INTRODUCTION

Choledochal cysts are one of the most common congenital biliary diseases in children. Significant potential complications associated with choledochal cysts include cholelithiasis, cholangitis, pancreatitis, secondary biliary cirrhosis, malignancy, and perforation [1]. Choledochal cyst perforation with subsequent bile peritonitis is an uncommon occurrence, with an incidence of 2%–12% [2-4]. The exact pathogenesis of...
perforation in choledochal cysts is unknown; however, the proposed mechanisms include mural immaturity of the ductal wall, pancreatic juice reflux due to an anomalous pancreaticobiliary ductal union (APBDU), and increased intraductal pressure due to impacted bile plugs [5-10].

Choledochal cyst perforation initially manifests as acute abdominal pain, but it is not often diagnosed preoperatively in actual practice when clinical and radiologic signs are subtle. A delay in the diagnosis of choledochal cyst perforation can be fatal. Therefore, an adequate diagnosis is critical for early surgical treatment [11,12]. Some radiologic findings of choledochal cyst perforation in children have been reported as a small case series, with diagnoses mostly after laparotomy [3,6,13-16]. Overall, data regarding the clinical and radiologic findings of choledochal cyst perforation in children are limited.

Therefore, the purpose of this study was to compare the clinical and radiologic findings between perforated and non-perforated choledochal cysts in children.

MATERIALS AND METHODS

Study Population

This retrospective study was conducted at two tertiary referral centers and was approved by the Institutional Review Boards of the Samsung Medical Center (IRB No. 2019-11-192) and Seoul National University Children’s Hospital (IRB No. H-2109-158-1259). The requirement for informed consent was waived, and patient information was anonymized prior to analysis.

Patients who underwent choledochal cyst excision were identified through a search of electronic medical records. In the database search, we identified 502 consecutive patients under 15 years of age at two institutions (214 and 288, respectively) between January 2000 and November 2019. Among them, choledochal cyst perforation was identified in 10 (4.7%) and 4 (1.4%) patients, respectively, at two institutions. Eventually, 14 children (male to female ratio, 3:11; mean age, 1.7 years old at the time of operation; range, 0.1–3.5 years) were included as cases (perforated group). The control group (non-perforated group) comprised 204 children with non-perforated choledochal cysts (male to female ratio, 61:143; mean age, 3.6 years; range, 0–13.8 years) at one institution. Each patient underwent preoperative hepatobiliary ultrasound (US), CT, or MR cholangiopancreatography (MRCP). In all patients, the diagnosis of choledochal cyst was confirmed by laparotomy, histological analysis of the bile ducts, and/or intraoperative cholangiography. Choledochal cyst perforation was confirmed by the identification of biliary peritoneal fluid during laparotomy. We also performed subgroup analyses for subjects with ascites to determine the influence of ascites on the diagnosis of choledochal cyst perforation.

The medical records were reviewed for clinical characteristics and laboratory data upon admission. Pancreatic enzymes, including serum amylase and lipase, and biochemical hepatic function tests, including aspartate aminotransferase, alanine aminotransferase, total bilirubin, albumin, and gamma-glutamyl transferase, were evaluated. Acute symptoms included abdominal pain, fever, vomiting, abdominal distension, tenderness, lethargy, and altered mental status. Acute pancreatitis was diagnosed when two of the following three criteria were present: acute abdominal pain, elevation in serum amylase or lipase to a level three times or greater than normal, and typical findings of acute pancreatitis on imaging [17].

Image Acquisition

All preoperative US examinations (n = 181) were performed by one of three pediatric radiologists (three radiologists with nine, four, and two years of experience in pediatric US when each first evaluated the study subjects). The US systems (Sequoia, Siemens Healthineers; LOGIQ E9, GE Healthcare) were equipped with high-resolution linear-array transducers (5–10 MHz, 9 MHz, and 6–15 MHz) and curved-array transducers (4 MHz, 1–5 MHz, and 6 MHz) were used for the examinations. The mean interval between US examination and surgery was 22 days (range, 0 days–6.2 months).

