Serum MMP-7 in the Diagnosis of Biliary Atresia

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BACKGROUND: The overlapping features of biliary atresia (BA) and other neonatal cholestasis with alternative causes (non-BA) have posed challenges for diagnosis. Matrix metalloproteinase-7 (MMP-7) has been reported to be promising in diagnosing BA. We aimed to validate the diagnostic accuracy of MMP-7 for BA in a large population sample.

METHODS: We enrolled 288 patients with neonatal obstructive jaundice from March 2017 to October 2018. Serum MMP-7 levels were measured by using an enzyme-linked immunosorbent assay. Receiver operating characteristic curves were constructed, and decision curve analysis was done. A Pearson correlation coefficient test was conducted to assess the correlation between MMP-7 levels and other characteristics.

RESULTS: The median serum MMP-7 levels were 38.89 ng/mL (interquartile range: 22.96–56.46) for the BA group and 4.4 ng/mL (interquartile range: 2.73–6.56) for the non-BA group (P < .001). The area under the receiver operating characteristic curve value was 0.9829 for MMP-7, and the sensitivity, specificity, positive predictive value, and negative predictive value were 95.19%, 93.07%, 97.27%, and 91.43%, respectively, at a cutoff value of 10.37 ng/mL. When MMP-7 was combined with γ-glutamyl transferase, the diagnostic accuracy was slightly improved without significance when compared with MMP-7 alone and had an area under the curve of 0.9880 (P = .08). Decision curve analysis also showed potential for MMP-7 to be used for clinical applications. A significant correlation was found with fibrosis stage from liver biopsy (R = 0.47; P < .001).

CONCLUSIONS: MMP-7 demonstrated good accuracy in diagnosing BA and holds promise for future clinical application. Furthermore, its correlation with liver fibrosis indicated its potential use as a therapeutic target or prognostic biomarker.

WHAT’S KNOWN ON THIS SUBJECT: Matrix metalloproteinase-7 was reported to have promising diagnostic accuracy for biliary atresia, but the related studies are rare with a small sample size, and the cutoff value has not yet been established.

WHAT THIS STUDY ADDS: We validated matrix metalloproteinase-7 efficacy in a larger population and found good performance in diagnosing biliary atresia. Also, a significant correlation was found with fibrosis stage, indicating its potential use as a therapeutic target or prognostic biomarker.
Biliary atresia (BA) is a serious liver disease affecting newborns, with higher incidence seen in the Asia-Pacific region (~1.06 in 10 000 live births) than within the United States (4.47 in 100 000).\(^1\)-\(^3\) It is characterized by inflammation and atresia of extra and intrahepatic bile ducts, resulting in obstructive jaundice and subsequent liver fibrosis. The Kasai portoenterostomy procedure has been the first-line treatment of BA since 1959, although the pathogenesis is largely unknown.\(^3\)-\(^8\) Several studies have proposed that early diagnosis and treatment is key to the restoration of bile flow and favorable prognosis.\(^3\)-\(^13\) However, many other non-BA cholestatic diseases, such as idiopathic cholestasis, Alagille syndrome, and progressive familial intrahepatic cholestasis, are similar to BA in symptoms and noninvasive laboratory and radiologic test results, leading to difficulties in the accurate diagnosis of BA. Our previous retrospective study showed that 14% of 602 patients with BA-like neonatal jaundice were found to be non-BA by using invasive diagnostic procedures such as intraoperative cholangiography and liver biopsy.\(^14\) Therefore, it is critical to develop a noninvasive diagnostic method with good reliability and validity to avoid unnecessary invasive procedures.\(^1\)

\(^{\gamma}\) glutamyl transferase (GGT), is 1 of the factors measured in biochemical liver function tests and is widely used to differentiate BA from non-BA, with an accuracy of 76% to 88% at a cutoff value of \(\sim 300 \text{ IU/L}.\(^{15,16}\) However, GGT alone is not enough to accurately diagnose BA. We have developed and validated a novel nomogram diagnostic model based on 5 variables, including sex, weight, direct bilirubin (DB), ln(GGT), and ln(alkaline phosphatase [ALP]), which achieved better sensitivity (85.7%), specificity (80.3%), and positive predictive value (PPV) (0.969). There is, however, still room for improvement.\(^17\) Although radiologic investigations (such as ultrasound, MRI, and hepatobiliary scintigraphy) were reported to be helpful in differentiating BA from other obstructive cholestasis, they are time consuming and costly.\(^18\)-\(^23\) Therefore, an effective biomarker would be extremely valuable for the preoperative diagnosis of BA.

