BMC Gastroenterology

RESEARCH

Open Access

Strain elastography for detecting advanced Fontan-associated liver disease: a retrospective study

Koji Imoto[1], Takeshi Goya[1], Yuki Azuma[1], Tomonobu Hioki[1], Tomomi Aoyagi[1], Hazumu Nagata[3], Akiko Nishizaki[2], Takamori Kakino[2], Ayako Ishikita[2], Kenichiro Yamamura[3], Ichiro Sakamoto[2], Masatake Tanaka[1*], Kohtaro Abe[2] and Yoshihiro Ogawa[1]

Abstract

Background The Fontan procedure has improved the prognosis of patients with a functional single ventricle; however, late complications—including Fontan-associated liver disease (FALD)—have surfaced as clinical concerns. FALD with signs of portal hypertension has been defined as advanced FALD (aFALD) due to its poor prognosis. Recently, noninvasive tests (NITs) have been found to predict liver fibrosis in FALD. Liver stiffness measurement excluding strain elastography (SE) was affected by hepatic congestion; however, to our knowledge, not many studies have evaluated the SE-derived Liver Fibrosis Index (LFI). This study aimed to determine the efficacy of NITs, especially LFI, for discriminating aFALD.

Methods In this retrospective study, 46 Japanese patients with FALD were included and classified into the aFALD (33 patients; 22 males and 11 females; median age: 28.0 years) and non-aFALD (13 patients; seven males and six females; median age: 22.0 years) groups based on the presence/absence of signs of portal hypertension.

Results The platelet count, FIB-4 index, Forns index, and LFI differed significantly between the two groups and demonstrated moderate accuracy for discriminating aFALD. The shear wave velocity (Vs) measured by Shear Wave Elastography (SWE) did not differ significantly between the two groups. The cut-off value of platelet counts below 185×10^3/μL had 78.8% sensitivity and 92.3% specificity. While 25/26 (96.2%) of the patients with FALD who had platelet counts below 185×10^3/μL were aFALD, 8/20 (40.0%) of the patients with FALD who had platelet counts above below 185×10^3/μL were also aFALD, indicating the need for additional markers. In the patients with FALD who had platelet counts above 185×10^3/μL, only SE indicated moderate diagnostic accuracy, and the LFI cut-off value of 2.21 had 100% sensitivity and 75.0% specificity.

Conclusions Using a two-step approach, discriminating aFALD with platelet counts below 185×10^3/μL by platelets alone, and for those with higher platelet counts, requiring LFI > 2.21 could discriminate aFALD with high accuracy. Early detection of aFALD and early intervention, including testing for aFALD, may lead to an improved prognosis of aFALD.

Keywords FALD, Fibrosis, Elastography, Portal hypertension

*Correspondence:
Masatake Tanaka
tanaka.masatake.656@m.kyushu-u.ac.jp
Full list of author information is available at the end of the article

Introduction

The Fontan procedure—a palliative operation widely performed in patients with single-ventricle congenital heart disease—has drastically improved the prognosis of these patients [1]. The procedure causes systemic venous return into the pulmonary circulation directly, and these long-term circulation alterations harm various organs [1, 2]. Liver damage in this context is known as Fontan-associated liver disease (FALD) [3]. The precise incidence of FALD is unknown due to the lack of a uniform definition of FALD; however, liver fibrosis develops in almost all patients with Fontan circulation [4–8]. The incidence of advanced liver fibrosis and cirrhosis increases in the years following the Fontan operation [4, 5, 8–10], increasing the risk of hepatocellular carcinoma (HCC) [9–13].

A liver biopsy is considered the gold standard for diagnosing and staging FALD fibrosis. However, it is invasive and has been linked to sampling error as well as intraobserver and interobserver variability [14, 15]. Furthermore, individuals with FALD are frequently treated with anticoagulants and/or antiplatelet medications, making liver biopsy a risky procedure for them. Recently, non-invasive tests (NITs)—including serum markers, non-invasive scores, and liver stiffness measurement (LSM)—have been shown to aid in estimating liver fibrosis in chronic liver diseases caused by HBV, HCV, and metabolic dysfunction-associated steatohepatitis [16]. There have been numerous reports on NITs for assessing liver fibrosis in FALD; however, the reported NITs varied, and the results were inconsistent across these studies [4–6, 17–20]. Recent studies conducted on a relatively large number of patients with FALD who had undergone liver biopsy revealed that platelet counts and non-invasive scores containing the platelet count as one of the variables—such as the AST-to-platelet ratio (APRI) and FIB-4 index—correlated with the severity of liver fibrosis [8, 21, 22].

