Research Square

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Clinical Characteristics and Genotype-Phenotype Correlation Analysis of 19 Cases of Alagille Syndrome

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Research Article

Keywords: Alagille syndrome, JAG1, NOTCH2, genotype–phenotype correlation, liver function

Posted Date: June 5th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9517428/v1

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Additional Declarations: No competing interests reported.

Abstract

Background & Aims: Alagille syndrome (ALGS) is an autosomal dominant disorder caused by JAG1 or NOTCH2 mutations and is the leading genetic cause of pediatric cholestatic liver disease. ALGS shows marked phenotypic heterogeneity and frequent misdiagnosis, with incompletely defined genotype–phenotype correlations. Although the ileal bile acid transporter (IBAT) inhibitors have revolutionized ALGS therapy, real-world data on Asian populations remain limited. We aimed to characterize the clinictreatment and features of Chinese pediatric ALGS patients, evaluate liver function changes with conventional treatment, and assess real-world maralixibat efficacy.

Methods: This retrospective study included 19 children diagnosed with ALGS at Shenzhen Children's Hospital (2011–2024). Clinical, genetic, and treatment data were analyzed, and comparisons were made between the JAG1 and NOTCH2 subgroups.

Results: The median age at onset was 1.9 (0.1–3.7) years. Common features included cholestasis (63%), hepatobiliary involvement (84%), cardiac involvement (37%), skeletal involvement (31.6%), and renal anomalies (16%); no ocular defects were observed. JAG1 mutations accounted for 68.4% of the cases, and NOTCH2 for 31.6%. JAG1 mutations were clustered in exons 5 and 26, whereas NOTCH2 mutations were concentrated in exon 34. Patients with JAG1 variants had higher baseline ALT levels ($P<0.05$). Conventional therapy significantly reduced TBIL and DBIL levels at 1 month, with sustained improvement at 1 year (both $P<0.05$). Maralixibat showed benefits in one of the three patients.

Conclusions: Chinese patients with ALGS exhibit distinct clinical and genetic characteristics. JAG1 is the major causative gene associated with more severe liver injury. Conventional and targeted IBAT therapies are effective in treating these conditions. Early genetic testing and personalized management can improve long-term outcomes.

Introduction

Alagille syndrome (ALGS) is a rare, autosomal dominant, multisystem disorder caused by pathogenic variants in the *JAG1* and *NOTCH2* genes. Initially, due to limited diagnostic tools, its prevalence was estimated to be 1 in 70,000 live births. With the advent of molecular diagnostics, the current prevalence is likely to be closer to 1 in 30,000 [1–3]. First described by Alagille et al. in 1969, ALGS is classically defined by a constellation of anomalies affecting the liver, heart, skeleton, eyes, kidneys, and vasculature, with intrahepatic bile duct paucity as the pathological hallmark [4]. These causal genes are integral components of the *NOTCH* signaling pathway. Pathogenic *JAG1* variants or deletions are detected in 94.3% of genetically confirmed cases, whereas pathogenic *NOTCH2* variants account for 2.5% of clinical cases [5, 6]. Owing to its low prevalence, high phenotypic heterogeneity, and nonspecific early manifestations, ALGS is frequently underdiagnosed or misdiagnosed in the pediatric population, leading to delayed intervention and adverse long-term outcomes.

Hepatic involvement is the most prominent feature of Alagille syndrome and is often identified in the neonatal period. Recent studies have indicated that 9%–95% of patients with ALGS exhibit liver involvement [7–9]. The severity of liver disease varies widely, and persistent cholestasis can lead to severe pruritus, malnutrition, growth retardation, liver fibrosis, cirrhosis, and end-stage liver disease [11–12]. Cardiac anomalies, most frequently pulmonary stenosis, are the second leading cause of mortality [12]. Extrahepatic manifestations, including butterfly vertebrae, skeletal dysplasia, renal parenchymal disease, and vascular malformations, further complicate the clinical course. Despite advances in genetic testing, data from Asian cohorts, particularly those involving Chinese children, remain limited. Genotype–phenotype correlation, differences in baseline liver function between distinct genotypes, longitudinal changes in liver biochemistry, and responses to conventional and emerging therapies have not yet been fully elucidated.

Although the understanding of ALGS pathogenesis has deepened in recent years, clinical management continues to pose major challenges. Until recently, treatment was largely supportive, encompassing nutritional support, choleretic drugs, antihistamines, and the management of extrahepatic manifestations [13–15]. In 2021, the ileal bile acid transporter (IBAT) inhibitor maralixibat received U.S. Food and Drug Administration (FDA) approval for treating cholestatic pruritus associated with ALGS, ushering in a new era of targeted therapy [16]. Maralixibat effectively reduces bile acid overload and alleviates cholestasis related complications. Nevertheless, real-world data on its efficacy, safety, and long-term sustainability in Chinese patients are notably lacking.

Therefore, this study aimed to systematically investigate the clinical characteristics, mutation spectrum, genotype–phenotype correlations, longitudinal changes in liver function, and treatment responses in a Chinese pediatric cohort with Alagille syndrome (ALGS). By integrating clinical, genetic, biochemical, and therapeutic data, we aimed to provide evidence for early diagnosis, risk stratification, personalized management, and future development of targeted therapies for Chinese children with ALGS.

Materials and methods

This study retrospectively analyzed the clinical data of 19 patients diagnosed with Alagille syndrome (ALGS) at Shenzhen Children's Hospital between January 2011 and December 2024. To exclude extrahepatic disorders, including biliary atresia (BA), infections, and metabolic diseases, a comprehensive panel of investigations was conducted, including serum ammonia, lactate, and blood glucose monitoring; blood gas analysis; bacterial culture; viral serology testing; thyroid function assessment; and serum amino acid analysis. Urine samples were used for routine urinalysis, cytomegalovirus nucleic acid detection, and organic acid profiling. Imaging examinations included liver and spleen ultrasonography and magnetic resonance cholangiopancreatography (MRCP).

ALGS should be suspected in patients with histological evidence of bile duct paucity (reduced bile duct-----only four patients underwent this procedure. All children were confirmed to carry heterozygous pathogenic variants of the *JAG1* or *NOTCH2* genes through molecular genetic testing.

The dataset encompassed demographic characteristics (including age, sex, height, and weight at admission), affected organ systems, liver function parameters at serial time points (baseline [at initial admission], 1 week, 2 weeks, 1 month, 4 months, and 1 year), administered therapeutic interventions, and molecular diagnosis of pathogenic genetic variants. The liver function parameters included the levels of alanine transaminase (ALT), aspartate transaminase (AST), γ-glutamyl transferase (GGT), total bilirubin (TBil), direct bilirubin (DB), and total bile acids (TBA). The collected data were statistically analyzed and plotted using GraphPad Prism 10 software.

