

ORIGINAL ARTICLE

Different clinical and genetic features of Alagille patients with progressive disease versus a jaundice-free course

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Key words

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Introduction

Alagille syndrome (ALGS) is an autosomal dominant disease and a highly variable disorder affecting multiple organ systems.¹ The diagnosis is based on clinical criteria and is determined by

Abstract

Background and Aim: Alagille syndrome (ALGS) is a multisystem disorder with variable clinical courses. This study investigated the clinical and genetic features of ALGS patients with different outcomes and analyzed the liver pathology at liver transplantation (LT) compared with that in biliary atresia (BA).

Methods: We report the clinical characteristics, outcomes, and genetic mutations of 25 children with ALGS followed for a median of 7.3 years. Patients were classified into (i) jaundice-free (JF) group (resolving jaundice after 2 years of age); (ii) progressive disease (PD) group (persistent jaundice or progressive cholestasis). In addition, we analyzed the explant liver in 10 ALGS patients compared with 20 age-matched BA patients at the time of LT.

Results: Nine patients (36%) in the JF group had a favorable outcome, with longer native liver survival than patients with PD ($n = 16$, $P < 0.001$). Fourteen of the PD group patients received LT or died. We identified 18 different *JAG1* mutations in 22 patients. Three unrelated probands in the JF group had the same de novo mutation in *JAG1*, c.2122-2125delCAGT. Compared with BA children, ALGS patients had lower METAVIR scores in liver pathology, higher serum albumin levels, and lower weight-for-age z-scores when receiving LT.

Conclusion: One-third of ALGS patients had JF and a favorable course. Children with ALGS presenting with persistent jaundice beyond 2 years of age should be cautioned for poor prognosis. ALGS patients tend to have a lesser extent of cirrhosis, and more growth problems than BA patients at the time of LT.

the presence of three out of five features (cholestatic liver disease, heart disease, vertebral anomalies, posterior embryotoxon, and characteristic facies).² ALGS may also involve other organ systems including the kidney, vasculature, and extremities.³⁻⁵

The liver histopathology in ALGS is characterized by a paucity of the interlobular bile duct, which is not always present in early infancy.^{6,7} Some patients might be diagnosed with biliary atresia (BA) and receive hepatoporoenterostomy (HPE) in infancy.⁸

Due to the rapid advancement of molecular diagnosis, the case number has increased, with an estimated incidence close to 1:30,000.^{9,10} *JAGGED1* (*JAG1*) and *NOTCH2* are two causative genes in ALGS patients. The majority of cases are caused by mutation of *JAG1*, and a small subset of *NOTCH2*.^{2,11} Both genes are involved in the Notch signaling pathway and play a key role in cell fate determination and cell differentiation.¹² One of the most intriguing aspects is the wide variety of hepatic manifestations in ALGS patients. Cholestasis usually develops in early infancy and may resolve gradually. However, many individuals can progress to end-stage liver disease (ESLD).⁵ Approximately 20–50% of ALGS patients need liver transplantation (LT) due to ESLD or nonhepatic causes. The most common indications for LT include uncontrolled itching, growth failure, complications of portal hypertension, decompensated cirrhosis, or liver failure.¹³ The present study aimed to identify the clinical course and genetic features of ALGS patients with different hepatic-outcome groups. The indication for LT and liver histopathology of ALGS patients were compared with the age-matched BA patients.

Methods

Patient selection and data collection. This retrospective study analyzed 25 patients admitted or referred to the clinics of National Taiwan University Hospital between 1990 and 2021 who were diagnosed with ALGS by clinical criteria.² Clinical data, sex, onset symptoms and age, ALGS-specific disease characteristics, indications for LT, and genetic mutations were obtained from the medical records. The weight-for-age *z*-scores were calculated based on the WHO International Child Growth Standards. Failure to thrive in this study was defined as a *z*-score <−2.¹⁴

Clinical course, follow-up, and outcomes. Patients were followed in the outpatient clinic every 3–6 months during the status of stable disease, and more frequently when indicated. The follow-up duration and the age at LT or death were recorded. The clinical course was divided into two groups: (i) jaundice-free (JF) group, defined as patients with resolved jaundice after 2 years of age or who were jaundice free since the time of diagnosis were included; (ii) progressive disease (PD) group, patients with persistent jaundice, and progressive cholestatic liver disease during the follow-up.

