Original Article

Non-invasive biomarkers for identification of vanishing bile duct syndrome among children with acute cholestatic hepatitis

Neng-Li Wang[1], Lian Chen[2], Jing Lin[3], Yi Lu[1], Wei-Yuan Fang[1], Xin-Bao Xie[1], Jian-She Wang[1]

[1]Center for Pediatric Liver Diseases, Children's Hospital of Fudan University, Shanghai, China; [2]Department of Pathology, Children's Hospital of Fudan University, Shanghai, China; [3]Department of Pediatrics, Icahn School of Medicine at Mount Sinai, NY, USA

Contributions: (I) Conception and design: NL Wang, XB Xie, JS Wang; (II) Administrative support: JS Wang; (III) Provision of study materials or patients: L Chen, Y Lu, WY Fang; (IV) Collection and assembly of data: NL Wang, L Chen, WY Fang; (V) Data analysis and interpretation: NL Wang, WY Fang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Xin-Bao Xie, MD; Jian-She Wang, PhD, MD. Center for Pediatric Liver Diseases, Children's Hospital of Fudan University, 399 Wanyuan Road, Minhang District, Shanghai 201102, China. Email: xxb116@163.com; jshwang@shmu.edu.cn.

Background: The identification of vanishing bile duct syndrome (VBDS) is still challenging before liver biopsy. This study tried to explore non-invasive biomarkers for identification of VBDS among children with acute cholestatic hepatitis.

Methods: Between January 2017 and December 2021, 192 children underwent native-liver biopsy for acute cholestatic hepatitis with onset after 6 months of age. VBDS was diagnosed by liver biopsy. Differences of liver biochemical indices were compared between children with and without VBDS. Diagnostic performances for VBDS were tested by receiver operating characteristic (ROC) curve analyses.

Results: Among the 192 patients, 24 (12.5%) were diagnosed with VBDS based on liver biopsy. At biopsy, their levels of total bilirubin (TB), direct bilirubin (DB), γ-glutamyl transpeptidase (GGT), total bile acid, triglyceride, and total cholesterol (TCH) were higher than patients without VBDS (all P<0.05). However, only GGT and TCH could distinguish patients with VBDS from patients without VBDS with an area under ROC curve (AUC) >0.850. Using GGT >446 U/L as a cut-off value, the sensitivity was 87.5%, the specificity was 91.6%, and the AUC was 0.948 (P<0.001). Using TCH >6.4 mmol/L as a cut-off value, the sensitivity was 100.0%, the specificity was 89.8%, and the AUC was 0.983 (P<0.001). A total of 28 patients had both GGT >446 U/L and TCH >6.4 mmol/L, including 21 patients with VBDS and 7 without VBDS (21/28 *vs.* 3/143, P<0.0001). Three patients with VBDS would be missed for GGT <446 U/L.

Conclusions: Both GGT and TCH can be used as non-invasive biomarkers for identification of VBDS among children with acute cholestatic hepatitis.

Keywords: Bile duct loss; diagnostic yield; hypercholesterolemia

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Introduction

Vanishing bile duct syndrome (VBDS) is a rare acquired condition characterized by progressive loss of intralobular bile ducts, and sometimes can even lead to end stage liver disease requiring transplant (1,2). Known causes of VBDS include drug induced liver injury (DILI), graft versus host disease (GVHD), autoimmune disease, etc. (3). The loss of bile ducts is possibly resulted from an inflammatory response directed at cholangiocytes (1). VBDS is a pathological diagnosis. A diagnosis of classical form of VBDS is established if no bile ducts are detected in >50% of portal tracts in a biopsy with at least ten portal areas (4). Mild or partial form of VBDS is defined as that bile ducts are absent in 25–50% of portal areas (3,4). VBDS typically arises in the setting of acute cholestatic hepatitis (4). Patients with

VBDS present as cholestatic jaundice, pruritus, fatigue, hypercholesterolemia, etc.

