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Metabolism-related hepatokines change in biliary atresia: ANGPTL6 as a potential biomarker

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Abstract

Objectives Biliary atresia (BA) is a severe obstructive cholangiopathy of early infancy that progresses to end-stage liver disease without any intervention. The aim of this study was to investigate the impact of drainage obstruction of bile on metabolism-related hepatokines and identify clinical biomarkers of BA.

Methods A total of 38 patients with BA and 12 age-matched controls were recruited. Blood samples were obtained for measuring liver function and hepatokine levels. Linear correlations between these changes in hepatokines and bilirubin/bile acid were subsequently examined to explore the hepatokines that may reflect the illness severity. Afterwards, ROC curve analysis was conducted to assess the diagnostic value of the hepatokines. Finally, prognostic analysis of the hepatokines was performed based on early cholangitis, the clearance of jaundice, native liver survival and liver transplantation.

Results The serum concentrations of TB, DB, ALT, AST, GGT, ALP and TBA in patients with BA were all increased compared with those in controls ($P < 0.05$). The plasma levels of ANGPTL4, HGF, FABP1, FGF21 and FGF23 were elevated in BA patients ($P < 0.05$), whereas the plasma ANGPTL6 level was decreased in BA patients ($P < 0.05$). The results of the correlation analysis revealed that ANGPTL6 was negatively linearly correlated with TB and DB and that FGF23 was positively linearly correlated with TBA. ROC curve analysis revealed that the AUC of ANGPTL6 for diagnosing BA was 0.9693, with a sensitivity of 0.8684 and a specificity of 1.0 at an optimal cut-off value of 1140.76 ng/ml. Prognostic analysis revealed that a lower plasma level of ANGPTL6 at KPE was associated with the occurrence of early cholangitis after KPE ($P < 0.05$).

Conclusions Among all of the hepatokines that were measured in this study, ANGPTL6 may be a potential diagnostic biomarker of BA and may be able to predict the occurrence of early cholangitis.

Clinical trial number : Not applicable.

Keywords Biliary atresia, Hepatokine, ANGPTL6, Biomarker, Early cholangitis

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Introduction

Biliary atresia (BA) is a rapidly progressive cholangiopathy of early infancy that destroys the extrahepatic and intrahepatic biliary tree and completely disrupts bile flow from the liver to the intestines, thereby leading to cholestasis and fibrosis [1]. Persistent jaundice, pale stools and variable levels of hepatosplenomegaly occur in infants with BA within the first few weeks after birth (secondary to fibroinflammatory obstruction of the bile ducts). Untreated children usually die of portal hypertension or hepatic encephalopathy caused by cirrhosis at approximately 1–2 years of age. BA occurs throughout the world, with variable geographical frequencies ranging from 100 to 500 per 100,000 live births in Asia [2] to 5–25 per 100,000 live births in Europe [3, 4]. The aetiology of BA remains unclarified; however, increasing evidence indicates that it is related to viruses [5, 6], toxins [7, 8] and gene sequence variations [9, 10]. BA accounts for approximately 60% of liver transplantations in children younger than 1-year-old. Complicated operations can be prevented only by the use of the Kasai procedure [11]. Hepatic portoenterostomy (HPE, also known as the Kasai procedure), which involves the excision of the obliterated extrahepatic biliary trees and the reestablishment of bile flow via the creation of a Roux-en-Y segment of the intestine, was originally proposed by Kasai in 1959 [12]. The success of each individual Kasai procedure can differ; however, a good result is more likely to be achieved if the surgery is performed earlier than 30–45 days of age [13, 14].

