

Serum Transforming Growth Factor- β , Matrix Metalloproteinase-7, and Acoustic Radiation Force Impulse Elastography for Staging Liver Fibrosis in Children with Biliary Atresia: A Cross-Sectional Study

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ABSTRACT

Introduction: Biliary atresia (BA) is the leading cause of pediatric cholestatic liver disease and liver transplantation, and its prognosis is driven by hepatic fibrosis. Liver biopsy remains the reference standard for fibrosis staging but is invasive, underscoring the need for noninvasive alternatives. This study evaluated the association between serum levels of transforming growth factor- β (TGF- β) and matrix metalloproteinase-7 (MMP-7) and acoustic radiation force impulse (ARFI) elastography with the histological fibrosis stage in children with BA.

Methods: This cross-sectional study enrolled children with suspected BA-related cholestasis at a national tertiary referral hospital in Jakarta, Indonesia, between January and June 2023. Serum TGF- β and MMP-7 levels were measured using enzyme-linked immunosorbent assay, and liver stiffness was assessed using ARFI elastography. Fibrosis was staged using liver biopsy and the Laennec scoring system, and dichotomized as F2–F3 or F4.

Results: Fifteen patients (10 girls; median age, 5 months) were analyzed; six had F2–F3 and nine had F4 fibrosis. Median TGF- β was marginally higher in F4 than in F2–F3 (1.081 vs. 1.057 ng/mL; $p = 0.77$), and MMP-7 did not differ between the groups ($p = 0.41$). ARFI staging agreed with histology in 13 of 15 patients (86.7%; $\kappa = 0.72$; $p = 0.011$), yielding 88.9% sensitivity and 83.3% specificity for F4.

Conclusion: In this cohort, serum TGF- β and MMP-7 did not discriminate between advanced and intermediate fibrosis, whereas ARFI elastography showed agreement with histology. ARFI, a promising minimally invasive tool for fibrosis staging in BA, warrants validation in prospective cohorts.

Biliary Atresia, Liver Fibrosis, Transforming Growth Factor-B, Matrix Metalloproteinase-7, Acoustic Radiation Force Impulse, Laennec Score

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INTRODUCTION

Biliary atresia (BA) is a progressive fibro-obliterative cholangiopathy of infancy that affects both the extra- and intrahepatic biliary tree [1]. If left untreated, the resulting cholestatic injury rapidly progresses to biliary cirrhosis, portal hypertension, and end-stage liver disease, and most affected children die within the first two years of life [2]. BA is the most frequent cause of neonatal cholestatic jaundice, accounting for approximately 25–30% of cases, and remains the leading indication for liver transplantation in the pediatric population [3]. Even after timely Kasai portoenterostomy (KPE), a considerable proportion of children experience ongoing fibrogenesis and ultimately require transplantation, which positions hepatic fibrosis as the principal determinant of long-term outcomes [4].

The histopathological hallmarks of BA reside in the portal tracts and comprise large-duct obstructive cholangiopathy, portal expansion with edematous fibroplasia, and ductular proliferation, with bile plugs and portal stromal edema representing the strongest histological predictors of the disease [5]. Accurate staging of fibrosis is clinically consequential because it informs prognostication, the need for and timing of therapy, screening and surveillance strategies, and the assessment of treatment response [6]. The Laennec scoring system refines conventional staging by subclassifying cirrhosis into stages 4A, 4B, and 4C according to septal thickness and nodule size, and these subclasses correlate with clinical stage and the severity of portal hypertension [7]. Nevertheless, liver biopsy is invasive, generally requires sedation in infants, carries a risk of bleeding, and is vulnerable to sampling error, which limits its suitability for repeated assessment [8]. These limitations have stimulated the search for non-invasive serum biomarkers that are safer, less costly, and suitable for serial monitoring [9]. Transforming growth factor- β 1 (TGF- β 1) is the archetypal profibrogenic cytokine: it drives the transdifferentiation of hepatic stellate cells (HSCs) into collagen-producing myofibroblasts, promotes extracellular matrix (ECM) deposition, and orchestrates macrophage infiltration, glycolytic induction, and epigenetic reprogramming during hepatic fibrogenesis [10]. Increased serum and tissue TGF- β 1 has been documented in children with BA [11]. Matrix metalloproteinase-7 (MMP-7), a protease involved in tissue remodeling and released by injured cholangiocytes, has more recently emerged as a sentinel marker of biliary epithelial injury, with high accuracy in distinguishing BA from other causes of neonatal cholestasis [12-14]. A systematic review and meta-analysis identified MMP-7, together with interleukin-33 and gamma-glutamyl transferase (GGT), as useful biomarkers for differentiating BA before KPE [15]. and several cohorts have linked elevated MMP-7 to the severity of liver fibrosis and native-liver outcome after KPE [16,17].

