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Review Article

Progress in Biomarkers Related to Biliary Atresia

Fanyang Kong, Rui Dong, Gong Chen, Song Sun, Yifan Yang, Jingying Jiang, Lingdu Meng, Huifen Chen, Jiajie Zhu and Shan Zheng*

Department of Pediatric Surgery, Children's Hospital of Fudan University, Shanghai Key Laboratory of Birth Defect, and Key Laboratory of Neonatal Disease, Ministry of Health, Shanghai, China

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Abstract

Biliary atresia (BA) is a congenital cholestatic disease that can seriously damage children's liver function. It is one of the main reasons for liver transplantation in children. Early diagnosis of BA is crucial to the prognosis of patients, but there is still a lack of reliable non-invasive diagnostic methods. Additionally, as some children are in urgent need of liver transplantation, evaluating the stage of liver fibrosis and postoperative native liver survival in children with BA using a straightforward, efficient, and less traumatic method is a major focus of doctors. In recent years, an increasing number of BA-related biomarkers have been identified and have shown great potential in the following three aspects of clinical practice: diagnosis, evaluation of the stage of liver fibrosis, and prediction of native liver survival. This review focuses on the pathophysiological function and clinical application of three novel BA-related biomarkers, namely MMP-7, FGF-19, and M2BPGi. Furthermore, progress in well-known biomarkers of BA such as gamma-glutamyltransferase, circulating cytokines, and other potential biomarkers is discussed, aiming to provide a reference for clinical practice.

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Introduction

Biliary atresia (BA) is an idiopathic neonatal liver disease characterized by inflammatory and fibrotic obliteration of intrahepatic and external biliary ducts. It is often manifested as neonatal jaundice, cirrhosis, and portal hypertension.[1] The etiology of BA is currently unknown. It may be associated with viral infection,[2] environmental toxins like biliatresone,[3,4] immune responses,[5] and genetic susceptibility.[6] BA is currently the main reason for liver transplantation in children,[7] with a high incidence in East Asian countries. According to a survey in Taiwan, there is approximately one patient with BA in every 5,000 live births.[8] The diagnosis of BA mainly depends on intraoperative cholangiography.[1,9,10] Kasai portoenterostomy (KPE) is the first-line treatment for BA, with the primary goal of re-establishing bile drainage.[11]

An early diagnosis of BA is very important for patients. Children diagnosed with BA who receive KPE within 90 days after birth are likely to have better jaundice clearance and native liver survival rates.[12] However, there is currently a lack of reliable non-invasive diagnostic methods, and distinguishing BA from other neonatal cholestatic diseases remains difficult. In addition, some patients will still develop cirrhosis after KPE and need liver transplantation.[13] The early identification of high-risk children in need of liver transplantation can help doctors change the treatment strategy and reasonably allocate the liver source to improve the prognosis of patients. Simply and efficiently identifying high-risk patients who need liver transplantation has been the focus of pediatric surgeons.

In recent years, serum biomarkers in patients with BA have shown great potential in clinical diagnosis and prognosis assessments. Many biomarkers with high specificity and sensitivity are gradually being discovered. They are less invasive compared to intraoperative cholangiography. These biomarkers can be used for an early diagnosis of BA, assessment of liver fibrosis in patients, and prediction of native liver survival after KPE.

In this review, recent research progress on serum biomarkers in BA is summarized. We focus on the novel biomarkers of BA and those with high clinical values, including MMP-7, FGF-19, and M2BPGi. We emphasize their role in the pathophysiology of BA and their clinical application according to recent studies. The latest research progress on well-known biomarkers like gamma-glutamyltransferase (GGT) and circulating cytokines, as well as other newly discovered biomarkers, are also discussed.

MMP-7

Matrix metalloproteinases (MMPs) are key enzymes involved in the degradation and deposition of all proteins in the extracellular matrix and play an important role in the process of tissue remodeling and fibrosis.[14] Huang *et al*.[15] suggested

Keywords: Biliary atresia; Biomarkers; Diagnosis; Liver fibrosis; Native liver survival.

Abbreviations: APRi, aspartate aminotransferase to platelet ratio index; BA, biliary atresia; CMV, cytomegalovirus; COMP, cartilage oligomeric matrix protein; ELISA, enzyme-linked immunosorbent assay; FGF-19, fibroblast growth factor-19; FXR, farnesoid X receptor; GGT, gamma-glutamyltransferase; HSCs, hepatic stellate cells; IL, Interleukin; KCs, kupffer cells; KPE, Kasai portoenterostomy; M2BPGi, mac-2 binding protein glycan isomer; MIP3a, macrophage inflammatory protein-3alpha; MMP-7, matrix metalloproteinase-7; PVR, human poliovirus receptor.

***Correspondence to:** Shan Zheng, Department of Pediatric Surgery, Children's Hospital of Fudan University, Shanghai Key Laboratory of Birth Defect, and Key Laboratory of Neonatal Disease, Ministry of Health, 399 Wan Yuan Road, Shanghai 201102, China. ORCID: https://orcid.org/0000-0002-9712-4573. Tel: +86-21-64932791, Fax: +86-21-64931901, E-mail: szheng@shmu.edu.cn

