (n=16), limbs (n=12), head and neck (n=6), and perineum (n=2). Histologically, lipoblastomas were divided into classic (n=15), lipoma-like (n=13) and myxoid (n=8) subtypes. They comprised lobules of mature adipose tissue of varying size and a fine capillary network surrounded by mucinous stroma. Single- or multivesicular lipoblasts positive for S-100 (29/36, 81%) were observed, with occasional mature adipocytes. Peripheral vessels and cytoplasm of primitive mesenchymal cells were diffusely positive for CD34 (36/36, 100%), whereas primitive mesenchymal cells and striated muscle tissue were positive for desmin (26/36, 72%). Most tumor cells were negative while only few were positive for P16 (8/36, 22%). FISH revealed PLAG1 breakage and rearrangement in 24/32 (75%) patients. In total, 28 patients were followed up post-operatively (range, 2-84 months; median, 41 months; 3 patients relapsed (n=2). Histologically, lipoblastomas were divided into classic (n=16), limbs (n=12), head and neck (n=6), and perineum (n=2). The most common type is one or more additional copies of chromosome 8, which contains structural abnormalities at 8q11-13 (including translocation, insertion, inversion, or circular chromosomes), resulting in pleomorphic adenoma gene 1 (PLAG1) rearrangement (1). PLAG1 is primarily composed of five exons, and codes from exon 4 produce a protein composed of 500 amino acids. Its oncogenic effect is associated with upregulation of multiple direct target genes, including growth factors, growth factor-binding proteins, growth factor receptors and cell cycle-associated proteins, such as insulin-like growth factor 2, vascular endothelial growth factor and mitogen-activated protein kinase (7-11). PLAG1 acts as a transcriptional regulator and is not expressed in adult tissue (12,13). It is hypothesized that this is due to the presence of negative control elements that inhibit PLAG gene expression) in exon 1 of PLAG1 in adults; however, ectopic PLAG1 in tumors results in loss of these elements and overexpression of the coding region (14). Tumors caused by overexpression of PLAG1 include salivary gland pleomorphic adenoma, lipoblastoma, hepatoblastoma and acute myeloid leukemia (15). Detection of PLAG1 rearrangement is helpful in the diagnosis of pleomorphic adenoma. Andreason et al (16) found that 16 (76.2%) of 21 pleomorphic...
adenomas showed copy-neutral PLAG1 rearrangements. Four other markers also serve a role in the development of lipoblastoma including CD34, S-100, desmin, and p16. It has been reported that the CD34+ fibroblastic stem cell may be the putative cell of origin for lipoblastoma (17). S-100-positive mono- and multi-vacular lipoblasts indicate tumor origin in adipose tissue (18). Aberrant immunoreactivity to desmin has been described in non-adipose mesenchymal tumors, except those with myogenic or myofibroblast differentiation (17,19). In the study by Kubota et al (20), PLAG1-positive spindle cells expressed desmin, but not other myogenic markers. Combining the immunological features of desmin, spindle cell morphology and ultrastructural features (invaginated nuclei, well-developed rough endoplasmic reticula, pinocytotic vesicles and desmin filaments), it was inferred that spindle cells in lipoblastoma may exhibit myofibroblastic differentiation. PLAG1 overexpression and activation are key events in lipoblastoma and this pathway is independent of p16. However, alterations in the retinoblastoma pathway during liposarcoma development serve a key role in overexpression of p16 (21,22). P16 immunohistochemistry has been reported to show high negative predictive value from lipoblastoma (87%) and benign adipocytic lesions (93%) in differentiating liposarcoma (23,24). Therefore, malignancy is unlikely in the absence of p16 expression.

Morphologically, lipoblastoma is primarily composed of primitive spindle mesenchymal cells and adipocytes at various stages of maturation. In particular, it contains lobules of mature adipocytes of different sizes divided by fiber septa, with a fine capillary network and mucinous stroma. In immuno-histochemistry, lipoblasts are usually S-100-positive and P16-negative, while CD34 and desmin expression is usually observed in primitive mesenchymal cells; these properties serve as a useful diagnostic marker (20,25). However, because lipoblastoma has its own characteristic genetic changes, fluorescence in situ hybridization (FISH) detection of PLAG1 fragmentation and rearrangement may be useful in diagnosis of lipoblastoma (26,27).

Furthermore, lipoblastoma often shows atypical morphology or occur in young and adult age groups and are easily misdiagnosed as lipoma, fibrous hamartoma of infancy, myxoid liposarcoma, primitive myxoid mesenchymal tumor of infancy and superficial angiomyxoma (28-30). Therefore, as a cytogenetic detection method, PLAG1 FISH is required to aid the diagnosis by pathologists. Currently, reports on this disease are mostly limited to case reports (4,5,8,26). Therefore, to gain a deeper understanding of the occurrence and development of lipoblastoma, changes in molecular structure and the effect of gene pathway during liposarcoma development serve a key role. In the study by Kubota et al (20), PLAG1-positive spindle cells expressed desmin, but not other myogenic markers. Combining the immunological features of desmin, spindle cell morphology and ultrastructural features (invaginated nuclei, well-developed rough endoplasmic reticula, pinocytotic vesicles and desmin filaments), it was inferred that spindle cells in lipoblastoma may exhibit myofibroblastic differentiation. PLAG1 overexpression and activation are key events in lipoblastoma and this pathway is independent of p16. However, alterations in the retinoblastoma pathway during liposarcoma development serve a key role in overexpression of p16 (21,22). P16 immunohistochemistry has been reported to show high negative predictive value from lipoblastoma (87%) and benign adipocytic lesions (93%) in differentiating liposarcoma (23,24). Therefore, malignancy is unlikely in the absence of p16 expression.