VBDS often has a poor prognosis. To establish a definite diagnosis, a liver biopsy is needed and should not be deferred when VBDS is suspected in clinical practices (5). However, repetitive biopsies are needed for its diagnosis in some instances because the loss of bile ducts is a gradual process (1). In addition, a non-invasive biomarker for VBDS is still absent at present. Therefore, it is challenging for clinicians to decide when to perform a liver biopsy. VBDS has been reported in adults in a relatively large cohort, and significant differences have been found in liver biochemical indices between adult patients with and without VBDS (3). We wondered whether these differences could be used as biomarkers for identification of VBDS among children with acute cholestatic hepatitis before liver biopsy.

This study enrolled children with acute cholestatic hepatitis who developed jaundice after 6 months of age and underwent native-liver biopsy. We compared the difference of liver biochemical indices between children with VBDS and those without VBDS based on liver biopsy. We aimed to explore non-invasive biomarkers for identification of VBDS among children with acute cholestatic hepatitis. We present this article in accordance with the STARD reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-305/rc).

Highlight box

Key findings

- Both γ-glutamyl transpeptidase (GGT) and total cholesterol (TCH) can be used as non-invasive biomarkers for identification of vanishing bile duct syndrome (VBDS) among children with acute cholestatic hepatitis who develop cholestatic jaundice after 6 months of age.

What is known and what is new?

- VBDS typically arises from acute cholestatic hepatitis. Patients without cholestasis are impossibly diagnosed with VBDS.
- Children with VBDS present cholestasis with elevated levels of GGT and TCH. The diagnosis of VBDS is unlikely if a child presents as cholestasis without high GGT and hypercholesterolemia. GGT and TCH can be used as biomarkers for identification of VBDS, and TCH has a better performance than GGT.

What is the implication, and what should change now?

- Both GGT and TCH should be routinely monitored among children with acute cholestatic hepatitis. VBDS is highly suspected if TCH >6.4 mmol/L and/or GGT >446 U/L are detected among children with acute cholestatic hepatitis.

Methods

Patients and definitions

This is a retrospective study from the Center for Pediatric Liver Diseases, Children's Hospital of Fudan University. Participants were identified by reviewing their medical records. Between January 2017 and December 2021, a total of 237 patients with acute cholestatic hepatitis, who developed cholestatic jaundice after 6 months of age, were admitted into this center. They denied a diagnosis of previous liver disease history. Among them, 45 patients were excluded for further analysis, because they did not undergo liver biopsy (*Figure 1*). This study enrolled the remaining 192 consecutive patients who performed native-liver biopsy during the course of acute cholestatic hepatitis. Cholestasis was defined as direct bilirubin (DB) >17.1 μmol/L when total bilirubin (TB) <85.5 μmol/L or DB >20% of TB when TB >85.5 μmol/L (6). Based on histologic findings of liver biopsy, the patients were divided into two groups: patients with VBDS and patients without VBDS. The study was approved by the ethics committees of Children's Hospital of Fudan University (No. 2022-43), and was conducted in full compliance with the Declaration of Helsinki (as revised in 2013). Informed consent was taken from the patients' parents or legal guardians at admission.

Liver biochemical tests

All the enrolled 192 patients underwent at least one tests of liver biochemical indices, including TB, DB, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bile acid (TBA), γ-glutamyl transpeptidase (GGT), albumin (ALB), triglyceride (TG), and total cholesterol (TCH). Test results were collected by reviewing their medical records. Tests at biopsy were defined as those carried out within five days before or after liver biopsy. If several tests were done during this period, only the test results obtained closest to liver biopsy were used for analyses.

Differences in liver biochemical indices at biopsy were compared between patients with and without VBDS. This study further tested the diagnostic performances of liver biochemical indices for identification of VBDS among children with acute cholestatic hepatitis, and also explored their cut-off values.

