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Diagnostic value of HA, PC-III, IV-C, and LN in infants with congenital biliary atresia

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Abstract

Hyaluronic acid (HA), type III procollagen III (PC-III), type IV collagen IV (IV-C), and laminin (LN) have certain diagnostic value for hepatobiliary diseases. No published studies have compared the diagnostic accuracy of these 4 indicators for the diagnosis of congenital biliary atresia (CBA) in infants. This study aimed to investigate the diagnostic value of HA, PC-III, IV-C, and LN in infants with CBA.

From January 2017 to December 2020, 185 infants with nonphysiological jaundice in the Second Department of General Surgery at the Children's Hospital of Hebei were enrolled in this study. Forty-six infants with CBA (CBA group) and 139 infants without CBA (noncongenital biliary atresia group) were diagnosed using ultrasonography, magnetic resonance imaging, intraoperative exploration, and intraoperative cholangiography. The levels of HA, PC-III, IV-C, and LN in the 2 groups were statistically analyzed. The diagnostic accuracy was determined using receiver operating characteristic curves and by calculating the area under the curve. Univariate and multivariate logistic regression analyses were performed to identify the independent risk factors.

Compared to the noncongenital biliary atresia group, the levels of HA, PC-III, IV-C, and LN were significantly increased in the CBA group (P <.05). The receiver operating characteristic analysis showed the optimal cutoff values for HA, PC-III, IV-C, and LN were 162.7, 42.5, 199.7, and 101.2 ng/mL, and the area under the curves were 0.892, 0.762, 0.804, and 0.768, respectively. The sensitivity values for the diagnosis of CBA were 76.82%, 71.61%, 70.32%, and 72.28%, and the specificity values for the diagnosis of biliary atresia were 70.22%, 70.44%, 66.34%, and 68.71%, respectively. In the multivariate model, HA ≥162.7 ng/mL (odds ratio [OR] = 5.28, 95% confidence interval [CI]: 3.15–8.37), PC-III ≥42.5 ng/mL (OR = 4.61, 95% CI: 2.54–7.16), IV-C ≥199.7 ng/mL (OR = 5.02, 95% CI: 2.98–7.64), and LN ≥101.2 ng/mL (OR = 6.25, 95% CI: 2.41–10.07) remained associated with the occurrence of CBA.

HA, PC-III, IV-C, and LN have high accuracy for the diagnosis of CBA in infants, and these factors are potential diagnostic biomarkers for CBA.

Abbreviations: AUC = area under the curve, BMI = body mass index, HA = hyaluronic acid, IV-C = type IV collagen, LN = laminin protein, PC-III = type III procollagen.

Keywords: biliary atresia, collagen IV, diagnostic value, hyaluronic acid, laminin, procollagen III

1. Introduction

Congenital biliary atresia (CBA) is one of the most common and refractory congenital diseases among children's biliary diseases; it is also the main cause of neonatal jaundice.[1] Presently, there are many theories about the etiology of CBA, such as the theory of congenital dysplasia, inflammation, and pancreaticobiliary junction deformity.[2,3] Inflammation and fibrosis can occur in the intrahepatic bile ducts when some or all of the extrahepatic bile ducts develop atresia. A clinical feature of CBA is that it is easily confused with physiological jaundice in the initial stage; it then develops into persistent jaundice with clay gray-white stool in the later stage. Infants with CBA require early Kasai or liver transplantation procedures; otherwise, by delaying treatment, the therapeutic effects of the surgeries and the prognosis of the infants would decrease.[4,5] If a patient has suffered from CBA for >3 months, then it will cause irreversible liver damage and even lead to the development of biliary cirrhosis, ultimately leading to death.[5–7] Therefore, early diagnosis of CBA in infants is crucial.

At present, there is no noninvasive diagnostic method for the detection of CBA that is 100% accurate; therefore, delays in CBA diagnosis and treatment and poor patient

This study was approved by the institutional review board of the Children's Hospital of Hebei in compliance with the Declaration of Helsinki and consent were waived for its retrospective nature.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

The authors declare that they have no competing interests.