Hepatokines (which are organ-specific cytokines) are released by liver tissue in an autocrine, paracrine, or endocrine manner. Hepatokines exert potent effects on the metabolic homeostasis of glucose, lipids and bile acids [15–17] and are potential biomarkers for diagnosing metabolic diseases [18]. Hepatokines include angiopoietin-like proteins (including ANGPTL3, ANGPTL4 and ANGPTL6), fibroblast growth factors (including FGF19, FGF21 and FGF23), and so on. ANGPTLs are circulating proteins that regulate angiogenesis, inflammation and carcinogenesis [19]. Specifically, ANGPTL3, ANGPTL4, and ANGPTL6 affect lipoprotein metabolism and consequently regulate of plasma lipid levels. FGFs are also mainly secreted proteins that affect energy metabolism [16]. In addition, canonical FGF functions include cell proliferation, differentiation and survival [20, 21]. Moreover, the FGF19 subfamily (FGF19, FGF21 and FGF23), which activates FGFRs in conjunction with the Klotho protein cofactor [22], controls glucose, lipid and bile acid metabolism [23]. In this study, metabolism-related hepatokines were examined in infants with BA to determine the influence of drainage obstruction of bile and explore the possibility of these hepatokines being used as biomarkers.

Materials and methods

Patients

Patients with BA ($n = 38$) and age-matched controls (C, $n = 12$) were recruited from Children's Hospital, Zhejiang University School of Medicine, from 2019 to 2020. Patients with BA were diagnosed based on the presence of fibrosing obstruction of extrahepatic biliary remnants resected after intraoperative cholangiography. All enrolled BA patients were confirmed as Ohi type 3 [24]. The majority of the patients underwent kasai portoenterostomy (KPE) after intraoperative cholangiography, with the exception of three patients for whom the guardians decided to stop treatment. The patients were enrolled in the study if they met the following criteria: no diseases of the cardiovascular system, nervous system, respiratory system, or urogenital system; no other digestive system diseases; no severe infections; and no history of operations. The control group consisted of infants of the same age as those with BA who had nondigestive diseases (such as children with umbilical polyps, hydronephrosis, and inguinal hernias). Written informed consent was obtained from the parents of each infant before enrolment. This study was approved by the Research Ethics Committee of Children's Hospital, Zhejiang University, School of Medicine.

Sample collections

Blood samples for liver function and cytokine measurements were obtained from patients at admission and prior to the determination of the diagnosis. Blood samples were prepared via centrifugation at 3,000 rpm for 10 min to separate the serum/plasma and stored at -80 °C until analysis.

Liver function tests

Serum levels of total bilirubin (TB), direct bilirubin (DB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GGT) and total bile acid (TBA) were determined using a Beckman Coulter AU5800 automatic analyser in the clinical biochemistry laboratory.

Plasma cytokine analysis

The plasma (12.5 μl) was analysed by using magnetic bead suspension technology with the MILLIPLEX MAP Human Liver Protein Panel (9-plex) on the Luminex 200 analyser, following the manufacturer's instructions. The 9-plex contains antibodies specific for ANGPTL3, ANGPTL4, ANGPTL6, FGF-19, FGF-21, FGF-23, fatty acid binding protein 1 (FABP1), hepatocyte growth factor (HGF) and α-Fetoprotein (AFP). Due to the fact that the AFP values in nearly one-third of the plasma samples were above the upper limit, this cytokine was excluded from the subsequent analysis. In addition, some values

Table 1 Demographic characteristics of the BA subjects and the controls

	BA subjects (*n* = 38)	Controls (*n* = 12)	*p* value
Age (days)	65 (55–77)	78 (51–144)	0.177
Gender			0.979
Girls	16 (42.1%)	5 (41.6%)	
Boys	22 (57.9%)	7 (58.3%)	
Number of births by C-section	18 (47.4%)	5 (41.7%)	0.730
Birth weight (g)	3259 ± 432	3177 ± 733	0.633
Feeding pattern			0.864
Any breast-feeding	32 (84.2%)	11 (91.7%)	
Exclusively formula-fed	6 (15.8%)	1 (8.3%)	

for HGF, FGF-19 and FGF-21 were below the detectable limits. Due to the fact that the lower limits of the standard curves of all of the abovementioned cytokines exceeded 0.001 ng/ml, as well as the fact that the rank-sum test was adopted to conduct the statistical analysis, these undetectable values were set to be 0.001 ng/ml for statistical purposes to avoid data loss.