Blood samples were collected from the children and their parents for further analysis. Genomic DNA was extracted using a blood genomic DNA extraction kit (MyGenostics Inc., Beijing, China; KingMed Gene Technology Co., Ltd., Beijing, China). Targeted regions were amplified, purified, and sequenced using high-NextSeq 500 (Illumina, Inc., San Diego, CA, USA). Sequencing was performed by Beijing MyGenostics Medical Research Center Co., Ltd. (Beijing, China), and Beijing KingMed Gene Technology Co., Ltd. (Beijing, China). The databases used for MAF annotation included 1000 Genomes, dbSNP, ESP, ExAC, and the MyGenostics MAF database. As a priority for pathogenicity annotation in accordance with ACMG guidelines, the pathogenicity of each variant was assessed using OMIM, HGMD, and ClinVar databases. For statistical analyses, numerical data are presented as medians, and categorical data as numbers and percentages.

Results

A total of 19 participants were included in this study, consisting of 9 males and 10 females. The median age of onset for the 19 children with ALGS was 1.5 months (range: 0.1–43 months), and some of the children (26.3%) developed the condition shortly after birth.

Table 1
Demographic and clinical characteristics of 19 children with Alagille syndrome. N = 19

Age(months)	**1.5(0–43)**
Gender(n, %)	
Male	9(47%)
Female	10(53%)
Clinical symptoms(n, %)	
Cholestasis	12(63%)
Abnormal liver enzymes	16(84%)
Butterfly vertebrae	1(5%)
Skeletal deformity	6(31.6%)
Cardiac features	7(37%)
Renal features	3(16%)
Vascular malformation	2(11%)
Genetic variation	
JAG1(n, %)	13(68%)
NOTCH2(n, %)	6(32%)

Cholestasis is the predominant clinical manifestation in children with ALGS, with jaundice being the most prominent feature. Seven patients (36.8%) presented with jaundice as the initial symptom. Additionally, elevated liver enzymes (transaminase levels > 2 times the upper limit of normal) were observed, with median AST and ALT values of 94 U/L and 82.5 U/L. Markedly elevated bilirubin levels were also noted; the median values for total bile acid (TBA), total bilirubin (TBil), and direct bilirubin (DBil) were 54.7 μmol/L (normal range: 0.5–10.0 μmol/L), 29.45 μmol/L (normal range: 3.42 ± 0.5 μmol/L), and 10.5 μmol/L (normal range: 0–8.6 μmol/L), respectively. The median GGT level in the 19 patients was 119 U/L. Thirteen patients (63%) had disease onset within the first three months of their lives. Liver biopsy findings in four patients were consistent with cholestatic pathological changes, indicating marked bile stasis in the cytoplasm and bile canaliculi of hepatocytes. In one of these cases, immunohistochemistry showed positivity for CK7 in interlobular bile ducts and ductular epithelium; Masson's trichrome staining revealed mild fibrous tissue proliferation in the portal areas; reticulin fiber staining indicated a regular distribution of reticulin fibers; periodic acid–Schiff (PAS) staining showed no red inclusions; and PAS with diastase (PAS- Radiological findings were as follows:Cardiovascular anomalies were present in the majority of patients (7, 37%), with pulmonary artery stenosis being the most common (4, 57%). Other cardiovascular findings included mitral regurgitation (1, 14%), tiny coronary artery fistula (1, 14%), and developmental anomalies of the internal jugular vein and cerebral arteries (1, 14%). Hepatic involvement was also frequent (7, 37%), mainly presenting as diffuse hepatomegaly (6, 85.7%) and biliary atresia (1, 14%). Multiple gallstones were observed in one case (14%). Renal involvement was detected in

3 patients (16%), with ultrasound showing diffuse parenchymal renal disease. Skeletal malformations occurred in 31.6% of patients, with a typical butterfly vertebra observed in one patient (5%). No ocular abnormalities were observed in any of the patients (Tables 1 and 2).

Table 2
Case series of 10 children with Alagille syndrome

Patient	Age(m)/gender	Genetic variation	Organs involved	Liver biopsy
1	2/F	*JAG1*	Cholestasis, biliary atresia, no ossification center of the coccyx was observed, pulmonary artery stenosis	N
2	2/F	*JAG1*	Cholestasis, hepatomegaly, pulmonary artery stenosis, renal parenchymal roughness, abnormal vascular development	Consistent with the pathological changes of cholestasis
3	1/F	*NOCTH2*	Cholestasis, delayed kidney development	N
4	3/F	*JAG1*	Cholestasis, hepatomegaly, congenital spina bifida, coronary fistula	N
5	74/M	*JAG1*	Cholestasis, hepatomegaly, butterfly vertebrae, scoliosis, pulmonary artery stenosis	Consistent with the manifestations of metabolic liver disease
6	43/F	*JAG1*	Cholestasis, Thoracic vertebrae midsection fusion, pulmonary artery stenosis	N
7	3/M	*JAG1*	N	N
8	34/F	*JAG1*	Diaphragmatic hernia, hepatomegaly	N
9	2/M	*JAG1*	Cholestasis, Portal vein cavernous transformation	The liver cells show degenerative changes, with bile accumulation in the cytoplasm and bile ducts, and the sinusoidal area expands
10	11/M	*JAG1*	N	N
11	1/F	*JAG1*	Cholestasis, pulmonary artery stenosis, renal parenchymal roughness	N
12	6/M	*NOTCH2*	Osteoporosis, compression fractures of vertebrae, lumbar spondylolisthesis, valgus knee	N
13	1/M	*NOTCH2*	Cholestasis, Cervical kyphosis	The boundaries of the liver lobules are not distinct. Hepatocyte edema and degeneration; Bile stasis in the bile ducts
14	4/M	*NOTCH2*	cholestasis	N
15	3/F	*JAG1*	N	N
16	2/F	*NOTCH2*	N	N
17	8/M	*JAG1*	Cholestasis, hepatomegaly, splenomegaly, portal hypertension	N
18	2/F	*JAG1*	Cholestasis,	N
19	2/M	*NOTCH2*	mitral regurgitation	N

The results of the genetic analysis are summarized in Tables 2 and 3. A total of 68% (13/19) of the patients carried *JAG1* pathogenic variants, while the remaining 32% (6/19) harbored *NOTCH2* pathogenic variants. *JAG1* variants were the most common genetic etiology (13/19, 68.4%), followed by *NOTCH2* variants (6/19, 31.6%). Among the *JAG1* variants, exons 5 and 26 were each affected in 2 patients, with the remaining variants distributed across 10 distinct exons. In contrast, *NOTCH2* variants were concentrated in exons 3, 4, 20, and 34, with exon 34 being affected in 3 patients. A diverse spectrum of mutational classes was identified, including missense variants (e.g., *JAG1 p.C220F, p.P1006T*), nonsense variants (e.g., *NOTCH2 p.Q445, JAG1 p.W404*), frameshift variants (e.g., *JAG1 p.D925Gfs3*), and splicing variants (e.g., *JAG1* c.2113-5C > A). Notably, the chromosomal locus chr20:10620418 was recurrently affected by *JAG1* variants (n = 2). The variant *p.R235* was also recurrently identified in patients with *JAG1* mutations. The gender distribution was well balanced (9 females, 10 males), with no gender predilection observed.