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prognoses have become problems that have yet to be solved by the world's medical community. The fecal colorimetric card method, an effective and convenient method of early screening for CBA, significantly shortens the time of diagnosis and improves prognosis.[8] It has high diagnostic sensitivity and specificity and is easy to implement; however, its results are susceptible to breast milk jaundice and partial physiologic jaundice. Most studies have shown that serum glutamyl transpeptidase (GGT) and bilirubin levels are of positive significance for the early diagnosis of CBA. The characteristics of CBA in liver function indices include continuous increases in direct bilirubin and GGT levels. However, other liver function indices lack specificity and sensitivity for diagnosis alone.[9] Infant choledochal cysts are associated with parenteral nutrition, and GGT levels can also increase in cholestasis and cholestasis syndrome; therefore, false-positive diagnoses of CBA due to increased GGT levels are inevitable. Ultrasonography is the first choice for the differential diagnosis of persistent jaundice in infants and young children. In recent years, the application of advanced ultrasound technology has led to a 90% accuracy in CBA diagnosis.[10] Approximately 20% of infants with type III CBA (hilar bile duct atresia) suffer from gallbladder and distal patent bile ducts; however, their gallbladder expansibility is still good, which interferes with the diagnosis. As there is no clinical diagnostic method with high sensitivity and specificity, we intend to explore a simple, noninvasive, and relatively efficient detection method.

The detection of serological markers has good sensitivity and repeatability, especially in younger children, which is convenient for dynamic monitoring of the current and developmental state of a disease.[11] Hyaluronic acid (HA), type III procollagen (PC-III), type IV collagen (IV-C), and laminin (LN) protein are biological diagnostic indicators of liver fibrosis. A large number of clinical studies have confirmed that HA, PC-III, IV-C, and LN tests have certain application value in the diagnosis and monitoring of hepatobiliary system diseases. However, there is no relevant research on the diagnostic direction of these indicators in children with CBA.[12,13]

Therefore, the aim of this study was to evaluate the diagnostic value of HA, PC-III, IV-C, and LN in children with CBA, and the relevant results could provide a reference for clinical diagnosis and treatment.

2. Material and methods

This retrospective study was approved by the Medical Ethics Committee of Hebei Children's Hospital and adhered to the ethical recommendations of the Declaration of Helsinki. Parents of the infants investigated in this study provided written informed consent for their infants' participation.

2.1. Inclusion and exclusion criteria

From January 2017 to December 2020, all patients with nonphysiological jaundice in the Second Department of General Surgery of Hebei Children's Hospital were recruited by querying the electronic medical records. The inclusion criteria were as follows: participants admitted to the hospital with jaundice pending investigation or pathological jaundice as a preliminary diagnosis (a direct bilirubin value >1.0 mg/dL if the total bilirubin was <5 mg/dL or a direct bilirubin value that represented >20% of the total bilirubin if the total bilirubin was >5 mg/dL); and complete clinical and imaging data of participants. The exclusion criteria were as follows: during hospitalization, participants did not cooperate with the treatment or refused to carry out the relevant examination or test; participants did not receive the operation due to other special reasons; and participants with other infectious diseases in conjunction with CBA.

2.2. Data acquisition

All patients were asked to be fed breast or formula milk after admission. The day after admission, the patients began fasting at 2 AM and 4 mL of venous blood was collected before 7 AM. Sodium citrate (180 ml:7.2 g) at a proportion of 1:9 was added to the venous blood for anticoagulation treatment. It was then centrifuged at 3000 rpm for 10 minutes to separate the serum immediately and stored in a refrigerator at −20°C. The AutoLumo A2000 Plus automatic chemiluminescent immunodetector provided by Antu Experimental Instrument Co., Ltd was used to measure the expression levels of HA, PC-III, IV-C, and LN. All experimental operations were performed in strict accordance with the reagent specifications. In addition, liver function-related indices such as alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin (TB), direct bilirubin (DB), and GGT were also detected.

2.3. Diagnosis criteria and grouping

2.3.1. Ultrasound examination.

For all infants, breast milk was prohibited for 4 hours prior to their ultrasound examination. If the infants were not cooperative, 10% chloral hydrate (0.5 mL/kg) could be provided via enema to slightly sedate them. A GE Voluson 730 Pro color ultrasonic diagnostic instrument was used. First, each liver and gallbladder were scanned with a high-frequency probe, and the size and structure of the gallbladder were observed, including the presence of fibrous tissue blocks in the hilar area, hepatosplenomegaly, expansion of the common bile duct, and ascites. If the ultrasound results indicated that the gallbladder body was smaller, that the gallbladder wall was rigid and irregular, or if there was a fibrous tissue mass in the hilar area, then the possibility of biliary atresia was considered to be high.

