Selective enlargement of left lateral segment liver volume as a potential diagnostic predictor for biliary atresia

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Abstract
Purpose To determine an early diagnostic indicator of biliary atresia (BA), we focused on morphological left–right differences of BA livers.
Methods Of 74 infants with suspected BA at our hospital in the last 12 years, 25 met the conditions for investigation: 15 infants with BA (BA group) and 10 with other pathologies (non-BA group). CT volumetry of the liver in each patient was performed using a 3D image analysis system. Patient characteristics, blood data, and proportion of the left lateral segment to the total liver volume (LLS ratio) were compared between the two groups.
Results Among the patient characteristics and liver function tests, only γ-glutamyl transpeptidase (GGT) were significantly higher in the BA group (p < 0.001). The LLS ratio was 0.321 (0.227–0.382) in the BA group and 0.243 (0.193–0.289) in the non-BA group (p = 0.01). The summary cut-off, area under the curve, sensitivity, and specificity were 0.322, 0.813, 53.3, and 100% for the LLS ratio and 94.26, 0.95, 86.7, and 100% for the GGT × LLS ratio, respectively.
Conclusions The LLS ratio is highly specific and may be an early diagnostic predictor of BA. Moreover, this segmental LLS enlargement may be associated with the etiology of BA.

Keywords Biliary atresia · Diagnosis · Volumetry · CT · Left lateral segment · Kasai portoenterostomy

Introduction
Biliary atresia (BA) is a rare disease of unknown etiology characterized by progressive cholangiopathy of the intrahepatic and extrahepatic bile ducts, leading to progressive obliteration of the biliary tree in the first and second months of life [1]. Although the prognosis of patients with BA has improved since the introduction of Kasai portoenterostomy (KP) in 1959 [2], BA is still the most common indication for pediatric liver transplantation. The current general conclusion is that the earlier the KP is performed, the better the result; early diagnosis and initiation of treatment are crucial to improving native liver survival in BA [3, 4]. Conversely, a definite diagnosis of BA must be achieved by direct cholangiography, which is invasive. Although many auxiliary diagnostic methods have been advocated, it remains challenging to establish a highly specific, non-invasive indicator [5].

In recent years, there have been reports of morphological and pathological differences between the left and right segments of BA [6]. In this study, we focused on morphological left–right differences of the liver as a potential diagnostic indicator for BA, and we conducted a retrospective investigation of preoperative imaging studies in patients with suspected BA.

Methods
This was a retrospective case–control study. We separated 37 of 74 infants who underwent contrast-enhanced abdominal CT. These identified infants were registered on our electronic medical record system as “suspected biliary atresia” between January 2010 and December 2021. Serum direct bilirubin levels in all the infants found to be above 0.5 mg/dl, and BA could not be ruled out based on ultrasonography (US) results alone. US findings could not clearly reveal the
gallbladder (including atrophic gallbladder) or cystic BA could not be ruled out due to the presence of cystic lesions. Hence, CT study was planned. Of these, 11 whose 1 mm slice CT images were not available and one with trisomy 18 and omphalocele who died of persistent jaundice without a final diagnosis were excluded. Finally, 25 infants were included in this study.

Of the 25 patients, 15 were diagnosed with BA (BA group), while 10 were not diagnosed with BA (non-BA group) (Fig. 1). In one patient with complete situs inversus, polysplenia, and the preduodenal portal vein, data were collected from the right lobe as the left lobe. In the BA group, there were no patients with asplenia. All patients in the BA group were diagnosed by cholangiography or pathological autopsy. Jaundice eventually disappeared in all patients in the non-BA group.

Sex, age (in days) at CT, body weight at CT, gestational age, and body weight at birth were retrospectively compared between the two groups in terms of patient characteristics. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), direct bilirubin (D-Bil), γ-glutamyltranspeptidase (GGT), platelets (Plt), and prothrombin time-international normalized ratio (PT-INR) were compared in the serum liver function tests.

We have extensively used a 3D image analysis system (SYNAPSE VINCENT, Fuji Film Co., Ltd., Tokyo, Japan) to convert digital imaging and communication in medical data from contrast-enhanced abdominal CT images to 3D images [7]. Total liver and LLS volumes were measured from the dominant portal vein or hepatic vein (Fig. 2). We examined liver volume/body weight and proportion of the left lateral segment to total liver volume (LLS ratio) to account for differences in body size.

Data are expressed as medians and ranges. We used the Mann–Whitney U test to compare the median of continuous variables and Fisher’s exact test to compare the proportions of categorical variables (such as sex) between the two groups. Receiver operating characteristic (ROC) analyses were also performed to evaluate the diagnostic performance of the volume ratio of LLS to the total liver and the combination of LLS volume ratio/GGT. Statistical significance was set at \( p < 0.05 \). All analyses were performed using R version 3.4.0 (R Core Team; R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/) [8].