Genetic mutation analysis. Molecular analysis was performed on 23 ALGS patients in our study cohort. Peripheral blood samples were collected from patients and genomic DNA was extracted from peripheral blood using Genra Puregene Blood Kit Plus (Qiagen, Germantown, Maryland). Genetic analysis was performed using either Sanger sequencing of the *JAG1* gene or panel-based next-generation sequencing (NGS) that included *JAG1* and *NOTCH2*.¹⁵ Whole exome sequencing was applied to identify novel disease-causing genes in one patient. Sequencing results were compared with the *JAG1* sequence (GenBank RefSeq: NM_000214.3).¹² The variant nomenclature was based on the Human Genome Variation Society (HGVS)

naming conventions.¹⁶ The interpretation of variants was based on the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) guidelines.¹⁷ The study was approved by the institutional review board. Informed consent was obtained from the subjects or their parents.

Comparisons of ALGS and BA patients who underwent LT. To analyze the hepatic manifestation and liver pathology of ALGS patients receiving LT, an 1:2 ratio of age-matched BA patients was selected for comparison. Data on the recipients' age, sex, weight-for-age *z*-score, serum bilirubin, albumin, prothrombin time-international normalized ratio (PT-INR), and pediatric end-stage liver disease (PELD) score at the pretransplant assessment were collected. The explant liver histology of 10 ALGS and 20 BA patients was reviewed by an experienced pediatric liver pathologist. Bile duct paucity was defined as a ratio of interlobular bile ducts to portal areas of <0.5.¹⁸ METAVIR scoring system was applied to grading the severity of fibrosis, which was divided into five levels: F0, normal; F1, portal fibrosis; F2, fibrosis with few septa; F3, numerous septa; and F4, cirrhosis.¹⁹

Statistical analysis. The STATA (version 14.0; StataCorp, College Station, TX, USA) and MedCalc (version 18.6; MedCalc Software, Ostend, Belgium) software packages were used for the statistical analyses. Normally distributed continuous data were compared between groups using the Student's *t*-test. The chi-square test or Fischer exact test was performed to compare categorical data between the groups. Descriptive data with continuous variables are reported as the mean ± SD or median (range). The *P* value below 0.05 indicated statistical significance. Receiver operating characteristic (ROC) curves were used to determine the ability of laboratory parameters at initial presentation to predict the occurrence of PD course in ALGS patients. Kaplan–Meier curves were applied to plot the probabilities of patient survival and native liver survival (NLS). The NLS between the JF and PD groups were compared using the log-rank test with the *P* value.

Results

General characteristics. Of the 25 ALGS patients, 13 (52%) were males. The median age at the first referral or admission was 2 months old (range, <1–80 months). Twenty-one patients had neonatal cholestasis as the onset symptom. One patient presented with hematemesis at the age of 1.3 years. Three patients were referred for further survey due to abnormal aminotransferases. Two of them sought medical help for a heart murmur, and another one had been diagnosed with pulmonary artery stenosis before referral. The major clinical features of our patients were cardiac disease (100.0%), characteristic facies (96.0%), cholestasis (92.0%), and butterfly vertebrae (78.3%); other features included pruritus (95.0%), hypercholesterolemia (73.9%), failure to thrive (60.0%), and xanthomas (47.4%) (Table S1, Supporting information).