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Materials and methods

Case selection. A total of 36 cases of lipoblastoma that were surgically resected and diagnosed at Shengjing Hospital of China Medical University, Shenyang, China, between January 2015 and January 2021 were collected. There were 22 males and 14 females, aged between 7 days and 33 years. Inclusion criteria included histopathologically confirmed lipoblastoma or lipoblastomatosis with hematoxylin- and eosin-stained sections, paraffin blocks and clinical data (age, sex, tumor location, size, surgery, complications and follow-up) available for all cases. Cases with missing IHC (S-100, CD-34, P-16 and desmin) analysis and cases with poorly preserved tissue blocks were excluded. The Institutional Review Committee of the hospital approved the study (ethical approval no. 2022PS104J). The need for written informed consent was waived in view of the retrospective nature. All cases were reviewed by two pediatric pathologists and lipoblastoma was classified into three subtypes: Classic, lipoma-like, and myxoid, as previously described (17,31).

Immunohistochemistry. All specimens were surgically excised, fixed in 3.7% neutral formaldehyde at room temperature for 24 h, routinely embedded in paraffin, sliced to 4-5 um thickness and stained with hematoxylin and eosin for ~45 min at room temperature by Roche fully automated system (VENTANA HE600; Roche) and histological characteristics were observed under a light microscope (DM 2500; Leica GmbH). The lesion area was selected and 3-μm-thick formalin-fixed paraffin-embedded sections were subjected to immunohistochemical staining with S-100, CD34 (cytoplasmic), desmin (cytoplasmic), and P16 using Envision kit (Elabscience Biotechnology Co., Ltd.) according to the manufacturer's instructions. Paraffin-embedded tissues were submerged three times in xylene for 5 min each. The sections were washed in 95% ethanol for 2 min, 90% ethanol for 2 min, 85% ethanol for 2 min, 80% ethanol for 2 min, 75% ethanol for 2 min and distilled water for 2 min to remove the xylene. The sections were then placed in EDTA PH 9.0 Antigen Repair Solution (E-IR-R104, Elabscience Biotechnology Co., Ltd.) for 20 min at 50 °C. After cooling to room temperature, the sections were removed. Place in distilled water for 5 min. Submerge sections in 3% H2O2 (E-IR-R115, Elabscience) for 10 min at room temperature. Rinse well with distilled water. Rinse 3 times with PBS buffer for 5 min each. Drop ready-to-use goat serum (E-IR-R217A, Elabscience) and block for 30 min at room temperature. Primary antibody was added at 4°C for 12 h. Rinse 3 times with PBS buffer for 5 min each. Add ready-to-use polyperoxidase-anti-mouse/rabbit IgG (E-IR-R214B, Elabscience) at room temperature for 30 min. Rinse 3 times with PBS buffer for 5 min each. Add freshly prepared 20x diluted to 1x DAB developer (E-IR-R214D, Elabscience) for approximately 2-3 min. The sections were submerged in Mayer hematoxylin stain for approximately 5 min, washed with water to remove the stain, rapidly fractionated with 1% ethanol hydrochloride for 30 seconds, rinsed with tap water, and returned to blue for 1 min. Sections were sequentially placed in 75% ethanol for 1 min, 80% ethanol for 1 min, 90% ethanol for 1 min, 95% ethanol for 1 min, anhydrous ethanol twice for 3 min each, submerged in xylene twice for 5 min, and xylene (second) for 5 min, and the tissue was sealed by adding neutral gum dropwise on a coverslip. Primary antibodies were as follows: S-100 rabbit polyclonal (cat. no. ZA-0225, ready-to-use), CD34 rabbit monoclonal
(cat. no. ZM-0046, ready-to-use), P16 mouse monoclonal (cat. no. ZM-0205, ready-to-use) and desmin rabbit monoclonal (cat. no. ZA-0610, ready-to-use), purchased from Zhongshan Jinqiao Biotechnology Co., Ltd. Staining intensity and positive area were independently interpreted by two pathologists.

**FISH.** FISH detected the breakage and rearrangement of PLAG1. (8q12; gene ID: 5324). A PLAG1 mRNA probe (cat. no. CL-003; HealthCare Biotechnology Co., Ltd.) was designed and synthesized using cDNA as a template. The length of the probe was 1,090 kb. Total RNA was extracted from 50 mg lipoblastoma tissue stored at -80˚C using RNAiso Plus (cat. no. 9108; Takara Biotechnology Co., Ltd.) and RNase-free (cat. no. 2270A; Takara Biotechnology Co., Ltd.), followed by PrimeScript™ RT kit (dNTP and RNase Inhibitor are included) (cat. no. RR037A; Takara Biotechnology Co., Ltd) for RT using PLAG1 forward primer: GCCGCAACA AGTGGTGACCTC; reverse primer: CCAGACGACTTGGCT GCATGAG. Thermocycling: pre-denaturation 95˚C, 5 min; 95˚C, 15 sec, PCR reaction 60˚C for 1 min, 35 cycles; solubility curve phase 95˚C, 15 sec, 50˚C, 1 min, 95˚C, 30 sec. The target gene cDNA fragment was inserted into a plasmid (cat. no. 3340; Takara Biotechnology Co., Ltd.) containing a specific RNA polymerase (cat. no. 2520A; Takara Biotechnology Co., Ltd.) promoter sequence, and the recombinant plasmid was then amplified, purified. The plasmid template was cleaved with restriction enzyme (cat. no. TP060A/B; Takara Biotechnology Co., Ltd.) to linearize. And then under the action of RNAase (cat. no. RR420Q; Takara Biotechnology Co., Ltd), starting from the promoter site, the cDNA was used as a template for in vitro transcription. In the in vitro transcription reaction system, nucleotide feedstock with digoxigenin labeling is provided, and the labeled RNA probe is obtained after in vitro transcription. The nucleotide sequences were PLAG1-red end: CTD-2245E20, CTD-2124P3, CTD-2359C13; PLAG1-green end: CTD-2283H1, RPL11-22H14, CTD-2005O24, CTD-2344J3, CTD-2266F8, CTD-2130C19. Paraffin tissue sections of 3 µm thickness were selected and baked at 65˚C for 2 h. Sections were dewaxed: xylene 10 min x2 times, 100, 85, 70% gradient ethanol dehydration and dried. Sections were placed in distilled water at 100˚C for 25 min, covered with pepsin (20 µg/ml; cat. no. 9001-75-6; Guangzhou LBP Medicine Science and Technology Co., Ltd.), incubated at 37˚C for 20 min, and then incubated with 2x saline-sodium citrate (SSC; cat. no. 6132-04-3; Guangzhou LBP Medicine Science and Technology Co., Ltd.) for 10 min x2 times at room temperature, fixed in ethanol gradient dehydration and dried. Using a Thermobrite in situ hybridizer (S500-24; Leica), the probe was co-denatured with the tissue in hybridization buffer at 85˚C for 5 min and hybridized at 42˚C for 16 h. Gradient washes were performed under SSC buffer (2X SSC at 37˚C for 1 min, 1X SSC at 37˚C for 10 min, 0.5X SSC at 37˚C for 10 min). The slides were placed in pre-warmed 0.3% NP-40/0.4X SSC at 68˚C for 2 min. The sections were removed and immersed in pre-warmed deionized water at 37˚C for 1 min. The slides were dried naturally in the dark. No blocking reagent was applied in this experiment. DAPI re-staining agent (5 µg/ml; cat. no. 220401; HealthCare Biotechnology Co., Ltd.) was dropped onto the hybridized area, immediately covered with a coverslip, and then observed under a fluorescence microscope at 100x magnification (Axio Imager.A2; ZEISS). PLAG1 breaks were considered positive if ≥10% of at least 100 cells (positive control, salivary gland tumors from HealthCare Biotechnology Co., Ltd.) showed PLAG1 breaks. The results were analyzed using Isis software version 5.9.1 (MetaSystems).