Liver stiffness measurement (LSM) is divided into two categories: magnetic resonance elastography (MRE) and ultrasonography (US)-based elastography, which are further divided into three methods: transient elastography (TE), shear wave elastography (SWE), and strain elastography (SE) [23]. LSM is a well-established tool for estimating the stage of liver fibrosis in chronic liver disease [23], and its utility in patients with FALD has been investigated using MRE [24–31], TE [17, 21, 32–42], and SWE [18, 43–45]. However, it has been demonstrated that the liver stiffness of MRE, TE, and SWE was increased by hepatic congestion in patients without liver fibrosis [46–54] and the Fontan operation itself [55, 56]. A recent study found that MRE and SWE were unrelated to the grade of liver fibrosis in a relatively large cohort of patients with FALD who had undergone biopsies [22]. Conversely, SE is less affected by inflammation [57] and hepatic congestion [58, 59]. Therefore, SE might be effective in diseases affected by liver congestion such as FALD. However, few studies have examined its utility in the context of FALD since SE is not yet as widespread as SWE and TE. Furthermore, it was reported that combinational elastography, which assesses SWE and SE simultaneously, had a higher predictive ability than SWE alone in distinguishing fibrosis stages in patients with cholestatic liver diseases [60] and chronic hepatitis B [60]. Therefore, we used combinational elastography to assess the liver status of patients with FALD in this study.

Patients with FALD who had clinical signs of portal hypertension, such as varices, ascites, and splenomegaly, showed a significantly higher mortality rate, need for liver transplantation, and HCC incidence than those without clinical manifestations [61–63]. Thus, it was proposed that FALD with signs of portal hypertension should be defined as advanced FALD (aFALD) [63]. This study aimed to assess the usefulness of NITs, especially SE, in discriminating aFALD.

Patients and methods

Patients

This retrospective study included 46 Japanese patients with FALD who underwent ultrasound (US) elastography and cardiac catheterization within a standardized protocol at Kyushu University Hospital between February 2017 and August 2023. Fourteen patients with FALD who did not undergo or underwent more of the following: laboratory testing, ultrasound elastography, cardiac catheterization, and imaging examinations were excluded. Thirty-three patients had aFALD and 13 patients had non-aFALD (Table 1). The median age of the patients was 28.0 years in the aFALD group and 22.0 years in the non-aFALD group. The proportion of males was 66.7% (22/11) in the aFALD group and 53.8% (7/6) in the non-aFALD. All patients underwent screening tests to rule out other liver diseases besides FALD, such as antinuclear antibodies, antimitochondrial antibodies (AMA), hepatitis B surface antigen, anti-hepatitis C antibody, free T4, and thyroid-stimulating hormone. An abdominal US was performed to rule out liver injury caused by fatty liver, a liver tumor, or bile duct obstruction. Liver injury from alcohol or drugs was also ruled out. In addition to the results of these tests, patients with FALD were defined as those with γ-GTP elevation and/or radiological abnormalities more than 10 years after surgery. FALD with clinical, endoscopic, or radiological signs of portal hypertension (varices, portosystemic collaterals, ascites, or splenomegaly) due to liver fibrosis was defined as aFALD [63]. The study was conducted per the principles outlined in the Declaration of Helsinki and authorized

Table 1 Clinical characteristics and hemodynamic data of patients with FALD

	non-aFALD	aFALD	*P* Value
Number of patients	**13**	**33**	
Patient charactaristics			
Age (y.o.)	**22.0 (19.5–31.5)**	**28.0 (24.0–33.0)**	**0.1394**
Gender (M/F)	**7/6 (53.8%)**	**22/11 (66.7%)**	**0.4309**
Fontan surgery elapsed years (years)	**18.0 (16.0–22.5)**	**25.0 (20.0–28.0)**	**0.0086**
Anticoagulats (Y/N)	**9/2 (81.8%)**	**24/11 (68.6%)**	**0.3797**
Laboratory data			
T-Bil (mg/dL)	**1.0 (0.8–1.6)**	**1.1 (0.8–1.5)**	**1.0000**
Albumin (g/dl)	**4.8 (4.3–4.9)**	**4.6 (4.3–4.8)**	**0.6415**
AST (U/L)	**26 (19–35)**	**24 (21–31)**	**0.6958**
ALT (U/L)	**27 (17–39)**	**24 (19–31)**	**0.6514**
ALP (U/L)	**82 (69–111)**	**93 (77–110)**	**0.5021**
GGT (U/L)	**77 (48–108)**	**94 (61–124)**	**0.2178**
Total cholesterol (mg/dL)	**156 (147–180)**	**146 (124–165)**	**0.1298**
Triglyceride (mg/dL)	**100 (61–117)**	**72 (55–101)**	**0.1436**
LDL cholesterol (mg/dL)	**98 (81–110)**	**80 (67–93)**	**0.0609**
TBA (μmol/L)	**7.0 (3.9–11.6)**	**12.1 (5.7–19.8)**	**0.0854**
Platelets ($\times 10^3$/μL)	**221 (203–275)**	**144 (113–174)**	**0.0001**
PT-INR	**1.94 (1.55–2.29)**	**1.68 (1.23–1.95)**	**0.2179**
NH_3 (μg/dL)	**36 (29–40)**	**47 (33–61)**	**0.0573**
BNP (pg/mL)	**10.6 (4.0–28.9)**	**12.1 (9.2–34.5)**	**0.4137**
Hemodynamic data			
IVCP (mmHg)	**11 (9–12)**	**12 (10–15)**	**0.1162**
PAP (mmHg)	**9 (8–10)**	**11 (9–12)**	**0.0806**
PCWP (mmHg)	**6 (5–10)**	**7 (4–10)**	**0.7740**
HR (bpm)	**77 (65–90)**	**72 (66–80)**	**0.5672**
Qp (L/min)	**3.70 (3.33–4.70)**	**3.86 (3.20–4.88)**	**0.6754**
Qs (L/min)	**3.40 (3.15–3.96)**	**3.90 (3.43–4.67)**	**0.1232**
PVR (W.U.)	**0.98 (0.49–1.25)**	**0.95 (0.52–1.33)**	**0.8046**
SVR (W.U.)	**23.1 (17.0–27.2)**	**20.4 (15.3–24.2)**	**0.2088**
SaO2 (%)	**94.5 (94.0–95.8)**	**94.0 (92.1–95.2)**	**0.2232**
CI (L/min/m2)	**2.36 (2.15–3.09)**	**2.59 (2.21–3.07)**	**0.9154**