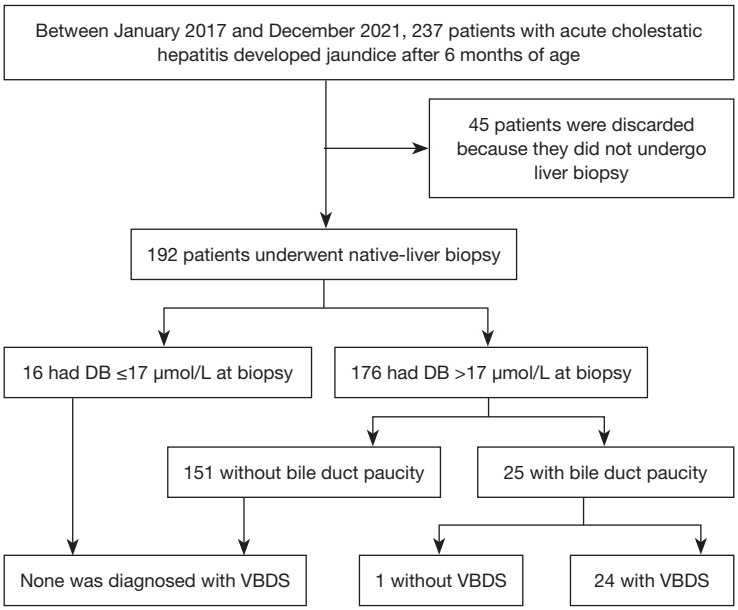

Figure 1 Flow diagram of patient enrollment. DB, direct bilirubin; VBDS, vanishing bile duct syndrome.

Liver histologic studies

Native-liver tissues were obtained by needle biopsy. Liver histologic studies were performed in the Department of Pathology. Liver tissue sections were read jointly by two pathologists and at least one hepatologist. Using 'bile duct paucity' as keywords, preliminary patients were identified by searching liver histologic reports of the enrolled 192 patients. Liver tissue sections of patients with bile duct paucity were further reviewed by a pathologist who was blind to the patients' clinical information. The loss of bile ducts was assessed in hematoxylin-eosin stained sections, and confirmed in both anti-CK7 and anti-CK19 (GeneTech, Shanghai, China) immunostained sections. Both the numbers of total portal areas and the numbers of portal areas without bile ducts were recorded for calculation of the fraction of portal areas without bile ducts.

The diagnosis of VBDS is established based on paucity of bile ducts in liver biopsy (4). In this study, patients with VBDS included both patients with classical form of VBDS and patients with partial form of VBDS. VBDS was diagnosed if one of the following elements was satisfied: (I) >25% of total portal areas absented bile ducts in a biopsy with at least ten portal areas; (II) at least three portal areas absented bile ducts in a biopsy with <10 portal areas. Although portal areas without bile ducts were detected, patients were still classified into group without VBDS if they did not satisfy any one of the above elements.

Statistical analysis

MedCalc Software (v20.026, https://www.medcalc.org; 2022) was used for statistical analyses. Continuous variables were presented as medians and interquartile ranges, and their differences between patients with and without VBDS were compared by the Mann-Whitney tests. The differences of categorical variables between the two groups were determined by Chi-square or Fisher's exact test. Diagnostic performances of liver biochemical indices for identification of VBDS among patients with acute cholestatic hepatitis were assessed by the receiver operating characteristic (ROC) curve analysis. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the ROC curve (AUC) were calculated. AUC >0.8 meant excellent performance. Patients with missing data were excluded from calculations. $P<0.05$ was considered significant.