The median follow-up time was 7.3 years (range, 2 months to 22 years). Five patients had received HPE for suspicion of BA in infancy in the early years. The histological diagnosis of bile duct paucity was established in 29.4% (5 of 17) of patients in the

Table 1 Comparisons of laboratory parameters at initial presentation in Alagille patients with progressive disease or jaundice-free course

	Progressive disease (<i>n</i> = 11) [†]	Jaundice free (<i>n</i> = 9)	<i>P</i> value
Refer age, median (range), months	1 (<1–16)	2 (<1–80)	0.206
Total bilirubin, mg/dL	7.3 ± 2.7	4.5 ± 3.5	0.055
Direct bilirubin, mg/dL	4.5 ± 2.1	2.1 ± 2.1	0.019
AST, U/L	124.6 ± 72.3	130.3 ± 74.2	0.862
ALT, U/L	114.8 ± 25.8	153.7 ± 142.6	0.460
GGT, U/L	528.9 ± 308.9	417.8 ± 337.8	0.453
CHO, mg/dL	321.2 ± 235.4	165.9 ± 70.1	0.090
TG, mg/dL	156.1 ± 100.2	85.7 ± 50.6	0.110
PT-INR	1.1 ± 0.1	1.0 ± 0.1	0.806
Albumin, g/dL	4.1 ± 0.3	4.5 ± 0.4	0.010

[†]Five patients with progressive disease had no initial data.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; PT-INR, prothrombin time-international normalized ratio; CHO, total cholesterol; TG, triglyceride.

first percutaneous needle biopsy. The rate of bile duct paucity increased to 61.1% (11 of 18) after the follow-up liver biopsy or when they received LT. Of the 21 patients who presented with neonatal cholestasis, jaundice gradually resolved in 6 patients during follow-up (range: 2 months to 2 years).

Difference in clinical course between the JF and PD groups. The study cohort was stratified into 9 JF and 16 PD subjects according to the laboratory values and clinical courses. The initial presentation of ALGS in the two groups revealed a significant difference in serum direct bilirubin (D-bil) (mean ± SD was 4.5 ± 2.0 mg/dL for the PD group and 2.1 ± 2.1 mg/dL for the JF group; *P* = 0.019) and serum albumin (mean ± SD was 4.1 ± 0.3 mg/dL for the PD group and 4.5 ± 0.4 mg/dL for the JF group; *P* = 0.010). The area under the ROC curve showed that D-bil > 3.5 mg/dL (sensitivity = 72.7%, specificity = 77.8%, diagnostic accuracy = 80.8%, *P* = 0.002), and albumin ≤ 4.2 g/dL (sensitivity = 81.8%, specificity = 88.9%,

diagnostic accuracy = 83.3%, *P* = 0.001) were optimal for predicting the PD outcome. There were no significant differences existed in total bilirubin (T-bil), aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, total cholesterol, triglycerides, and PT-INR between the two groups (Table 1).

In the PD group, variceal upper gastrointestinal bleeding occurred in 6 of the 16 patients. Two patients had a history of bone fractures. LT was performed in 10 (40.0%) ALGS patients at a median age of 3.7 years (range, 1.5–13.1 years). Of these, 90% were from a living donor, and 10% were from a deceased donor. One patient was still on the waiting list for LT. Four patients died of ESLD without LT; two patients died at 0.5 and 3.6 years after LT due to sepsis. In the JF group, three patients did not present cholestasis during the whole course. One patient who had a history of ventricular septal defect and bilateral peripheral pulmonary stenosis (PPS) received total correction at

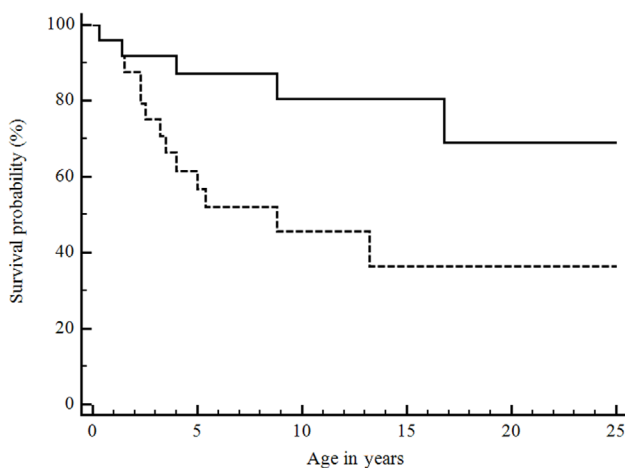


Figure 1 The overall and native liver survival (NLS) rates of patients with Alagille syndrome. Kaplan–Meier survival plot comparing overall and NLS at 10 years were 45.6 and 80.5%, respectively. (—), Overall survival; (---), NLS.