The ethics review board of our hospital approved the study design (approval no. 2111105). The requirement for informed consent was waived due to data anonymization. We recruited all patients by opt-out methods and published this research content on our hospital’s homepage.

![Fig. 1](image1.png)

**Fig. 1** Flowchart of patients included at our institution during the study period. Of 74 infants with suspected biliary atresia (BA) at our hospital during the last 12 years, 37 infants who underwent contrast-enhanced abdominal CT, 25 infants with thin-slice CT images available, and definitive diagnosis or exclusion of BA were included: 15 infants were diagnosed with BA (BA group) and 10 infants were not diagnosed with BA (non-BA group). Eleven infants without thin-slice CT images were excluded from the study. Only one patient who died of continued jaundice was excluded because BA could not be ruled out.

![Fig. 2](image2.png)

**Fig. 2** 3D image analysis of the patient with biliary atresia. The total liver volume was 259 ml, and the LLS volume was 84 ml measured from the dominant portal vein.
Results

Fourteen patients in the BA group were diagnosed by intraoperative cholangiography, and one patient was diagnosed by pathological autopsy. In the non-BA group, the diagnoses were infantile hepatitis in two, biliary dilatation in one, liver cyst in one, blood disease in one, and unknown in five. They were distinguished from BA by scintigraphy in three, cholangiography in two, and other modalities in five. All patients eventually improved to be jaundice free.

There were no significant differences in sex, age at CT, weight at CT, gestational age, or birth weight between the BA and non-BA groups (Table 1). In the liver function test, AST, ALT, D-Bil, Plt, and PT-INR levels were statistically equivalent between the two groups. Only GGT was 586 U/l (185–875 U/l) in the BA group, which was higher than 170 U/l (61–389 U/l) in the non-BA group ($p < 0.001$) (Table 2).

The total and right liver volume/body weight was 48.28 (42.13–68.91) ml/kg and 25 (20–43.1) ml/kg, respectively, in the BA group versus 48.97 (30.36–80) ml/kg and 23.17 (13.57–61.07) ml/kg, respectively, in the non-BA group ($p = 0.5$ and $0.26$, respectively). The LLS volume/body weight was 14.6 (9.57–25.1) ml/kg in the BA group versus 12.1 (6.79–16.8) ml/kg in the non-BA group ($p = 0.07$) (Fig. 3). The LLS ratio was 0.321 (0.227–0.382) in the BA group and 0.243 (0.193–0.289) in the non-BA group ($p = 0.01$) (Fig. 4).

ROC analysis of the LLS ratio showed a cut-off of 0.322, area under the curve (AUC) of 0.813, sensitivity of 53.3%, and specificity of 100% (Fig. 5). Moreover, the GGT × LLS ratio had a cut-off of 94.26, AUC of 0.95, sensitivity of 86.7%, and specificity of 100% (Fig. 6).

### Table 1 Patients’ characteristics

|                | BA group | Non-BA group | $p$ value |
|----------------|----------|--------------|-----------|
| N              | 15       | 10           |           |
| Sex, men, %    | 3 (20)   | 6 (60)       | 0.087     |
| Age, day       | 33 (4–119) | 38 (15–172) | 0.781     |
| Body weight, kg| 3.8 (2.4–5.8) | 3.1 (2.6–5) | 0.148     |
| Gestational age, week | 39 (37–40) | 38 (26–41) | 0.475     |
| Body weight at birth, g | 3012 (2140–3338) | 2572 (786–3621) | 0.134     |

Data are reported as numbers or median (range).

**BA** biliary atresia

### Table 2 Serum liver function test findings

|                        | BA group  | Non-BA group | $p$ value |
|------------------------|-----------|--------------|-----------|
| N                      | 15        | 10           |           |
| Aspartate aminotransferase, U/l | 159 (23–329) | 105.5 (38–321) | 0.506    |
| Alanine aminotransferase, U/l | 87 (5–239)    | 66.5 (14–249) | 0.760    |
| Direct-type bilirubin, mg/dl | 5.4 (1.2–9.7)  | 4.5 (0.5–10.2) | 0.318    |
| γ-Glutamyltranspeptidase, U/l | 54.8 (185–1773) | 170 (61–389) | $< 0.001$ |
| Platelets, 10$^3$/μl | 310 (219–576) | 376.5 (183–579) | 0.657    |
| Prothrombin time- international normalized ratio | 1.1 (0.9–1.9) | 1 (0.9–1.2) | 0.531    |

Bold indicates statistically significant $p$ value.

Data are reported as numbers or median (range).