In parallel, ultrasound-based elastography has gained traction as an imaging alternative to biopsy. Acoustic radiation force impulse (ARFI) elastography quantifies liver stiffness by generating shear waves within the parenchyma and measuring their propagation velocity, and can be incorporated into a standard abdominal ultrasound examination [18]. In infants with suspected BA, ARFI shear-wave velocity correlates strongly with histological fibrosis and reliably predicts advanced fibrosis before KPE [19]. The technique also performs well in detecting hepatic fibrosis and portal hypertension in other chronic liver diseases [20]. Despite these advances, most available evidence originates from East Asian, European, and North American centers, and few studies have evaluated circulating biomarkers and elastography simultaneously against histology within the same pediatric BA cohort; such data remain scarce for Indonesian children. Therefore, this study aimed to evaluate the association of serum TGF- β , serum MMP-7, and ARFI elastography with the degree of liver fibrosis determined by the Laennec histopathological score in children with BA.

METHODS

Study Design and Setting

This cross-sectional study was conducted in the pediatric inpatient wards of a national tertiary referral hospital in Jakarta, Indonesia, between January and June 2023. The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

Participants

All pediatric patients aged <18 years who were admitted with cholestasis suspected to be caused by BA and who underwent liver biopsy, either percutaneously or during intraoperative cholangiography, during the study period were eligible, provided that their parents or legal guardians signed a written informed consent. Patients with acute or acute-on-chronic liver failure were excluded. Patients who had undergone one or more, but not all, of the index examinations were considered dropouts and were excluded from the analysis.

Data Collection

Primary data were obtained through history taking and physical examination, and secondary data, including demographic characteristics, anthropometry, and laboratory parameters (hemoglobin, leukocyte and platelet

counts, aminotransferases, bilirubin fractions, albumin, GGT, and alkaline phosphatase), were retrieved from the medical records.

Serum Biomarker Measurement

Venous blood samples were collected, and serum was separated and stored until analysis. Serum TGF- β and MMP-7 concentrations were quantified using commercial enzyme-linked immunosorbent assay (ELISA) kits, according to the manufacturer's instructions.

ARFI Elastography

ARFI elastography was performed by a designated, experienced operator. The shear-wave velocity (m/s) was measured in the right hepatic lobe, and the median of the valid measurements was recorded. ARFI results were categorized into fibrosis stages F2–F3 or F4 using predefined cut-off values.

Histopathological Assessment

Liver specimens were processed for routine histology and evaluated by experienced pathologists. Fibrosis was graded using the Laennec scoring system (Table 1). Because no patient had stage F0–F1 fibrosis, the patients were categorized into two groups: F2–F3 and F4 (stages 4A–4C).

Table 1. Laennec scoring system for histological staging of liver fibrosis

Stage	Name	Septa	Criteria	Score
0	No definite fibrosis	–	–	0
1	Minimal fibrosis	+/-	No septa or rare thin septa; possible portal expansion or mild sinusoidal fibrosis	1
2	Mild fibrosis	+	Occasional thin septa; possible portal expansion or mild sinusoidal fibrosis	2
3	Moderate fibrosis	++	Moderate number of thin septa; up to incomplete cirrhosis	3
4A	Cirrhosis, mild (definite or probable)	+++	Marked septation with rounded contours or visible nodules; most septa thin (one broad septum allowed)	4
4B	Moderate cirrhosis	++++	At least two broad septa, but no very broad septa and fewer than half of the biopsy length composed of minute nodules	5
4C	Severe cirrhosis	+++++	At least one very broad septum or more than half of the biopsy length composed of minute nodules (micronodular cirrhosis)	6

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA). The normality of numerical variables was assessed; normally distributed data are presented as mean $\pm$ standard deviation (SD) and non-normally distributed data as median (minimum–maximum). Differences in numerical variables between the two fibrosis groups were analyzed using the Mann–Whitney U test. The association between categorical variables was analyzed using the chi-square test or Fisher's exact test when any expected cell count was <5 . Agreement between ARFI and histological staging was quantified using Cohen's kappa (κ), and the sensitivity, specificity, and predictive values of ARFI for F4 fibrosis were calculated with histology as the reference standard. All tests were two-sided, and $p < 0.05$ was considered statistically significant.

Ethical Considerations

The study protocol was approved by the Institutional Health Research Ethics Committee and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the parents or legal guardians of all participants.

RESULTS

During the study period, 20 patients met the inclusion criteria and were invited to participate. Five patients were excluded because they did not complete the full study protocol, leaving 15 patients for the final analysis. Five patients (33.3%) were boys and ten (66.7%) were girls. The median age was 5 months (range, 1–38 months), and all participants had a clinical diagnosis of BA at the time of the study. Based on liver biopsy, six patients (40.0%) had F2–F3 fibrosis and nine (60.0%) had F4 fibrosis. The baseline clinical and laboratory characteristics are summarized in Table 2.