**Statistical analysis.** SPSS 26.0 software (IBM Corp.) was used for statistical analysis of clinical pathological data. Values are expressed as median. Continuous variables that conformed to normal distribution were analyzed by one-way ANOVA with LSD method for post hoc tests and continuous variables that did not conform to normal distribution were analyzed by Kruskal-Wallis rank sum test. Fisher's exact test was used for categorical variables. P<0.05 was considered to indicate a statistically significant difference. Disease-free survival curves were constructed using the Kaplan-Meier method.

**Results**

**Clinical features.** Clinicopathological characteristics of lipoblastoma series (n=36) are shown in Tables I and II. The study included 22 males and 14 females (male to female ratio, 1.6:1.0) with age ranging from 7 days to 33 years (median, 1.5 years; mean, 3.2 years). A total of 28 and eight patients were aged ≤3 and >3 years (8/36, 22%), respectively. The median ages of patients with classic, lipoma-like and myxoid subtypes were 10 months (range, 7 days to 3 years), 2 years (range, 10 months to 7 years) and 4 years (range, 3 months to 33 years), respectively. There was a significant difference in age between the groups. The sites included the extremities (n=12, 33%), head and neck (n=6, 17%), trunk (n=16, 44%) and perineum (n=2, 6%); in most cases, the site was the abdomen (8/36 cases, 22%). Tumor size ranged from 1.7 to 16.2 cm (median, 4.7 cm; mean, 5.5 cm), without statistically significant differences between subtypes. In our case, lipoblastoma was more frequent in males, in patients no older than 3 years of age, and in the extremities. Patients are slightly older in the mucinous subtype.

Myxoid lipoblastomas were yellow-to-white, medium in texture and partly translucent. Classic and lipomatous lipoblastomas appeared more homogeneous, with a yellow appearance and medium texture, accompanied by fibrous septa and localized hemorrhage. Histologically, all subtypes of lipoblastoma exhibited fibrous septa (data not shown). Classic lipoblastoma (n=15) had lobular architecture and variable amounts of mature adipose tissue, with scattered lipoblasts, spindle cells and myxoid stroma accounting for <50% of the section (Fig. 1A). This subtype presented with mature banded morphology and a small amount of plexiform vascular tissue with a predominantly myxoid background. The lipoma-like subtype (n=13) consisted primarily of mature adipocytes of varying sizes surrounded by fibrous tissue with few lipoblasts or myxoid stroma (Fig. 1B). Myxoid lipoblastomas (n=8) were cytologically diverse, with a myxoid background accounting for >50% of the entire morphology, including a myxoid pool, stellate- and spindle-shaped primitive mesenchymal cells, a small number of adipocyte components, no pathological mitosis (Fig. 1C) and vascular plexiform, resembling myxoid liposarcoma.

**Molecular characteristics.** FISH identified PLAG1 breakage and rearrangement in 24 of 32 (75%) lipoblastoma
samples (Table II). There were no statistically significant differences between the subgroups (Table I). Representative FISH images are shown in Figs. 2 and 3. The \textit{PLAG1} gene breakage probe uses orange-red dye to label \textit{PLAG1} 3' end region (460 kb) and green dye to label the \textit{PLAG1} 5' end region (580 kb) with the 50 kb \textit{PLAG1} gene in the middle. In Fig. 2, orange-red and green signal are separated in the tumor cells, which represents breakage and rearrangement of \textit{PLAG1} in this tumor cell. By contrast, in Fig. 3, tumor cells did not undergo breakage and rearrangement of \textit{PLAG1} so the orange-red and green signals were not separated. In the classic and myxoid subgroups of lipoblastoma, FISH-negative detection rates were 27 and 29%, respectively, compared with 20% in the lipoma-like subtype. Therefore, the highest probability of \textit{PLAG1}-positive rearrangement was detected using FISH in the lipoma-like subgroup. Also, two of three relapsed patients tested negative for \textit{PLAG1} fragmentation and rearrangement. One patient failed the trial. Although S-100, CD34, P-16 and desmin IHC were not associated with recurrence in patients with lipoblastoma patients by Kaplan-Meier analysis (Fig. S1A-D), patients with positive \textit{PLAG1} fragmentation and rearrangement had a risk of relapse of only 0.57% of those with negative \textit{PLAG1}. Patients who were positive for \textit{PLAG1} fragmentation and rearrangement had a 99.49% lower risk of recurrence than those who were negative (Fig. S1E). However, there were only 3 patients with recurrence in the present study, including one patient who was not detected, which requires further verification with large samples.