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *ALP* Alkaline Phosphatase, *BNP* brain natriuretic peptide, *CI* cardiac index, *CVP* central venous pressure, *FALD* Fontan-associated liver disease, *GGT* γ-glutamyl transpeptidase, *HR* heart rate, *IVCP* inferior vena cava pressure, *LDL* low-density lipoprotein, *NH3* ammonia, *PAP* pulmonary artery pressure, *PCWP* pulmonary capillary wedge pressure, *Qp* pulmonary blood flow, *Qs* systemic blood flow, *PVR* pulmonary vascular resistance, *SaO2* arterial oxygen saturation, *SVR* systemic vascular resistance, *TBA* total bile acid, *T-Bil* total bilirubin, *PT-INR* prothrombin time-international normalized ratio, *Vs* shear wave velocity

by Institutional Review Board for Clinical Research of Kyushu University Hospital and Medical Institutions as a retrospective study (approval number: 23202–01), with information disclosed in an opt-out format. Therefore, written informed consent was waived by Institutional Review Board for Clinical Research of Kyushu University Hospital and Medical Institutions.

Patient characteristics, laboratory tests, and serum markers of liver fibrosis

Patient characteristics such as age, sex, initial diagnosis, dominant ventricle, type of Fontan procedure, and the time-lapse (in years) since the procedure were examined. Laboratory tests including total bilirubin (T-Bil), albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total cholesterol, triglyceride, low-density lipoprotein (LDL) cholesterol, total bile acid (TBA), creatinine (Cr), prothrombin time-international normalized ratio (PT-INR), ammonia, brain natriuretic peptide (BNP), and complete blood counts were measured. Serum markers for liver fibrosis—including type IV collagen 7S, hyaluronic acid, type III procollagen-N-peptide (P-III-P),

and Mac-2 binding protein glycan isomer (M2BPGi)—were also measured.

Non-invasive scores of liver fibrosis

The Fibrosis-4 (FIB-4) index, Forns index, AST-to-platelet ratio index (APRI), the model for end-stage liver disease (MELD), and MELD excluding the INR (MELD-XI) were calculated using the published formulas shown below [16].

$$\text{FIB-4 index} = (\text{Age} \times \text{AST})/(\text{platelet count} \times \sqrt{\text{ALT}})$$

$$\text{Forns index} = 7.811 - 3.131 \times \ln(\text{platelet count}) + 0.781 \times \ln(\text{GGT}) + 3.467 \times \ln(\text{Age}) - 0.014 \times (\text{total cholesterol})$$

$$\text{APRI} = \text{AST}/\text{AST(upper limit of normal)}/\text{platelet count} \times 100$$

$$\text{MELD} = 9.57 \times \ln(\text{Cr}) + 3.78 \times \ln(\text{T-bil}) + 11.20 \times \ln(\text{PT-INR}) + 6.43$$

$$\text{MELD-XI} = 11.76 \times \ln(\text{Cr}) + 5.11 \times \ln(\text{T-bil}) + 9.44$$

Hemodynamic data

Hemodynamic data such as cardiac catheterization, including inferior vena cava pressure (IVCP), pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), heart rate (HR), pulmonary blood flow (Qp), systemic blood flow ratio (Qs), pulmonary vascular resistance (PVR), systemic vascular resistance (SVR), arterial oxygen saturation (SaO_2), and cardiac index (CI), were examined. Imaging tests included at least one of the following: US, CT, and MRI. Cardiac catheterization was performed within five years of US elastography.