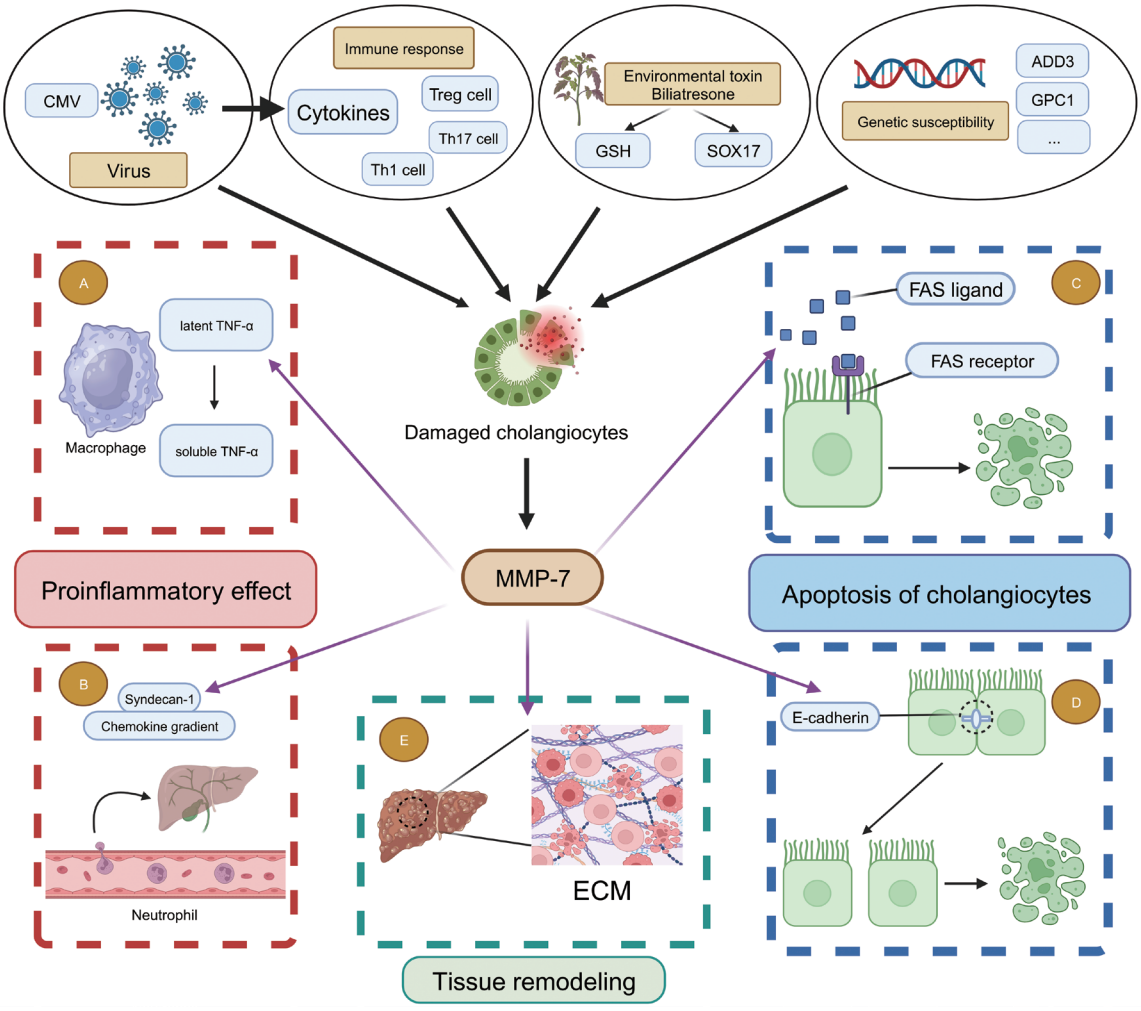

Fig. 1. Overview of how MMP-7 may be involved in the pathophysiology of biliary atresia. Viral infection, environmental toxin, immune responses, and genetic susceptibility, which are thought to be the causes of BA, may damage cholangiocytes, leading to the release of MMP-7. (A) MMP-7 can cleave latent tumor necrosis factor-alpha secreted by macrophages, leading to the activation of tumor necrosis factor-alpha and pro-inflammatory effects. (B) MMP-7 can shed the ectodomain of syndecan-1 and establish a local chemokine gradient, resulting in the influx and activation of neutrophils. (C) MMP-7 activates the FAS ligand, which can induce apoptosis of cholangiocytes by binding to the FAS receptor. (D) MMP-7 can shed E-cadherin and reduce cell-to-cell contact. Reduced E-cadherin can finally lead to apoptosis of cholangiocytes. (E) MMP-7 can degrade collagen type IV and other extracellular matrix, leading to tissue remodeling and participating in liver fibrosis. (Figure created on biorender.com). CMV, cytomegalovirus; GSH, glutathione; TNF-α, tumor necrosis factor-alpha; ECM, extracellular matrix.

that matrix metalloproteinase-7 (MMP-7) was overexpressed in liver biopsy samples and there was a significant difference when comparing the control group (children with no liver diseases) and the liver transplantation group among children with BA. Lertudomphonwanit *et al*.[16] found that MMP-7 is also highly expressed in the sera of patients with BA, through large-scale, quantitative serum proteomics. Consequently, the significance of MMP-7 in BA has been receiving increasing attention.

There is a lack of research on the role of MMP-7 in the pathophysiology of BA, which may be presumed from lessons learned from other diseases.[17] The first step is likely to be the damage to cholangiocytes from various causes, leading to the release of MMP-7.[17,18] As previously mentioned, viral infections, environmental toxins, immune responses, and genetic susceptibility are possible triggers for BA. Specifically, the main viruses investigated in BA include cytomegalovirus (CMV), human herpesvirus-5, human papillomavirus, Epstein-Barr virus, and rotavirus rhesus.[5] CMV infection is thought to be the most closely related to BA. This infection may cause disequilibrium of cytokine expression and reduction of regulatory T cells, resulting in an inflammatory response and subsequent bile duct injury.[5] Biliatresone, a natural toxin found in plants, can damage extrahepatic cholangiocytes through decreased glutathione and SOX17 levels.[19] Immune responses led by Th1, Th17, and Treg cells can also participate in the injury of the bile duct.[5] Genome-wide association studies were carried out and identified several genes as susceptibility factors of BA. A previous review has summarized common genetic variants in BA.[20] Many of these genetic variants, like ADD3 and GPC1,[21,22] can directly or indirectly cause biliary developmental defects and biliary tract damage. It is important to note that these triggers have been mostly studied in experimental models. Whether they can cause damage to the biliary tract in humans still warrants further investigation. An overview of how MMP-7 may be involved in the pathophysiology of BA is shown in Figure 1. Firstly, MMP-7 can degrade collagen type IV; fibronectin; gel-