\textbf{Immunohistochemical characteristics.} Immunohistochemical results are presented in Table SI. S-100-positive mono- or multivesicular lipoblasts were observed (29/36, 81%), with occasional mature adipocytes (Fig. 1F). CD34 (36/36, 100%) staining was diffusely strong in the cytoplasm of primitive spindle mesenchyme and peripheral vessels and abundant in blood vessels, highlighting a zonal pattern (Fig. 1G). Most tumor cells were negative while only few were positive for P16 (8/36, 22%; Fig. 1H). Desmin (26/36, 72%) staining was positive in primitive mesenchymal cells and striated muscle tissue in the dense fibrous septum (Fig. 1I). However, P16 IHC was less likely to be expressed in the lipoma-like subtype than in the other two subtypes (Table I).

\textbf{Follow-up.} In total, 28 cases were clinically followed up (range, 2-84 months; median, 41 months), of which 3 patients relapsed, 8 were lost to follow-up and others were alive without disease.

\textbf{Discussion} Here, 36 lipoblastoma cases underwent morphological, S-100, CD34, desmin and P16 immunohistochemical and \textit{PLAG1} FISH analysis. Other studies with similar sample size have mainly focused on the morphology and immunophenotyping (19,32). However, the present study attempted to diagnose at the molecular level. Similar to other cases (17-20), the majority of the present cases (28/36, 78%) were detected within three years of age. By contrast with the large series studied by Coffin \textit{et al} (19) (n=59), who reported a range of clinical associations in up to 17% of lipoblastomas, the present study did not identify any syndromic association, except for one case with complications of subcutaneous emphysema (case 20). According to other reports, more than one-fifth of

\begin{table}[h]
\centering
\caption{Characteristics of 36 patients with lipoblastoma.}
\begin{tabular}{|l|c|c|c|c|}
\hline
Characteristic & Total (n=36) & Classic subtype (n=15) & Lipoma-like subtype (n=13) & Myxoid subtype (n=8) & P-value \\
\hline
Male & 22 & 9 & 8 & 5 & 1.00$^a$
\hline
Age, months & & & & & 0.01$^b$
\hline
Mean & 38.98 & 15.08 & 33.08 & 93.38 & \\
Median (range) & 18.00 (0.23-396) & 10 (0.23-36) & 24 (10-84) & 48 (3-396) & \\
\hline
Location & & & & & 0.91$^a$
\hline
Extremities & 12 & 4 & 5 & 3 & \\
Head and neck & 6 & 4 & 1 & 1 & \\
Trunk & 16 & 6 & 6 & 4 & \\
Perineum & 2 & 1 & 1 & 0 & \\
\hline
Size, cm & & & & & 0.24$^c$
\hline
Mean & 5.54 & 4.58 & 6.46 & 5.85 & \\
Median (range) & 4.70 (1.70-16.20) & 4.00 (2.50-8.20) & 5.60 (1.70-16.20) & 5.10 (2.20-10.50) & \\
\hline
S-100$+$ & 29 & 12 & 10 & 7 & 1.00$^a$
\hline
CD-34$+$ & 36 & 15 & 13 & 8 & -
\hline
P-16$+$ & 8 & 5 & 0 & 3 & 0.03$^a$
\hline
Desmin$+$ & 26 & 9 & 10 & 7 & 0.40$^a$
\hline
FISH $PLAG1+$ & 24 & 11 & 8 & 5 & 1.00$^a$
\hline
\end{tabular}
\end{table}

\footnotesize{$^a$Fisher’s exact test; $^b$Kruskal-Wallis rank sum test; $^c$one-way ANOVA. -, not applicable; FISH, fluorescence \textit{in situ} hybridization; \textit{PLAG1}, pleiomorphic adenoma gene 1.}
Table II. Clinicopathological characteristics of lipoblastoma.

### A, Classic subtype (n=15)

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex/age</th>
<th>Location</th>
<th>Size, cm</th>
<th>PLAG1 FISH</th>
<th>Complete resection</th>
<th>Follow-up, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>M/7 m</td>
<td>Left armpit</td>
<td>5.6x5.4</td>
<td>+, 69%</td>
<td>Yes</td>
<td>AWOD, 78</td>
</tr>
<tr>
<td>3</td>
<td>M/10 m</td>
<td>Retroperitoneum</td>
<td>4.8x4.8</td>
<td>+, 30%</td>
<td>Yes</td>
<td>Lost to follow-up</td>
</tr>
<tr>
<td>4</td>
<td>F/6 m</td>
<td>Right neck</td>
<td>2.8x2.2</td>
<td>+, 39%</td>
<td>Yes</td>
<td>AWOD, 74</td>
</tr>
<tr>
<td>8</td>
<td>F/7 m</td>
<td>Right armpit</td>
<td>8.0x5.0</td>
<td>+, 28%</td>
<td>Yes</td>
<td>Lost to follow-up</td>
</tr>
<tr>
<td>10</td>
<td>M/1 y</td>
<td>Neck</td>
<td>4.0x3.0</td>
<td>-, 2%</td>
<td>Yes</td>
<td>AWOD, 64</td>
</tr>
<tr>
<td>12a</td>
<td>F/7 d</td>
<td>Abdominal wall</td>
<td>4.2x3.5</td>
<td>-, 2%</td>
<td>Yes</td>
<td>Lost to follow-up</td>
</tr>
<tr>
<td>15</td>
<td>M/3 y</td>
<td>Left scapular region</td>
<td>8.2x5.2</td>
<td>+, 35%</td>
<td>Yes</td>
<td>Lost to follow-up</td>
</tr>
<tr>
<td>16a</td>
<td>M/10 m</td>
<td>Armpit</td>
<td>3.1x3.1</td>
<td>+, 33%</td>
<td>Yes</td>
<td>AWOD, 54</td>
</tr>
<tr>
<td>18</td>
<td>F/1 y</td>
<td>Suprachlavicular fossa</td>
<td>2.5x2.0</td>
<td>-, 6%</td>
<td>Yes</td>
<td>AWOD, 53</td>
</tr>
<tr>
<td>19</td>
<td>M/8 m</td>
<td>Left maxilla</td>
<td>3.0x2.0</td>
<td>-, 3%</td>
<td>Yes</td>
<td>AWOD, 54</td>
</tr>
<tr>
<td>20</td>
<td>M/10 m</td>
<td>Mediastinum</td>
<td>4.0x4.0</td>
<td>+, 39%</td>
<td>Yes</td>
<td>Lost to follow-up</td>
</tr>
<tr>
<td>21</td>
<td>M/1 y</td>
<td>Perineum</td>
<td>3.8x2.7</td>
<td>+, 35%</td>
<td>Yes</td>
<td>AWOD, 39</td>
</tr>
<tr>
<td>25</td>
<td>M/2 y</td>
<td>Left armpit</td>
<td>5.7x5.0</td>
<td>+, 32%</td>
<td>Yes</td>
<td>AWOD, 31</td>
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<tr>
<td>31</td>
<td>F/3 y</td>
<td>Left chest wall</td>
<td>2.8x2.2</td>
<td>+, 57%</td>
<td>Yes</td>
<td>AWOD, 11</td>
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<tr>
<td>32</td>
<td>F/3 y</td>
<td>Right upper mediastinum</td>
<td>6.2x5.2</td>
<td>+, 45%</td>
<td>No</td>
<td>AWOD, 5</td>
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</table>