Combinational elastography of the SWE and SE

Patients fasted for more than 4 h, elevated their right upper limbs in a supine position, and had SWE and SE (Combinational Elastography) evaluated simultaneously by three experienced hepatologists (K.I., T.H., and T.A.) using the ARIETTA 850 (FUJIFILM Medical Co., Ltd., Tokyo, Japan). The region of interest was placed at least 10 mm below the liver capsule on the B-mode image, and SWE and SE were measured using Shear Wave Measurement (SWM) and Real-time Tissue Elastography (RTE), respectively. The data was represented as the median value of 10 LSMs, and its reliability was screened according to the following criteria: success rate 60% (percentage of valid measurements out of all measurements), and interquartile range < median 30%. SWM quantified the shear wave velocity (Vs). RTE quantified nine features, including the mean and standard deviation of the relative strain value, the ratio and complexity of the blue area in the region of interest, skewness, kurtosis, entropy, inverse difference moment, and angular second moment. The liver fibrosis index (LFI) for each frame was calculated using the following nine features and the formula below, as previously reported [64, 65].

$$\text{LFI} = (-0.009 \times \text{means}) - (0.005 \times \text{SD}) + (0.023 \times \text{percentage area}) + (0.025 \times \text{complexity}) + (0.775 \times \text{skewness}) - (0.281 \times \text{kurtosis}) + (2.083 \times \text{entropy}) + (3.042 \times \text{inverse difference moment}) + (39.979 \times \text{angular second moment}) - 5.542$$

Statistical analysis

Quantitative variables were presented as median values with interquartile ranges while categorical variables were presented as frequencies with percentages. As test of significance, comparisons between categorical and quantitative variables were performed using the chi-square test and the Wilcoxon rank-sum test, respectively. In this report, *p*-values less than 0.05 were considered statistically significant. The diagnostic accuracies were evaluated using receiver operating characteristic (ROC) analyses. Optimal cut-off values were chosen to maximize the sum of the sensitivity and specificity on the Youden index. The relationships between the LFI and other variables were evaluated using Spearman's rank correlation coefficient. Statistical analyses were performed using JMP® 16.0.0 (SAS Institute Inc., Cary, NC).

Results

Clinical characteristics of patients with FALD

Table 1 shows the clinical characteristics and hemodynamic data of the patients with FALD. The median time elapsed since the Fontan procedure was significantly longer in the aFALD group than in the non-aFALD group (25.0 vs. 18.0 years, $P = 0.0086$). The rate of use of anticoagulants did not differ significantly between the aFALD and non-aFALD groups, although anticoagulant use tended to be more common in the latter group [aFALD 24/11 (68.6%) vs. non-aFALD 9/2 (81.8%), $P = 0.3797$). The platelet counts in the aFALD group were significantly lower than those in the non-aFALD group (aFALD 144 $\times 10^3/\mu l$ vs. non-aFALD 221 $\times 10^3/\mu l$, $P = 0.0001$). Hemodynamic data did not differ significantly between the aFALD and non-aFALD groups, although IVCP and PVP tended to be high (IVCP; aFALD 12 mmHg vs. non-aFALD 11 mmHg, $P = 0.1162$, PVP; aFALD 11 mmHg vs. non-aFALD 9 mmHg, $P = 0.0806$). Table 2 shows the diagnosis and type of Fontan procedure for patients with FALD. Double outlet right ventricle ($n = 12$) was the most frequent initial diagnosis. Fontan procedures included an extracardiac conduit in 34 patients and a lateral tunnel in 12 patients. Four patients were diagnosed with asplenia

Table 2 Diagnosis and type of Fontan procedure in patients with FALD

Characteristics	
Initial diagonosis	
DORV	**12 (26.1%)**
DILV	**8 (17.4%)**
TA	**7 (15.2%)**
PA/IVS	**3 (6.5%)**
MA	**3 (6.5%)**
Unbalanced AVSD	**3 (6.5%)**
ccTGA	**2 (4.4%)**
Others	**8 (17.4%)**
Dominant ventricle	
RV	**26 (56.5%)**
LV	**19 (41.3%)**
Balanced	**1 (2.2%)**
Type of Fontan procedure	
Lateral tunnel	**12 (26.1%)**
Extra-cardiac conduit	**34 (73.9%)**
Heterotaxy	**9 (19.6%)**
Asplenia	**4 (8.7%)**
Polysplenia	**5 (10.9%)**

AVSD atrioventricular septal defect, *ccTGA* congenitally corrected transposition of the great arteries, *DILV* double inlet left ventricle, *DORV* double outlet right ventricle, *FALD* Fontan-associated liver disease, *PA/IVS* pulmonary atresia with intact ventricular septum, *MA* mitral atresia, *LV* left ventricle, *RV* right ventricle, *TA* tricuspid atresia

and five were diagnosed with polysplenia. All patients with asplenia were non-aFALD, whereas only one patient with polysplenia was non-aFALD.

Non-invasive tests (NITs) of patients with FALD

The NITs of the patients with FALD are summarized in Table 3. The serum markers of liver fibrosis did not differ significantly between the aFALD and non-aFALD groups. Among the non-invasive scores, the FIB-4 index, Forns index, and APRI were significantly higher in the aFALD group than in the non-aFALD group (FIB-4 index: aFALD 1.04 vs. non-aFALD 0.56, $P=0.0003$, Forns index: aFALD 5.35 vs. non-aFALD 2.60, $P=0.0001$, APRI: aFALD 0.56 vs. non-aFALD 0.41, $P=0.0023$, respectively). MELD and MELD-XI did not differ significantly between the aFALD and non-aFALD groups. The LFI derived from SE was significantly higher in the aFALD group compared with the non-aFALD group (aFALD 2.48 vs. non-aFALD 1.82, $P=0.0008$). However, the shear wave velocity (Vs) measured by SWE did not differ significantly between the aFALD and non-aFALD groups (aFALD 2.06 vs. non-aFALD 1.83, $P=0.0970$). The correlation between histological fibrosis and NITs was investigated in patients with FALD who were able to obtain tissue samples (Supplemental Table 1). It was observed that a considerable number of NITs, including Type IV collagen 7S and hyaluronic acid, exhibited variability within the same histological fibrosis, although the LFI demonstrated a certain degree of consistency with the aforementioned histological fibrosis.