Results

Patients of VBDS

The enrolled 192 patients, including 125 boys and 67 girls, underwent liver biopsy at ages ranging from 7 months to

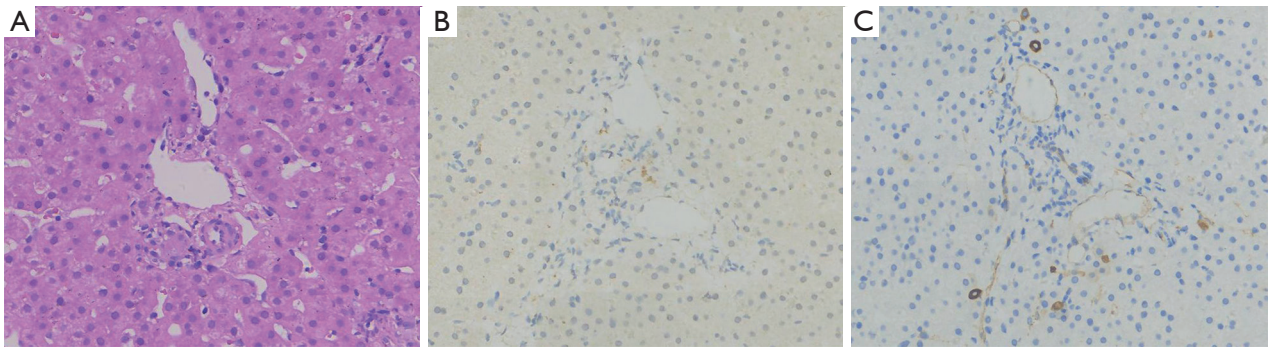

Figure 2 Liver histologic studies of patient 10. Bile ducts absent in portal areas by hematoxylin-eosin (×200, A), CK19 (×200, B), and also CK7 (×200, C) staining. A few hepatocytes are CK7-positive in CK7 staining sections.

15 years, with a median age of 5 years. The median time frame from the development of jaundice to biopsy was 27 days (range, 6 to 172 days). By searching liver histologic reports, 25 patients with bile duct paucity were identified. Among them, one case was not diagnosed with VBDS, because he only had two portal areas without bile ducts in a biopsy with nine portal areas. Other 24 patients, including 17 boys and 7 girls, satisfied the diagnostic criteria, and were diagnosed with VBDS (*Figure 2*). The overall ratio of positive diagnosis of VBDS were 12.5% (24/192). DILI was the most common cause (n=13), and the implicated drugs included piperacillin-tazobactam (n=3), azithromycin (n=3), Chinese herbal medicine (n=3), etc. (Table S1). Sixteen patients had cholestatic jaundice ameliorated (DB <17 μmol/L) but still elevated transaminase at biopsy, and none of them was diagnosed with VBDS. Their levels of ALT, AST, GGT, and TCH were similar to other 152 patients without VBDS (all P>0.05).

At biopsy, all the 24 patients with VBDS presented as cholestasis with high GGT and hypercholesterolemia (*Table 1*). The median level of DB was 128 μmol/L (range, 20 to 327 μmol/L). The levels of GGT were prominently elevated with a median of 932 U/L (range, 151 to 2,860 U/L), while ALT was only mildly increased (median and range: 205 U/L; 56 to 1,080 U/L). The median of TCH concentrations was 13.9 mmol/L (range, 6.8 to 39.9 mmol/L).

Difference between patients with and without VBDS

There was no difference on age and gender between patients with and without VBDS (both P>0.05) (*Table 2*). The levels of TB, DB, TBA, and GGT at biopsy were higher in the group with VBDS than the group without VBDS at biopsy (all P<0.05). However, the levels of ALT, AST, and ALB showed no difference. The patients with VBDS had higher levels of TG and TCH than the patients without VBDS (both P<0.05). Hypercholesterolemia (TCH >5.2 mmol/L) was diagnosed in all the 24 patients with VBDS, but only in 30 (17.9%) of the 168 patients without VBDS (24/24 *vs.* 30/168, P<0.0001).

Biomarkers for identification of VBDS

Based on ROC curve analyses, TB, DB, TBA, GGT, TG, and TCH at biopsy shown some diagnostic values to distinguish patients with VBDS from those without (all P<0.05, *Table 3*). However, only GGT and TCH had AUC >0.850 (*Figure 3*). Using GGT >446 U/L as a cut-off value, the sensitivity was 87.5%, the specificity was 91.6%, the PPV was 60.0%, the NPV was 98.1%, and the AUC was 0.948 (P<0.001). Using TCH >6.4 mmol/L as a cut-off value, the sensitivity was 100.0%, the specificity was 89.8%, the PPV was 61.5%, the NPV was 100.0%, and the AUC was 0.983 (P<0.001).