### B, Lipoma-like subtype (n=13)

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex/age</th>
<th>Location</th>
<th>Size, cm</th>
<th>PLAG1 FISH</th>
<th>Complete resection</th>
<th>Follow-up, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td>M/2 y</td>
<td>Left chest wall</td>
<td>6.0x4.0</td>
<td>-, 1%</td>
<td>No</td>
<td>AWOD, 68</td>
</tr>
<tr>
<td>11</td>
<td>M/2 y</td>
<td>Scrotum</td>
<td>1.7x1.3</td>
<td>+, 22%</td>
<td>Yes</td>
<td>AWOD, 63</td>
</tr>
<tr>
<td>13</td>
<td>M/5 y</td>
<td>Abdominal cavity</td>
<td>5.6x4.6</td>
<td>+, 35%</td>
<td>Yes</td>
<td>AWOD, 57</td>
</tr>
<tr>
<td>14a</td>
<td>F/3 y</td>
<td>Right parotid gland</td>
<td>3.4x3.3</td>
<td>ND</td>
<td>Yes</td>
<td>AWOD, 57</td>
</tr>
<tr>
<td>17</td>
<td>M/3 y</td>
<td>Right upper arm</td>
<td>7.2x5.0</td>
<td>-, 5%</td>
<td>Yes</td>
<td>Relapse after 54 months</td>
</tr>
<tr>
<td>21</td>
<td>F/1 y</td>
<td>Right popliteal fossa</td>
<td>9.7x5.0</td>
<td>+, 42%</td>
<td>Yes</td>
<td>AWOD, 43</td>
</tr>
<tr>
<td>23b</td>
<td>M/5 y</td>
<td>Mesentery</td>
<td>3.0x3.0</td>
<td>ND</td>
<td>NO</td>
<td>Relapse after 51 months</td>
</tr>
<tr>
<td>26</td>
<td>M/3 y</td>
<td>Mesentery</td>
<td>16.2x13.8</td>
<td>+, 31%</td>
<td>Yes</td>
<td>AWOD, 29</td>
</tr>
<tr>
<td>27</td>
<td>M/1 y</td>
<td>Right thigh</td>
<td>5.4x3.3</td>
<td>+, 23%</td>
<td>Yes</td>
<td>AWOD, 26</td>
</tr>
<tr>
<td>29</td>
<td>F/10 m</td>
<td>Abdomen</td>
<td>7.7x6.5</td>
<td>ND</td>
<td>Yes</td>
<td>AWOD, 18</td>
</tr>
<tr>
<td>30</td>
<td>F/7 y</td>
<td>Right foot</td>
<td>4.5x2.2</td>
<td>+, 42%</td>
<td>Yes</td>
<td>AWOD, 16</td>
</tr>
<tr>
<td>34</td>
<td>M/2 y</td>
<td>Left hip</td>
<td>4.1x2.6</td>
<td>+, 26%</td>
<td>Yes</td>
<td>AWOD, 3</td>
</tr>
<tr>
<td>35</td>
<td>F/1 y</td>
<td>Mesentery</td>
<td>9.5x9.4</td>
<td>+, 45%</td>
<td>Yes</td>
<td>AWOD, 3</td>
</tr>
</tbody>
</table>

### C, Myxoid subtype (n=9)

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex/age</th>
<th>Location</th>
<th>Size, cm</th>
<th>PLAG1 FISH</th>
<th>Complete resection</th>
<th>Follow-up, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/4 y</td>
<td>Right shoulder</td>
<td>4.6x4.4</td>
<td>+, 32%</td>
<td>Yes</td>
<td>Lost to follow-up</td>
</tr>
<tr>
<td>5a</td>
<td>F/3 m</td>
<td>Behind the right ankle</td>
<td>2.2x1.8</td>
<td>+, 41%</td>
<td>Yes</td>
<td>Lost to follow-up</td>
</tr>
<tr>
<td>6a</td>
<td>M/11 y</td>
<td>Right sole</td>
<td>3.8x2.8</td>
<td>+, 50%</td>
<td>Yes</td>
<td>AWOD, 71</td>
</tr>
<tr>
<td>9</td>
<td>M/8 y</td>
<td>Left thigh</td>
<td>10.0x5.0</td>
<td>-, 2%</td>
<td>Yes</td>
<td>Lost to follow-up</td>
</tr>
<tr>
<td>24a</td>
<td>M/1 y</td>
<td>Back</td>
<td>7.1x2.3</td>
<td>ND</td>
<td>Yes</td>
<td>AWOD, 32</td>
</tr>
<tr>
<td>28</td>
<td>M/33 y</td>
<td>Mediastinum</td>
<td>10.5x3.5</td>
<td>-, 2%</td>
<td>No</td>
<td>Relapse after 15 months</td>
</tr>
<tr>
<td>33</td>
<td>F/4 y</td>
<td>Right thoracic cavity</td>
<td>5.6x3.4</td>
<td>+, 82%</td>
<td>Yes</td>
<td>AWOD, 3</td>
</tr>
<tr>
<td>36</td>
<td>F/1 y</td>
<td>Neck</td>
<td>3.0x2.9</td>
<td>+, 47%</td>
<td>Yes</td>
<td>AWOD, 2</td>
</tr>
</tbody>
</table>