2.3.2. Magnetic resonance examination.

For all infants, breast milk was prohibited for 4 hours prior to their magnetic resonance (MR) examination. If the infants were not cooperative, 10% chloral hydrate (0.5 mL/kg) could be provided via enema to slightly sedate them. A Siemens 3.0T Skyra II MRI Scanner was used for this examination. Each patient was placed in a supine position and wore earplugs. Family members accompanied the patients. The MR imaging scanning range was in the horizontal axial position of the hepatic portal, including the intrahepatic bile duct, common bile duct, pancreatic duct, and gallbladder. If the MR imaging results showed that the gallbladder was thin and cord-like or that the common bile and common liver ducts were small and undeveloped, the patient had a high possibility of biliary atresia.

2.3.3. Operation exploration.

Children with positive imaging results underwent laparoscopic exploration combined with choledochography. After successful induction of general anesthesia, laparoscopic exploration and cholecystography were performed. If the extrahepatic bile duct did not develop, biliary atresia was diagnosed. Infants who were diagnosed with biliary atresia by the above-mentioned methods were classified into the CBA group, whereas those who were not were classified into the noncongenital biliary atresia (NCBA) group.

2.4. Statistical analysis

All statistical analyses were performed using Statistical Package for Social Sciences software (version 23.0; SPSS Inc., Chicago,

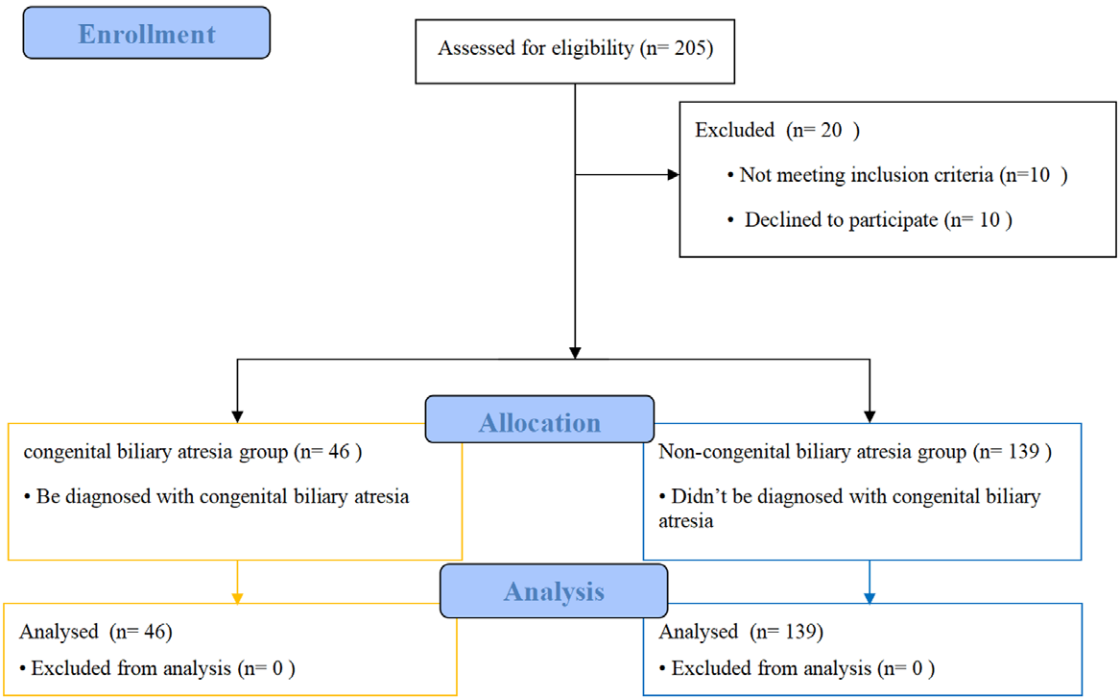

Figure 1. Flow diagram of study participants: congenital biliary atresia group (orange); noncongenital biliary atresia group (blue).