Table 3
Genetic traits of children with ALGS

Patient	Gene	Exon	Genetic mutation information	Chromosomal location	Homozygous/Heterozygous	Family results	ACMG Pathogenicity analysis
1	*JAG1*	exon4	*c.659G > T(p.C220F)*	*chr20-10639151*	heterozygous	spontaneous variant	Likely pathogenic
2	*JAG1*	exon10	*c.1333C > T(p.Q445)*	*chr20-10630185*	heterozygous	spontaneous variant	pathogenic
3	*NOTCH2*	exon4	*c.504C > A(p.C168)*	*chr1-120539867*	heterozygous	spontaneous variant	pathogenic
4	*JAG1*	exon24, exon20	*c.3016C > A(p.P1006T),c.2413C > T(p.R805W)*	*chr20-10621793,chr20-10624471*	heterozygous	mother	VUS
5	*JAG1*	exon9	*c.1211G > A(p.W404)*	*chr20-10630918*	heterozygous	spontaneous variant	pathogenic
6	*JAG1*	exon17	*c.2173dupG(p.D725Gfs*3)*	*chr20-1062584410625844*	heterozygous	spontaneous variant	pathogenic
7	*JAG1*	exon23	*c.2779G > A*	*chr20-10622245*	heterozygous	mother	uncertain
8	*JAG1*	exon5	*c.703C > T(p.R235X)*	*chr20:10637098*	heterozygous	father	pathogenic
9	*JAG1*	exon16	*c.2113 + 5G > A(splicing)*	*chr20-10625999*	heterozygous	spontaneous variant	uncertain
10	*JAG1*	exon26	*c.3385C > A(p.H1129N)*	*chr20:10620418*	heterozygous	spontaneous variant	uncertain
11	*JAG1*	exon5	*c.703C > T(p.R235X)*	*chr20:10637098*	heterozygous	father	pathogenic
12	*NOTCH2*	exon34	*c.6449_6450delCT*	*chr1:120458894–120458896*	heterozygous	spontaneous variant	pathogenic
13	*NOTCH2*	exon20	*c.3226G > A(p.G1076S)*	*chr1-120480591*	heterozygous	mother	VUS
14	*NOTCH2*	exon3	*c.214C > T*	*chr1-120548153*	heterozygous	father	uncertain
15	*JAG1*	exon26	*c.3385C > A*	*chr20-10620418*	heterozygous	father	uncertain
16	*NOTCH2*	exon34	*c.6314G > A*	*chr1-120459031*	heterozygous	father	uncertain
17	*JAG1*	exon26	*c.3577C > T*	*chr20-10620226*	heterozygous	spontaneous variant	uncertain
18	*JAG1*	exon13	*c.1655C > T(p.P552L)*	*chr20-10628673*	heterozygous	father	uncertain
19	*NOTCH2*	exon34	*c.6236C > T(p.A2079V)*	*chr1-120459109*	heterozygous	spontaneous variant	uncertain

VUS: Clinical significance is unknown.

Table 2 Case series of 10 children with Alagille syndrome

Table 3 Genetic traits of children with ALGS

Tables 1 and 2 *are attached at the end of the article.*

This study analyzed and compared the liver function data from the 1-month and 1-year follow-up periods with the baseline data(Fig. 1) using the paired-samples Wilcoxon signed-rank test. The results demonstrated that total bilirubin (TBIL) and direct bilirubin (DBIL) levels were significantly reduced following one month of intervention (TBIL: Z = − 1.992, P = 0.046, r = 0.407; DBIL: Z = − 2.023, P = 0.043, r = 0.422), with moderate effect sizes. Although other liver function indices, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and total bile acid (TBA), also showed a downward trend after treatment, the differences were not statistically significant (all P > 0.05). After one year of therapy, TBIL levels remained significantly lower than the baseline values (Z = − 1.992, *P* = 0.046, *r* = 0.407), indicating a moderate effect size. DBIL levels exhibited a downward trend, but the difference was not statistically significant (*P* = 0.075). Notably, although the median GGT and TBA levels also declined from baseline, the changes did not reach statistical significance, likely due to large data variability (wide interquartile ranges).

Note

A, AST level change; B, ALT level change; C, GGT level change; D, TBA level change; E, TBIL level change; F, DBIL level change. The box plot shows the median (horizontal line within the box), interquartile range (box), and range (whiskers).

Baseline liver function parameters were compared between patients with *JAG1* (n = 13) and *NOTCH2* mutations (n = 6) (Fig. 2). Patients with *JAG1* mutations exhibited significantly higher baseline alanine aminotransferase (ALT) levels than those with *NOTCH2* mutations (median: 114.0 U/L vs. 53.5 U/L; U = 11.0, *P* = 0.019), with a large effect size (r = 0.538). No statistically significant differences were observed between the two groups for other indices, including aspartate aminotransferase (AST), gamma-(GGT), total bile acids (TBA), total bilirubin (TBIL), and direct bilirubin (DBIL) (all *P* > 0.05). However, the between-*P* = 0.061) with a moderate effect size (r = 0.421).

Note

G, AST level change between genotypes; H, ALT level change between genotypes; I, GGT level change between genotypes; J, TBA level change between genotypes; K, TBIL level change between genotypes; L, DBIL level change between genotypes. The box plot shows the median (horizontal line within the box), interquartile range ((box, and range (whiskers).

Analysis revealed a gradual reduction in AST levels over time; nevertheless, the overall difference across time points did not achieve statistical significance ($\chi^2 = 9.429$, df = 3, *P* = 0.093) (Table 4).

Table 4
Comparison of AST levels in ALGS patients at different time points [M (IQR)]

Timepoint	AST (U/L)	Effective sample size
baseline	117.0 (55.0-440.0)	19
1 week	148.0 (243.0-369.8)	6
1 month	59.0 (46.0-348.5)	8
1 year	76.5 (30.0-174.5)	6
Note: Due to the inconsistent sample size at each time point, the Friedman test only included patients with complete data from all four follow-up visits (n = 5).		

Longitudinal changes in AST levels were evaluated using repeated measures analysis of variance (RM-ANOVA). Preliminary data validation was performed first, and no extreme outliers were identified on boxplots or via inspection of standardized residuals. The Shapiro–Wilk test indicated that the data at some time points deviated significantly from a normal distribution (P < 0.05); however, RM-ANOVA is known to be robust to violations of normality. Mauchly's test of sphericity revealed a violation of the sphericity assumption (Mauchly's W = 0.007, $\chi^2 = 4.903$, df = 2, P = 0.086). Accordingly, the degrees of freedom were adjusted using the Greenhouse–Geisser correction (ε = 0.502).

The descriptive statistics for AST levels at each time point are summarized in Table 5. The results revealed a gradual reduction in the mean AST level from 379.4 U/L at baseline to 97.5 U/L at the 1-year follow-up. However, substantial interindividual variability was observed, with a standard deviation of 818.7 U/L at baseline.