*aCase was lipoblastomatosis, infiltrating the skeletal muscle tissue; †primary tumor was 15x12x11 cm at the age of 1 year and recurred 51 months after incomplete resection, but the patient survived without disease for 33 months after re-excision. F, female; M, male; d, days; m, months; y, years; FISH, fluorescence in situ hybridization; AWOD, alive without disease; ND, not detected; PLAG1, pleiomorphic adenoma gene 1.
lipoblastomas occur in patients >3 years of age, consistent with the proportion reported in the present study (17,31). The present findings differ from those of other studies showing that lipoblastoma occurs most frequently in extremities, since lipoblastomas in the present cases occurred most frequently in the trunk (19,32-35). The patients were predominantly male and exhibited median tumor size of 4.7 cm. In certain studies, the recurrence rate in children reached 25% (1,6); here, only 3 (8%) recurrences occurred, 2 of which recurred because the tumor was too close to the adjacent organ with incomplete resection (in case 23, following recurrence the patient returned for further resection and was diagnosed with lipoma-like lipoblastoma, which matured into lipoma). The reason may be that the infant had relapsed after 51 months and the lipoblasts had matured and progressed. In another case (case 17), recurrence occurred in situ in the superficial subcutaneous fascia of the right upper arm 54 months after complete resection. The longest (case 17) and shortest (case 28) intervals between recurrences were 54 and 15 months, respectively.

Notably, recurrence occurred in two of four patients (50%; at 1 and 33 years of age, respectively) with incomplete tumor resection; three patients (case 7, 23, and 32) were young and
or (36) conducted a DDX6 -PLAG1, skeletal muscle tissue can be observed in lipoblastomatosis, lipoblastomas (34). Similar to intramuscular lipoma, residual recommended (6). A total of seven cases had lipoblastoma resected tumors. Close follow‑up for at least five years is recommended regardless of age. The clinical outcome primarily depends on the complete‑ness of resection, with a high recurrence rate in incompletely resected tumors. Close follow‑up for at least five years is recommended (6). A total of seven cases had lipoblastoma resected tumors. Close follow‑up for at least five years is recommended regardless of age.

Moreover, NGS not only detects PLAG1 or HMGA2 rearrangements with high sensitivity but also identifies PLAG1‑associated fusion genes. Numerous fusion gene partners [dead‑box helicase 6 (DDX6), klf transcription factor 10 (KLF10), kat8 regulatory nsl complex subunit 1 like (KANSL1L), hyaluronan synthase 2 (HAS2), collagen type III alpha 1 chain (COL3A1), rad51 paralog b (RAD51L1), collagen type I alpha (36) conducted a meta‑analysis and found that lipoblastomatosis has a higher risk of recurrence than localized lipoblastoma (odds ratio=5.1; 95% confidence interval, 1.9‑15.9).

The clinical outcome primarily depends on the complete‑ness of resection, with a high recurrence rate in incompletely resected tumors. Close follow‑up for at least five years is recommended (6). A total of seven cases had lipoblastoma resected tumors. Close follow‑up for at least five years is recommended regardless of age.

The primary genetic feature of lipoblastoma is chromosomal translocation (minor inversions, insertion and circular chromosomes), resulting in the rearrangement of PLAG1, which encodes a zinc finger transcription factor that is expressed during fetal life and is present at low levels or absent in most adult organs (9). In lipoblastoma, exons 2 or 3 of PLAG1 most commonly combine with exon 1 at the N‑terminus of partner genes (the fourth exon is the coding region containing the initiation codon) (12) so that the entire coding sequence is retained under transcriptional control of a more active promoter (37), resulting in subsequent upregulation (14,38). In a mouse model, overexpression of PLAG1 was found to induce tumorigenesis (39). Here, 75% of cases showed PLAG1 breakage and rearrangement, greater than the 60‑70% reported in the literature (31,34,38). Coiled‑Coil‑Helix -Coiled‑Coil‑Helix Domain Containing 7 (CHCHD7‑PLAG1) fusion, which also results in promoter swap and PLAG1 activation, has been reported as a recurrent event in salivary gland pleomorphic adenoma (40‑42). Two studies reported that hyaluronan synthase 2 (HAS2) (8q24.1) and serine and arginine rich splicing factor 3 (SRSF3) (6p21.3‑p21.1) fusion genes are prone to local recurrence in lipoblastoma (9,28). At present, RNA next‑generation sequencing (NGS) serves a key role in the classification and diagnosis of soft tissue tumors, including defining the tumors, especially in cases where the morphology is atypical and immunohistochemistry cannot indicate the specific tumor type (31). It has been suggested that even if FISH and immunohistochemistry results are negative, the tumor may still be a lipoblastoma because high mobility group at‑hook 2 (HMGA2) is an upstream regulatory activator of PLAG1 (43). In the absence of chromosome 8 abnormality involving the PLAG1 locus, HMGA2 induces activation and overexpression of PLAG1; therefore, PLAG1 FISH and immunohistochemistry results may be negative in cases with HMGA2 rearrangement.

