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 hepatobiliary 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.[6–7] 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
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.\textsuperscript{18} 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.\textsuperscript{19} Infant choleodochal 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.\textsuperscript{10} Approximately 20% of infants with type III CBA (hilar biliary 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 diagnostic 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.\textsuperscript{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.\textsuperscript{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 cholechochography. 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,
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 ≥101.2 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. 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...
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, in any manner, it can cause serious hepatic fibrosis, irreversible damage, 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, in any manner, it can cause serious hepatic fibrosis, irreversible damage, and even threaten the life safety of children.\(^{15–17}\) Therefore, in any manner, it can cause serious hepatic fibrosis, irreversible damage, and even threaten the life safety of children.\(^{15–17}\) Therefore, in any manner, it can cause serious hepatic fibrosis, irreversible damage, and even threaten the life safety of children.\(^{15–17}\) Therefore, in any manner, it can cause serious hepatic fibrosis, irreversible damage, and even threaten the life safety of children.\(^{15–17}\) Therefore, in any manner, it can cause serious hepatic fibrosis, irreversible damage, and even threaten the life safety of children.\(^{15–17}\) Therefore, in any manner, it can cause serious hepatic fibrosis, irreversible damage, and even threaten 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the inspection process owing to their young age, and the fast-
ing 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 exam-
ination 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 diagnos-
tic 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; there-
fore, 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 nor-
mal liver tissue. When liver fibrosis occurs, a large amount of
LN is deposited in liver cells, which play a role in cell adhe-
sion. 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 col-
lagen 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 import-
ant 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.[10] 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 inten-
sity of the system under certain conditions, the chemilumines-
cence 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 clin-
ical blood sample indexes, the chemiluminescence detection
method has high accuracy and sensitivity and is widely used
in clinical settings.[16] 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.[11]

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 analy-
sis 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 fac-
tors 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 exper-
imental research to make the research conclusion more con-
vincing, 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 indi-
cators 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 arti-
cle. 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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