Table 5
Descriptive statistics of AST at each time point (mean ± standard deviation)

Timepoint	Sample size	Mean value(U/L)	Standard deviation(U/L)	Minimum value(U/L)	Maximum value(U/L)
Baseline	18	379.4	818.7	22.0	3551.0
1 Week	10	262.6	265.8	34.0	886.0
2 Week	7	176.0	119.1	34.0	321.0
1 Month	6	164.7	186.8	46.0	485.0
4 Month	5	120.8	45.6	187.0	187.0
1 Year	6	97.5	78.1	209.0	209.0

The repeated-*P* = 0.662, partial $\eta^2 = 0.114$), indicating the absence of a significant overall temporal trend in the data. Furthermore, the time × genotype interaction was not significant (F = 0.265, *P* = 0.659, partial $\eta^2 = 0.117$), suggesting that the pattern of AST changes over time did not differ significantly between the genotype groups.

In this study cohort, 3 patients (15.8%) received maralixibat, whereas 16 (84.2%) did not. There were no statistically significant differences between the treatment and the non-*P* > 0.05). Although GGT levels showed a trend toward being higher in the treatment group (318.0 vs. 135.0 U/L), the difference was not statistically significant (*P* = 0.063). These findings indicate that the two groups were comparable at baseline (Table 6).

Table 6
Baseline characteristics: maralixibat vs. control

Variate	Total	Text group(n = 3)	Non-test group(n = 16)	p
Continuous variable				
year(month)	1.5	26	4.7	
AST(U/L)	379.4	247.0	405.9	0.769
ALT(U/L)	284.6	276.7	286.2	0.981
GGT(U/L)	165.5	318.0	135.0	0.063
TBA(umol/L)	69.3	92.0	65.5	0.567
TBIL(umol/L)	86.1	72.0	85.3	0.839
DBIL(umol/L)	50.3	48.7	50.6	0.964
Classified variable	N(%)	N(%)	N(%)	p
gender(male/female)	9/10 (47/53)	1/2 (33/67)	8/8 (50/50)	
genotype(JAG1/NOTCH2)	13/6 (68/32)	3/0 (100/0)	10/6 (63/37)	0.517
cholestasis(exist/non)	12/7 (63/37)	2/1 (67/33)	10/6 (63/37)	

AST levels in the maralixibat group increased transiently during the early treatment phase (1 week to 1 month) and then gradually decreased, whereas those in the untreated group continuously declined. At 1 year, the mean AST value in the untreated group (75.5 U/L) was lower than that in the treated group (141.5 U/L), although the difference was not significant ($P = 0.247$). Similar trends were observed for ALT levels (Fig. 3).

Only one patient (Patient 2) achieved a reduction of > 50% in both AST and ALT after treatment, meeting the criterion for efficacy. The other two patients showed some degree of decline but did not reach a 50% threshold. Patient 8 lacked one-year follow-up data; at the four-month assessment, AST and ALT had decreased by 26.3% and 33.3% from baseline, respectively.

Discussion

This study systematically reviewed the clinical features and genotype–phenotype correlations of Alagille syndrome (ALGS) by analyzing 19 confirmed cases, aiming to further delineate the clinical and genetic landscape of ALGS in the Chinese population and to support precision diagnosis and individualized management of the disease.

Our study cohort exhibited the typical characteristics of Alagille syndrome (ALGS), with a prominent pattern of multisystem involvement. Pathogenic mutations were predominantly in *JAG1* (68%), while *NOTCH2* mutations accounted for 32%, a distribution consistent with previously reported genotypic profiles of ALGS [17]. Cholestasis was the most prominent clinical feature of ALGS in this cohort, with an 84% incidence of hepatobiliary involvement, mainly manifesting as cholestatic jaundice and hepatomegaly. These findings confirm that the hepatobiliary system is the primary organ system affected by ALGS. Notably, 7 patients in this study presented with cholestasis as the initial symptom, and 13 patients developed abnormal liver function during infancy, indicating that hepatobiliary injury in ALGS can occur early in the disease course, particularly within the first 3 months of life. Previous studies have also documented that ALGS may present with direct hyperbilirubinemia in the neonatal period, with variable severity [8]. These observations underscore the importance of early liver function monitoring for disease surveillance and early recognition of liver dysfunction. Liver biopsy was performed in 4 children in this cohort, all of whom demonstrated histological evidence of cholestasis. One case additionally showed positive CK7 immunohistochemistry indicative of small bile duct proliferation. Historically, due to limited diagnostic modalities, liver biopsy was considered essential for establishing a diagnosis of ALGS, with pathological findings typically showing cholestasis accompanied by bile duct paucity, a feature reported to be present in 100% of patients with ALGS [7–9]. However, with advances in molecular genetic testing, invasive diagnostic procedures are no longer required. Accordingly, only 4 patients in our study cohort underwent liver biopsy for confirmation.

Cardiovascular abnormalities were the second most common manifestation in the present study (37%), with pulmonary stenosis being the most frequent (57%). Notably, no clinical features of tetralogy of Fallot were observed in this cohort. Meanwhile, the proportions of concomitant vascular malformations (11%) and renal anomalies (16%) in our patient group were slightly lower than those reported in Western studies [7, 18–19], which may be attributable to the relatively small sample size or racial differences. Skeletal anomalies occurred in 31.58% of cases, and only 1 patient (5.26%) exhibited the typical butterfly vertebra, suggesting that skeletal phenotypes may be relatively rare in Chinese children with ALGS. Consistent with another Chinese case series [20], none of the patients in our study presented with ocular manifestations, which may indicate a lower prevalence of ocular abnormalities in the Chinese ALGS population than in other populations.

Internationally, up to 97% of ALGS cases have been attributed to pathogenic variants in *JAG1*, whereas variants in *NOTCH2* account for fewer than 1% of the affected individuals [21–23]. In the present cohort, *JAG1* mutations were the predominant genetic cause (68.4%), followed by *NOTCH2* mutations (31.6%). The proportion of *NOTCH2* mutations in our study was slightly higher than that reported in some European and American cohorts, suggesting

potential ethnic disparities in the mutational spectrum of ALGS [24]. Regarding the distribution of mutations, *JAG1* variants were scattered across multiple exons, with relative clustering in exons 5 and 26. In contrast, *NOTCH2* mutations were notably concentrated in exons 3, 4, 20, and 34; exon 34 harbored mutations in 3 cases, indicating that this region represents a mutational hotspot for *NOTCH2* in Chinese pediatric patients and may serve as a priority target for genetic screening. This study is the first to identify the recurrent variant at chr20:10620418 in *JAG1*, implying that this locus may constitute a novel mutational hotspot within the *JAG1* gene and may have functional significance in the pathogenesis of ALGS.