Table 1. Clinical studies on MMP-7 from 2018 to 2023

Region	Cut-off value, ng/mL	Sensitivity, %	Specificity, %	Sample size of BA group	Sample size of non-BA cholestasis group	Reference
China	52.85	98.67	95.00	75	60	33
China	10.37	95.19	93.07	187	101	32
China	26.73	96.70	95.60	214	226	35
China	1.43	97.30	83.20	36	64	37
Japan	18.60	100.00	90.00	27	29	36
India	4.99	96.00	90.40	25	21	40
Iran	7.80	95.50	94.5	22	32	34
Iran	1.90	84.60	45.10	13	31	39
UK	69.00	68.00	93.00	32	27	38
Meta-analysis	/	96.00	91.00	–		31

BA, biliary atresia; MMP-7, matrix metalloproteinase-7; UK, United Kingdom.

atin type I, III, IV, and V; laminin; entactin; and elastin, leading to tissue remodeling.[23,24] Secondly, MMP-7 can promote inflammation through macrophages and neutrophils. MMP-7 can cleave latent tumor necrosis factor-alpha to its soluble form and subsequently induce infiltration of macrophages.[25] Besides, it can shed the ectodomain of syndecan-1, thereby establishing a local chemokine gradient that controls the influx and activation of neutrophils.[26,27] Finally, MMP-7 may play a crucial role in cell apoptosis. A study has shown that MMP-7 could shed and activate FAS ligands, thereby mediating epithelial cell apoptosis through FAS receptor.[28] Another study found that MMP-7 can also shed E-cadherin, which is a cell-cell adhesion molecule, leading to reduced cell-to-cell contact and subsequent cell apoptosis.[29,30] It can be seen from the above studies that MMP-7 may be involved in various aspects of the development of BA. However, further studies are required to confirm these findings.

The role of MMP-7 in the diagnosis of BA seems to be clear. The results of some important clinical studies on MMP-7 from 2018 to 2023 are shown in Table 1.[31–40] According to the systematic review by He *et al*.,[31] the sensitivity, specificity, and area under the curve of MMP-7 in the diagnosis of BA were 96%, 91%, and 0.9847, respectively. It is worth noting that the studies by Jiang *et al*.[32] and Yang *et al*.[33] were comparable, because they used the same enzyme-linked immunosorbent assay (ELISA) kit to detect serum MMP-7 concentration, both were conducted in China, and the median ages of the patients in the BA group were similar in the two studies. We found that the cut-off values produced by the two studies considerably differed. Although the sample size in the study by Jiang *et al*.[32] was larger compared to that of Yang *et al*.,[33] the former was a single-center study with fewer subjects from different regions. The subjects in the study by Jiang *et al*.[32] seemed to have more severe liver damage because they had higher ALT and AST levels. This suggests that patients' liver function may have an impact on the cut-off value of MMP-7. Grouping patients according to liver function and exploring their cut-off value of MMP-7 may be the direction of future research. Rohani *et al*.,[34] Chi *et al*.,[35] Sakaguchi *et al*.[36] and Wu *et al*.[37] used another kind of ELISA kit, but their cut-off values were also very different. The sample sizes of Rohani *et al*.,[34] Wu *et al*.[37] and Sakaguchi *et al*.[36] were relatively small and their cut-off values may not be accurate. Besides, the time point of blood sample collection, methods of sample storage, and the regions of the patients in these studies were different, along with the disease distribution in the control group. Interestingly, both Yang *et al*.[33] and Sakaguchi *et al*.[36] found that MMP-7 levels in patients were positively correlated with age, while Rohani *et al*.[34] suggested that there was no significant relationship between serum MMP-7 levels and age after adjusting for possible confounders (including GGT). Recently, Wu *et al*.[41] suggested that the age-adjusted MMP-7 ratio could distinguish between BA and cholestasis, but there was no significant improvement in its sensitivity and specificity. This may indicate that the degree of liver injury, rather than age, is a crucial factor affecting serum MMP-7 levels. Current studies in this field have been mainly conducted in Asia, and studies in other regions and cross-regional studies are lacking. A recent study in the UK has shown that MMP-7 may also hold significance in the diagnosis of BA among Western patients.[38] However, we found the sensitivity of MMP-7 in the diagnosis of BA was much lower in Western studies than in Asian studies, and the cut-off value was much higher. In addition to the use of different ELISA kits, this may also reflect ethnic differences in BA. Although most researchers have recognized the role of MMP-7 in the diagnosis of BA, some have questioned it. A study in Iran found the capability of the MMP-7 to distinguish BA from the non-BA cholestasis group fell significantly short of expectations.[39] We note that this study used a different ELISA kit compared to other studies. Besides, in this study, serum samples were stored at −20°C instead of −70°C or −80°C as in other studies, which may have led to protein degradation. The composition of disease in the control group may also be an important factor influencing the results. According to the study, non-BA cholestasis diseases such as inspissated bile syndrome, tyrosinemia, galactosemia, and hemophagocytic lymphohistiocytosis were included in the control group in this study, while the control group of the other studies did not involve these diseases. Therefore, studying the expression level of MMP-7 in other cholestatic diseases may help to improve the diagnostic accuracy of MMP-7 in BA.

Although the diagnostic significance of serum MMP-7 is steadily increasing, the ability of MMP-7 to assess the stage of liver fibrosis in children remains controversial. A study by Lertudomphonwanit *et al*.[16] determined that there was no significant correlation between serum MMP-7 s and the stage of liver fibrosis in patients, while Jiang *et al*.[32] and Chi *et al*.[35] reported contrasting findings. It is worth noting that Lertudomphonwanit *et al*.[16] and Jiang *et al*.[32] used different systems to evaluate histological fibrosis. Besides, Leung *et al*.[42] used shear wave velocity to measure liver stiffness, an