Preoperative CT examinations (n = 68) were conducted using multidetector CT machines (LightSpeed 16 or LightSpeed VCT XT, GE Healthcare; SOMATOM Definition Flash, Siemens Healthineers) with a low-dose technique based on each patient’s weight and with automatic exposure control. Two phases (arterial and portal phase, n = 12) and a single portal phase (n = 56) were obtained after injection of intravenous contrast material (2 mL/kg [maximum 120 mL] iomeprol, 300 mg iodine/mL; Iomeron 300, Bracco). Imaging parameters were 80–100 kV and 27–80 mA with a 2–5 mm section thickness (ST). The mean interval between US and CT examinations was 20.5 days (range, 0 days–7.9 months), and the mean interval between CT examination and surgery was 27.4 days (range, 1 day–8.9 months).

Preoperative MRCP examinations (n = 194) were
performed using a 1.5T or 3T unit (Achieva, Philips Healthcare; MAGNETOM Avanto, Siemens Healthineers). The protocol included axial and coronal single-shot spin-echo T2-weighted images (repetition time/echo time = 820–7742/52–120 ms, ST = 3–6 mm, field of view = 140–250 mm, matrix = 200–384 x 128–256), non-breath-hold, respiratory-triggered, heavily T2-weighted turbo spin-echo images (677–2400/150–187 ms, 3–5 mm, 140–250 mm, 200–256 x 160–250), and three-dimensional (3D) MRCP (1200–4600/188–750 ms, 2–3 mm, 170–250 mm, 200–256 x 126–256). The 3D acquisition images were reformatted using a standard maximum intensity projection algorithm to create a rotating display. MRCP studies were performed during natural sleep or sleep using sedatives. The mean interval between US examination and MRCP was 15.1 days (range, 0 days–7.3 months), and the mean interval between MRCP examination and surgery was 14.7 days (range, 0 days–9.4 months).

Image Analysis
Two pediatric radiologists (with 11 and 5 years of pediatric imaging interpretation experience) retrospectively reviewed all images in consensus. Although the reviewers knew that all patients had undergone choledochal cyst excision, they were blinded to all other clinical information. The reviewers were requested to prioritize the MRCP data, and CT and US images were analyzed.

The parameters assessed using the imaging studies included the type, maximum diameter, and shape of choledochal cysts, presence of APBDU, presence of dilated common channels containing bile plugs, common bile duct (CBD) stone/sludge, choledochal cyst wall thickening, gallbladder contraction, the presence of discontinuity of the bile duct wall, and the presence of ascites (amount, temporal change in the amount of ascites, complex ascites, and presence of pseudocyst). The type of choledochal cyst was classified according to the Todani classification [18]. The maximum choledochal cyst diameter was measured using a transverse scan. The choledochal cysts were classified as fusiform when its shape is close to cylindrical and cystic when close to spherical [19]. The presence of APBDU was assessed using MRCP, CT, or intraoperative cholangiography. The presence of a dilated common channel containing bile plugs was evaluated in patients with APBDU [20]. Choledochal cyst wall thickening was defined as a cyst wall greater than 1.5 mm [21]. A small amount of ascites was defined as grade 1, whereas a large amount of ascites was defined as grade 2 or 3 according to the International Ascites Club [22]. If more than two preoperative imaging studies of any modality (US, CT, MRCP, or abdominal radiograph) were conducted within one week, the two studies were compared to estimate whether any temporal change had occurred in the amount of ascites. Complex ascites was defined as free peritoneal fluid with low-level echoes, increased density, or septation. Pseudocysts were defined as encapsulated, loculated fluid collection, and the location of the pseudocysts was assessed. Gallbladder contraction was defined as a collapsed lumen of the gallbladder with wall thickening.

Statistical Analysis
Descriptive data were expressed as the mean ± standard deviation and were tested using the Mann–Whitney U test after evaluating for normality with the Shapiro–Wilk test. Differences in categorical variables were expressed as counts and percentages and were analyzed using Fisher’s exact test. Statistical analyses were performed using IBM SPSS Statistics for Windows (version 23.0; IBM Corp.). Statistical significance was set at \( p < 0.05 \).