Table 3 The noninvasive assessment of the patients with FALD

Variables	non-aFALD	aFALD	*P* Value
(Serum markers)			
Type IV collagen 7S (ng/mL)	**5.0 (4.3–5.8)**	**5.7 (4.8–7.0)**	**0.0508**
Hyaluronic acid (ng/mL)	**22 (9.5–26.5)**	**27 (16.5–44.5)**	**0.1124**
P-III-P (U/mL)	**11.0 (8.8–13.3)**	**11.7 (9.0–13.7)**	**0.5816**
M2BPGi (C.O.I.)	**0.26 (0.21–0.33)**	**0.32 (0.26–0.50)**	**0.1033**
(Noninvasive tests)			
Forns index	**2.60 (1.78–3.86)**	**5.35 (4.08–6.35)**	**0.0003**
FIB-4 index	**0.56 (0.41–0.67)**	**1.04 (0.77–1.27)**	**0.0001**
APRI	**0.41 (0.29–0.47)**	**0.56 (0.46–0.79)**	**0.0023**
MELD	**11.5 (8.1–13.8)**	**9.4 (5.5–12.3)**	**0.3055**
MELD-XI	**5.1 (3.2–9.0)**	**5.0 (3.5–9.1)**	**0.9029**
(Elastography)			
LF Index	**1.82 (1.47–2.36)**	**2.48 (2.26–2.76)**	**0.0008**
Vs (m/s)	**1.83 (1.46–2.09)**	**2.06 (1.80–2.95)**	**0.0970**

APRI AST to Platelet Ratio Index, *FALD* Fontan-associated liver disease, *FIB-4 index* fibrosis-4 index, *LF Index* Liver Fibrosis Index, *MELD* model for end-stage liver disease, *M2BPGi* Mac-2 binding protein glycan isomer, *P-III-P* type III procollagen-N-peptide, *Vs* shear wave velocity

Relationship between LFI and other indicators of liver fibrosis

Figure 1 shows the relationship between LFI and other indicators of liver fibrosis. Type IV collagen 7S and platelet counts had a significant correlation with the LFI (type IV collagen 7S: $R=0.335$, $P=0.0243$, platelet counts: $R=-0.332$, $P=0.0258$, respectively). The non-invasive scores and SWE had no significant correlation with the LFI. Figure 2 shows the relationship between the LFI and laboratory data. Albumin, total cholesterol, and LDL cholesterol—which are related to the liver's synthetic function—all showed significant correlations with the LFI (albumin: $R=-0.401$, $P=0.0063$, total cholesterol: $R=-0.468$, $P=0.0014$, LDL cholesterol: $R=-0.393$, $P=0.0083$, respectively). The LFI also showed a significant correlation with total bile acid and ammonia levels (total bile acid: $R=0.479$, $P=0.0010$, ammonia: $R=0.396$, $P=0.0078$, respectively).

Diagnostic accuracies of platelet counts, noninvasive scores, and US elastography for aFALD

Platelet counts, FIB-4 index, Forns index, APRI, and LFI all had moderate diagnostic accuracies (Table 4), but Vs