IL). Continuous data with normality were presented as mean ± standard deviation and compared using 1-way analysis of variance. Continuous data with abnormalities were presented as median (interquartile range) and compared using the Kruskal–Wallis test. Univariate logistic regression analysis was performed to evaluate the relationship between each categorical variable and CBA. The Mann–Whitney *U* test or *t* test was used to evaluate continuous variables when appropriate and depending on the data distribution (equal variance and normality). Multivariate logistic regression analysis was used to evaluate the risk of CBA, and *P* values < .05 were interpreted as statistically significant in all statistical analysis models.

3. Results

3.1. General information

A total of 205 were assessed for eligibility. Ten patients did not meet the inclusion criteria, and 10 patients declined to participate. In total, 185 patients were enrolled in this study. The flow diagram of the study is shown in Figure 1. There were 112 male and 73 female patients with a mean age of 33 ± 4.6 days (range 26–38 days). During the follow-up period, 46 patients were diagnosed with CBA and were assigned to the CBA group (CBA group), whereas the remaining 139 patients were not diagnosed with CBA and were assigned to the NCBA group. Of the 139 infants who were not diagnosed with CBA, 95 had obstructive jaundice and 44 had citrin protein deficiency. Table 1 shows the baseline characteristics of the study population and the levels of ALT, AST, TB, DB, and GGT in the 2 groups. There were no significant differences in sex, age, or body mass index (BMI) between the 2 groups. However, the levels of ALT, AST, TB, DB, and GGT were higher in the CBA group than in the NCBA group, which is consistent with the findings of Jiang et al.[10]

3.2. Comparison of HA, PC-III, IV-C, and LN levels between the 2 groups

The results showed that the levels of HA, PC-III, IV-C, and LN in children with biliary atresia were significantly higher than those in children without biliary atresia (*P* < .01, Table 2). Representative intraoperative cholangiography findings in the children with CBA are shown in Figure 2.

Receiver operating characteristic analysis was performed to determine the optimal cutoff value for HA, PC-III, IV-C, and LN levels, which could be associated with the occurrence of CBA. The statistical result shows that the critical HA, PC-III, IV-C, and LN values were 162.7 ng/mL (AUC = 0.892 sensitivity = 76.82%, specificity = 70.22%), 42.5 ng/mL (AUC = 0.762 sensitivity = 71.61%, specificity = 70.44%), 199.7 ng/mL (AUC = 0.804 sensitivity = 70.32%, specificity = 66.34%), and 101.2 ng/mL (AUC = 0.768, sensitivity = 72.28%, specificity = 68.71%).

3.3. Univariate and multivariate logistic analyses

In the univariate analysis, HA ≥162.7 ng/mL, PC-III ≥42.5 ng/mL, IV-C ≥199.7 ng/mL, and LN ≥101.2 ng/mL were found to be the significant risk factors for CBA. Other factors such as age, sex, BMI, ALT, AST, TB, DB, and GGT were not associated with the occurrence of CBA. Detailed information is presented in Table 3.

In the multivariate model, HA ≥162.7 ng/mL, PC-III ≥42.5 ng/mL, IV-C ≥199.7 ng/mL, and LN ≥ 01.2 ng/mL were independent risk factors associated with CBA after adjustment for confounding factors such as sex, age, and BMI (*P* =.006, .002, .011, and .007, respectively), and the adjusted odds ratio values were 5.28 (3.15–8.37), 4.61 (2.54–7.16), 5.02 (2.98–7.64), and 6.25 (2.41–10.07) respectively. Detailed information is presented in Table 4.

4. Discussion

Jaundice is one of the most common diseases affecting newborns. Jaundice is the main clinical manifestation of many diseases such as CBA and choledochal cysts. Long-term jaundice symptoms can lead to liver fibrosis, cirrhosis, and serious liver dysfunction.[14] Biliary atresia, characterized by fibrosis and inflammation of the intrahepatic and extrahepatic bile ducts, is a type of idiopathic cholestasis disease with a high risk coefficient

Table 1

Demographic data in 2 groups ($\bar{\chi}\pm s$).