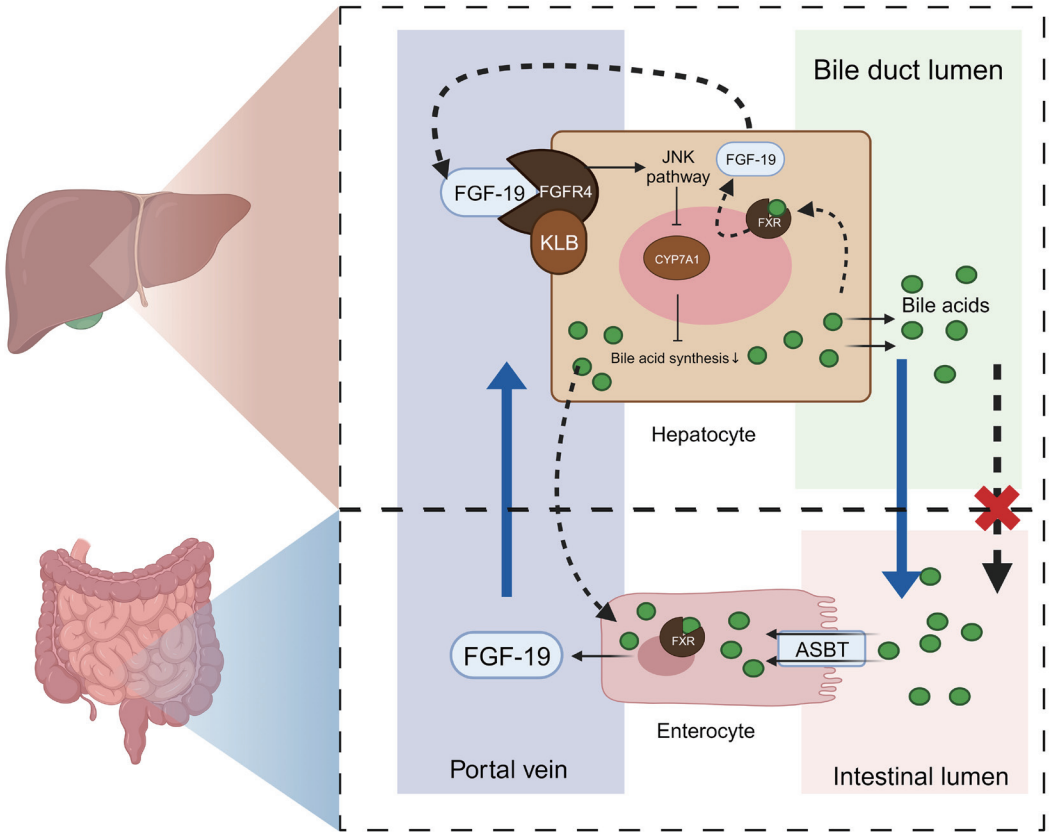

Fig. 2. Function of FGF-19 in physiological conditions and biliary atresia. Bile acids are synthesized in the liver and released into the duodenum after meals. When bile acids reach the distal ileal, they are transported into the enterocytes via the apical sodium-dependent bile acid transporter. After they get into enterocytes, FXR on the nucleus is signaled, leading to the transcription of FGF-19. FGF-19 reaches the liver via the portal circulation and binds to the fibroblast growth factor receptor-4–b-Klotho complex on hepatocytes. Subsequently, cholesterol 7 alpha-hydroxylase is inhibited due to the activation of the intracellular Jun N-terminal kinase pathway. As a result, the synthesis of bile acid is downregulated. However, bile acids cannot reach the distal ileal in BA. It seems that excess bile acids can activate FXR in hepatocytes and induce the expression of FGF-19, which may activate the fibroblast growth factor receptor-4–b-Klotho complex on the membrane of hepatocytes and downregulate bile acid synthesis. Besides, bile acids in systemic circulation may also induce enterocytes to secret FGF-19, leading to the upregulation of FGF-19 in serum. Dashed lines represent potential pathways in BA. (Figure created on biorender.com). FGF-19, fibroblast growth factor-19; JNK, Jun N-terminal kinase; FGFR4, fibroblast growth factor receptor 4; KLB, b-Klotho; CYP7A1, cholesterol 7 alpha-hydroxylase; FXR, farnesoid X receptor; ASBT, apical sodium-dependent bile acid transporter.

indirect measure of fibrosis. They found that MMP-7 significantly correlates with increased liver stiffness in patients with BA (n = 187), supporting the findings of Jiang *et al*.[32] and Chi *et al*.[35]

In addition, many researchers have tried to screen out high-risk children who may need liver transplantation after KPE based on their serum MMP-7 concentrations. Chi *et al*.[35] tracked dynamic changes in MMP-7 concentrations and patient prognosis in children with BA from diagnosis to liver transplantation. They summarized four patterns of MMP-7 changes in these patients after KPE and found that changes in serum MMP-7 concentrations were a significant predictor of survival with the native liver in 2 years at 6 weeks post-KPE and the most accurate predictor at 3 months post-KPE. However, Sakaguchi *et al*.[36] suggested that serum MMP-7 concentrations in patients before KPE as well as 1 and 4 weeks after KPE could not predict whether patients would need liver transplantation 1 year after KPE. According to Wu *et al*.,[37] serum levels of MMP-7 6 months after KPE may predict the need for liver transplantation in patients with BA during the first 3-4 years after KPE. These three studies tracked changes in MMP-7 concentrations after KPE at different times. Long-term detection of MMP-7 levels after KPE may be necessary for doctors to predict the prognosis of patients.

FGF-19

Cholestasis is one of the main characteristics of BA. Studies *in vivo* and *in vitro* have confirmed that the accumulation of bile acids in cholestasis can trigger a hepatocyte-specific inflammatory response, leading to damage of the hepatic tissue and fibrosis.[43] Fibroblast growth factor-19 (FGF-19) is an endocrine factor mainly secreted by the small intestine and plays an important role in the negative feedback regulation of bile acid synthesis.[44,45] It is mainly expressed in the small intestine and is not expressed in the liver under physiological conditions.[45–47] Figure 2 shows the function of FGF-19 in physiological conditions and BA. In healthy conditions, bile acids are synthesized in the liver and stored in the gallbladder. After a meal, they are released into the duodenum, and 95% of them are reabsorbed in the ileum.[45] Bile acids are transported into enterocytes via the apical sodium-dependent bile acid transporter.[48] Subsequently, bile acids signal the farnesoid X receptor (FXR), which facilitates the transcription of FGF-19.[49] FGF-19 reaches the liver via the portal vein