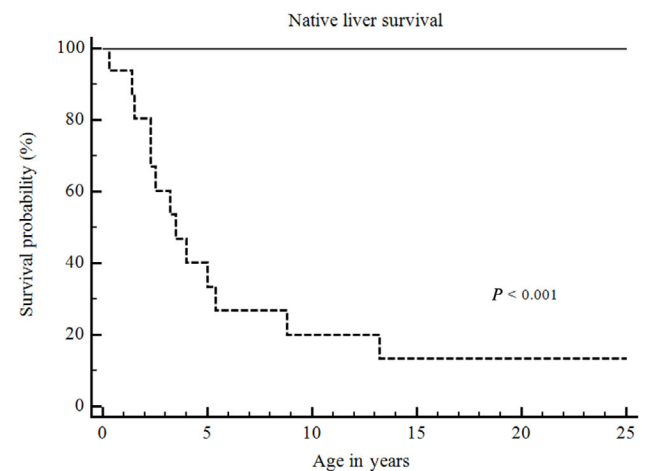


Figure 2 Comparison of the native liver survival (NLS) rate of jaundice-free (JF) and progressive disease (PD) groups of patients with Alagille syndrome. There were significant differences in the NLS between the PD and the JF group (log-rank, *P* < 0.001). (—), Jaundice-free; (---), PD.