At biopsy, 171 patients simultaneously tested TCH and GGT. Among them, 28 had both GGT >446 U/L and TCH >6.4 mmol/L (*Table 4*), including 21 patients with VBDS and 7 without VBDS (21/28 *vs.* 3/143, P<0.0001). Three patients with VBDS would be missed for GGT <446 U/L. The sensitivity was 87.5%, the specificity was 95.2%, the PPV was 75.0%, and the NPV was 97.9%.

Discussion

VBDS typically arises from acute cholestatic hepatitis (4), and has been reported in children as isolated cases (7-10).

Table 1 Clinical findings of 24 pediatric patients with vanishing bile duct syndrome at biopsy

Patient	Gender	Age	TB	DB	ALT	AST	GGT	TBA	TG	TCH	Time frame† (days)	No. of portal areas with/without bile ducts	Etiologic diagnosis	Outcome
P1	Male	7 years	336	188	526	417	1,114	518	5.2	19.6	31	3/6	Unknown	Alive
P2	Female	11 months	244	140	190	294	2,120	249	3.5	27.1	37	1/10	DILI	Alive
P3	Female	7 years	200	122	482	172	796	229	6.2	18.6	20	2/3	DILI	Alive
P4	Male	13 years	256	131	122	47	1,067	170	1.9	13.9	71	2/7	Unknown	Alive
P5	Male	7 years	106	58	378	381	738	167	1.0	6.8	28	4/8	Unknown	Alive
P6	Male	7 months	126	70	128	207	259	102	2.4	7.1	20	2/8	DILI	Alive
P7	Male	3 years	161	125	80	79	194	423	2.9	19.7	27	2/4	DILI	Alive
P8	Male	10 years	395	327	214	143	1,156	536	3.1	21.6	38	7/8	Unknown	Alive
P9	Male	17 months	35	29	203	157	1,111	64	3.2	9.4	11	1/3	DILI	Alive
P10	Male	14 months	150	126	358	279	2,616	142	7.2	22.3	19	2/6	DILI	Alive
P11	Female	15 months	390	323	211	270	1,113	305	2.8	13.9	84	3/10	DILI	Death
P12	Male	15 months	30	20	208	189	470	145	1.8	39.9	63	3/9	DILI	Alive
P13	Male	13 months	205	185	56	109	634	53	6.4	11.4	21	1/6	Unknown	Alive
P14	Female	5 years	271	244	174	126	899	429	3.2	9.4	36	1/6	DILI	Loss to follow-up
P15	Male	12 years	220	197	1,080	319	1,794	140	2.7	11.6	25	1/5	Unknown	Alive
P16	Female	8 years	96	76	694	305	892	131	2.6	11.8	33	4/6	DILI	Alive
P17	Male	12 years	199	104	162	64	151	406	4.1	8.5	43	2/7	Unknown	Alive
P18	Male	5 years	121	113	196	201	517	460	2.7	33.3	31	4/9	Unknown	Alive
P19	Male	8 months	165	132	345	299	2,860	368	4.4	16.8	60	0/15	DILI	Loss to follow-up
P20	Male	2 years	75	65	101	160	1,443	143	3.8	36.8	74	1/9	Unknown	Alive
P21	Male	11 years	193	152	639	146	966	26	2.6	9.1	28	2/11	DILI	Alive
P22	Female	2 years	251	208	162	369	616	453	1.6	9.5	27	0/13	DILI	LT
P23	Male	5 years	308	248	317	292	1,043	149	3.3	11.6	29	3/3	GVHD	Alive
P24	Female	8 years	102	78	180	110	659	17	2.1	15.6	32	4/5	Unknown	Alive

†, Time frame from the development of jaundice to liver biopsy. TB (μmol/L), total bilirubin; DB (μmol/L), direct bilirubin; ALT (U/L), alanine aminotransferase; AST (U/L), aspartate aminotransferase; GGT (U/L), γ-glutamyl transpeptidase; TBA (μmol/L), total bile acid; TG (mmol/L), triglyceride; TCH (mmol/L), total cholesterol; DILI, drug induced liver injury; LT, liver transplantation; GVHD, graft versus host disease.