and interacts with fibroblast growth factor receptor-4 and coreceptor b-Klotho on the membrane of the hepatocytes.[48] Through subsequent activation of both extracellular signal-regulated kinase and Jun N-terminal kinase pathways, the transcription of the rate-limiting cytochrome P450 enzyme, cholesterol 7 alpha-hydroxylase, is downregulated, resulting in a downregulation of bile acid synthesis.[45,48] In BA, the enterohepatic circulation of bile acids is blocked. However, recent studies have shown that hepatocytes can also express FGF-19 during cholestasis.[50,51] Another study found that elevated circulating FGF-19 in patients with BA is of hepatic origin.[52] Since FXR is also expressed in hepatocytes,[48] we can infer that hepatocytes can express and secrete FGF-19 on their own in BA, resulting in reduced bile acid synthesis. Thus, FGF-19 may reflect the degree of cholestasis in BA. Furthermore, enterocytes can sense highly elevated levels of bile acids in the systemic circulation to induce FGF-19,[53] indicating that bile acids may also have the ability to activate intestinal FXR-FGF-19 from the basolateral side of enterocytes.

Recently, FGF-19 has been used to predict native liver survival in BA. Johansson *et al*.[52] found that serum FGF-19 was significantly reduced after KPE, particularly in the group of patients that went on to survive with their native liver at the age of 2 years.[52] They focused on the origin and changes of FGF-19 in the sera of patients with BA. However, their study only included 14 children. To further explore the value of FGF-19 as a biomarker for KPE outcomes, Nyholm *et al*.[54] analyzed the sera of 74 children with BA and found that patients with continued elevations of serum bilirubin after KPE had significantly higher serum levels of FGF-19 at KPE. When serum FGF-19 concentration at KPE exceeded 109 pg/mL, the native liver survival was significantly decreased, suggesting that the increased level of FGF-19 at KPE may indicate a poor prognosis. Importantly, this study revealed a positive correlation between serum primary bile acids and FGF-19 at the time of KPE. However, Johansson *et al*.[52] did not find this correlation. The discrepancy in the results of the two studies may be attributed to the administration of ursodeoxycholic acid, an antagonist to FXR. It also indicated that ursodeoxycholic acid may influence the synthesis of FGF-19. In addition, Nyholm *et al*.[54] suggested that serum FGF-19 was associated with ductular reaction in patients with BA. As FGF-19 has a direct ability to enhance proliferation, dedifferentiation, and transformation of cultured cholangiocytes,[55] the specific mechanism of FGF-19 in BA-related ductular reaction is worth exploring. Although the study by Nyholm *et al*.[54] had a relatively large sample size, their serum and biopsy samples were stored for more than 14 years. The degradation of protein and mRNA may have affected the accuracy of the results. Besides, the study by Nyholm *et al*.[54] did not track changes in FGF-19 in children with BA after KPE. If the serum level of FGF-19 and the degree of ductular reaction can be tracked after KPE, the relationship between FGF-19 and ductular reaction can be clearly demonstrated. Furthermore, according to Johansson *et al*.,[52] the change of FGF-19 after KPE may also be an important factor in predicting the prognosis of children with BA. Follow-up studies tracking the changes of FGF-19 in patients after KPE are required.

As increased serum FGF-19 levels may reflect liver injury and predict mortality in both primary biliary cholangitis and alcoholic hepatitis,[51,56] they could serve as potential prognostic biomarkers for BA. However, only two studies are insufficient to support the current conclusions. More studies with larger sample sizes from different regions are needed to verify the role of FGF-19 in BA. The role of FGF19 in ductular reaction also needs to be investigated, as FGF19 may also be a biomarker of bile duct injury in patients with BA.

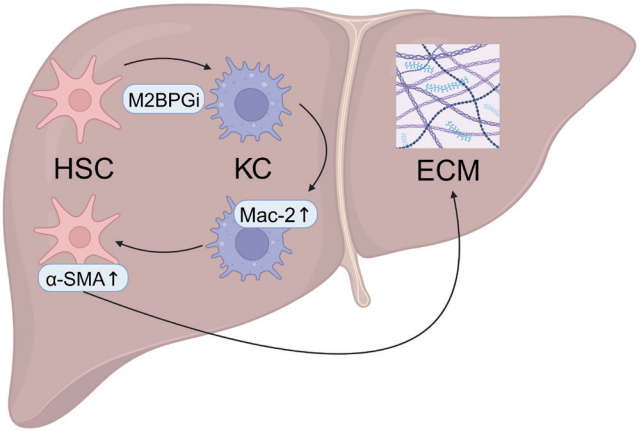

Fig. 3. Role of M2BPGi in the progression of liver fibrosis. Firstly, M2BPGi is secreted by HSCs. Next, M2BPGi enhances Mac-2 expression by KCs. Finally, Mac-2$^+$ KCs markedly increased α-SMA expression by HSCs, leading to the activation of HSCs and the production of extracellular matrix. (Figure created on biorender.com). M2BPGi, mac-2 binding protein glycan isomer; HSC, hepatic stellate cell; KC, kupffer cell; α-SMA, alpha-smooth muscle actin; ECM, extracellular matrix.

M2BPGi

Liver biopsy is still considered the gold standard for stratifying hepatic fibrosis.[57] However, this technique is invasive, and histologic interpretations may vary.[58] Mac-2 binding protein glycan isomer (M2BPGi), also called WFA-M2BP, is a novel marker of liver fibrosis, which has been confirmed in BA,[59] primary biliary cirrhosis,[60] autoimmune hepatitis,[61] and non-alcoholic fatty liver disease.[62,63] Although M2BPGi may be a common marker for evaluating liver fibrosis, M2BPGi COI values seem to differ among the causes of liver fibrosis.[64] Therefore, it is worth studying in BA.