Table 2 Genetic mutations and phenotypes of patients with Alagille syndrome

Patient no.	Sex	Onset symptoms/age	Outcome	Exon/intron	Mutation	Protein (dbSNP)	Mutation type	Novel	Phenotype*
Progressive disease									
1	Female	Cholestasis/<1 month	LT	Exon 1	c.53_73delITCGCCCTGCTCTGTGCCCCTGC	p.Leu18_Leu25del	In-frame deletion	+	L, H, F, V
2 [‡]	Female	UGI bleeding/1 year 4 months	LT	Exon 2	c.384G>A	p.Trp128Ter	Nonsense	+	L, H, F, V
3	Male	Cholestasis/3 months	Death	Intron 2	c.387+21>G	—	Splicing	+	L, H, F, V, E
4	Male	Cholestasis/2 months	LT	Exon 6	c.765C>A	p.Tyr255Ter (rs1131695)	Nonsense	—	L, H, F
5	Male	Cholestasis/1 month	Bone fracture, Death	Intron 6	c.866+3A>G	— (rs1555829065)	Splicing	—	L, H, F, V, E
6	Female	Cholestasis/1 month	LT	Exon 20	c.2376 C>A	p.Tyr792Ter	Nonsense	+	L, H, F, V, E
7	Female	Cholestasis/1 month	LT	Exon 23	c.2779_2782dupGTCC	p.His928ArgfsTer25	Frameshift	—	L, H, F, V
8	Male	Cholestasis/1 month	LT	Exon 23	c.2824C>T	p.Gln942Ter (rs1195992553)	Nonsense	—	L, H, F
9	Male	Cholestasis/1 month	LT	Exon 23	c.2824C>T	p.Gln942Ter (rs1195992553)	Nonsense	—	L, H, F, V
10	Male	Cholestasis/<1 month	LT	Exon 23	c.2894_2899delTTAACA	p.Phe965_Lys967delinsTer	In-frame deletion, nonsense	+	L, H, F, V
11	Female	Cholestasis/<1 month	Death	Exon 24	c.2923dupA	p.Thr975AsnfsTer8	Frameshift	+	L, H, F, V, E
12	Male	Cholestasis/<1 month	LT evaluation	Exon 24	Whole gene deletion	—	Large deletion	—	L, H, V
13	Male	Cholestasis/<1 month	ICH, bone fracture	Exon 24	Whole gene deletion	—	Large deletion	—	L, H, F, V
14	Male	Cholestasis/2 months	Death	Exon 24	Whole gene deletion	—	Large deletion	—	L, H, F, E
15	Female	Cholestasis/3 months	LT	Exon 24	Exon 1–5 deletion	—	Large deletion	—	L, H, F, V
16	Female	Cholestasis/<1 month	LT/death	Exon 24	NA	—	—	—	L, H, F, V
17	Female	Cholestasis/1 month	LT/death	Exon 24	NA	—	—	—	L, H, F, V
18	Female	Cholestasis/2 months	Jaundice free at 3 months	Intron 3	c.439+1G>A	— (rs863223648)	Splicing	—	L, H, F, E
19	Male	Heart murmur/ <1 month	Total correction of CHD at 10 years	Exon 4	c.689_690insTGTA	—	Frameshift	+	L, H, F, V
20	Male	Cholestasis/2 months	Jaundice free at 8 months	Exon 14	c.1875C>G	p.Tyr625Ter	Nonsense	+	L, H, F, V
21	Female	Cholestasis/4 months	Jaundice free at 2 years	Exon 15	c.1976 G>A	p.Trp659Ter	Nonsense	+	L, H, F, V
22	Female	Cholestasis/1 month	Jaundice free at 2 months	Exon 16	c.2089_2099TGGAAAGGAAAdelinsAGT	p.Trp697SerfsTer7	Frameshift	+	L, H, F, V
23	Female	Heart murmur/4 months	Jaundice free at 3 months	Exon 17	c.2122_2125delCAGT	p.Gln708ValfsTer34 (rs727504412)	Frameshift	—	L, H, F, V
24	Female	Abnormal liver function/6 years 8 months	Event free	Exon 17	c.2122_2125delCAGT	p.Gln708ValfsTer34 (rs727504412)	Frameshift	—	L, H, F, V
25	Male	Cholestasis/2 months	Jaundice free at 29 months	Exon 17	c.2122_2125delCAGT	p.Gln708ValfsTer34 (rs727504412)	Frameshift	—	L, H, F
26	Male	Cholestasis/1 month	Jaundice free at 7 months	Exon 17	ND	—	Frameshift	—	L, H, F, V

*Affected systems: liver (L), heart (H), face (F), vertebrae (V), and eye (E).

[‡]Two linked variants were identified in patient no. 2, both were classified as pathogenic variants.

+, present; –, absent; CHD, congenital heart disease; LT, liver transplantation; NA, not available; ND, not detected; UG1, upper gastrointestinal.

Table 3 Comparisons of clinical, biochemical, and pathology features of Alagille syndrome (ALGS) patients with age-matched biliary atresia (BA) patients at the time of liver transplantation (LT)

	ALGS (<i>n</i> = 10)	BA (<i>n</i> = 20)	<i>P</i> value
Age at LT, median (range), years	3.7 (1.5–13.1)	3.5 (1.3–12.4)	0.87
<6 years, <i>n</i> (%)	9 (90.0)	17 (85.0)	
≥6 years, <i>n</i> (%)	1 (10.0)	3 (15.0)	
Sex			
Male, <i>n</i> (%)	4 (40.0)	11 (55.0)	
Female, <i>n</i> (%)	6 (60.0)	9 (45.0)	0.350
Weight-for-age <i>z</i> -score	−2.7 ± 1.2	−0.5 ± 1.7	0.005
Total bilirubin, mg/dL	14.1 ± 12.8	14.7 ± 15.4	0.908
PT-INR	1.1 ± 0.2	1.2 ± 0.2	0.095
Albumin, g/dL	4.1 ± 0.5	3.4 ± 0.5	<0.001
PELD score	7.8 ± 8.7	7.7 ± 8.2	0.988
METAVIR score [†]			
F0, <i>n</i>	1	0	
F1, <i>n</i>	0	0	
F2, <i>n</i>	1	0	
F3, <i>n</i>	4	0	
F4, <i>n</i>	2	20	<0.001
Graft survival			
1 year, %	90.0	90.0	1.000
5 years, %	80.0	85.0	0.729

[†]Histopathology of the liver was not available for reassessment in two ALGS patients.