Table 2. Baseline characteristics of study participants (n = 15)

Characteristic	Value
Sex, male : female, n	5 : 10
Age (months)*	5 (1–38)
Body weight (kg)*	5.90 (4.00–15.00)
Hemoglobin (g/dL)	9.34 ± 1.69
Leukocytes (×10 ³ /μL)*	13.80 (3.47–64.00)
Platelets (×10 ³ /μL)*	179 (33–851)
AST (U/L)	136.20 ± 66.35
ALT (U/L)	79.13 ± 25.83
Total bilirubin (mg/dL)*	2.53 (0.28–11.78)
Direct bilirubin (mg/dL)	13.09 ± 10.14
Indirect bilirubin (mg/dL)	9.38 ± 7.08
Albumin (g/dL)	3.40 ± 0.92
GGT (U/L)*	338 (67–2032)
ALP (U/L)	403.23 ± 145.55

Note: Data are presented as mean ± SD or *median (minimum–maximum) for non-normally distributed variables. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.

The serum TGF-β concentrations ranged from 0.171 to 6.288 ng/mL, with a mean of 1.665 ng/mL. TGF-β showed a numerical increase with advancing histological fibrosis, from a median of 1.057 ng/mL in the F2–F3 group to 1.081 ng/mL in the F4 group; however, the difference was not significant ($p = 0.77$). Serum MMP-7 levels were 6.48 ± 8.78 ng/mL in the F2–F3 group and 6.06 (0.24–30.11) ng/mL in the F4 group, with no significant difference between the groups ($p = 0.41$) (Table 3).

Table 3. Serum TGF-β and MMP-7 according to histological fibrosis stage

Biomarker	F2–F3 (n = 6)	F4 (n = 9)	p-value†
TGF-β (ng/mL)*	1.057 (0.171–4.532)	1.081 (0.298–6.208)	0.77
MMP-7 (ng/mL)	6.48 ± 8.78	6.06 (0.24–30.11)*	0.41

Note: Data are presented as mean ± SD or *median (minimum–maximum). †Mann–Whitney U test. MMP-7, matrix metalloproteinase-7; TGF-β, transforming growth factor-β.

ARFI elastography classified two patients (13.3%) as F2, four (26.7%) as F3, and nine (60.0%) as F4. ARFI staging was concordant with histology in 13 of 15 patients (86.7%); one patient with histological F2–F3 fibrosis was upstaged to F4 by ARFI, and one patient with histological F4 fibrosis was downstaged to F2–F3. The association between ARFI and histological staging was statistically significant ($p = 0.011$) and showed a substantial agreement ($\kappa = 0.72$). For the detection of F4 fibrosis, ARFI had a sensitivity of 88.9% (8/9), specificity of 83.3% (5/6), positive predictive value of 88.9% (8/9), and negative predictive value of 83.3% (5/6) (Table 4), respectively.

Table 4. Cross-tabulation of ARFI elastography and histological fibrosis stage

ARFI stage	Histology F2–F3	Histology F4	Total	p-value†
F2–F3	5	1	6	0.011
F4	1	8	9	
Total	6	9	15	

Note: †Fisher's exact test. Overall agreement, 86.7%; Cohen's $\kappa = 0.72$. ARFI, acoustic radiation force impulse.

DISCUSSION

In this cross-sectional study of children with BA, ARFI elastography showed substantial agreement with histological fibrosis staging, whereas serum TGF- β and MMP-7 levels did not discriminate between intermediate (F2–F3) and advanced (F4) fibrosis. Although TGF- β displayed a numerical upward trend with increasing fibrosis stage, neither serum biomarker reached statistical significance in this cohort.

Girls outnumbered boys by a ratio of approximately 2:1 in our cohort, in line with the slight female predominance described in the epidemiological series of BA [21]. The mean age of 9.7 months reflects the age at data collection rather than at symptom onset or diagnosis, because most patients had received initial care at referring hospitals before transfer to our center. This observation underscores the importance of early recognition and evaluation of cholestatic jaundice in infancy, as advocated by international guidelines [22]. The success of KPE declines with advancing age and fibrosis [3,4]. We found no significant association between serum MMP-7 and histological fibrosis stage. The MMP-7 levels observed here were considerably lower than those reported [16], and fall within a very wide spectrum of published diagnostic thresholds, ranging from approximately 1.43 ng/mL in a Taiwanese cohort to 52.8 ng/mL on a single-plex platform in a large North American cohort [23]. The Childhood Liver Disease Research Network explicitly demonstrated that MMP-7 cut-off values differ according to assay technology [23]. Therefore, differences in quantification methods and ELISA kits likely contribute to the discrepancy between our values and those of previous studies. Differences in fibrosis stratification are also relevant: we used a histological score dichotomized into F2–F3 and F4, whereas Kerola et al. applied a different categorization of fibrosis severity [16]. Biologically, MMP-7 is primarily a marker of cholangiocyte injury and is most accurate for diagnosing BA at presentation [15]. Its relationship with fibrosis is modulated by disease stage and biliary drainage after KPE [24]. The absence of F0–F1 cases in our cohort further restricted the spectrum of fibrosis and reduced the ability to detect a gradient.