PLAG1 expression has been observed in the absence of PLAG1 rearrangements, suggesting an alternative mechanism underlying alterations in genes upregulates PLAG1 expression, such as increasing the PLAG1 copy number, as proposed previously (38,44). Thus, the diagnostic role of PLAG1 immunohistochemistry is limited, particularly in morphologically difficult cases of mature lipoblastoma, where only sparsely positive immature adipocytes and spindle cells are typically identified; this finding is consistent with the results of Lopez‑Nunez et al (17). However, if PLAG1 FISH is positive in adipose tumor, an accurate diagnosis can be made using a combination of morphology and immunohistochemistry. Therefore, it was hypothesized that when lipoblastoma is suspected, FISH detection of PLAG1 may replace PLAG1 immunohistochemistry.
2 chain, ras-related protein rab-2a (RAB2A), CHCHD7, serine and arginine rich splicing factor 3 (SRSF3), heterogeneous nuclear ribonucleoprotein e (HNRNPC), protein-1-isosacparte (d-aspartate) o-methyltransferase domain containing 1 (PCMTD1), tyrosine 3-monoxygenase/tryptophan 5-monoxygenase activation protein zeta (YWHAZ), ctd small subunit α, boc cell adhesion associated, oncogene regulated, zinc finger e-box binding homeobox 2, runx1 partner transcriptional co-repressor 1, Versican, peptidase inhibitor 15 and eukaryotic translation elongation factor alpha 1 (PLAG1) have been identified in lipoblastoma (8,14,17,31,37,44-52). These fusions lead to overexpression of PLAG1 (17,37). Although only the YWHAZ promoter is fused to PLAG1, it does not contribute to protein expression (49). The rearrangement of PLAG1 [a transcriptional activator of Insulin Like Growth Factor 2 (IGF2)] in lipoblastoma activates the MAPK and PI3K/AKT signaling pathways by directly increasing expression of IGF2 and promoting the differentiation of CD34-positive primitive mesenchymal cells into lipoblasts (14,53). Pleomorphic adenoma and lipoblastoma with PLAG1 rearrangement differ in their partner genes (13,54). In salivary gland tumors, the primary targets of translocation are DNA-binding transcription factors (PLAG1 and HMGA2) involved in growth factor signaling and cell cycle regulation as well as co-activators of Notch [mastermind like transcriptional coactivator 2, (MAML2)] and cAMP (target of rapamycin complex 1, (TORC1)] signaling pathways. These fusion genes, which are also involved in molecular tumor pathways, serve a key role in tumorigenesis. Therefore, timely identification of the associated genetic alterations and molecular classification of these childhood lesions are important for proper follow-up, evaluation of potential recurrence and avoidance of secondary surgery.

The histological diagnosis of lipoblastoma with typical morphological features is relatively straightforward in infancy and early childhood. In first-born infants, tumors are predominantly composed of primitive mesenchymal cells with extensive myxoid stromal and minimal lipoblastoid components; therefore, primitive myxoid mesenchymal tumor of infancy (PMMTI) should be considered, which exhibits a more aggressive behavior (55). PMMTI has typical cellular atypia, strong mitotic activity and distinct round cellular component compared with lipoblastoma, as reported by Warren et al (50). PMMTI can overlap with undifferentiated myxoid lipoblastoma, which resembles myxoid lipoblastoma. Notably, RNA NGS has been used to assess internal tandem repeats of BCL6 corepressor, a characteristic change in PMMTI (56). Lipoblastoma-like tumors of the vulva (LLTV) occur in adults, mostly commonly at age 17-46 years. Most often, LLTV presents as a unilateral, severely myxoid, gelatinous, well-circumscribed, lobulated vulvar mass. The morphology includes lobulated and varied proportions of mature adipocytes; mild lipoblasts; spindle cells with short, thick nuclei and prominent branching vessels with minimal nuclear atypia in a diffuse myxoid background. In LLTV, mitosis without necrosis is rare. Therefore, it also shows histological overlap with lipoblastoma (57). Here, two cases of lipoblastoma occurred in the perineal region (cases 11 and 22); both were males aged <2 years. FISH showed PLAG1 rearrangement; therefore, LLTV was excluded. In children, the morphological appearance of a lipoma-like subtype requires differential diagnoses, including lipoma, lipoblastomatosis, fibrous hamartoma of infancy, atypical lipomatous tumor/well-differentiated liposarcoma and non-neoplastic lesions with post-traumatic fat necrosis (such as post-traumatic pseudolipoma) (Table III). Microscopically, lipoblastomatosis may have a spindle cell component in fascicular cells, lack lipoblasts and show more invasive growth in the surrounding tissue (58). In cases of post-traumatic fat necrosis, morphology is characterized by chronic inflammatory changes, fat necrosis and hematoma formation. A clinical history is helpful for diagnosis (59). Although lipoblastoma can be differentiated from liposarcoma based primarily on age, when lipoblasts mature, especially in older adults or deep in the limbs, mediastinum, abdominal pelvis or retroperitoneum, they tend to be larger. In these cases, tumors present with extensive myxoid or lipomatous morphology and rare lipoblasts, especially focal adipocytes and stromal cells, with nuclear atypia and local invasiveness. In such cases, other diseases such as myxoid liposarcoma and atypical lipomatous tumor/well-differentiated liposarcoma should be considered (58,60). With fine-needle biopsy specimens, it is difficult to histologically distinguish lipoblastoma, which may require further molecular detection (61). (PLAG1 and DDIT3) and (PLAG1 and MDM2) genetic fusion testing may confirm this diagnosis. In addition, insulin-induced lipatrophy should be considered if there is a clinical history of diabetes or malnutrition, as these cases may exhibit myxoid changes and pseudolipoblasts (62). The morphology of the classic subtype of lipoblastoma is more typical (31). In case 34, lipoblastoma with fibrolast morphology which is the fourth class of lipoblastoma (31) was focally present but surrounded by classic lipoblastoma. Thus, it was classified as a classic subtype. The fifth class of lipoblastoma, consisting primarily of multicellular lipoblasts, some of which have central nucleus and granular eosinophilic cytoplasm lacking a myxoid component, was not observed in the present study. The tumor was named lipoblastoma with hibernoma-like features (38). Studies have reported that P16 effectively differentiates benign lesions from liposarcoma (24,63). It is necessary to combine CD34-positive primitive mesenchymal cells with a more characteristic histological morphology in lipoblastoma with clinical information and biological behavior to diagnose lipoblastoma. Clinical features, histological morphology, biological behavior, immunohistochemical expression, and genetic changes of the 12 tumors that are difficult to differentiate from lipoblastoma are summarized in Table III.

In clinical practice, rapid FISH detection is favored by pathologists for soft tissue tumors because of its rapidity, low cost and high diagnostic efficiency. Here, the frequency of PLAG1 rearrangement (75%) in lipoblastoma was higher than that reported in previous studies (17,38); however, 4 lipoblastomas were not successfully detected. Quality control review was performed to rule out factors that were more likely to be associated with short formalin fixation time, too old specimens and DNA degradation. In addition, the present study lacked a control group for other adipose tumors and only tested PLAG1 for lipoblastoma.

In the classic and myxoid subgroups of lipoblastoma, FISH-negative detection rates were 27 and 29%, respectively,
Table III. Clinicopathological features of the differential diagnoses of lipoblastoma.