M2BPGi is mainly secreted by hepatic stellate cells (HSCs) in liver fibrosis and is involved in the interaction between HSCs and Kupffer cells (KCs).[65] The role of M2BPGi in the progression of liver fibrosis is shown in Figure 3. Studies have found that HSCs are the source of M2BPGi.[65,66] Exogenous M2BPGi can enhance Mac-2 expression by KCs.[65] Furthermore, HSCs can be activated by KCs in the co-culture of HSCs and KCs. Activated HSCs differentiate into myofibroblast-like cells, characterized by the upregulation of alpha-smooth muscle actin (α-SMA).[67] These activated HSCs can produce extracellular matrix proteins and play an important role in liver fibrosis.[68] Inhibition of Mac-2 expression has been found to significantly impair the ability of KCs to enhance α-SMA expression by HSCs.[65] Therefore, M2BPGi may be a juxtacrine-acting messenger sent by HSCs to KCs during liver fibrosis.

Several studies from Japan have shown that M2BPGi shows great potential in the evaluation of liver fibrosis in BA. A study by Yamada *et al*.[59] may have been the first to examine the value of M2BPGi in patients with BA. The study included 64 children with BA who underwent living donor liver transplantation; their blood samples were collected the day before transplantation. It was found that M2BPGi showed the strongest ability to predict grade F4 fibrosis (METAVIR fibrosis scores) in children with BA. The area under the curve value of M2BPGi was 0.917. There was high sensitivity (94.1%) and specificity (92.3%) when the cut-off value was 3.53 (C.O.I). However, 79.7 % of patients in the study developed grade F4 fibrosis. There were very few children with mild liver fibrosis, which may have led to a biased conclusion. Ueno *et al*.[69]

Table 2. Studies on the diagnostic value of gamma-glutamyl transferase in biliary atresia

Region	Cut-off value, IU/L	Sensitivity, %	Specificity, %	Sample size of BA group	Sample size of non-BA cholestasis group	Reference
China	314	64.00	71.67	75	60	33
China	185	86.02	73.27	187	101	32
China	5.8*	78.60	79.60	1,512	216	75
China	350.0	59.30	85.40	150	575	74
China	216	83.33	84.37	36	64	37
Egypt	286	76.70	80.00	30	30	76
Iran	434.5	77.30	77.80	22	32	34
Iran	230	84.60	90.30	13	31	39
Meta-analysis	/	80.00	79.00	–		31

*The value here is In (GGT). BA, biliary atresia; GGT, gamma-glutamyltransferase.

used the same method to test serum M2BPGi of 37 children with BA and also found that the median M2BPGi in patients with F4 liver fibrosis was significantly higher compared to patients with F0–F3 liver fibrosis. Despite the small sample size, the liver fibrosis stage in their patients was more evenly distributed. Furthermore, Ueno *et al*.[70] tracked serum M2BPGi of 11 children with BA and suggested that the increase of serum M2BPGi in patients may be associated with the progression of liver fibrosis and the decline of liver function.

The research objects of the above three studies covered patients with BA who underwent liver transplantation, those with cirrhosis, and those with normal liver function. All results suggested that M2BPGi could help predict the stage of liver fibrosis in children with BA, especially in children with F4 liver fibrosis. To better understand the value of M2BPGi, studies from different regions with larger sample sizes and long-term follow-ups are warranted.

GGT

GGT is an enzyme that mainly exists in the cell membranes of the liver, kidney, pancreas, and other organs and plays an important role in the transport of amino acids.[71] It is generally considered a sensitive but not highly specific indicator of liver function and is widely used in clinical practice.[71] As the levels of GGT in the sera of BA patients are usually high,[16,72,73] GGT has been widely used for the diagnosis of BA in recent decades. A previous study has shown that serum levels of GGT>300 U/L or a daily increase of 6 U/L could distinguish BA from neonatal hepatitis, with an accuracy of 85% and 88%, respectively.[72] However, only 29 patients with BA were included in this study. In recent years, the diagnostic value of GGT in BA has been extensively studied, and some of the results are shown in Table 2.[31–34,37,39,74–76] A study by Rendon-Macias *et al*.[73] suggested that combining patient age with GGT levels could improve the reliability of diagnosis. However, the small sample size of their study affected the statistical power of the study. Chen *et al*.[77] enrolled 1,338 children with BA and 131 children with obstructive jaundice and divided them into different age groups, aiming to investigate the cut-off value of GGT in different age groups. Although a large number of patients were included in this study, information on patients younger than 30 days of age is lacking. Recently, Weng *et al*.[74] conducted a multicenter study that divided patients into different age groups. The cut-off value of GGT in patients younger than 30 days was reported in this study. Interestingly, Chen *et al*.[77] and Weng *et al*.[74] both found that the cut-off value of GGT peaks between 61 and 90 days after birth. This interesting finding may indicate that the diagnostic cut-off value of GGT is not simply positively correlated with age but fluctuates with age. Although GGT may not be as accurate as MMP-7 for the diagnosis of BA, it can be used as an alternative when MMP-7 testing is unavailable. Besides, the abovementioned studies were conducted mainly in China. Studies should be conducted in different regions to generalize the conclusion.

Circulating cytokines

The inflammatory response is one of the important reasons for biliary tract injury in patients with BA.[5] As circulating cytokines play an important role in immune inflammatory responses in the systemic and local environment, changes in these inflammatory molecules in serum are generally considered potential biomarkers of tissue damage, and damage to the hepatobiliary system is no exception.[78] Previous studies have confirmed the presence of an inflammatory response in the liver of patients with BA, which is mainly characterized by the excessive production of cytokines, including cytokines of T cells, macrophages, and other pro-inflammatory cells.[79] Recently, many researchers have attempted to use circulating cytokines as non-invasive biomarkers to diagnose BA and predict the post-KPE progression of patients.

Interleukin-8 (IL-8), a chemokine involved in neutrophil recruitment, is closely associated with bile duct response and liver fibrosis.[80–83] Studies have shown that IL-8 is highly expressed in the sera of patients with BA and is involved in disease progression.[84–86] Udomsinprasert *et al*.[87] studied the plasma of 82 children with BA and 25 healthy controls. They screened out 17 cytokines with high expression levels in the plasma of children with BA at the time of KPE. When the cut-off value of IL-8 was 2.29 pg/mL, the sensitivity and specificity of IL-8 for the diagnosis of BA were 90.2% and 92.0%, respectively. Furthermore, they found that patients with high plasma IL-8 levels had a significantly reduced survival rate. The primary disadvantage of this study is that the control group did not include patients with non-BA cholestasis. In a study by Godbole *et al*.,[83] which included 115 patients with BA, IL-8 was markedly overexpressed in the sera of these patients at the time of KPE compared with normal controls but was not correlated with the native liver survival rates of children after KPE. Madadi-Sanjani *et al*.[88] also found that IL-8 was not an effective predictor of the stage of cirrhosis and the need for liver transplantation in patients after KPE.