Matrix metalloproteinase-7 (MMP-7), a protease responsible for tissue remodeling, was discovered to be associated with liver fibrosis in patients with BA.\(^24,25\) Lately, the Bezerra group\(^26\) identified that MMP-7 was superior to all other potential biomarkers and had a significantly higher concentration in patients with BA when compared with non-BA using a high-throughput proteomic assay (SOMAscan). This revealed its potential role in the pathogenesis of BA and thereby its use as a potential biomarker and therapeutic target.\(^26\) Recently, Yang et al\(^27\) compared serum MMP-7 concentration among patients with BA and without BA and healthy control infants and confirmed its diagnostic accuracy with a cutoff value of 52.85 ng/mL. The area under the curve (AUC) was 0.99 with a sensitivity, specificity, and PPV of 98.67%, 95%, and 98.28%, respectively.\(^27\) However, most recently, Wu et al\(^28\) found that a serum MMP-7 level of \(>1.43 \text{ ng/mL}\) was predictive of BA in infants with cholestasis with a sensitivity of 97.30% and a specificity of 83.20%. The cutoff value was different in the 2 studies, although the patients were all from a Chinese cohort. Therefore, we conducted a single-center validation diagnostic test for serum MMP-7 levels in a larger patient population to further evaluate diagnostic accuracy and the cutoff value.

**METHODS**

**Study Design**

This is a single-center diagnostic test to validate the use of serum MMP-7 in the diagnosis of BA. We evaluated the diagnostic accuracy of using MMP-7 alone and GGT alone or in combination as well as assessing the correlation of MMP-7 with patient age, liver function testing, and liver biopsy.

This study was reviewed and approved by the ethics committee of the Children’s Hospital of Fudan University (Shanghai, China) with a waiver of requirement for informed consent because of the use of left blood samples from routine investigations along with patient anonymity. The study was performed in compliance with the Declaration of Helsinki and other relevant regulations.

**Study Subjects**

This study was conducted at Children’s Hospital of Fudan University, an urban, tertiary-care academic children’s hospital in Shanghai, China. Infants between 30 and 150 days of age with obstructive jaundice (defined as a DB serum level \(>17 \text{ μmol/L}\) and \(>20\%\) of total bilirubin [TB]) were recruited from March 2017 to October 2018. Blood samples were obtained from routine laboratory tests at admission, and the sera were stored at \(-80^\circ\text{C}\) immediately after extraction. Intraoperative cholangiography and subsequent histologic examination of liver biopsies were used to confirm the diagnosis of BA. The gallbladders of some patients were seen to be completely atrophic, and the injection of contrast was hard to achieve, so BA in the infant would be diagnosed at once. Otherwise, a cholangiography would be performed to further evaluate the anatomy of the intrahepatic bile ducts before a final diagnosis was made. Patients without BA were confirmed by intraoperative cholangiography demonstrating a patent biliary tree. Percutaneous needle liver biopsy was also used to exclude BA. These were also confirmed by genetic tests.
demonstrating specific gene mutations or the resolution of jaundice without surgical intervention during follow-up. The follow-up information was collected from outpatient clinical records and telephone communication. Patients with non-BA were further divided into 2 groups: those with and without diagnostic surgery (Supplemental Fig 3).

**Parameters**

Baseline assessments, including demographic features, medical history, physical examination, and laboratory and radiographic tests, were performed on all patients. The laboratory variables included complete blood count and biochemical liver function tests. The histologic features of all liver biopsy specimens were measured and recorded by the same pathologist (G.C.). The grades of inflammation and stages of fibrosis were defined according to the Metavir scale system, ranging from A1–3 to F0–4.29

**Serum MMP-7 Measurement**

On the day of laboratory test, serum samples from each patient were obtained before the final diagnosis. MMP-7 concentration was measured by using an enzyme-linked immunosorbent assay (Cloud-Clone Corp, Wuhan, China). The serum samples from the patients with BA were diluted 16 times to accommodate the concentration range of the kit (0–10 ng/mL), whereas samples from the patients without BA were diluted 4 times. The person performing the measurements was blinded to the test result and final diagnosis. Each sample was provided with 2 technical replicates, and the mean was recorded.