RESULTS
Clinical Characteristics and Laboratory Data
The clinical characteristics and laboratory data of the perforated and non-perforated groups are presented in Table 1. Choledochal cyst perforation occurred only in patients under four years of age. Acute symptoms, such as fever (57%, 8/14) \( (p < 0.001) \) occurred more frequently in the perforated group than in the non-perforated group. The white blood cell (WBC) count (13000 ± 4500/µL) \( (p = 0.004) \), C-reactive protein (CRP) \( (3.1 ± 3.1 \text{ mg/dL}) \) \( (p < 0.001) \) and serum amylase \( (675.6 ± 490.1 \text{ U/L}) \) \( (p = 0.004) \) were higher, and the albumin \( (3.4 ± 0.6 \text{ g/dL}) \) \( (p < 0.001) \) levels were lower in the perforated group than in the non-perforated group. The white blood cell (WBC) count (13000 ± 4500/µL) \( (p = 0.004) \), C-reactive protein (CRP) \( (3.1 ± 3.1 \text{ mg/dL}) \) \( (p < 0.001) \) and serum amylase \( (675.6 ± 490.1 \text{ U/L}) \) \( (p = 0.002) \) levels were higher, and the albumin \( (3.4 ± 0.6 \text{ g/dL}) \) \( (p < 0.001) \) levels were lower in the perforated group than in the non-perforated group. No significant differences were noted in sex, acute pancreatitis, mortality, or other biochemical hepatic function tests between the two groups. Three patients in the perforated group underwent abdominal paracentesis \( (n = 1) \) or percutaneous fluid drainage \( (n = 2) \), which revealed biliary ascites.

None of the patients in the perforated group had a history of trauma. Twelve patients in the perforated group underwent one-stage cyst excision surgery with hepaticojejunostomy, and the remaining two patients
underwent two-stage procedures with initial drainage followed by delayed excision. The location of perforation was identified during surgery in 10 patients (mid-CBD, n = 4; between the cystic duct and common hepatic duct, n = 3; distal CBD, n = 1; gallbladder, n = 1; and left intrahepatic duct, n = 1), whereas the precise location was not found in four cases. The mean postoperative follow-up was 7.8 ± 6.4 years in the perforated group and 10.4 ± 5.4 years in the non-perforated group. All except one patient in both groups recovered without incident, but one patient with choledochal cyst perforation died due to pulmonary hypertension and cardiac failure three years after surgery.

**Imaging Findings**

All patients except one had either type I or IV choledochal cysts; one patient had a type V choledochal cyst. The type, size, and shape of the choledochal cysts did not differ between the perforated and non-perforated groups (Table 1). No significant differences were noted in the presence of APBDU (45% [5/11] vs. 41% [81/199]).

| Table 1. Comparisons of Clinical and Radiological Findings between Perforated and Non-Perforated Groups |
|-------------------------------------------------------------|
| Variables | Perforated Group (n = 14) | Non-Perforated Group (n = 204) | P  |
|---|---|---|---|
| Male | 3/14 (21) | 61/204 (30) | 0.762 |
| Age at operation, year | 1.7 ± 1.2 | 3.6 ± 3.8 | 0.231 |
| Acute symptoms | 14/14 (100) | 129/204 (63) | 0.003 |
| Abdominal pain | 9/14 (64) | 86/204 (42) | 0.162 |
| Fever | 8/14 (57) | 13/204 (6) | < 0.001 |
| Acute pancreatitis | 9/14 (64) | 51/107 (48) | 0.270 |
| Mortality | 1/14 (7) | 0/204 (0) | 0.064 |
| Laboratory data | | | |
| WBC, x 10^9/µL | 13.0 ± 4.5 | 9.7 ± 3.7 | 0.004 |
| CRP, mg/dL | 3.1 ± 3.1 | 0.8 ± 2.5 | < 0.001 |
| Amylase, U/L | 675.6 ± 490.1 | 262.2 ± 457.0 | 0.002 |
| Lipase, U/L | 1315.0 ± 1516.3 | 1084.5 ± 2776.8 | 0.066 |
| AST, U/L | 121.9 ± 132.5 | 94.9 ± 113.6 | 0.240 |
| ALT, U/L | 98.7 ± 125.4 | 104.5 ± 142.2 | 0.713 |
| Total bilirubin, mg/dL | 2.0 ± 1.5 | 2.7 ± 3.3 | 0.292 |
| Albumin, g/dL | 3.4 ± 0.6 | 4.3 ± 0.5 | < 0.001 |
| GGT, U/L | 369.6 ± 221.0 | 340.5 ± 446.6 | 0.091 |
| Radiologic findings | | | |
| Type I, choledochal cyst | 7/14 (50) | 122/203 (60) | 0.576 |
| Type IV, choledochal cyst | 7/14 (50) | 81/203 (40) | |
| Size of choledochal cyst, mm | 18.8 ± 15.6 | 27.7 ± 19.8 | 0.089 |
| Fusiform shape of cyst | 11/14 (79) | 169/204 (83) | 0.715 |
| APBDU | 5/11 (45) | 81/199 (41) | 0.762 |
| Dilated common channel with bile plugs | 3/5 (60) | 29/81 (36) | 0.356 |
| CBD stone/sludge | 9/14 (64) | 99/204 (49) | 0.282 |
| Cyst wall thickening | 8/14 (57) | 65/204 (32) | 0.076 |
| Gallbladder contraction | 4/14 (29) | 64/203 (32) | 1.000 |
| Ascites | 14/14 (100) | 33/204 (16) | < 0.001 |
| Small | 6/14 (43) | 30/33 (91) | 0.001 |
| Large | 8/14 (57) | 3/33 (9) | |
| Temporal change in the amount | 9/12 (75)* | 1/27 (4)† | < 0.001‡ |
| Complex | 10/14 (71) | 3/33 (9) | < 0.001‡ |
| Pseudocyst | 8/14 (57) | 0/33 (0) | < 0.001‡ |