### A, Lipoblastoma with predominant myxoid morphology

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Features</th>
<th>First author, year (Refs.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myxoid liposarcoma</td>
<td>Myxoid liposarcoma is rare in children, usually occurs in 30-60-year-old adults. Histomorphologically, mature adipocytes in the lobules are concentrated in the periphery, whereas in lipoblastoma, maturation occurs in the center of the lobule and the periphery is composed of more primitive cells, lacking the enrichment phenomenon cells around blood vessels. The focal nuclei are atypical and pleomorphic, with pathological mitosis. A characteristic pulmonary edema morphology is observed due to the pooling of matrix mucins. Tumor cells express S-100 protein and NY-ESO-1 to varying degrees and are negative for CD34, desmin, keratin, SMA, MDM2 and CDK4. In this tumor, rearrangement of chromosome 12q13 (CHOP/DDIT3) with translocation partners 16p11 (FUS-TLS) or 22p11 (EWSR1) results in disruption of the CHOP gene on chromosome 12.</td>
<td>Coffin, 2012 (58)</td>
</tr>
<tr>
<td>PMMTI</td>
<td>PMMTI primarily occurs in infants, mainly on the trunk, neck, and extremities. Histomorphologically, there are mainly round cell components, primitive mesenchymal cells and myxoid matrix, curvilinear-plexiform vascular morphology, pseudolipoblasts, cellular atypia, and frequent mitosis. S-100 expression is negative on histochemistry. BCOR-ITD or YWHAE gene rearrangement and lack of PLAG1 gene rearrangement are seen in this tumor.</td>
<td>Warren, 2021 (47); Deen, 2013 (52); Andersson, 2019 (53)</td>
</tr>
<tr>
<td>Invasive angiomyxoma</td>
<td>Invasive angiomyxoma primarily occurs in young and middle-aged females. Histomorphologically, there are spindle and asteroid cell with unclear boundaries, thin-walled or thick-walled blood vessels of varying sizes distributed in a myxoid matrix rich in slender collagen fibers, atypical tumor cells, small round or oval nuclear, and no mitosis. Tumor cells express vimentin, desmin, ER, and PR; most nuclei express HMGA2; CD34 and S-100 are not expressed. HMGA2 (12q14.3) rearrangement is seen in this tumor.</td>
<td>Yang, 2021 (28)</td>
</tr>
<tr>
<td>LLTV</td>
<td>LLTV primarily occurs in adult females, primarily in the vulva or groin. Histomorphologically, there are lobular appearance, mature adipocytes interspersed with spindle cells, lipoblasts, myxoid matrix, branching vessels, and no banded mature morphology. On histochemistry the tumor loses nuclear expression of RB protein (usually mosaic morphology) and is negative for S-100, PLAG1, and HMGA2 expression. The tumor has no DDIT3T fusion and no evidence of PLAG1 gene alteration, and associates with chromosomal 13q alteration.</td>
<td>Stenman, 2005 (54)</td>
</tr>
<tr>
<td>Lipoatrophy</td>
<td>Lipoatrophy primarily occurs in adults with a clinical history of insulin-dependent diabetes or starvation (malnutrition or anorexia). Histomorphologically, there are presence of lobular architecture, myxoid changes, and pseudolipoblasts.</td>
<td>Jermendy, 2000 (62)</td>
</tr>
<tr>
<td>Superficial angiomyxoma</td>
<td>Superficial angiomyxoma is rare in infants and young children, more common in middle-aged people (median age 40 years). Histomorphologically, there are abundant myxoid matrix, sparse spindle or asteroid cells, and slender capillaries, lobulated structures with indistinct boundaries. Lack of lipoblasts at different developmental stages are key to differential diagnosis. Tumor cells express CD34; some cells are positive for SMA, MSA, and desmin; S-100 is not expressed.</td>
<td>Iwashita, 2020 (29)</td>
</tr>
</tbody>
</table>

### B, Lipoblastoma with predominant mature lipoma-like morphology

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Features</th>
<th>First author, year (Refs.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipofibromatosis</td>
<td>Lipofibromatosis primarily occurs in infants (congenital subgroup) to 14 years of age. Histomorphologically, there are infiltration in skeletal muscle, spindle cell components forming long thin fascicles, mature adipose tissue, and absent of lipoblasts. Spindle cells express vimentin, CD34, and</td>
<td>Mirkovic, 2015 (57)</td>
</tr>
</tbody>
</table>
compared with 20% in the lipoma-like subtype. The higher negative detection rate in the first two groups indicated that in certain cases, lipoblastoma may not result in cytogenetic segregation of the target gene, which leads to undetected rearrangements by FISH (64). RNA NGS may improve diagnostic accuracy. Therefore, RNA NGS is necessary, especially for uncommon age groups or morphologically atypical populations. Lipoblastomas mature into regular lipomas or are similar to fibrolipoma (25,34). Here, subjects with a median age of up to three years had the lipoma-like subtype. Whether older individuals have a higher tendency to develop the lipoma-like subtype or mature lipoma requires further experimental verification, clinical observation and molecular characterization to clarify the occurrence and development of the disease.

Patients with lipoblastoma are usually within the age of three years; however, the disease cannot be ruled out in patients older than three years and may also occur in adults with mature adipose tissue with prominent lobular structures. Immunohistochemistry showing S-100-positive single or multivesicular adipocytes and CD34- and desmin-positive primitive mesenchymal cells as well as FISH results indicating \textit{PLAG1} gene breakage and rearrangement are key to diagnosis and differential diagnosis.

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All data generated or analyzed during this study are included in this published article.

Authors' contributions
WZ collected and analyzed data and wrote the paper. WZ, SZ, ZY and YZ performed immunohistochemistry and FISH. ZW conceived and supervised the study, WZ and ZW confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate
The study was approved by the Institutional Review Committee of Shengjing Hospital of China Medical University (approval no. 2022PS104J). The requirement for written informed consent was waived due to the retrospective nature of the study.

Patient consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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4. Jandali D, Heilingoetter A, Ghai R, Jeffe J and Al-Khudari S: The authenticity of all the raw data. All authors have read and approved the final manuscript.