**Statistical Analyses**

Baseline characteristics of patients in the BA and non-BA groups were demonstrated by using frequency distributions and descriptive statistics. Sex and stages of liver biopsy were described by n (%). Continuous variables, including age, GGT, TB, DB, total bile acid (TBA), alanine aminotransferase (ALT), aspartate aminotransferase (AST), ALP, platelets, and the AST/platelet ratio index (APRI), were expressed as mean ± SD and median and quartiles (quartile 1 [Q1], quartile 3 [Q3]). By using univariate analysis, the x² test was conducted for sex, whereas the Mann-Whitney U test was performed for all continuous variables because of a failing Shapiro-Wilk W-test for normal distribution.

Receiver operating characteristic (ROC) curves were constructed to calculate the best cutoff point and AUC for MMP-7 alone, GGT alone, and MMP-7 combined with GGT. The sensitivity, specificity, PPV, and negative predictive value (NPV) were used to show diagnostic accuracy. Decision curve analysis (DCA) was performed to finalize the ranges of threshold probabilities within which MMP-7, GGT, or MMP-7 combined with GGT were clinically valuable for the diagnosis of BA. The Pearson correlation coefficient test was applied to assess the correlations between MMP-7 and other clinical characteristics, including grade of inflammation and stage of fibrosis, by using liver biopsy. Statistically significant differences were defined as a P < .05. All data analyses were performed by using Stata 14 software (Stata Corp, College Station, TX).

**RESULTS**

**Study Population**

A total of 288 eligible infants were enrolled, of whom 187 were diagnosed with BA, and of those, 34 had BA splenic malformation syndrome or other congenital malformations, including congenital heart disease, renal malformation, or congenital intestinal malrotation. One hundred one patients were confirmed to have cholestasis with other causes of non-BA, and of these, 38 underwent diagnostic surgery. Fifty-two of patients without BA underwent genotyping tests. The mean follow-up period for the patients was 482 ± 180 days. The final diagnosis for patients without BA included cytomegalovirus (CMV) hepatitis (n = 26), Alagille syndrome (n = 8), citrin deficiency (n = 2), progressive familial intrahepatic cholestasis (n = 6), parenteral nutrition–associated cholestasis (n = 3), intrahepatic bile duct dysplasia (n = 1), congenital absence of a gallbladder (n = 1), gallbladder duplication (n = 1), neonatal sclerosing cholangitis (n = 1), and idiopathic cholestasis (n = 52; Supplemental Tables 4 and 5).

The demographic and baseline characteristics of the study subjects in the BA and non-BA groups are summarized in Table 1. The median age of the infant patients was 59 days (interquartile range [IQR]: 48–69) in the BA group and 67 days (IQR: 51–84) in the non-BA group (P = .006). The majority of the patients without BA were boys (75.25%), whereas the sex distribution in the BA group was the opposite, with the male population representing 43.32% and the female population representing 56.68% (P < .001). The median level of GGT and TB were found to be higher in the BA group (P < .001) when compared with the non-BA group (P = .004). However, the 2 groups were comparable in DB, TBA, ALT, AST, ALP, platelets, and the APRI. All patients with and without BA with diagnostic surgery underwent liver biopsy. However, the specimens of 15 patients with BA and 10 patients without BA were too small and too close to the liver capsule for the pathologist to make a judgment on the inflammation grade or fibrosis stage, and another 16 patients without BA underwent needle liver biopsy. Inflammation and fibrosis stages of 172
patients with BA and 44 patients without BA were obtained, both showing significant differences between these 2 groups ($P < .001$).

### Serum MMP-7 Concentration From Each Group

The median serum MMP-7 levels were 38.89 ng/mL (IQR: 22.96–56.46) for the BA group and 4.40 ng/mL (IQR: 2.73–6.56) for the non-BA group ($P < .001$). The non-BA group was further divided into 2 groups, 1 with diagnostic surgery and the other without surgery. The

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$^a$ $P$ between the BA and non-BA groups. $\chi^2$ test were applied to sex and inflammation and fibrosis stages of liver biopsy, and the rest were tested by using a Mann-Whitney U test.
median serum MMP-7 levels were 4.94 ng/mL (IQR: 2.52–7.58) for the group with diagnostic surgery and 4.25 ng/mL (IQR: 3.07–6.07) for the nonsurgery group, which showed no statistical significance ($P = .57$; Fig 1). Furthermore, the serum MMP-7 concentrations were also calculated for each different diagnosis (Supplemental Fig 4, Supplemental Tables 4 and 5).