Data are the numbers of patients, nominator/denominator with the percentage in parentheses, or mean ± standard deviation. *All nine patients showed increased ascites for an average of 3.5 days (range, 8–9 days). †One patient showed decreased ascites at a 4-day interval. ‡P values are based on subgroup analysis of patients with ascites, comparing perforated group (n = 14 or 12) and non-perforated group (n = 33 or 27). ALT = alanine aminotransferase, APBDU = anomalous pancreaticobiliary ductal union, AST = aspartate transaminase, CBD = common bile duct, CRP = C-reactive protein, GGT = gamma-glutamyl transferase, WBC = white blood cell.
Perforated vs. Non-Perforated Pediatric Choledochal Cysts

Fig. 1. Perforated choledochal cyst with a large amount of ascites and a pseudocyst in a 2-year-old girl (clinical manifestations: abdominal pain, fever, high levels of white blood cells, C-reactive protein, and serum amylase, and low levels of albumin).
A. US image shows a pseudocyst in the right subhepatic space (arrows), as well as the choledochal cyst (asterisk). B, C. MR cholangiopancreatography images at 4 days after US shows a pseudocyst in the right subhepatic space (arrows), a large amount of ascites (increase in the amount of ascites compared to US), and choledochal cyst (asterisks). US = ultrasound

(p = 0.762), dilated common channel containing bile plugs (60% [3/5] vs. 36% [29/81]) (p = 0.356), CBD stone/sludge (64% [9/14] vs. 49% [99/204]) (p = 0.282), cyst wall thickening (57% [8/14] vs. 32% [65/204]) (p = 0.076), or gallbladder contraction (29% [4/14] vs. 32% [64/203]) (p = 1.000) between the two groups. There were no cases of discontinuity of the bile duct wall in the perforated group. All 14 patients had ascites in the perforated group, but only 16% (33/204) of the non-perforated group had ascites (p < 0.001).

Subgroup Analysis of Patients with Ascites

Separate comparisons were performed in a subgroup of patients with ascites between the perforated group (n = 14) and the non-perforated group (n = 33). Patients in the perforated group had more frequent fever (57% [8/14] vs. 21% [7/33]) (p = 0.037), higher WBC counts (13000 ± 4500/µL vs. 10000 ± 3800/µL) (p = 0.027), higher CRP levels (3.1 ± 3.1 mg/dL vs. 0.4 ± 0.5 mg/dL) (p < 0.001), and lower albumin levels (3.4 ± 0.6 g/dL vs. 4.3 ± 0.4 g/dL) (p < 0.001) than in the non-perforated group with ascites. Of the 59% (16/27) of patients with acute pancreatitis in the non-perforated group with ascites, three patients had large amounts of ascites, but with a normal range of CRP and albumin levels.