Thus, although IL-8 may be a potential auxiliary diagnostic indicator, its value in predicting native liver survival after KPE remains controversial. Further prospective cohort studies are required to validate the existing findings.

Interleukin-33 (IL-33) is a nuclear cytokine that is released after cell death as a consequence of severe tissue injury.[89] Previous reviews have explored the pathophysiological function of IL-33 in liver inflammation.[90,91] An early study by Dong *et al*.[92] included 18 infants with BA, 12 infants with non-icteric choledochal cysts (CCs), and 10 healthy controls (HCs) and suggested that the level of IL-33 expression in serum was significantly elevated in patients with BA, as compared with the CC and HC groups. Recently, Behairy *et al*.[93] found that serum IL-33 in patients with BA was significantly higher compared to patients with non-BA cholestasis and normal controls. When the cut-off value of IL-33 was 20.8 pg/mL, the specificity and sensitivity for the diagnosis of BA were 95% and 96.7%, respectively. At a cut-off value of ≥45.3 pg/ml, IL-33 can detect liver fibrosis of significant fibrosis (F3) with a specificity of 72.2% and a sensitivity of 66.7%. Although the study included only 30 patients with BA and 30 patients with non-BA cholestasis, it showed that IL-33 may assist in the diagnosis of BA and the evaluation of the grade of liver fibrosis. It is worth noting that Chen *et al*.[94] also explored the value of IL-33 in the diagnosis of BA in a sample size similar to that in the study by Behairy *et al*.[93] Interestingly, their cut-off values varied widely (20.8 pg/mL vs. 314.1 pg/mL), and the study by Chen *et al*.[94] reported much lower specificity and sensitivity. This disparity may be attributed to the different detection methods used in the two studies. Further investigation into this aspect is warranted.

In addition, other circulating cytokines may also have clinical value in the diagnosis and evaluation of BA. Chen *et al*.[94] screened Th17-related cytokines in the sera of patients with BA and found that the serum levels of macrophage inflammatory protein-3alpha (MIP3a) may also aid the diagnosis of BA, with a specificity of 80.00% and a sensitivity of 90.48%. Vejchapipat *et al*.[95] suggested that serum IL-18 levels significantly increased with the degree of jaundice in medium-term survivors of BA, while Urushihara *et al*.[96] also found that the change in serum IL-18 levels may related to the native liver survival of patients with BA. Wu *et al*.[97] found that a preoperative serum IL-12p40 level of >33 pg/mL can significantly predict 3-year survival with native liver. Adawy *et al*.[98] suggested that IL-13 receptor alpha 2 (IL-13Rα2) may reflect liver fibrosis in patients with BA. However, their studies only included a small number of cases in a single region and there is a lack of further research to validate their conclusions.

Other potential biomarkers

In addition to the above widely studied biomarkers, an increasing number of BA-related biomarkers are gradually being discovered, which may also hold potential diagnostic or prognostic value.

Biomarkers that can be used to diagnose BA have always been the focus of attention. Li *et al*.[99] found that human poliovirus receptor (PVR) expression was upregulated in the bile ducts of patients with BA and RRV-induced BA mice. Furthermore, PVR may be involved in the pathogenesis of BA by regulating the NK cell-mediated bile duct injury.[99] Besides, the concentration of PVR in the sera of children with BA was significantly higher than that in the sera of healthy controls. This suggests that PVR may be a potential biomarker of BA. However, more studies that compare the serum levels of PVR in patients with BA and non-BA cholestasis are warranted. Madadi-Sanjani *et al*.[100] found that serum caspase-3 activity in children with BA was significantly higher than that in other patients with non-BA cholestasis, suggesting that caspase-3 is also a potential biomarker of BA. Kong *et al*.[101] found increased expression of leukocyte cell-derived chemotaxin 2 (LECT2) mRNA in the liver tissues of children with BA. Another study found that LECT2 was also highly expressed in the sera of children with BA.[102] Dong *et al*.[103] used miRNA microarray analysis to screen differentially expressed microRNAs (miRNAs) in the sera of patients with BA and those with non-BA neonatal cholestasis. They found that the expression levels of miR-4429 were significantly downregulated whereas those of miR-4689 were significantly upregulated in the sera of patients with BA, suggesting that miR-4429 and miR-4689 could serve as potential diagnostic biomarkers of BA. Peng *et al*.[104] found that patients with BA had lower plasma levels of miR-140-3p compared to cholestatic disease controls. At the optimal threshold, their sensitivity and specificity in diagnosing BA were 66.7% and 79.1%, respectively. Similarly, a study by Zahm *et al*.[105] found that the miR-200b/429 cluster was significantly increased in the sera of patients with BA relative to infants with non-BA cholestatic disorders. These miRNAs appear to have a significant value in the diagnosis of BA, although studies with larger sample sizes are lacking.

Biomarkers that reflect liver fibrosis in BA are also being explored. Udomsinprasert *et al*.[106] showed that the serum cartilage oligomeric matrix protein (COMP) levels in children with BA were much higher compared to the healthy control group, and higher levels were positively correlated with liver stiffness and liver fibrosis. Xiao *et al*.[107] revealed that serum exosomal long non-coding RNA-H19 (lncRNA-H19) in children with BA is positively correlated with the severity of fibrosis liver injury. Yoneyama *et al*.[108] found that serum miR-214 levels were significantly increased in patients with BA having liver fibrosis stage F3–4, suggesting that serum miR-214 levels may be also used as a non-invasive predictor of liver fibrosis in BA.