In this study, we enrolled 192 children who underwent native-liver biopsy for acute cholestatic hepatitis and a total of 24 children were diagnosed with VBDS. To our best knowledge, this was the largest cohort of pediatric VBDS patients, though it was unclear that 12 of them belonged to partial form of VBDS or classical form of VBDS for specimens had less than 10 portal areas. The overall ratio of positive diagnosis of VBDS was 12.5% in this cohort. It might be overestimated, because patients with rapidly resolved jaundice were more likely to reject a liver biopsy. However, given the adverse outcome for VBDS, we suggest that the occurrence of VBDS should be routinely monitored among patients with acute cholestatic hepatitis.

In this cohort, cholestatic jaundice had already ameliorated at biopsy in 16 children, in whom none was diagnosed with VBDS. It is consistent with the findings from adult DILI, where patients without cholestasis are impossibly diagnosed with VBDS (11). In adult VBDS,

Table 2 Differences between patients with and without vanishing bile duct syndrome

Characteristics	Patients with VBDS (n=24)	Patients without VBDS (n=168)	P
Age (years)	5.0 (1.2, 8.0)	4.5 (2.0, 8.0)	0.5109
Time frame (days)[†]	31.0 (26.0, 40.5)	24.0 (16.0, 44.5)	0.1077
Gender (No. of male/female)	17/7	108/60	0.6494
Total bilirubin (μmol/L)	196.0 (113.5, 253.5)	90.0 (55.5, 176.0)	0.0017
Direct bilirubin (μmol/L)	128.5 (77.0, 192.5)	69.0 (35.5, 131.0)	0.0031
Alanine aminotransferase (U/L)	205.5 (162.0, 368.0)	301.0 (146.0, 599.5)	0.2303
Aspartate aminotransferase (U/L)	195.0 (134.5, 296.5)	227.0 (112.5, 466.0)	0.2656
γ-glutamyl transpeptidase (U/L)	932.5 (625.0, 1135.0)	126.0 (60.0, 222.0)	<0.0001
Total bile acid (μmol/L)	168.5 (135.5, 414.5)	92.0 (30.0, 259.7)	0.0032
Albumin (g/L)	38.2 (35.5, 39.6)	38.5 (34.7, 42.0)	0.5980
Triglyceride (mmol/L)	3.0 (2.5, 3.9)	1.9 (1.2, 2.9)	0.0001
Total cholesterol (mmol/L)	13.9 (9.5, 20.6)	4.1 (3.3, 4.8)	<0.0001

Data are shown as median (interquartile range). [†], time frame from the development of jaundice to biopsy. VBDS, vanishing bile duct syndrome.

Table 3 Performance of liver laboratory indexes on identification of vanishing bile duct syndrome