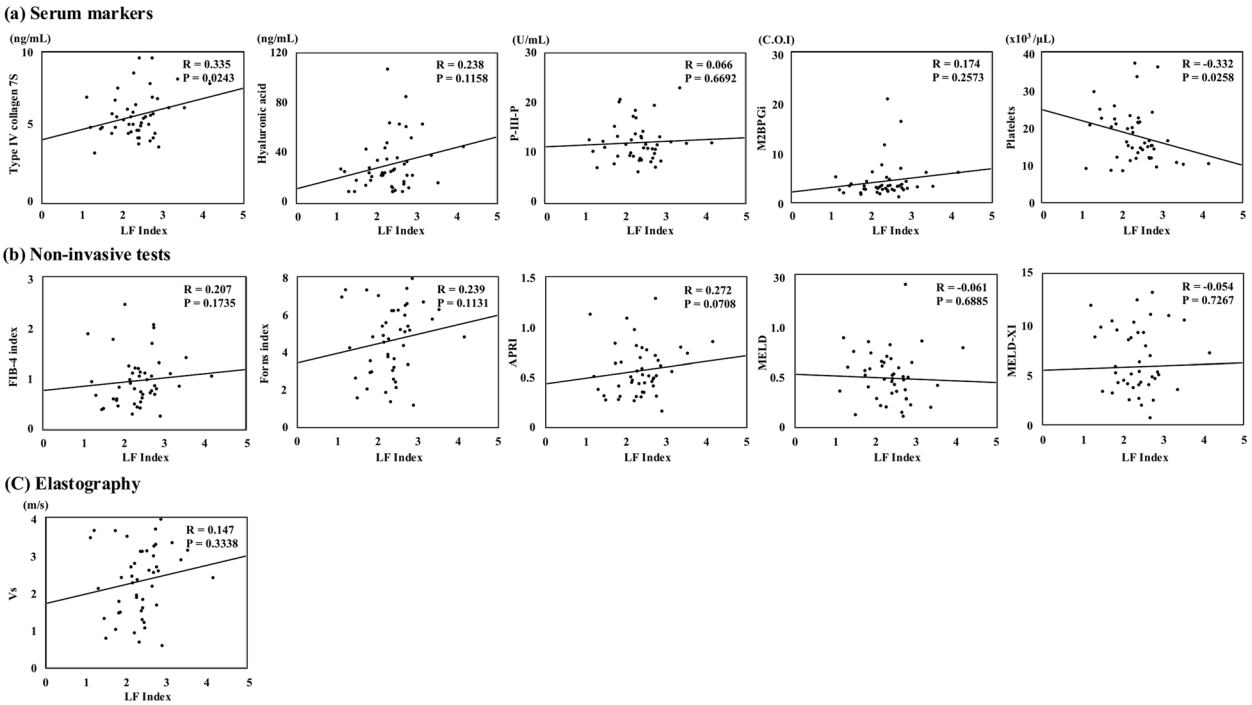

Fig. 1 Relationship between the LF Index and other fibrosis indicators. APRI, AST to Platelet Ratio Index; FIB-4 index, fibrosis-4 index; LF Index, Liver Fibrosis Index; MELD, model for end-stage liver disease; M2BPGi, Mac-2 binding protein glycan isomer; P-III-P, type III procollagen-N-peptide; Vs, shear wave velocity

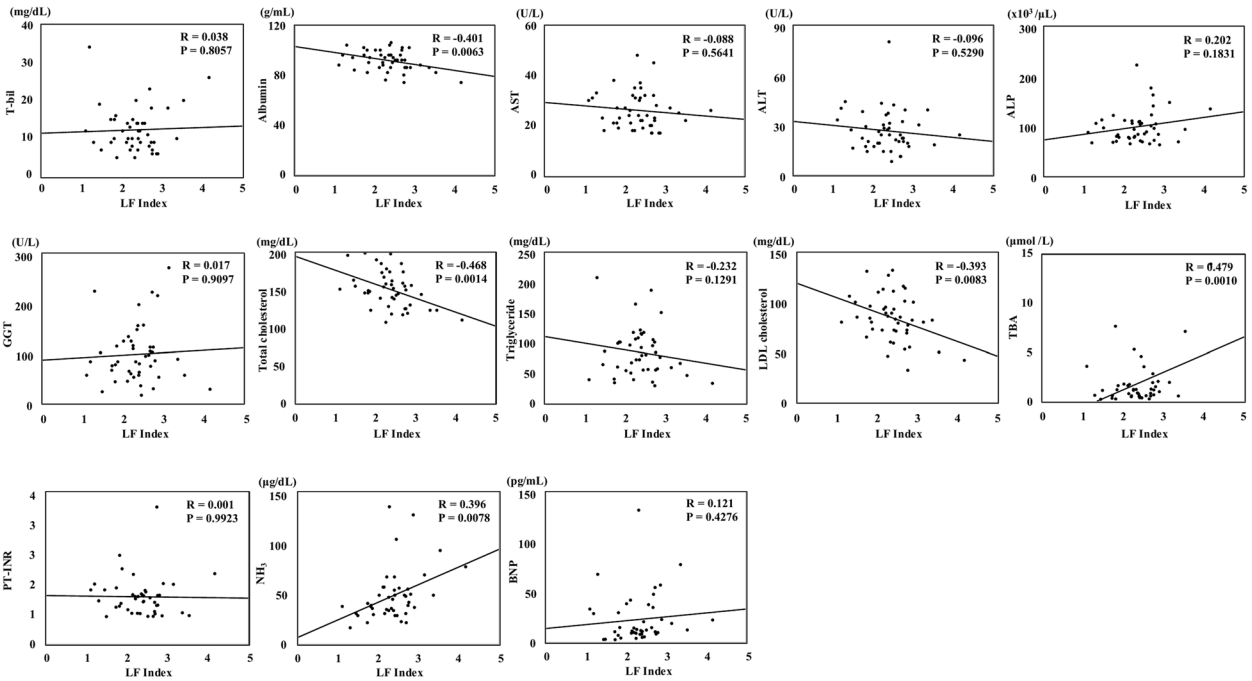

Fig. 2 Relationship between the LF Index and laboratory data. ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, Alkaline Phosphatase; BNP, brain natriuretic peptide; GGT, γ-glutamyl transpeptidase; LF Index, Liver Fibrosis Index; LDL, low-density lipoprotein; NH_3, ammonia; TBA, total bile acid; T-bil, total bilirubin; PT-INR, prothrombin time-international normalized ratio

Table 4 Diagnostic accuracy of serum markers, noninvasive tests, and ultrasound elastography for advanced FALD