Statistical analysis

In this study, SPSS Statistics 20 and GraphPad Prism 7 were employed for statistical analysis. The data are presented as the mean ± standard deviations (SDs) or medians (Interquartile ranges). An unpaired t test was adopted to determine clinical differences between the two groups for normally distributed data, and a Mann–Whitney U test was used for nonnormally distributed data. A chi-square test was used to compare the demographic variables between the two groups. Linear correlation analysis was performed by a Pearson correlation or a Spearman rank correlation test. To evaluate the discriminatory ability of these cytokines, receiver operating characteristic (ROC) curves were drawn, and the area under the curve (AUC) was calculated. A p value < 0.05 with a two-tailed test was considered to be statistically significant.

Results

Demographic characteristics

The demographic characteristics of the BA patients and the controls were reviewed (Table 1). The median age of the patients with BA was 65 days, and 57.9% of them were boys. The average birth weight of the BA patients was 3259 g, and 18 infants (47.4%) were delivered by C-section. Only 15.8% of the BA patients were fed exclusively with formula milk. There were no significant differences observed in age, gender, birth pattern, birth weight or feeding pattern between the BA patients and the control patients.

Table 2 Liver function of the BA subjects and the controls

	BA subjects (*n* = 38)	Controls (*n* = 12)	*P* value
Total bilirubin (μmol/L)	169.2 ± 38.1	17.0 ± 12.5	< 0.001
Direct bilirubin (μmol/L)	93.1 ± 18.4	3.9 ± 2.9	< 0.001
Alanine transaminase (U/L)	156 ± 109	36 ± 14	< 0.001
Aspartate transaminase (U/L)	249 ± 153	54 ± 16	< 0.001
gamma glutamyl transpeptidase (U/L)	534 ± 470	67 ± 62	< 0.001
Alkaline phosphatase (U/L)	621 ± 217	346 ± 113	< 0.001
Total bile acids (μmol/L)	143.7 ± 40.8	14.1 ± 6.4	< 0.001

Liver function

The liver function of the BA subjects and the controls are shown in Table 2. The serum concentrations of TB, DB, ALT, AST, GGT, ALP and TBA in the patients with BA were 169.2 μmol/L, 93.1 μmol/L, 156 U/L, 249 U/L, 534 U/L, 621 U/L and 143.7 μmol/L respectively, which were significantly greater than those in the controls ($P < 0.05$).

Plasma metabolism-related hepatokine levels

Metabolism-related hepatokines were examined in BA patients and controls (Table S1). Compared to controls, the plasma levels of ANGPTL4, HGF, FABP1, FGF21 and FGF23 were elevated in BA patients ($P < 0.05$), whereas the plasma ANGPTL6 level was decreased in BA patients ($P < 0.0001$). There were no significant differences observed in the plasma concentrations of ANGPTL3 and FGF19 between the BA patients and the controls (Fig. 1).

Linear correlation analysis between altered hepatokines and TB/DB/TBA

Due to the fact that a higher serum TB/DB/TBA level reflects a more sereve disease scenario, we conducted a linear correlation analysis between those altered hepatokines and TB/DB/TBA in the BA group to determine which liver proteins were related to disease severity. The results demonstrated that ANGPTL6 was negatively linearly correlated with TB and DB (Fig. 2A), and FGF23 was positively linearly correlated with TBA (Fig. 2B).

ROC curves analysis of ANGPTL6 and FGF23

Due to the fact that ANGPTL6 and FGF23 may be related to the disease severity of BA, ROC curve analysis was used to further explore their diagnostic values of these hepatokines. The AUC of ANGPTL6 for diagnosing BA was 0.9693, with a sensitivity of 0.8684 and a specificity of 1.0 at an optimal cut-off value of 1140.76 ng/ml (Fig. 3A), whereas the AUC of FGF23 was only 0.7018, with a sensitivity of 0.4737 and a specificity of 1.0 at an optimal cut-off value of 0.12 ng/ml (Fig. 3B).