PELD, pediatric end-stage liver disease; PT-INR, prothrombin time-international normalized ratio.

10 years of age and only had abnormal aminotransferases during the 20-year follow-up.

The Kaplan–Meier plots showed that NLS and overall survival at 10 years were 45.6% and 80.5%, respectively (Fig. 1). The PD group was associated with poorer NLS than the JF group (log-rank, $P < 0.001$) (Fig. 2). Fourteen patients (87.5%) in the PD group and one patient (11.1%) in the JF group had failure to thrive ($P = 0.03$).

Genetic analysis results. Genetic mutations were found in 22 of the 23 individuals (95.7%) (Table 2). Eleven novel *JAG1* mutations were identified, and the other 11 were reported mutations. No mutation in *NOTCH2* was found in our ALGS patients. Eighteen different *JAG1* mutations were identified in the 22 patients, including 6 nonsense mutations (33.3%), 5 frameshift mutations (27.8%), 3 splice site mutations (16.7%), 2 large deletions (11.1%), and 2 in-frame deletions (11.1%). Patients 22, 23, and 24 in the JF group were found to have the same de novo mutation in *JAG1*, c.2122-2125delCAGT. The three unrelated probands harboring the 4-bp deletion all had a relatively favorable outcome with JF status at follow-up. Four patients who had large genetic deletions were all in the PD group.

Comparisons of ALGS and BA patients who underwent LT. The clinical and biochemical features of 10 ALGS and 20 age-matched BA patients who underwent LT are presented in Table 3. Explant liver pathology scores were analyzed. Although more than one indication generally led to the

decision for transplantation, the most common indication for LT in ALGS patients was failure to thrive (7 of 10), intractable pruritus unresponsive to medical management (4 of 10), progressive cholestasis (3 of 10), and gastrointestinal bleeding (2 of 10). Three patients (30%) had biliary stricture after LT, and radiological intervention was used for further management (Table S2).

By contrast, the major indications for LT in BA were portal hypertension with complications, such as esophageal variceal bleeding, and cirrhosis with decompensation. Children with ALGS had lower weight-for-age *z*-scores ($P = 0.005$) and higher serum albumin levels ($P < 0.001$) than age-matched children with BA at the time of LT. The mean *z*-score improved from −2.21 at LT to −0.76 at the 2-year after LT in the ALGS patients. The METAVIR scores were significantly lower in ALGS than BA children when receiving LT ($P < 0.001$). No significant differences were detected in the pretransplant T-bil, PT-INR, PELD score, and graft survival between ALGS and BA patients (Table 3).

Discussion

ALGS is a complex disease involving a multiorgan system with a highly variable penetrance, phenotypes, and disease severity. Although ALGS is generally considered a benign syndrome of intrahepatic cholestasis,²⁰ progressive liver dysfunction associated with the necessity of LT or with death can also occur.^{21,22}

There have been no good parameters, such as genetic mutations or the extent of bile duct paucity in pathology, for predicting disease progression. In this report, we first proposed two distinct groups of patients who had very different disease courses: one group with JF, benign or slowly progressing courses, and the other group with PD that mostly necessitated LT in early childhood (<6 years of age). Patients with a JF outcome were less likely to develop failure to thrive. Significantly higher serum D-bil (>3.5 mg/dL) and lower albumin (≤4.2 g/dL) at the initial presentation were correlated with the PD outcome. This result indicates initial liver function represented by bilirubin excretion and albumin synthesis may well predict the outcome of ALGS patients, as the reported series by Liu *et al.*²³ Kamath *et al.* also reported that cases with total bilirubin above 3.8 mg/dL, presence of fibrosis and xanthoma were associated with severe outcomes.²⁴ Previous studies showed that 21–47% of patients with ALGS are estimated to require LT.^{5,25} In our study, 68.8% (11 of 16) of cases in the PD group underwent LT or died before 6 years of age. Kamath *et al.* proposed that the estimated transplant-free survival was 24% at the age of 18.5 years.²⁶ This indicated that if ALGS patients are among the PD group, the clinician should be on alert for severe outcomes and prepare for LT early in childhood.