**Diagnostic Value of MMP-7 for BA**

The AUC was found to have a value of 0.9829 (95% confidence interval [CI]: 0.9702–0.9957) for MMP-7 alone, which was greater than the AUC value of 0.8723 (95% CI: 0.8296–0.9149) for GGT alone. The cutoff value for MMP-7 was 10.37 ng/mL, with a sensitivity, specificity, PPV, and NPV of 95.19%, 93.07%, 97.27%, and 91.43%, respectively. When MMP-7 was combined with GGT, the AUC value was 0.9880, with sensitivity, specificity, PPV, and NPV values of 95.70%, 98.02%, 98.90%, and 95.52%, respectively. However, there were no significant differences when compared with MMP-7 alone ($P = .08$). The results of DCA confirmed and supported the use of MMP-7 in the prediction of BA because the ranges of the threshold probabilities were wide and practical with a net benefit of >50%, which is stable and better than GGT alone but close to MMP-7 combined with GGT (Table 2, Fig 1).

Furthermore, we also analyzed the diagnostic value of MMP-7 in subgroups of patients with relatively low GGT (<300 IU/L) and at ages between 30 and 60 days. Both showed good performance in diagnosing BA (Supplemental Fig 5).

**Correlation of MMP-7 With Multiple Clinical Characteristics**

Correlation analysis was performed on MMP-7 with multiple clinical characteristics, including age and laboratory parameters in the entire cohort as well as in the BA and non-BA groups separately. A moderate

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**FIGURE 1**

Serum MMP-7 concentration in the BA and non-BA groups and diagnostic accuracy for MMP-7 alone, GGT alone, and MMP-7 combined with GGT. A, Boxes and whiskers represent the median and IQR. A Mann-Whitney U test was applied. B, ROC plots. The AUC value is 0.9829, 0.8723, 0.9880 for each. C, DCA showing wide and practical ranges of threshold probabilities for MMP-7 with a stable net benefit of 50% or more, which is much better than for GGT alone. NS, no significance. *P < .0001.
correlation with GGT level was observed in all 3 groups, whereas age was found to correlate in the BA group alone (Supplemental Fig 6).

**Correlation of MMP-7 With Inflammation Grade and Fibrosis Stage in Liver Biopsies**

A total of 216 liver biopsy results were obtained, including from 172 patients with BA and 44 patients without BA. Serum MMP-7 concentration was also analyzed with the inflammation grades and fibrosis stages from liver biopsy (summarized in Table 3). A significant correlation was found with the fibrosis stage by using the Pearson correlation coefficient test ($R = 0.47; P < .001$), whereas no significant differences were seen with different inflammation grades ($R = 0.12; P = .07$; Fig 2).

**DISCUSSION**

It is currently challenging to accurately diagnose BA on the basis of existing diagnostic approaches because of overlapping similarities between BA and other causes of non-BA cholestasis. Furthermore, current diagnostic methods can be costly, time consuming, and highly invasive. Matrix metalloproteinases (MMP) and their endogenous inhibitors have been found to be involved in the activation of hepatic stellate cells and increase extracellular matrix, both of which are associated with the fibrogenic mechanism of BA. This has been found based on reports looking at MMP expression in liver specimens at different time points in patients with BA, 1 during the Kasai procedure and the other from liver transplant. Among all MMPs, MMP-7 is the most consistent marker, as observed in several studies using animal models of BA. Moreover, recent diagnostic tests have further confirmed its diagnostic accuracy as a biomarker for BA. However, a cutoff value has not been agreed on at present.

In our study, conducted at the largest liver center for pediatric patients in China, we aimed to validate the diagnostic accuracy of serum MMP-7 levels. We found the following. First, Serum MMP-7 concentration was significantly higher in the BA group, when compared with the non-BA group, either with or without diagnostic surgery. Second, the AUC of MMP-7 was greater than that of GGT alone, and the DCA further validated its clinical benefit; when MMP-7 and GGT were combined, there was no significant improvement in their discriminatory ability. The performance remained good in a subgroup of patients with low GGT (<300 IU/L) and between ages 30 and 60 days. Third, Serum MMP-7 levels were correlated with the fibrosis stage using liver biopsy, whereas no significance was found within different grades of inflammation.