Variables	Cut off	Sensitivity	Specificity	AUROC
(Serum markers)				
Platelets ($\times 10^3$/μL)	**185.0**	**78.8**	**92.3**	**0.87**
(Noninvasive tests)				
FIB-4 index	**0.71**	**84.7**	**84.9**	**0.88**
Forns index	**3.01**	**93.9**	**69.2**	**0.84**
APRI	**0.45**	**79.8**	**76.9**	**0.79**
(Elastography)				
LFIndex	**1.88**	**96.9**	**62.5**	**0.82**
Vs (m/s)	**2.06**	**51.5**	**76.9**	**0.66**

APRI AST to Platelet Ratio Index, *FALD* Fontan-associated liver disease, *FIB-4 index* fibrosis-4 index, *LF Index* Liver Fibrosis Index, *Vs* shear wave velocity

derived from SWE had low diagnostic accuracy (AUROC 0.66). The most appropriate cut-off value for diagnosing aFALD by platelet counts was 185 $\times 10^3$/μL, with 78.8% sensitivity and 92.3% specificity. While 25/26 (96.2%) of the patients with FALD who had platelet counts $\leq 185 \times 10^3$/μL were aFALD, 8/20 (40.0%) of the patients with FALD who had platelet counts $> 185 \times 10^3$/μL were also aFALD, indicating the need for the identification of additional markers.

Diagnostic accuracies of noninvasive scores and US elastography for aFALD with platelet counts $> 185 \times 10^3$/μL

To discriminate aFALD among the patients with FALD who had platelet counts of $> 185 \times 10^3$/μL, we assessed the diagnostic accuracy of noninvasive scores and US elastography in this population (Table 5). The AUROC for diagnosing aFALD was 0.69, 0.61, 0.57, and 0.51 for the FIB-4 index, Forns index, APRI, and SWE, respectively, which was insufficient to diagnose aFALD. On the other hand, the AUROC was 0.84 using SE, indicating moderate diagnostic accuracy. The most appropriate SE cut-off value was 2.21, with 100% sensitivity and 75.0% specificity. Using a two-step approach—discriminating aFALD with platelets $\leq 185 \times 10^3$/μL by platelets alone, and for those with higher platelets, requiring LFI > 2.21—yielded a combined sensitivity and specificity of 100% and 69.2%, respectively.

Table 5 Diagnostic accuracy of serum marker, noninvasive tests, and ultrasound elastography for advanced FALD with platelet $\geq 185 \times 10^3$/μl

Variables	Cut off	Sensitivity	Specificity	AUROC
(Serum markers)				
Platelets ($\times 10^3$/μL)	**239.0**	**87.5**	**41.8**	**0.57**
(Noninvasive tests)				
FIB-4 index	**0.49**	**87.5**	**50.0**	**0.69**
Forns index	**3.01**	**75.0**	**66.7**	**0.61**
APRI	**0.45**	**75.0**	**59.4**	**0.57**
(Elastography)				
LFIndex	**2.21**	**100**	**75.0**	**0.84**
Vs (m/s)	**1.57**	**87.5**	**41.8**	**0.51**

APRI AST to Platelet Ratio Index, *FALD* Fontan-associated liver disease, *FIB-4 index* fibrosis-4 index, *LF Index* Liver Fibrosis Index, *Vs* shear wave velocity

Discussion

FALD is one of the crucial complications of the Fontan procedure because the prevalence of advanced liver fibrosis and cirrhosis increases with the number of postoperative years [4, 5, 8–10], and patients with signs of portal hypertension or advanced fibrosis have poor prognoses [8, 62]. Therefore, an accurate assessment of the liver condition is required to determine the prognosis of patients undergoing the Fontan procedure by NITs.

Platelet counts and noninvasive scores, which include platelet counts as a variable (FIB-4 index and Forns index), were correlated with aFALD in our study (Tables 1 and 3). The platelet count cut-off value of 184.6 $\times 10^3$/μL could identify severe fibrosis (CHFS 3–4) in FALD in a previous report [8]. This aligned with our results; however, 8/20 (40.0%) of the patients with FALD who had platelet counts of $> 185 \times 10^3$/μL had aFALD in our study, highlighting the need for additional markers to be identified. Among the patients with FALD who had platelet counts of $> 185 \times 10^3$/μL, only SE showed moderate diagnostic accuracy (Table 5). These results suggest that the combination of platelet counts and LFI could more accurately distinguish aFALD.