Serum TGF- β increased numerically from the F2–F3 to the F4 group, a positive trend that is consistent with the linear rise in TGF- β 1 across fibrosis stages reported [25]. This trend is biologically plausible, as TGF- β 1 participates in virtually every key step of hepatic fibrogenesis, including HSC activation, hepatocyte apoptosis, ECM production, and the induction of other profibrogenic mediators such as connective tissue growth factor [26,27]. However, TGF- β is not a liver-specific or fibrosis-specific marker. TGF- β signaling operates at all stages of chronic liver injury, from inflammation to fibrosis, cirrhosis, and hepatocarcinogenesis, and exerts pleiotropic, context-dependent effects on immunity, cell proliferation, and tissue repair [28,29]. Illustrating this complexity, Vejchapipat et al. observed higher serum TGF- β 1 levels in post-KPE BA patients with good outcomes than in those with persistent jaundice, suggesting a reparative role [26]. These factors, together with the small sample size, likely explain why the observed trend did not reach significance and suggest that serum TGF- β alone is insufficient for fibrosis staging in BA. In contrast, ARFI elastography correctly classified 13 of 15 patients, with only one overstaged and one understaged case. This performance is concordant with the findings of Takahashi et al., who reported a significant association between ARFI shear-wave velocity and fibrosis stage, with cut-off values of 1.34 m/s for F2–F4, 1.44 m/s for F3–F4, and 1.80 m/s for F4 [30]. A meta-analysis of 29 diagnostic studies further concluded that ARFI has satisfactory diagnostic accuracy for liver fibrosis in non-viral liver diseases, particularly for stages F3 and F4 [31]. In pediatric BA specifically, ARFI values correlate strongly with histological fibrosis ($r > 0.70$) [18], and reliably identify advanced fibrosis before KPE [19]. Moreover, ultrasonography is recommended as a first-line investigation in cholestatic infants because it is inexpensive, free of ionizing radiation, and usually does not require sedation [22]. Incorporating ARFI into this examination adds fibrosis information at minimal additional cost.

From a clinical perspective, our findings support a complementary rather than competing role for these modalities. Serum MMP-7 appears to be best suited for the early diagnosis of BA [15], whereas ARFI elastography may serve as a non-invasive tool for fibrosis staging, risk stratification, and serial monitoring after KPE, potentially reducing the need for repeated biopsies in selected patients [32]. In resource-limited settings, where access to repeated histological assessments is constrained, the integration of ARFI into routine ultrasonography may be particularly valuable. This study has several limitations. First, the sample size was

small and derived from a single center, which limits the statistical power and generalizability; therefore, the results should be regarded as preliminary. Second, no patient had F0–F1 fibrosis, introducing spectrum bias and preventing the evaluation of these modalities in early fibrosis. Third, the cohort was heterogeneous with respect to age at sampling and KPE status, both of which may influence biomarker levels and liver stiffness [32]. Fourth, ARFI is operator-dependent, and its accuracy is lower for early fibrosis and for discriminating between adjacent stages [31]. Finally, receiver operating characteristic analysis to derive population-specific cut-off values was not feasible in this study. Future multicenter studies with larger samples that include the full fibrosis spectrum, standardized ARFI protocols and operator training, homogeneous pre-KPE populations, and formal diagnostic accuracy analyses are warranted to confirm these findings.

CONCLUSION

In children with BA, serum TGF- β showed a non-significant positive trend with fibrosis stage, and serum MMP-7 was not associated with histological fibrosis; neither biomarker alone was adequate to stage fibrosis. ARFI elastography demonstrated substantial agreement with Laennec histological staging and represents an effective, minimally invasive tool for assessing liver fibrosis in BA. Larger prospective studies are required to validate these findings and establish population-specific cut-off values.

DECLARATIONS

None

CONSENT FOR PUBLICATION

The Authors agree to be published in the Journal of Society Medicine.

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COMPETING INTERESTS

The authors declare no conflicts of interest in this case report.

AUTHORS' CONTRIBUTIONS

All authors have read and approved the final version of the manuscript and agree to be held accountable for all aspects of the work presented.

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