Group	CBA group (N = 46)	NCBA group (N = 139)	*P* value
Gender (male/female)	30/16	82/57	.325
Age (d)	34 ± 5.13	33 ± 4.35	.274
BMI (kg/m^2)	15.24 ± 0.9	15.53 ± 1.0	.187
ALT (U/L)	55.26 ± 10.88	15.31 ± 2.77	.002
AST (U/L)	151.29 ± 25.36	70.61 ± 8.82	.013
TB (μmol/L)	196.62 ± 31.24	104.74 ± 15.41	.026
DB (μmol/L)	159.42 ± 30.33	112.58 ± 20.22	.029
GGT (U/L)	886.45 ± 102.26	119.64 ± 20.49	<.001

ALT = alanine transaminase, AST = aspartate transaminase, BMI = body mass index, CBA = congenital biliary atresia, DB = direct bilirubin, GGT = glutamyl transpeptidase, NCBA = noncongenital biliary atresia, TB = total bilirubin.

Table 2

The level of HA, PC-III, IV-C, and LN between 2 groups ($\bar{\chi}\pm s$, ng/mL).

Group	HA	PC-III	IV-C	LN
Reference range, ng/mL	0–120	0–15	0–30	0–130
Group CBA (N = 46)	256.7 ± 56.9	76.2 ± 17.6	584.4 ± 106.3	278.4 ± 40.2
Group NCBA (N = 139)	64.2 ± 21.5	9.5 ± 3.7	17.9 ± 6.6	73.2 ± 19.7
t value	2.714	3.304	6.432	2.432
P value	.011	.002	.001	.019

CBA = congenital biliary atresia, HA = hyaluronic acid, IV-C = type IV collagen, LN = laminin, NCBA = noncongenital biliary atresia, PC-III = type III procollagen.

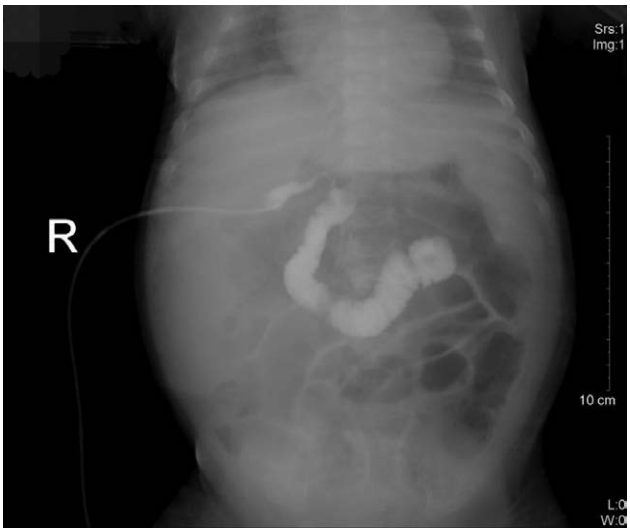

Figure 2. The representative intraoperative cholangiography in patients with congenital biliary atresia.

and poor prognosis. If it is not found and treated in a timely manner, it can cause serious hepatic fibrosis, irreversible damage, and even threaten the life safety of children.[15–17] Therefore, attention should be paid to the etiology, early diagnosis, and treatment of neonatal jaundice. However, the etiology of biliary atresia remains unclear. There are many theories for CBA, such as the theory of congenital dysplasia (biliary dysplasia leads to biliary malformations), the theory of inflammation (dysplasia of the hilar bile duct plate in the perinatal period causes bile extravasation, stimulates the surrounding tissues to induce an inflammatory response, and causes atresia), and the theory of pancreaticobiliary junction malformation (the opening of the pancreatic duct is abnormal or connected to the bile duct).

Table 3

Univariate analysis of factors associated with congenital biliary atresia.

Risk factors	CBA group (N = 46)	NCBA group (N = 139)	*P* value
Age (d)	34 ± 5.13	33 ± 4.35	.347
BMI (kg/m^2)	15.24 ± 0.9	15.53 ± 1.0	.239
Gender			.288
Male, n (%)	30 (65.22)	82 (58.99)	
Female, n (%)	16 (34.78)	57 (41.01)	
ALT (U/L)	55.26 ± 10.88	15.31 ± 2.77	.125
AST (U/L)	151.29 ± 25.36	70.61 ± 8.82	.098
TB (μmol/L)	196.62 ± 31.24	104.74 ± 15.41	.119
DB (μmol/L)	159.42 ± 30.33	112.58 ± 20.22	.155
GGT (U/L)	886.45 ± 102.26	119.64 ± 20.49	.062
HA			.001
≥162.7 ng/mL (%)	36	10	
<162.7 ng/mL (%)	10	129	
PC-III			.003
≥42.5 ng/mL (%)	37	19	
<42.5 ng/mL (%)	9	120	
IV-C			<.001
≥199.7 ng/mL (%)	38	15	
<199.7 ng/mL (%)	8	124	
LN			.004
≥101.2 ng/mL (%)	39	28	
<101.2 ng/mL (%)	7	111	