**BA** biliary atresia
Discussion

Our study showed that LLS volumetry using preoperative CT images could be useful for BA diagnosis with high specificity, especially when combined with the serum GGT level. This result also suggests that BA shows morphological characteristics of the liver that are different from those of other cholestatic diseases from an early stage, which may be useful for an early diagnosis of BA.

Peng et al. [9] reported that left lateral discordant enlargement of the liver is more prominent in patients with early BA than in other cholestatic children, which is consistent with our present study. Their investigation using indirect indices drawn from a plane of MRI images was novel; however, as stated in the manuscript, there were problems with objectivity and reproducibility. SYNAPSE VINCENT (Fuji Film Medical Co., Ltd., Tokyo, Japan), a 3D image analysis workstation widely used for radio-diagnosis, provides highly automated volume-rendering data by intuitive operation. Recently, it has been applied for preoperative three-dimensional evaluation in hepatobiliary surgery [7] and transplantation [10]. Therefore, we conducted this study using SYNAPSE VINCENT to
accurately and directly measure the regional volume of the liver using CT images.

There have been many attempts to diagnose BA using imaging tests. A meta-analysis [5] showed that summary sensitivity and specificity were 77% (95% CI 74–80%) and 93% (95% CI 91–94%) for US in 23 studies, 96% (95% CI 92–98%) and 58% (95% CI 51–65%) for MRCP in five studies, and 96% (95% CI 94–97%) and 73% (95% CI 70–76%) for hepatobiliary scintigraphy in 18 studies using image diagnostic methods. The specificity in our study was the highest compared to other imaging studies. Enlargement of the LLS was considered valuable in terms of specificity.

There have also been many studies on the early diagnosis of BA using general blood chemistry test data. Chen et al. [11] reported that GGT and D-Bil levels could be helpful tools for early diagnosis of BA. There was no significant difference in D-Bil levels between the BA and non-BA groups in our study, and only GGT levels showed a significant difference between the two groups. Our study showed a sensitivity of 90%, specificity of 86.7%, and AUC of 0.94 (Supplemental Fig. 2). Another meta-analysis [12] showed a summary sensitivity of 80%, specificity of 79%, and AUC of 0.96. Because the diagnostic accuracy of GGT alone was insufficient, we combined GGT with the LLS ratio to achieve higher sensitivity and specificity.

Serum matrix metalloproteinase-7 (MMP-7) has recently received considerable attention. An observational study showed that diagnostic sensitivity and specificity were 98.67 and 95%, respectively [13]. MMP-7, a protease responsible for tissue remodeling, is associated with liver fibrosis in patients with BA [14]. Selective LLS enlargement in our study indicates inflammation in the prefibrotic stage. The median LLS ratio was 0.329 (0.286–0.346) in the four neonates in this study, which was higher than the median in all patients and the cut-off for ROC analysis. Therefore, it may lead to an earlier diagnosis than MMP-7.

We have previously found significant atrophy of the LLS of the BA livers resected at liver transplantation, which was associated with severe inflammation and fibrosis [6]. A liver heterogeneously affected by BA could lead to such a change. In other words, the selectively attacked LLS of the liver in BA patients could be swollen in the early stages. As a result, the LLS could change to be atrophic in the end stages.

The presented segmental LLS enlargement in BA may be unexplainable by the viral infection theory, in which inflammation would impact the whole liver. In fetal life portal blood supply, the right liver receives blood supply from only the fetal portal vein, while the left liver receives mainly from the umbilical vein [15]. In addition, a large prospective study [16] on newborn screening using D-Bil measurements within the first 60 h of life showed that all known infants in the study population with BA were detected, suggesting their BA onset in fetal life. These findings might support the explanation that exposure of the left liver to a minute mixture of maternal blood-derived substances or maternal blood itself is the pathogenesis of BA. Allogeneic maternal cells that migrate to the umbilical vein can readily engraft into the LLS. Therefore, the maternal microchimerism theory [17, 18] seems to reflect the selective enlargement of LLS. Further studies are required to elucidate the etiology of BA.

**Limitations**

This study has some limitations. First, the sample size was so small that a multivariate analysis was not possible. Second, this was a retrospective single-center study. This could have led to a selection bias. Third, the diseases causing jaundice in the control group were not uniform. Despite these limitations, this is the first study to report the morphological differences between the left and right segments using 3D volume analysis with CT as an early diagnostic method for BA. Moreover, the selective enlargement of the LLS may be utilized as a US finding without radiation. Further research in large numbers regarding the left–right difference is needed.

**Conclusions**

Our study demonstrated a new diagnostic method using morphological left–right differences of BA livers in 3D CT analysis before KP. In addition, the BA-specific LLS enlargement observed in this study may support a better understanding of the etiology of BA.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00383-022-05227-7.

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**Author contributions** All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by KS. The first draft of the manuscript was written by KS and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.
Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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