The variant *NM_000214.3: c.2122_2125delCAGT p. (Gln708Valfs*34)* is the most prevalent pathogenic variant of *JAG1* reported internationally, located within exon 17 of the *JAG1* gene. A retrospective study identified this frameshift variant in 5 unrelated patients (5/115, 4.35%), and it has been previously documented in the Human Gene Mutation Database (HGMD accession number: CD972288). According to the published literature, this variant is the most frequently detected mutation in patients with ALGS [11, 25]. However, this variant was not identified in the present study. Given the relatively small sample size, it remains inconclusive whether this variant type is less prevalent in the Chinese population than in other populations. The p.R235 variant was recurrently detected in *JAG1* and was exclusively inherited from the father in all cases, suggesting that this locus may represent a mutational hotspot in JAG1. Further studies with larger sample sizes are required to validate the significance of this hotspot. The identified mutations were predominantly missense, nonsense, frameshift, and splice-site variants, most of which were heterozygous de novo. Specifically, 11 cases (57.9%) were de novo mutations, while 8 cases (42.1%) were inherited from a parent, with paternal inheritance predominating (6 cases). Notably, phenotypic variability was observed among family members harboring identical mutations, such as patient 4 and his mother. The mother carried two *JAG1* mutations but exhibited a milder phenotype. Similar intrafamilial phenotypic heterogeneity has been documented in previous studies. For instance, Zhang et al. reported a child with classic ALGS features whose mother carried the same pathogenic *JAG1* variant *(c.3112C > G, p. Leu1038Val)*, but displayed no overt ALGS phenotype [26]. These findings highlight the marked variable expressivity and intrafamilial heterogeneity in ALGS, consistent with autosomal dominant inheritance, and support the notion that both familial inheritance and de novo mutations contribute to the genetic etiology of ALGS. Internationally, pathogenic variants of *JAG1* are the most common, identified in 94.3% of individuals with ALGS. Pathogenic variants in *NOTCH2* are considerably rarer, accounting for 2.5% of ALGS cases, with 19 distinct pathogenic variants (six of which are recurrent) reported to date. In contrast to *JAG1*, most *NOTCH2* variants are missense (68%) [6, 27–28]. ACMG-based pathogenicity analysis in the present study revealed that 47.4% (9/19) of the variants were classified as definitely pathogenic, among which 44.4% (4/9) were *JAG1* pathogenic mutations. Variants of uncertain significance (VUS) constituted 42.1% (8/19) of all the detected variants. Differences in pathogenic mutation rates have distinct implications for the genetic confirmation of Alagille syndrome (ALGS) in the Chinese population. For cases with rarer clinical presentations, a comprehensive evaluation is required rather than relying solely on genetic testing to establish a diagnosis. Although the rate of variants of uncertain significance (VUS) in our cohort was lower than that reported in the ClinVar database, such variants still represent a major challenge in current genetic diagnosis, likely related to the expression patterns of ALGS-associated genes [29]. Thus, the clinical interpretation of VUS remains a hurdle for precise molecular diagnosis, and further validation is warranted through co-segregation analysis within pedigrees and functional studies. For instance, Patient 4 harbored two VUS (p.P1006T and p.R805W) and exhibited a relatively mild clinical phenotype without cholestasis, suggesting that these two variants may confer low penetrance or require biallelic involvement to exert pathogenicity.

Previous studies have reported no significant genotype–phenotype correlations between individuals harboring *JAG1* and *NOTCH2* variants [29–32]. However, other investigations have identified subtle distinctions: patients with ALGS caused by *JAG1* variants more commonly present with facial dysmorphism and cardiac involvement than those carrying *NOTCH2* variants [20, 27, 33]. In the present cohort, children with *JAG1* mutations were more likely to exhibit the classic ALGS triad (cholestasis, cardiac anomalies, and skeletal defects). In contrast, the *NOTCH2* mutation group displayed several uncommon skeletal phenotypes, including osteoporosis, vertebral compression fractures, lumbar spondylolisthesis (Patient 12), and cervical lordosis (Patient 13). This observation appears to conflict with international reports, which indicate that individuals with *NOTCH2* mutations have a lower penetrance of major clinical features than those with *JAG1* mutations. Specifically, skeletal abnormalities and facial features are rarely documented in patients with *NOTCH2*-related ALGS. One study of patients with *NOTCH2* mutations demonstrated a statistically significant reduction in the prevalence of skeletal anomalies and dysmorphic features compared to the *JAG1* mutation group [34]. Notably, Patient 12 carried a pathogenic *NOTCH2* mutation but did not present with cholestasis, suggesting that *NOTCH2*-related ALGS may be characterized predominantly by skeletal and renal phenotypes with relatively milder hepatic involvement.

The histopathological findings from liver biopsies in 4 patients in this study further supported the existence of genotype–phenotype correlations in ALGS. Patient 2 (harboring a *JAG1* mutation) and Patient 13 (carrying a *NOTCH2* mutation) exhibited cholestatic liver injury. Notably, Patient 9, with a *JAG1* mutation, developed cavernous transformation of the portal vein, a rare vascular anomaly that may be related to the role of *JAG1* in vascular development. Positive immunohistochemical staining for CK7, indicative of small bile duct proliferation (Patient 13), was consistent with the characteristic pathological changes of bile duct paucity observed in ALGS [26, 35].

As a multisystem hereditary disorder mediated by *JAG1*/*NOTCH2* mutations, Alagille syndrome (ALGS) is characterized by cholestasis resulting from bile duct dysplasia, which is the central driver of liver injury, progressive hepatic fibrosis, and even end-stage liver disease [36–38]. Therefore, dynamic monitoring of liver function and effective interventions are critical steps toward improving long-term prognosis. Management strategies for ALGS focus on controlling cholestasis and its associated complications, including nutritional support, fat-soluble vitamin deficiency (FSVD), and pruritus [17]. In current clinical practice, the initial treatment for pediatric ALGS patients primarily consists of conventional choleretic and hepatoprotective therapy. Standard pharmacotherapy includes ursodeoxycholic acid (UDCA), cholestyramine, and rifampicin, while surgical interventions may also be applied to promote bile excretion and alleviate pruritus [12–15, 39]. Ursodeoxycholic acid, a synthetic bile acid, is typically used as a first-line treatment to improve