ALT = alanine transaminase, AST = aspartate transaminase, BMI = body mass index, CBA = congenital biliary atresia, DB = direct bilirubin, GGT = glutamyl transpeptidase, HA = hyaluronic acid, IV-C = type IV collagen, LN = laminin, NCBA = noncongenital biliary atresia, PC-III = type III procollagen, TB = total bilirubin.

Table 4

Multivariate logistic regression analysis of factors associated with congenital biliary atresia.

Factors	Odds ratio	95% CI	*P* value
HA ≥162.7 ng/m–L	5.28	3.15–8.37	.006
PC-III ≥42.5 ng/mL	4.61	2.54–7.16	.002
IV-C ≥199.7 ng/mL	5.02	2.98–7.64	.011
LN ≥101.2 ng/mL	6.25	2.41–10.07	.007

CI = confidence interval, HA = hyaluronic acid, IV-C = type IV collagen, LN = laminin, PC-III = type III procollagen.

Currently, Doppler ultrasound and MR are the most commonly used noninvasive diagnostic methods for CBA. Although these are easy to perform, they have a certain misdiagnosis rate.[18] Intraoperative exploration by cholecystography is the gold standard for the diagnosis of biliary atresia; however, this operation causes great damage to children. If the preoperative diagnosis is incorrect and the operation is performed, it will cause unnecessary damage and affect the physical and mental health of the patient. However, if the correct diagnosis is not made in time, irreversible liver damage will occur.[19] Therefore, differentiating and diagnosing biliary atresia as early as possible and reducing unnecessary surgical trauma is an urgent problem in clinical practice.

Doppler ultrasound is a commonly used examination method for abdominal diseases, and it is also commonly used to distinguish biliary atresia from nonbiliary atresia. Ultrasound physicians diagnose the disease by detecting the size and shape of the gallbladder, the presence of fibrous masses in the hilar region, and the shape of the bile duct. The identification of the formation of fibrous masses or the trigonometric cord sign is very helpful for the diagnosis of biliary atresia.[20–22] Therefore, Doppler ultrasound plays an increasingly important role in the examination and diagnosis of biliary diseases, particularly biliary atresia. However, children often do not cooperate during

the inspection process owing to their young age, and the fasting period before the examination is difficult for the children to accept. The accuracy of Doppler ultrasound examination is largely limited by the quality and sensitivity of the examination instrument and the clinical experience and subjective judgment ability of the operator; therefore, Doppler ultrasound cannot be regarded as the gold standard for the diagnosis of biliary atresia. MR cholangiopancreatography is also a first-line clinical examination method for biliary atresia, which has the advantages of being noninvasive, having a high success rate, and not requiring radiation. A relatively static liquid shows a high signal in the influence, while a flowing liquid shows signal loss. The signal pair ratio directly shows the shape and patency of the bile duct with high diagnostic specificity.[23,24] However, owing to the long examination time, it is difficult to ensure good sedation of patients.

The activation of stellate cells is a key step in the process of liver fibrosis: these can be transformed into fibroblasts through a series of steps and participate in the development of liver fibrosis.[25] In this process, stellate cells can synthesize large amounts of extracellular matrix (ECM). The main components of ECM are HA, PC-III, IV-C, and LN. With the development of liver fibrosis, the level of ECM in serum changes accordingly. Therefore, the detection of serum HA, PC-III, IV-C, and LN is helpful for understanding the degree of liver fibrosis.[26] With the further development of biliary atresia, liver fibrosis will typically also appears; therefore, we boldly use the serological indicators of liver fibrosis in the diagnosis of CBA in children as a diagnostic method and clinical thinking innovation.