Imaging findings revealed a large amount of ascites (57%, 8/14) in the perforated group (p = 0.001) (Fig. 1). Short-term temporal changes in the amount of ascites were also more frequent in the perforated group (75%, 9/12) than in the non-perforated group with ascites (4%, 1/27) (p < 0.001) (Fig. 2). The perforated group exhibited increased ascites for an average of 3.5 days (range, 8–9 days) in 75% (9/12) of the cases. In contrast, the cases in the non-perforated group with ascites did not show any change in the amount of ascites (Fig. 3), except in one patient who demonstrated decreased ascites at a four-day interval. Complex ascites was more common in the perforated group (71%, 10/14) than in the non-perforated group with ascites (9%, 3/33) (p < 0.001). Pseudocysts (57%, 8/14) were only observed in the perforated group (p < 0.001) (Fig. 1). Pseudocysts appeared in the perihepatic spaces, and the precise location of the pseudocysts was in the right subhepatic space (n = 5), gastrohepatic recess (n = 5), porta hepatis (n = 1), and gallbladder fossa (n = 1).

DISCUSSION

Our study demonstrated that children with perforated choledochal cysts had acute symptoms, laboratory abnormalities, and ascites more frequently than those with non-perforated choledochal cysts. In the subgroup of patients who had ascites, identifying large amounts of ascites, increasing the amount of ascites during a short time, complex ascites, and perihepatic pseudocysts may be helpful in ensuring a high degree of accuracy in the diagnosis of choledochal cyst perforation.

Although the pathogenesis of choledochal cyst perforation has yet to be elucidated, the fact that perforation developed most often during infancy could indicate that mural immaturity of the ductal wall may be an essential contributory factor [5,6]. Ohkawa et al. [7] first suggested the presence of APBDU as a risk factor for choledochal cyst perforation, as it may cause pancreatic juice reflux into the biliary tree, resulting in rupture of the
fragile cyst wall. Ando et al. [9] reported that impacted bile plugs in the dilated common channel might cause an abrupt increase in intraductal pressure. However, our study did not find any difference between the perforated and non-perforated groups in the presence of APBDU and dilated common channels containing bile plugs. Yamaguchi [4] also reported that only 23% (6/26) of patients with perforated choledochal cysts had APBDU. Even if not accompanied by APBDU, cholestasis itself increases the pressure of the bile in the biliary tree, which may contribute in part to choledochal cyst perforation [13]. Choledochal cyst perforation may derive from high intraductal pressure applied to the cyst wall, which is weakened by intrinsic immaturity or repeated cholangitis.

Bile peritonitis caused by choledochal cyst perforation is usually sterile, but it can be associated with sepsis when accompanied by acute bacterial cholangitis. Spillage of sterile bile itself can also cause an intense inflammatory reaction that can lead to acute symptoms, such as abdominal pain and fever. Hyperamylasemia and hypoalbuminemia were more common in the perforated group. Similarly, Urushihara et al. [20] described how amylase entry into the bile duct through APBDU could enter the blood due to the high intraductal pressure, indicating cholangio-venous reflux. Albumin could be used as a marker of nutritional status and disease severity.
with hypoalbuminemia possibly representing a critically ill condition [23]. Our study revealed that choledochal cyst perforation occurred only in young children under four years of age. Diao et al. [2] reported an incidence of choledochal cyst perforation of 15% in infants and 4% in older children aged >10 years. They concluded that the incidence of choledochal cyst perforation decreased with age. Our study confirmed this tendency in age distribution.

Large amounts of ascites and bile duct dilatation have been reported to be helpful in the radiologic diagnosis of choledochal cyst perforation. For example, Chen et al. [13] described preoperative US findings of choledochal cyst perforation, including bile duct edema, bile duct dilatation, and ascites. US is the imaging modality of choice for children with choledochal cysts. In an emergency setting, CT is helpful, especially for abnormalities in the retroperitoneal space [15,24]. MRCP is a valuable diagnostic tool that can noninvasively depict anomalies of the biliary tree and pancreatic duct. Although MRCP has superior soft tissue resolution and multiplanar capability, it was difficult to precisely identify the discontinuity of the bile duct wall in our study, which is consistent with previous studies [14,16,25]. MRCP can specifically evaluate the extent of biliary peritonitis, including perihepatic pseudocysts [14,16,25], which was a characteristic finding of choledochal cyst perforation in our study and in previous studies [14,25,26]. Our subgroup analysis in patients with ascites also showed that the perforated group had an increase in the amount of ascites in a short time, possibly due to the acute process of chemical or septic peritonitis.