bile flow and is widely administered to patients with cholestatic liver disease, regardless of the presence or severity of pruritus, as cholestasis may improve irrespective of symptom intensity [40–41]. Given its favorable safety profile, UDCA is routinely recommended as a first-line therapy [42]. In the present study cohort, nearly all children received conventional choleretic treatment with UDCA as the foundational agent. Medications were further adjusted according to the individual clinical status, such as the use of reduced glutathione to lower liver enzymes and supplementation with fat-soluble vitamins. Our results demonstrated that serum levels of total bilirubin (TBIL) and direct bilirubin (DBIL) decreased significantly after one month of treatment (P = 0.046 and P = 0.043, respectively), with moderate effect sizes (r = 0.407 and 0.422, respectively). Moreover, the improvement in TBIL persisted at one-year post-treatment (P = 0.046). These findings suggest that impaired bilirubin metabolism is a relatively reversible component of liver injury in ALGS. They further indicated that conventional comprehensive regimens centered on choleresis, hepatoprotection, nutritional support, and symptomatic management can rapidly and sustainably improve core markers of cholestasis, with clear clinical value in preventing hepatotoxicity and extrahepatic complications related to bilirubin accumulation. Nevertheless, liver enzyme parameters, including AST, ALT, and GGT, showed a downward trend but did not reach statistical significance. Notably, the median GGT level decreased markedly at 1 year (from 186.7 to 97.0 U/L), yet the interquartile range (IQR) expanded substantially (38.0–761.8 U/L), indicating highly heterogeneous GGT responses likely influenced by multiple factors such as genotype, age, and comorbidities. Repeated-measures analysis of variance (ANOVA) revealed a declining trend in AST levels over time; however, the temporal effect was not statistically significant (P = 0.662), and the interaction between time and genotype was also non-significant (P = 0.659). This observation may be attributed to several factors, including the following. First, only 5 patients had complete data across all four follow-up time points, resulting in severely limited statistical power. Second, the baseline AST standard deviation was as high as 818.7 U/L, reflecting considerable heterogeneity within the cohort. Extreme values in certain patients (e.g., Patient 17 with AST 3551 U/L) may have masked the overall trends. These findings emphasize that individualized trajectories, rather than population mean values, should be emphasized in the prognostic evaluation of ALGS. Regarding genotype–liver function correlations, children with *JAG1* mutations exhibited significantly higher baseline ALT levels than those with *NOTCH2* mutations (P = 0.019, r = 0.538), with a similar trend observed for AST (P = 0.061). These results suggest that *JAG1* variants may be associated with more severe hepatocellular injury, providing novel evidence for genotype–phenotype stratification in ALGS. *JAG1* is a transmembrane ligand of the Notch signaling pathway.

Haploinsufficiency of *JAG1* protein resulting from heterozygous mutations in the *JAG1* gene is sufficient to disrupt normal bile duct development, leading to earlier and more pronounced elevations in transaminases. Accordingly, such patients require more intensive liver function monitoring and earlier therapeutic intervention [36–37, 43]. In contrast, children with *NOTCH2* mutations displayed relatively milder hepatobiliary involvement. These findings support the notion that distinct disease-causing genes act through different components of the Notch signaling pathway to generate divergent phenotypes, providing molecular targets for personalized risk stratification.

Surgical intervention is generally not considered a first-line treatment for Alagille syndrome. However, it may still be indicated in pediatric patients with refractory cholestasis who show inadequate response to medical therapy. In the present cohort, surgical procedures were performed in 4 children. The efficacy of surgical management has been well established in international literature. In a large, multicenter North American study investigating biliary diversion in infants with cholestasis, biliary diversion surgery in 20 patients with ALGS resulted in reduced serum cholesterol levels, regression of xanthomas, and a significant decrease in patient-reported pruritus [14, 17].

In recent years, the management of Alagille syndrome has evolved from conventional supportive care to the era of precision therapy targeting the ileal bile acid transporter. Maralixibat, the first globally approved targeted agent for cholestasis in ALGS, exerts its therapeutic effect by inhibiting the apical sodium-dependent bile acid transporter (ASBT), also known as the IBAT. ASBT is primarily responsible for mediating the reabsorption of bile acids from the small intestine back to the liver. Approximately 95% of bile acids are recycled to the liver via ASBT. Preliminary clinical studies have demonstrated considerable potential of maralixibat in alleviating pruritus and improving serum biochemical markers in pediatric patients [44–47]. In the present study, baseline characteristics of the 3 children receiving maralixibat were comparable to those of the untreated group (all P > 0.05), providing a valid basis for efficacy comparison. Individual response analysis revealed that one patient (Patient 2) achieved a greater than 50% reduction in AST and ALT levels, meeting the criteria for clinical response and indicating a clear hepatoprotective effect of maralixibat in selected pediatric ALGS patients. Although the remaining two patients showed decreasing trends, the reductions did not reach the predefined threshold. These findings are generally consistent with the results of the ICONIC study, in which 42% of patients achieved a greater than 50% decrease in serum bile acids following 48 weeks of maralixibat treatment [48], suggesting substantial interindividual variability in the real-world effectiveness of this agent. The Italian MAREA study (Maralixibat Expands Treatment Landscape in Alagille Syndrome), a real-world study, enrolled a total of 13 patients. After 24 weeks of treatment, 77% of patients achieved a reduction in serum bile acid levels exceeding 25% [49]. Notably, Patient 2 harbored a *JAG1* mutation and had a high baseline GGT level (158 U/L). Following treatment, AST and ALT levels decreased by 72.1% and 61.2%, respectively, suggesting that *JAG1*-mutated patients with elevated GGT may exhibit a more favorable response to maralixibat. This observation is consistent with findings reported by Gonzales et al., who demonstrated that baseline GGT level could predict the therapeutic efficacy of IBAT inhibitors [49]. For Patient 8, 4-month data were used in place of 1-year data due to missing long-term follow-up. AST and ALT decreased by 26.3% and 33.3%, respectively; with prolonged follow-up, these reductions might approach the 50% threshold for clinical response. This implies that some patients may require a longer treatment duration to achieve optimal efficacy. Regarding safety, maralixibat demonstrated a favorable safety profile. Among 37 patients in the U.S. expanded access program, only 3 patients (8%) experienced mild gastrointestinal treatment-related adverse events. Two patients required dose reduction due to diarrhea, and one patient discontinued treatment because of mild liver enzyme elevation. The MERGE study, conducted in the same cohort, further confirmed the durability of therapeutic response and safety over up to 7 years of treatment [49].

Furthermore, transient elevations in transaminases observed early during treatment were likely associated with bile acid redistribution and adaptive hepatocellular responses, whereas levels trended downward during long-term follow-up, consistent with findings from international multicenter studies [49]. Although between-group comparisons did not reach statistical significance due to the limited sample size, the present study nonetheless provides preliminary real-world evidence supporting the use of maralixibat in Chinese pediatric patients with ALGS. Future studies with larger sample sizes and randomized controlled designs are warranted to determine the optimal initiation timing, dosage, and long-term safety profile, as well as to identify predictive biomarkers of therapeutic response.

The non-significant improvements in most parameters in this cohort may be attributed to several factors. First, hepatic lesions in ALGS are characterized primarily by bile duct paucity, in which hepatocellular injury represents a secondary change; conventional choleretic therapy alone may be insufficient to reverse established bile duct loss. Second, the median follow-up duration in this study was only 1 year, whereas hepatic progression in ALGS is generally slow; longer-term follow-up may reveal more pronounced treatment effects. Third, extreme values in some patients (e.g., Patient 17) introduced substantial variability and interfered with statistical comparisons, suggesting that subgroup or sensitivity analyses should be considered in future real-world studies. Fourth, given the retrospective design of this study, uniformity of therapeutic regimens and standardization of follow-up could not be fully ensured.