HA is a high-molecular-weight polysaccharide synthesized by stellate cells. HA is degraded in the endothelial cells of the hepatic sinuses through blood circulation. Owing to the further development of liver fibrosis, the HA degradation ability of sinusoidal endothelial cells is significantly reduced, resulting in a significant increase in serum HA levels; therefore, HA is the most valuable serological index reflecting liver fibrosis.[27] LN is a noncollagen glycoprotein synthesized by liver stromal cells and is present in small amounts in normal liver tissue. When liver fibrosis occurs, a large amount of LN is deposited in liver cells, which play a role in cell adhesion. Several studies have confirmed that serum LN levels can accurately and sensitively evaluate the degree of liver fibrosis and determine the presence of active liver fibrosis.[28] PC-III is an amino-terminal polypeptide formed before the secretion of type III collagen, which is released by stellate cells. It can accurately reflect the synthesis and metabolism of type III collagen in the extracellular matrix of the liver and has strong sensitivity. It is commonly used for clinical diagnosis of early liver fibrosis. As the level of PC-III also increases following the formation of fibrosis in other tissues, its specificity for the diagnosis of liver fibrosis is weak.[29] IV-C is an important component of the basement membrane of small blood vessels in the dise cavity and the collecting duct of the liver. When liver fibrosis develops further, the basement membrane is destroyed, and a large amount of IV-C release increases serum levels.[30] Therefore, the levels of HA, PC-III, IV-C, and LN can be specifically and accurately evaluated. In this study, serum HA, PC-III, IV-C, and LN levels were measured using chemiluminescence. According to the principle of linear quantitative relationship between the concentration of the substance to be measured and the chemiluminescence intensity of the system under certain conditions, the chemiluminescence method further determines the content of the substance to be measured through the detection of chemiluminescence intensity by the instrument. In the detection process of clinical blood sample indexes, the chemiluminescence detection method has high accuracy and sensitivity and is widely used in clinical settings.[31] Of course, other diseases apart from CBA also increase HA, PC-III, IV-C, and LN levels. During hepatic fibrosis, the production of LN and HA increases and these are released into the blood. Therefore, the levels of serum HA, PC-III, IV-C, and LN also increase in diseases with symptoms of hepatic fibrosis, such as chronic hepatitis and liver cirrhosis. Therefore, HA, PC-III, IV-C, and LN can also be used to diagnose these diseases with diagnostic value.[12]

The results of this study showed that the serum HA, PC-III, IV-C, and LN levels were significantly higher in children with biliary atresia than in those without biliary atresia, suggesting that HA, PC-III, IV-C, and LN levels could play a better role in the diagnosis of children with CBA and have higher diagnostic sensitivity and specificity. Moreover, logistic regression analysis showed that HA ≥162.7 ng/mL, PC-III ≥42.5 ng/mL, IV-C ≥199.7 ng/mL, and LN ≥101.2 ng/mL were independent risk factors of CBA. Therefore, children who meet these criteria should receive more clinical attention.

It is undeniable that there are still some limitations in this study. First, this was a retrospective study with a certain bias, which may have an impact on the accuracy of the results. Second, the current study included only the medical records from the second Department of General Surgery of Hebei Children's Hospital from January 2017 to December 2020 for retrospective analysis, and the sample size was small. We should carry out multicenter and large-sample clinical experimental research to make the research conclusion more convincing, which is the direction of our future efforts. Third, in this study, we only explored the sensitivity and specificity of HA, PC-III, IV-C, and LN in the diagnosis of CBA separately. We did not explore the diagnostic value of ≥2 of these indicators in combination; however, this is the direction of our future efforts. Finally, we only considered the inconvenience of Doppler ultrasound and MR cholangiopancreatography in disease screening and did not compare their sensitivity and specificity with HA, PC-III, IV-C, and LN in the diagnosis of CBA. This is not only a deficiency of this study but also one of the research topics we need to pursue.

5. Conclusion

The detection of HA, PC-III, IV-C, and LN has high accuracy for diagnosing CBA in infants, and they are the potential diagnostic biomarkers for CBA.

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Author contributions

Y.K.B. conceived and designed the study and wrote the article. P.W., Y.W.Q., and L.Y. collected data. W.D.L., L.G., H.L.J., and Y.X.A. analyzed the data. Y.X.G. designed the study and reviewed the articles.

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