In contrast, there are fewer novel serum biomarkers for predicting the native liver survival of patients with BA. In the study by Udomsinprasert *et al*.,[106] a significant reduction in survival rate was observed in patients with BA and high circulating COMP levels (cut-off value: 128.47 ng/mL). However, traditional biomarkers may be useful in predicting the prognosis of patients with BA. Huang *et al*.[109] conducted a retrospective chart review of 90 patients with BA and concluded that serum total bilirubin ≤ 4.85 mg/dL at 1 week after HPE can predict a higher chance of native liver survival. Recently, Harpavat *et al*.[110] measured total serum bile acid levels of 137 patients 6 months after KPE and found that patients with levels of ≤ 40 μmol/L had better liver function, fewer complications, and lower cumulative incidence of liver transplant/death.

The biomarkers mentioned in this chapter also have great potential in clinical practice, but most of them lack follow-up studies to confirm their clinical values. Besides, their role in the pathophysiology of BA needs to be explored.

Comparison and summary

An increasing number of serum biomarkers with diagnostic and prognostic value in BA have been discovered and promoted in recent years. Most of them are listed in Table 3,[16,31–37,40,42,52,54,59,69,70,72,75–77,83,87,92–100,102-108,110–113] including all the biomarkers mentioned in this review. Among them, MMP-7 is currently the most reliable biomarker for the diagnosis of BA, which may help clinicians assess the stage of liver fibrosis and predict post-KPE outcomes to a certain extent. Some studies have evaluated the diagnostic value of

Table 3. Emerging serum biomarkers of biliary atresia

Function	Biomarker	Reference
Diagnosis	MMP-7	16,31–37,40
	GGT	31–34,37,72,75–77
	IL-33	92–94
	MIP3a	94
	PVR	99
	Caspase-3	100
	LECT2	102
	miR-4429 and miR-4689	103
	miR-140-3p	104
	miR-200b/429	105
Assessing liver fibrosis	MMP-7	32,35,42
	M2BPGi	59,69,70
	APRi	59,111–113
	IL-13Rα2	98
	COMP	106
	lncRNA-H19	107
	miR-214	108
Predicting native liver survival after KPE	MMP-7	35,36
	FGF-19	52,54
	Total bile acid	110
	IL-8	83,87
	IL-18	95,96
	IL-12p40	97
	COMP	106

There was a duplication of references between biomarkers because some studies involved multiple biomarkers at the same time. MMP-7, matrix metalloproteinase-7; FGF-19, fibroblast growth factor-19; M2BPGi, mac-2 binding protein glycan isomer; GGT, gamma-glutamyltransferase; IL, Interleukin; lncRNA, long non-coding RNA; miRNA, microRNA; MIP3a, macrophage inflammatory protein-3alpha; PVR, human poliovirus receptor; LECT2, leukocyte cell-derived chemotaxin 2; COMP, cartilage oligomeric matrix protein; APRi, aspartate aminotransferase to platelet ratio index.

GGT while studying MMP-7.[32–34,37] They also concluded that compared to GGT, MMP-7 showed better sensitivity and specificity for diagnosing BA. However, efforts to improve the diagnostic reliability of GGT are still necessary, because measurement of MMP-7 is not available in most cases. Besides, other biomarkers like circulating cytokines and miRNAs also have potential in the diagnosis of BA. Further studies to confirm their role are warranted.

FGF-19 is a new predictor of outcomes in BA. Although there is little research on FGF-19, it still shows strong potential as a prognostic biomarker. Previously, clinicians often followed serum levels of bilirubin to predict disease progression after KPE.[114–116] A recent study by Harpavat *et al*.[110] found that total serum bile acid levels 6 months after KPE were related to a lower cumulative incidence of liver transplant/death, indicating that serum bilirubin levels after KPE can reliably predict poor outcomes, including complications from progressive liver disease and the invariable need for a liver transplant. According to a study by Nyholm *et al*.,[54] serum FGF-19 levels at the time of KPE can be used to predict native liver survival of children with BA. Compared with total serum bile acid, FGF-19 may be able to reflect the prognosis of patients with BA at an earlier stage and may also reflect the degree of ductular reaction. However, the cut-off value of FGF-19 in predicting native liver survival and the ability to predict complications after KPE still remain to be explored.

The role of M2BPGi in the evaluation of liver fibrosis in BA is often compared with aspartate aminotransferase to platelet ratio index (APRi). APRi was first proposed by Wai *et al*.[117] to assess liver fibrosis in chronic hepatitis C and was widely used for the assessment of BA in the past few years.[111–113,118,119] A study by Yamada *et al*.[59] reported that M2BPGi had a better diagnostic ability to detect fibrosis of the native liver with grade F4 fibrosis compared to APRi when using the METAVIR fibrosis score. Although the ages of the patients in this study and another study by Ueno *et al*.[69] varied considerably, the latter study also reported similar findings. This indicates that M2BPGi shows a higher accuracy in predicting F4 liver fibrosis in BA. It is also important to note that these studies did not include children with BA diagnosed less than 3 months ago. Early assessment of the stage of liver fibrosis in children with BA would facilitate the selection of children directly for liver transplantation, avoiding KPE wherever appropriate.

We are excited to see more and more biomarkers associated with BA being discovered. As clinical studies advance,

there is an urgent need to understand the role of these biomarkers in the development and progress of the disease. For example, our understanding of MMP-7 is mostly based on studies on other diseases,[17] and there is still a lack of research in BA. This knowledge gap also exists with regard to biomarkers like FGF-19, M2BPGi, and several others. Therefore, elucidating the pathophysiological role of biomarkers in BA will be an important area of future research.

In conclusion, MMP-7 is currently the most reliable biomarker for the diagnosis of BA. FGF-19 and M2BPGi are novel biomarkers for evaluating native liver survival and liver fibrosis in patients with BA, respectively. GGT and other circulating cytokines could serve as potential diagnostic biomarkers of BA. However, more high-quality, large-size, multicenter clinical trials are warranted to confirm the value of these biomarkers and to elucidate their pathophysiological role in BA.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Conceptualization, writing of original draft, reviewing, and editing (FK); and conceptualization, reviewing, and editing (RD, GC, SS, YY, JJ, LM, HC, JZ, and SZ). All authors approved the final version of the manuscript.

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