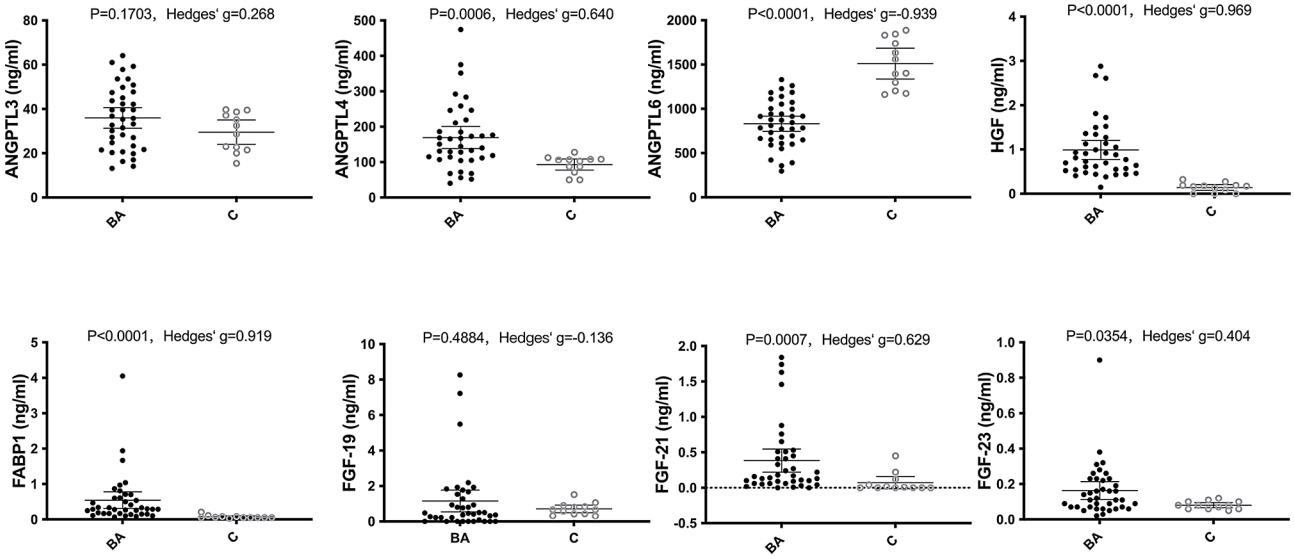

Fig. 1 Plasma metabolism-related hepatokines of the BA subjects and the controls

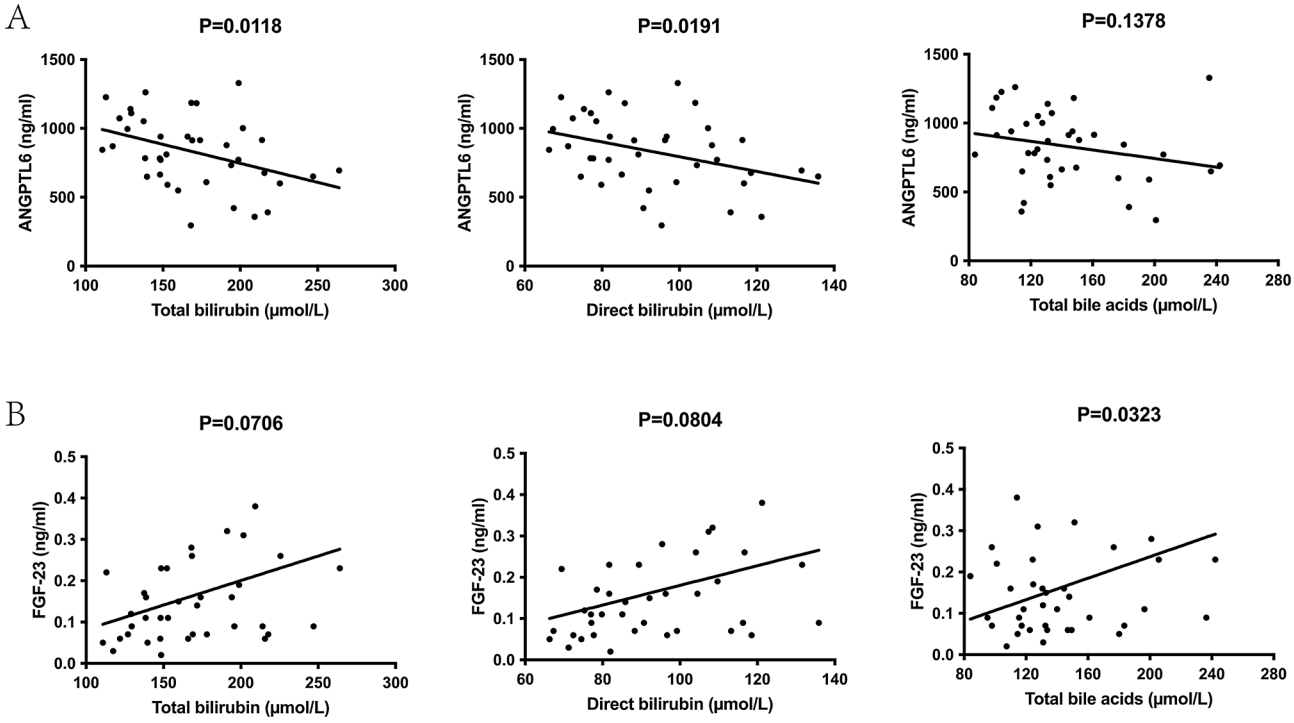

Fig. 2 Linear correlation analysis between changed hepatokines and TB/DB/TBA in BA group. (**A**) ANGPTL6 and TB/DB/TBA; (**B**) FGF23 and TB/DB/TBA

Prognostic analysis of ANGPTL6

Given that ANGPTL6 exhibited an excellent diagnostic value in BA, we further explored whether plasma ANGPTL6 levels can predict the outcome of BA after the performance of kasai portoenterostomy (KPE). In our study, a lower plasma level of ANGPTL6 in BA patients at the time of KPE was associated with the occurrence of early cholangitis after KPE ($P<0.05$) (Fig. 4A). Internal validation was conducted using 1000 repetitions of bootstrap resampling. However, the plasma ANGPTL6 level