Eighteen different mutations were identified in the *JAG1* gene of the 22 unrelated ALGS patients. Previous studies have revealed no reliable genotype–phenotype correlation in ALGS.¹⁰ In our cohort, we found that large gene deletions were identified only in the PD group. Notably, the frameshift mutation c.2122-2125delCAGT in the *JAG1* gene was detected in three unrelated probands in the JF group, which were all de novo mutations. Whether the 4-bp deletion (2122-2125del) is a hotspot mutation is not yet clear. From the literature review, 21 patients (including our three cases) from different countries carrying the same frameshift mutation, and almost every patient had features affecting the liver, heart, and face (Table S3).^{1,12,27–35} Of the

reviewed studies, only four cases had the outcomes described. Three patients died, and the other patient developed liver failure; three mortality cases were reported 20 years ago.^{27–30} It is not clear whether the poor outcome was related to medical care facilities in the previous era. It deserves further investigations to clarify this site as a mutation hotspot and its relationship with patient outcome.

In our study, the major indication for LT was failure to thrive in ALGS contrary to portal hypertension or cirrhosis-related complications in BA patients, implying different pathophysiologies of the two infantile cholestasis diseases. A significantly lower METAVIR score at LT indicated less extent of cirrhosis in ALGS patients than in BA patients. However, the PELD score revealed no significant difference between our ALGS and BA patients before LT. Our findings are in line with previous studies comparing ALGS and BA liver by computed tomography image and pathology.^{36,37} Both studies revealed less cirrhotic changes of the liver in patients with ALGS than in patients with BA. Defects of Notch signaling may affect liver repair mechanisms and results in absent reactive ductular cells and less portal septa fibrosis.³⁶ In our study, children with ALGS had higher serum albumin levels but lower weight-for-age *z*-scores. The higher albumin level is consistent with a lower extent of cirrhosis in the ALGS patients. ALGS is known to be associated with growth problems, partly because of liver disease and partly due to genetic factors, the latter may play a more important role given the less severe degree of cirrhosis at LT. However, improved weight-for-height *z*-score after LT supports the role of liver disease on growth.

There was no significant difference in the graft survival rate in either ALGS or age-matched BA patients, but 30% of ALGS patients developed biliary stricture after LT in our study. This rate was higher than that of BA patients (12%) with the same liver transplant team.³⁸ This result could facilitate the development of better posttransplant monitoring strategies in ALGS patients.

The limitations of this study were the relatively small size of our patient cohort. Nonetheless, the prevalence of major phenotypes of our ALGS patients was consistent with that in earlier reports and can be assumed to represent a larger cohort of patients. We have proposed two distinct disease-progression courses of ALGS syndrome. A future study with a larger case number may be needed to verify our findings.

In conclusion, this study highlighted the different disease courses of ALGS patients and warrants particular attention in ALGS patients predicted to experience PD and poor outcomes. Genetic analysis is essential in the diagnosis of ALGS in current practice. Further investigations are necessary for the hotspot mutation in *JAG1*, c.2122–2125 del, and its outcome association. In those ALGS patients who need LT for failure to thrive, improved growth parameters are achievable.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1. Clinical features of Alagille syndrome patients.

Table S2. Alagille syndrome patients received liver transplantation.

Table S3. Reported cases of Alagille syndrome with a mutation in *JAG1*, c.2122-2125delCAGT.