Three patients with non-perforated choledochal cysts in our study had large amounts of ascites accompanied by acute pancreatitis. This may be important for determining the timing of surgery when differentiating between perforated and non-perforated choledochal cysts with acute pancreatitis. Early surgical treatment is preferred for perforated choledochal cysts because the condition could be fatal if left undrained. In contrast, patients with non-perforated choledochal cysts with acute pancreatitis often undergo surgery after acute pancreatitis has improved, since acute pancreatitis may increase perioperative morbidity [27]. Identifying temporal changes in the amount of ascites and the presence of pseudocysts may be helpful in differentiating perforated choledochal cysts from those with acute pancreatitis. Patients with perforated choledochal cysts also showed more features of acute illness, including fever, elevated WBC and CRP, and low albumin levels, compared with patients with non-perforated choledochal cysts and acute pancreatitis. Bile leakage can be confirmed with hepatobiliary scintigraphy and abdominal paracentesis [20,24], and radionuclide extravasation from the biliary tree during scintigraphy is pathognomonic for perforation [20,24,25,28]. However, hepatobiliary scintigraphy is relatively insensitive for the detection of subacute or chronic perforation of the biliary tree [29]. Scintigraphy has less radiation exposure; however, a conservative approach to radiation risks in children is part of standard medical care [30]. Abdominal paracentesis can be diagnosed with ascitic fluid bilirubin levels of >6 mg/dL, but carries the risk of infection [24,31].

One-stage cyst excision surgery with biliary reconstruction is the standard treatment for uncomplicated choledochal cysts. Choledochal cyst perforation is managed by two- or one-stage surgery, with a recent trend toward one-stage definitive surgery in patients with stable clinical conditions [26,32,33]. Two-stage surgeries include biliary drainage in the first stage and definitive repair later in the second stage. This approach has a low risk of anastomotic site leakage and is usually indicated in patients with unstable conditions [9]. One-stage surgery has potential cost-effectiveness, including shortened hospital stays and lower costs, and no burden of biliary drainage, although it carries a risk of infection and presents technical difficulties [3,32,33].

The main limitations of this study were the potential bias in the inclusion and exclusion criteria due to its retrospective design and the small study population of the case group. Our study included cases from other institutions. However, large-scale research is needed to elucidate the pathogenesis of choledochal cyst perforation. The imaging techniques used in this study were not standardized over a period of two decades. A further limitation is the lack of histological and intraoperative assessment of particular perforation sites. However, the identification of perforation sites of choledochal cysts in 10 patients during surgery ensured that the radiologic interpretations were correct. Although imaging does not show the precise defect of choledochal cyst perforation, choledochal cyst perforation should be studied by recognizing the presence and nature of ascites.

In conclusion, the diagnosis of choledochal cyst perforation requires a high level of vigilance in acutely ill children younger than four years of age who have choledochal cysts and ascites. The perforated group demonstrated large amounts of ascites, an increase in the amount of ascites in a short time, complex ascites,
and perihepatic pseudocysts more commonly than the non-perforated group with ascites. Familiarity with the characteristic imaging findings combined with a careful evaluation of the clinical features of choledochal cyst perforation should enable timely diagnosis and prompt management.

Availability of Data and Material
The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest
So-Young Yoo who is on the editorial board of the Korean Journal of Radiology was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

Author Contributions
Conceptualization: all authors. Data curation: Yu Jin Kim, Soo-Hyun Kim, Tae Yeon Jeon. Formal analysis: Yu Jin Kim, Soo-Hyun Kim, Tae Yeon Jeon. Investigation: Yu Jin Kim, Soo-Hyun Kim, So-Young Yoo, Ji Hye Kim, Soo-Min Jung, Sanghoon Lee, Jeong-Meen Seo, Tae Yeon Jeon. Methodology: all authors. Project administration: Yu Jin Kim, Soo-Hyun Kim, Tae Yeon Jeon. Resources: Yu Jin Kim, Soo-Hyun Kim, So-Young Yoo, Ji Hye Kim, Soo-Min Jung, Sanghoon Lee, Jeong-Meen Seo, Tae Yeon Jeon. Supervision: Yu Jin Kim, Soo-Hyun Kim, Tae Yeon Jeon. Validation: all authors. Visualization: Yu Jin Kim, Soo-Hyun Kim, Tae Yeon Jeon. Writing—original draft: Yu Jin Kim, Soo-Hyun Kim. Writing—review & editing: Yu Jin Kim, Soo-Hyun Kim, Tae Yeon Jeon.

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