at the time of KPE was not related to the clearance of jaundice (Fig. 4B, C), native liver survival (Fig. 4D, E), or liver transplantation (Fig. 4F) with respect to BA after KPE.

Discussion

BA is characterised by progressive fibrogenesis of the biliary system and obliteration of the extrahepatic and intrahepatic biliary tree, which disrupts bile flow from

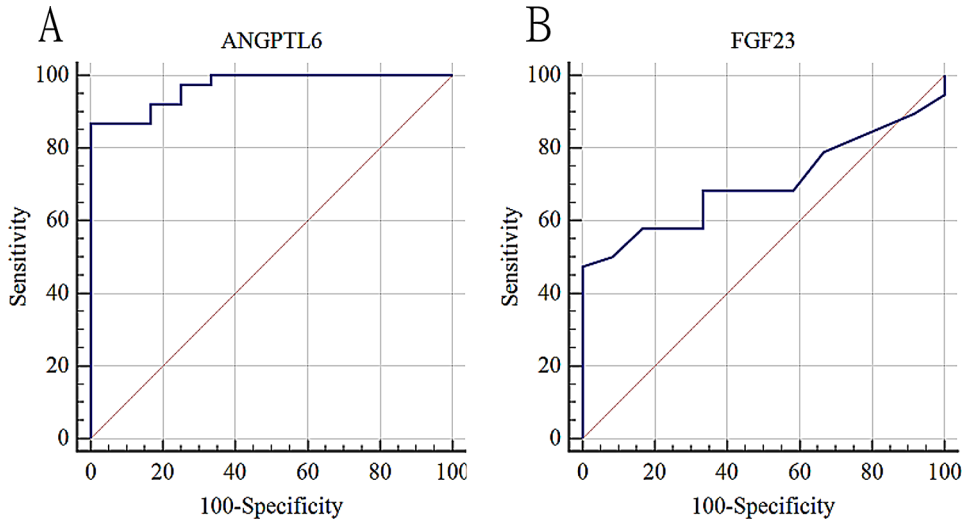

Fig. 3 ROC curves analysis. (**A**) ANGPTL6; (**B**) FGF23

the liver to the intestines. For this reason, BA exerts the greatest and most direct impact on the liver and gut, which constitute the body's major metabolic pools. Thus, metabolism related hepatokines were investigated in this study, with the aim of identifying clinical biomarkers contributing to the diagnosis, severity assessment and outcome prediction of BA.