Variables	AUC	P	Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
TB (μmol/L)	0.698 (0.628, 0.762)	0.0001	>95	87.5 (67.6, 97.3)	51.2 (43.4, 59.0)	20.4 (17.1, 24.1)	96.6 (90.8, 98.8)
DB (μmol/L)	0.687 (0.616, 0.751)	0.0003	>64	87.5 (67.6, 97.3)	47.0 (39.3, 54.9)	19.1 (16.1, 22.5)	96.3 (90.0, 98.7)
ALT (U/L)	0.576 (0.503, 0.647)	0.1487	≤214	62.5 (40.6, 81.2)	63.1 (55.3, 70.4)	19.5 (14.3, 25.9)	92.2 (87.4, 95.2)
AST (U/L)	0.570 (0.497, 0.641)	0.1454	≤417	100.0 (85.8, 100.0)	29.8 (23.0, 37.3)	16.9 (15.6, 18.3)	100.0
GGT (U/L)	0.948 (0.906, 0.975)	<0.0001	>446	87.5 (67.6, 97.3)	91.6 (86.3, 95.3)	60.0 (47.1, 71.7)	98.1 (94.6, 99.3)
TBA (μmol/L)	0.686 (0.615, 0.752)	0.0008	>130	79.2 (57.8, 92.9)	58.8 (50.9, 66.4)	21.8 (17.5, 26.9)	95.1 (89.8, 97.7)
ALB (g/L)	0.533 (0.460, 0.606)	0.5588	≤40	83.3 (62.6, 95.3)	38.3 (30.9, 46.2)	16.3 (13.5, 19.4)	94.1 (86.5, 97.6)
TG (mmol/L)	0.753 (0.681, 0.815)	<0.0001	>2.5	75.0 (53.3, 90.2)	69.4 (61.3, 76.7)	28.6 (22.2, 35.9)	94.4 (89.4, 97.2)
TCH (mmol/L)	0.983 (0.950, 0.997)	<0.0001	>6.4	100.0 (85.8, 100.0)	89.8 (83.7, 94.2)	61.5 (49.8, 72.1)	100.0

95% CIs in parentheses. AUC, area under ROC curve; ROC, receiver operating characteristic; PPV, positive predictive value; NPV, negative predictive value; TB, total bilirubin; DB, direct bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; TBA, total bile acid; ALB, albumin; TG, triglyceride; TCH, total cholesterol.

the elevation of alkaline phosphatase (ALP) was more obvious than ALT and AST (3). ALP is usually used as an indicator for bile duct injury in adults, while GGT is a preferred indicator for bile duct injury in children (12). Similarly, we found that GGT was markedly elevated, while ALT and AST were only mildly elevated in pediatric VBDS. Apart from high GGT, hypercholesterolemia had also been reported previously in children with VBDS (9,13). In our cohort, all the 24 children with VBDS had hypercholesterolemia and high GGT. Our data demonstrate that high GGT and hypercholesterolemia are common features of children with VBDS. Therefore, we infer that the diagnosis of VBDS is unlikely if a child presents as cholestasis without high GGT and hypercholesterolemia. Due to the small sample size, further researches are needed to confirm our findings.