The above findings have confirmed a promising diagnostic accuracy for serum MMP-7 as a biomarker for BA and suggest it is superior to GGT, which is currently widely used in clinical diagnosis. However, compared
with a previous study from the Bezerra group, the median serum MMP-7 level and cutoff values were lower in our patients, although the same kit and protocol were used. However, in opposition to this is a study from the Wu group using a different kit (enzyme-linked immunosorbent assay; DuoSet, R&D Systems, Inc, Minneapolis, MN). These discrepancies may be due to differences in the sample collection or dilution algorithm. The serum samples were separated in our biochemistry department, as described in our protocol, and stored at \(-80^\circ\text{C}\) before measurement. The period between sample collection and measurement ranged from several days to several months, which may interfere with concentration levels because of degradation. The serum samples from the Wu study were stored for up to 10 years, which may explain the low concentration values seen. The sera from patients with and without BA were diluted by either 16 times or 4 times, as recommended by the protocol, and none were found to exceed the measurement range. Furthermore, we are currently working on a project measuring fresh and frozen serum samples, and also different dilution algorithms, in the hope of further standardizing MMP-7 measurement.

Moreover, as in the previous study, we have also found that serum MMP-7 levels were positively correlated to GGT in all patients, with a slightly improved diagnostic accuracy but no significant difference seen when using MMP-7 combined with GGT. MMP-7 correlated with age only in the BA group, just as reported previously. The reason for this may be that the process of liver fibrosis is much quicker with age in patients with BA. In addition to the previous study, most patients enrolled in the current study underwent liver biopsy, and the specimens were scored by the same pathologist for both inflammation and fibrosis stage. The Pearson correlation coefficient test showed that serum MMP-7 levels were well correlated to the fibrosis stage. This was paralleled with the correlation between MMP-7 and age in the BA group. So far, most of the previous studies have focused on the correlation between MMP-7 and liver fibrosis after the Kasai procedure. This study confirmed a correlation between MMP-7 levels and liver fibrosis in the early stages of BA, indicating its potential use as a noninvasive biomarker for evaluating liver fibrosis before the Kasai procedure or liver biopsy, therefore aiding the direction of treatment of individuals in the future. Furthermore, it may also be used as a noninvasive measurement of liver fibrosis during follow-up after the Kasai procedure, serving as a prognostic biomarker for BA.

However, our study has some limitations remaining. Firstly, this study was conducted in a single center, although the sample size was large. The application of a new biomarker requires samples from those of different races and regions to confirm efficacy for the majority of the population. A prospective study will provide stronger evidence for determining the diagnostic accuracy of a new biomarker. However, the blood samples for the enrolled patients were collected and measured together.

![Graph](https://www.aappublications.org/news)
in batches to maximize the use of the kits. However, the person conducting the measurement of MMP-7 concentration was blinded to diagnosis to avoid investigator bias and simulate a prospective study design. Secondly, the BA and non-BA groups in our study were not age matched because many of the patients without BA showed low possibility of BA and were always referred to their local hospitals first and had been followed up as neonatal physiologic jaundice for some time before referral to us, thereby delaying the time of the first visit to our hospital. However, because age has no significant correlation with serum MMP-7 levels in non-BA group, according to our results and also those of previous studies, the discriminatory ability of MMP-7 between BA and non-BA was still valid in this study. Furthermore, our subgroup analysis in patients between 30 and 60 days of age further confirmed its value for the early diagnosis of BA.

CONCLUSIONS
The use of MMP-7 as a marker to differentiate BA from non-BA holds great promise. However, the protocol used to obtain and measure the blood samples requires further standardization before clinical application. The mechanism by which MMP-7 is expressed in BA pathogenesis and liver fibrosis deserves further study to determine its value as a therapeutic target and/or prognostic biomarker.

ACKNOWLEDGMENT
We sincerely thank Dr Lian Chen for her guidance in histology examinations.

ABBREVIATIONS
ALP: alkaline phosphatase
ALT: alanine aminotransferase
APRI: aspartate aminotransferase/platelet ratio index
AST: aspartate aminotransferase
AUC: area under the curve
BA: biliary atresia
CI: confidence interval
CMV: cytomegalovirus
DB: direct bilirubin
DCA: decision curve analysis
GTT: γ-glutamyl transferase
IQR: interquartile range
MMP: matrix metalloproteinase
MMP-7: matrix metalloproteinase-7
NPV: negative predictive value
PPV: positive predictive value
Q1: quartile 1
Q3: quartile 3
ROC: receiver operating characteristic
TB: total bilirubin
TBA: total bile acid

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