With an improved understanding of the pathogenesis of Alagille syndrome (ALGS), therapeutic strategies are shifting from symptomatic management toward etiological intervention. The first clinical guideline focusing on ileal bile acid transporter inhibitors (IBATis) for cholestatic pruritus was recently published. This guideline recommends that in pediatric patients with ALGS, although ursodeoxycholic acid (UDCA) should not be regarded as the sole agent for pruritus, IBATis are indicated as second-line therapy following trial treatment with UDCA and rifampicin [49–50]. Maralixibat was approved by the U.S. FDA in 2021 for the treatment of cholestatic pruritus in ALGS, and accumulating evidence supports its long-term benefits in improving quality of life and delaying liver transplantation [16]. Gene therapy represents a potential curative strategy for ALGS. As both *JAG1* and *NOTCH2* exert pathogenic effects via haploinsufficiency, antisense oligonucleotides (ASOs) have emerged as promising therapeutics, with over 30 years of development and multiple ASO drugs already approved for various human diseases. In a study by Zhang L et al., administration of an ASO in an ALGS mouse model increased Jag1 protein expression, which sufficiently ameliorated bile duct (BD) development and reduced plasma bile acid and triglyceride levels. Specifically, ASOs targeting the 5' uORF of *Jag1* mRNA significantly elevated Jag1 protein abundance, improved hepatic BD development, and restored liver function. These findings highlight a novel therapeutic opportunity: directly enhancing endogenous *JAG1* protein levels in patients with ALGS may improve bile duct development and thus confer clinical benefit [51]. Advances in organoid and induced pluripotent stem cell (iPSC) technologies have provided novel platforms for personalized drug screening and mechanistic investigations in ALGS.

In the era of precision medicine, the management of Alagille syndrome (ALGS) requires comprehensive integration of genotype, clinical phenotype, and biomarker profiles. Future multi-center prospective cohort studies are warranted to establish genotype-based therapeutic stratification models, explore combination therapeutic regimens (such as IBAT inhibitors combined with UDCA or FXR agonists), and develop efficacy prediction models tailored to the Chinese population. Meanwhile, the value of multidisciplinary collaboration (including hepatology, cardiology, nutrition, and other specialties) in improving long-term outcomes of pediatric patients should be emphasized.

Conclusion

This study characterized clinical manifestations, genotype–phenotype relationships, longitudinal liver function, and treatment responses in 19 Chinese pediatric patients with Alagille syndrome. Cholestasis and elevated liver enzymes were the predominant features, accompanied by relatively high rates of cardiovascular and skeletal anomalies. *JAG1* mutations (68.4%) constituted the primary genetic etiology, while *NOTCH2* mutations (31.6%) were more closely linked to skeletal defects. Patients harboring *JAG1* variants exhibited significantly higher baseline ALT levels, indicating more severe hepatocellular injury. Conventional comprehensive therapy significantly reduced total and direct bilirubin levels at 1 month and sustained the effect at 1 year. Preliminary observations suggested that maralixibat may provide beneficial effects in selected individuals. These data highlight the importance of early genetic diagnosis, genotype-stratified management, and targeted interventions to improve long-term prognosis in ALGS.

Abbreviations

ACMG
American College of Medical Genetics and Genomics
ALGS
Alagille syndrome
ASBT
apical sodium-dependent bile acid transporter
ASO
antisense oligonucleotide
BA
biliary atresia
BD
bile duct

DBIL
direct bilirubin
FDA
U.S. Food and Drug Administration
FSVD
fat-soluble vitamin deficiency
GGT
γ-glutamyl transferase
HGMD
Human Gene Mutation Database
IBAT
ileal bile acid transporter
IBATis
ileal bile acid transporter inhibitors
iPSC
induced pluripotent stem cell
IQR
interquartile range
MAREA
Maralixibat Expands Treatment Landscape in Alagille Syndrome
MRCP
magnetic resonance cholangiopancreatography
PAS
periodic acid–Schiff
PASD
periodic acid–Schiff with diastase
RM-ANOVA
repeated-measures analysis of variance
TBA
total bile acids
TBIL
total bilirubin
UDCA
ursodeoxycholic acid
VUS
variants of uncertain significance.

Declarations

Ethics approval and consent to participate

The studies involving humans have been approved by the Medical Ethics Committee of Shenzhen Children's Hospital (approval number: 202200502). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was obtained from the legal guardians of the patients.

Consent for publication

No information or images of this manuscript can identify the participants. Not applicable.

Availability of data and materials

The datasets generated during the current study are available in the NCBI repository under BioProject accession number PRJNA1466752. Direct link: https://www.ncbi.nlm.nih.gov/bioproject/PRJNA1466752.

Competing Interests

The authors report no conflicts of interest.

Funding

This study was supported by Shenzhen Medical Research Fund (Grant number C2401020), Shenzhen Science and Technology Innovation Program (Grant number JCYJ20220818102801004), Shenzhen Clinical Research Center（20220819113341005).

Author's contributions

H.C. conceived the study, collected and analyzed clinical data, and drafted the original manuscript. Y.Z. prepared and revised Figures 1 and 2. Z.Z. prepared and revised Figures 3, 4, and 5. Z.L., B.L., and S.M. constructed and formatted all tables. D.D. supervised the project, critically revised the manuscript for intellectual content, and provided final approval. All authors have read and approved the final manuscript for submission.

Acknowledgements

The authors gratefully acknowledge Dr. Yigui Zou for his valuable academic advice, insightful suggestions on research design, and critical revision of the manuscript. His professional input greatly improved the scientific quality, logical structure, and academic presentation of this work.