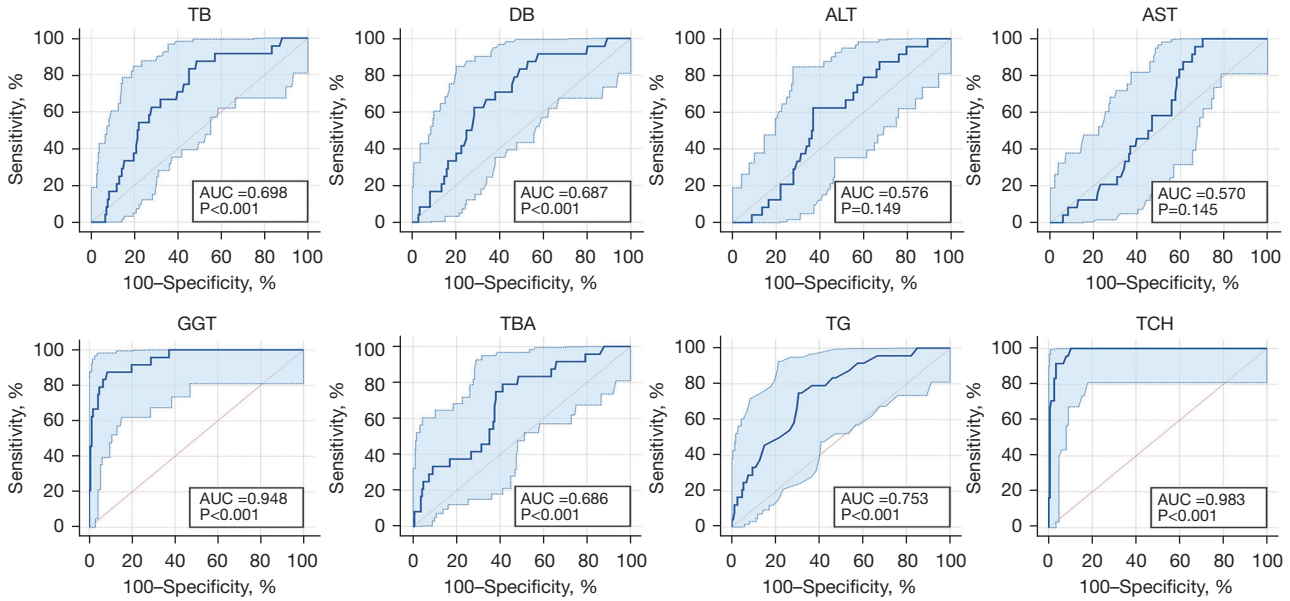

Figure 3 Diagnostic performances of liver biochemical indices for vanishing bile duct syndrome. TB, total bilirubin; AUC, area under ROC curve; ROC, receiver operating characteristic; DB, direct bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; TBA, total bile acid; TG, triglyceride; TCH, total cholesterol.

Table 4 Performance of GGT and TCH for identification of vanishing bile duct syndrome

Indicators	VBDS confirmed by liver biopsy		Total	P
	Positive	Negative		
GGT >446 U/L				<0.0001
Positive	21	14	35	
Negative	3	152	155	
TCH >6.4 mmol/L				<0.0001
Positive	24	15	39	
Negative	0	132	132	
GGT >446 U/L and TCH >6.4 mmol/L				<0.0001
Positive	21	7	28	
Negative	3	140	143	

GGT, γ-glutamyl transpeptidase; TCH, total cholesterol; VBDS, vanishing bile duct syndrome.

Identification of VBDS is still a challenge before liver biopsy. This study tried to explore non-invasive biomarkers for identification of VBDS among children with acute cholestatic hepatitis. Similar to adult VBDS (3), significant differences were also found in liver biochemical indices between children with and without VBDS. We further found that both GGT and TCH could be used as non-invasive biomarkers for identification of VBDS with AUC >0.85. Using GGT >446 U/L as a cut-off value, the specificity could be 91.6%, but three children with VBDS would be missed. In addition, 14 out of the 166 patients without VBDS also had GGT >446 U/L. It might be attributed to that elevation of GGT levels could result from many other causes, such as sclerosing cholangitis, bile

duct obstruction, etc. (14). Interestingly, TCH had a better performance for identification of VBDS than GGT. Using TCH >6.4 mmol/L as a cut-off value, the specificity could be 89.8%, and none of patients with VBDS was missed. The combination of GGT and TCH did not further improve the diagnostic value. Therefore, both GGT and TCH can be used as non-invasive biomarkers for identification of VBDS among children with acute cholestatic hepatitis. We suggest that both GGT and TCH should be routinely monitored among children with acute cholestatic hepatitis. VBDS is highly suspected if TCH >6.4 mmol/L and/or GGT >446 U/L are detected among children with acute cholestatic hepatitis, and liver biopsy is suggested.

Conclusions

Children with VBDS present as cholestasis with high GGT and hypercholesterolemia. The diagnosis of VBDS is unlikely if a child presents as cholestasis without high GGT and hypercholesterolemia. Both GGT and TCH can be used as non-invasive biomarkers for identification of VBDS among children with acute cholestatic hepatitis, and TCH has a better performance than GGT. These markers are still potential, and additional tests are needed to confirm the diagnosis of VBDS.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-23-305/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-23-305/dss

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-23-305/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-23-305/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the ethics committees of Children's Hospital of Fudan University (No. 2022-43) and was conducted in full compliance with the Declaration of Helsinki (as revised in 2013). Informed consent was taken from the patients' parents or legal guardians at admission.

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