Enzyme-linked immunosorbent assay (ELISAs), metabolomics and proteomics represent widely accepted and adopted methods for analyzing cytokines in plasma or serum samples. Via screening with metabolomics and validation with ELISAs, Zhang et al. [26] demonstrated an increase in Apo C-II in BA. Moreover, Xia et al. [27] confirmed an increase in FGF21 in BA via ELISAs. Ellis et al. [28] and Pakarinen et al. [29] identified an elevation of FGF19 in BA via ELISAs. Additionally, Bezerra et al. [30] used large-scale, quantitative serum proteomics to identify matrix metalloproteinase-7 (MMP-7) as a lead biomarker in infants with BA. In subsequent years, other researchers [31, 32] determined similar conclusions in other large cohorts. In this study, based on previous research, a series of metabolism-related hepatokines (including FGF19 and FGF21) were detected with multiplex magnetic bead suspension arrays.

In our study, among the measured hepatokines, ANGPTL6 was the most relevant hepatokine with respect to the occurrence, severity and prognosis of BA. The plasma ANGPTL6 level was observed to be decreased in BA infants and was negatively linearly correlated with TB and DB. Moreover, a lower plasma level of ANGPTL6 in BA patients at the time of KPE was associated with the occurrence of early cholangitis after KPE. This finding positions ANGPTL6 as a potential tool for early risk stratification—identifying high-risk patients who could benefit from intensified monitoring or prophylactic therapies.

ANGPLT6 (which is a member of the ANGPTL family), is secreted into the systemic circulation predominantly from the liver and can promote angiogenesis. In addition, ANGPTL6 can protect the body from high-fat diet-induced obesity and insulin resistance resulting from increased energy expenditure [33, 34]. When BA occurs, the amount of lipids absorbed from the gut significantly decrease because of the disruption of bile flow from the liver to the intestines. Thus, the secretion of ANGPTL6 is also suppressed. For this reason, ANGPTL6 is a promising target for diagnosing BA and assessing the extent of metabolic disorders.

In our research, the plasma FGF19 level in BA patients was not different from that in control infants, although there was a trend of a higher plasma FGF19 concentration in the BA group. This result is inconsistent with the results of previous studies [28, 29], which may be attributed to the use of different control infants. In fact, the median level of circulating FGF19 in BA that was observed in this study was similar to that reported in the other two studies (470 pg/ml vs. 320 pg/ml and 223 pg/ml, respectively).

However, the relatively small sample size is one of the limitations of our study, and the findings need to be verified in larger cohorts. While our current cohort lacks cholestatic controls, ANGPTL6's significant elevation in BA infants justifies its prioritization for further studies against other cholestasis etiologies. In addtion, further studies examining mRNAs and proteins levels in tissue samples are needed to explore the specific mechanisms underlying the changes in these hepatokines.