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Figures

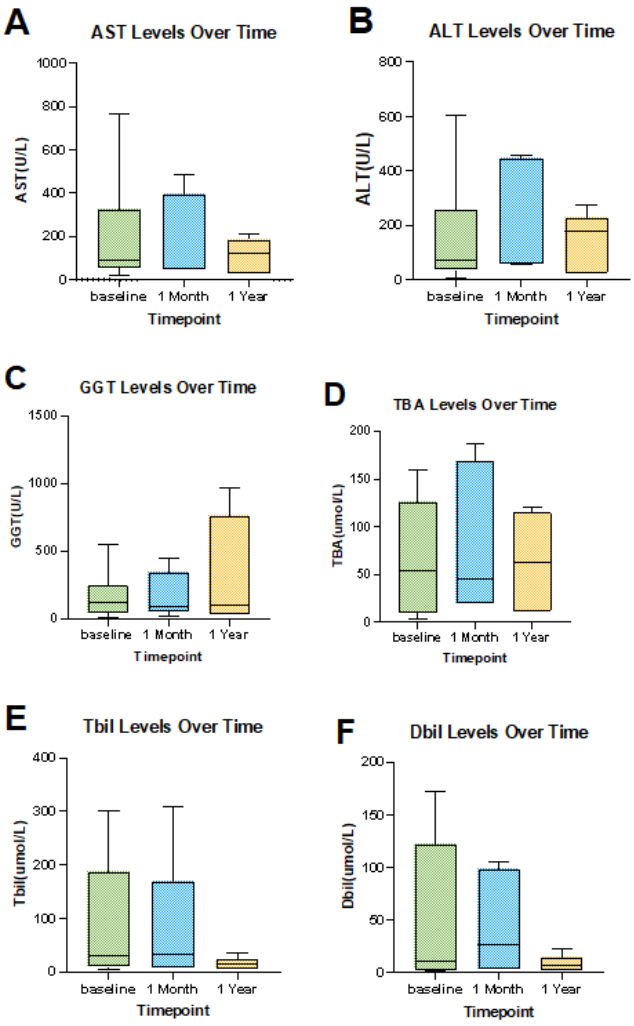


Figure 1

Liver function before and after treatment in ALGS

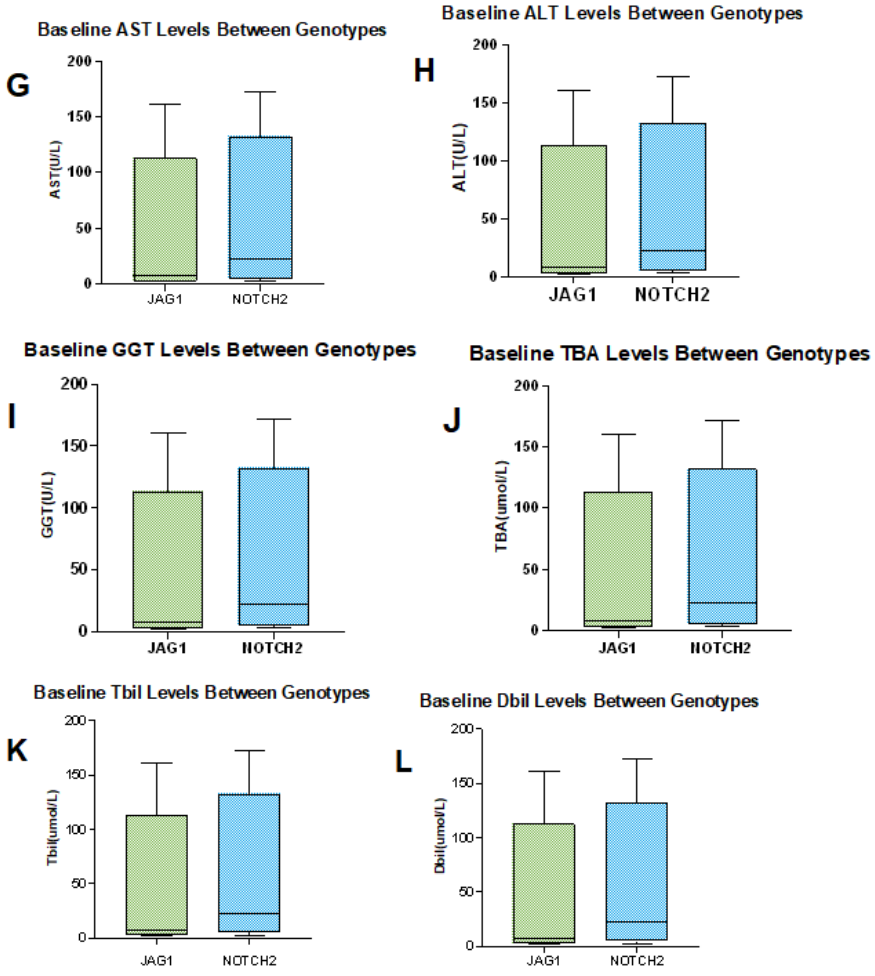


Figure 2

Baseline liver function by genotype in ALGS

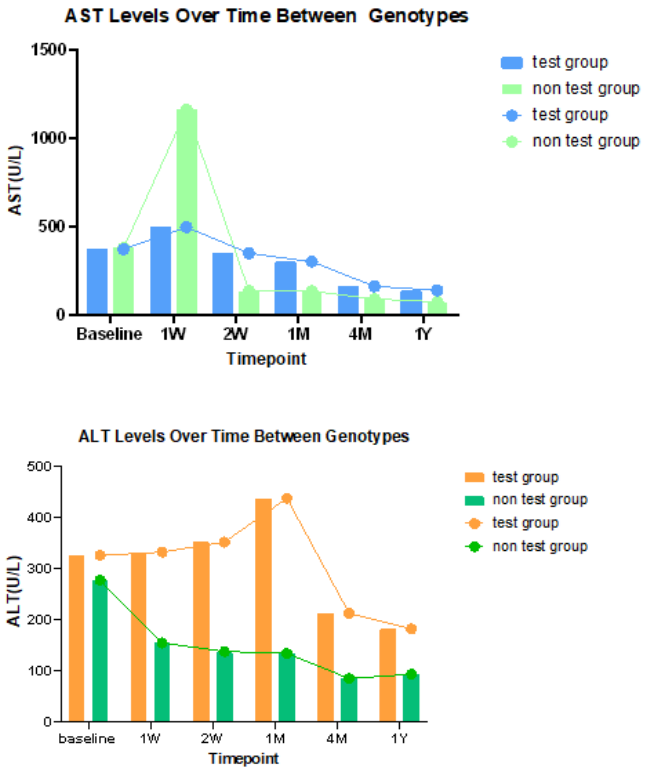


Figure 3

AST and ALT changes over time between two groups

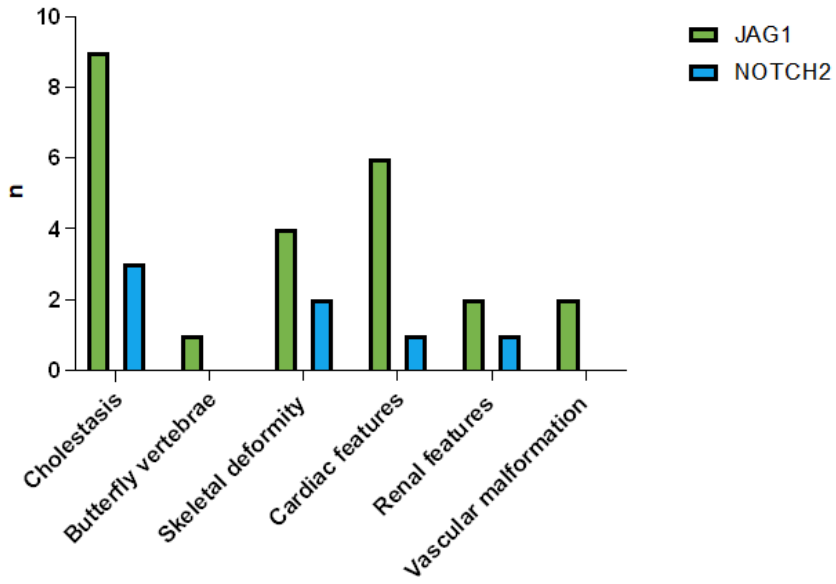


Figure 4

Distribution of clinical manifestations by genotype