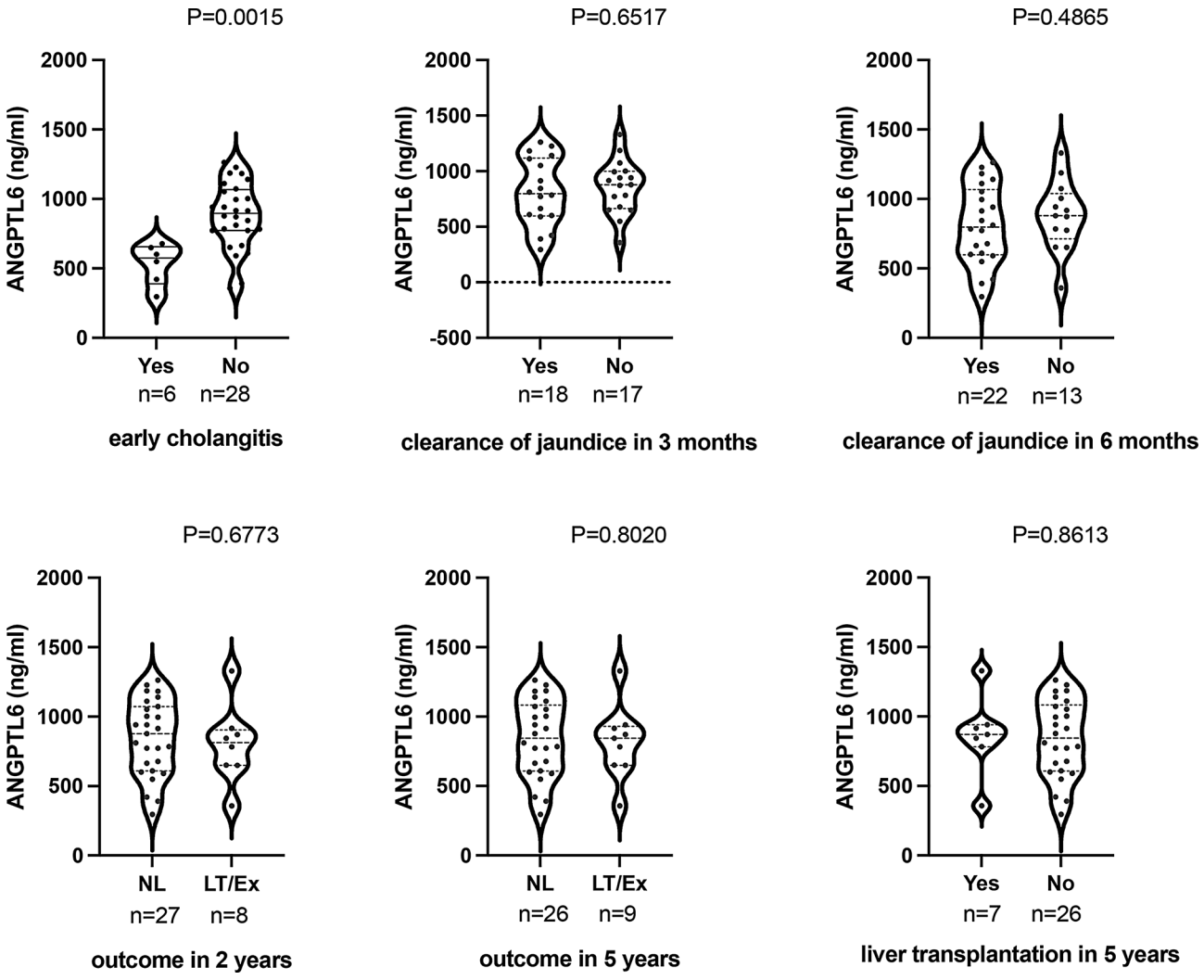

Fig. 4 Prognostic analysis of ANGPTL6. Plasma ANGPTL6 concentration at the time of KPE according to early cholangitis (**A**), clearance of jaundice in 3 months (**B**), clearance of jaundice in 6 months (**C**), outcome in 2 years (**D**), outcome in 5 years (**E**), liver transplantation in 5 years (**F**). Early cholangitis refers to the cholangitis which episodes within the first month after KPE, following the accepted diagnostic criteria [25]. An outlier was excluded in the early cholangitis group. Abbreviations: NL, native liver; LT, liver transplantation; Ex, exitus

Supplementary Information

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Supplementary Material 1

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Author contributions
P.S. conceived and designed the experiments. F.D. and H.S. performed the experiments. T.J. and D.F. collected and analyzed the data. P.S., F.D. and H.S. wrote the manuscript. All authors reviewed and approved the final submitted version.

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Data availability
Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate
The study was approved by the Institutional Ethics Committee of The Children´s Hospital, Zhejiang University School of Medicine (2019-IRB-018; March 11,2019). Informed consent was obtained from all subjects involved in the study.

Consent for publication
Informed consent was obtained from all subjects involved in the study.

Competing interests
The authors declare no competing interests.

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