LSM is divided into MRE and US elastography, with the latter subdivided into TE, SWE, and SE. SWE is the method that uses a focused acoustic radiation force impulse within the liver. This focused acoustic radiation force impulse gives rise to shear waves in the liver, and the speed of the waves is measured. MRE is a method in which a pneumatic passive driver is placed over the right upper quadrant abdominal wall, and modified phase-contrast pulse sequences are used to track mechanically induced shear waves within the liver [23]. On the other hand, SE evaluates tissue deformation by manual compression or physiological motion, while SWE and MRE measure the speed of shear waves in tissues. The precise mechanism through which SE exhibits a lesser response to hepatic congestion and inflammation is yet to be elucidated; however, the difference in measurement mechanisms may be related to SE being less affected by hepatic congestion. The lack of correlation between Vs (SWE) and LFI in this study was presumably due to the congestion affecting SWE (Fig. 1). The diagnostic accuracy of

LFI for discriminating aFALD was moderate and comparable to those of platelet counts, the FIB-4 index, and the Forns index (Table 4). LFI had a significant correlation with platelet counts and type IV collagen 7S, which are commonly used as indicators of fibrosis, as well as with albumin, total cholesterol, ammonia, and total bile acid, which are indicators of protein synthesis, detoxification, and portal hypertension, implying that LFI may primarily reflect liver fibrosis (Figs. 1 and 2). However, it should be noted that congestion-related factors (fluid status, CVP, heart failure symptoms) were not controlled and could confound the association between elastography results and true fibrosis.

To the best of our knowledge, only one report on SE in the FALD setting exists. Koizumi et al. investigated TE, SWE, SE, and hepatic vein waveforms, which were previously linked to the liver fibrosis of FALD [66], as alternative markers of CI in patients with FALD [67]. They discovered that hepatic vein waveforms were useful indicators for predicting decreased CI and LFI increase over time following the Fontan procedure; however, no direct correlations between LFI and liver fibrosis or signs of portal hypertension were identified in their study. To the best of our knowledge, ours is the first to show that LFI derived from SE can discriminate patients with FALD who have signs of portal hypertension. SE might also be useful in assessing the liver condition in patients with heart diseases other than FALD.

Since a of 73 Fontan patients discovered that the presence of esophageal varices, along with other clinical manifestations of portal hypertension, was associated with an increased risk of death, heart transplantation, and HCC [61], the European Association for The Study of the Liver and the European Reference Network on Rare Liver Diseases proposed screening for esophageal varices for staging [63]. Recently, the term "cirrhosis" was replaced by the term "advanced chronic liver disease" based on NITs at the Baveno VI conference, as cirrhosis is diagnosed pathologically by invasive liver biopsy [68]. Interestingly, the conference identified patients who can avoid screening endoscopy for varices based on the criterion consisting of platelet counts and LSM (platelet counts $>150\times10^3/\mu L$ and LSM by TE <20 kPa) [68]. It is consistent with our findings that aFALD can be distinguished by the criterion of platelet counts and LFI derived from SE. SE can be a useful tool for aFALD detection, and the early detection of aFALD has the potential to improve the prognosis of patients by providing an opportunity for intervention—including the testing of patients by hepatologists—at an earlier stage.

There was a high incidence of asplenia in the non-aFALD group in the current study. The relationship between asplenia and non-aFALD in this study was unclear, perhaps due to the small sample size.

The study has several limitations. First, the small sample size and the retrospective design could have taken a toll on the study's power and the generalizability of its results. The results may differ for studies conducted on larger Fontan populations. The findings need to be validated in a larger, prospective, longitudinal, and multicenter cohort to adjust for various cofounders and avoid biases. Second, the discrepancy between cardiac catheterization and abdominal US could influence the patient's condition. Some patients had additional medication that altered their hemodynamics. A prospective study with synchronized elastography and catheterization is required. Third, the relationship between histological findings and NITs was not sufficiently investigated because only a small number of patients underwent liver biopsies. Whether or not FALD is advanced has been shown to have significant prognostic value in patients with FALD [62]. However, further research is required to validate and noninvasive findings.

Conclusions

Platelet counts, noninvasive scores that include platelet counts as a variable (FIB-4 index and Forns index), and SE-derived LFI are useful indicators for diagnosing aFALD. Using a two-step approach, discriminating aFALD with platelets $\leq185\times10^3/\mu L$ by platelets alone, and for those with higher platelets, requiring LFI >2.21 could discriminate aFALD with high accuracy. Early aFALD detection and prompt intervention, including testing for aFALD, may lead to improved prognosis for aFALD.

Abbreviations

aFALD	Advanced Fontan-associated liver disease
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMA	Antimitochondrial antibodies
APRI	AST-to-platelet ratio
AST	Aspartate aminotransferase
AUROC	Area under the receiver operating characteristic curve
BNP	Brain natriuretic peptide
CHFS	Congestive liver fibrosis score
CI	Cardiac index
Cr	Creatinine
CVP	Central venous pressure
FALD	Fontan-associated liver disease
FIB-4	Fibrosis-4
GGT	Gamma-glutamyl transferase
HCC	Hepatocellular carcinoma
HR	Heart rate
IVCP	Inferior vena cava pressure
LDL	Low density lipoprotein
LFI	Liver Fibrosis Index
LSM	Liver stiffness measurement
MELD	Model for end-stage liver disease
MELD-XI	Model for end-stage liver disease excluding INR
MRE	Magnetic resonance elastography

M2BPGi	Mac-2 binding protein glycan isomer
NITs	Non-invasive tests
PAP	Pulmonary artery pressure
PCWP	Pulmonary capillary wedge pressure
PT-INR	Prothrombin time-international normalized ratio
PVR	Pulmonary vascular resistance
P-III-P	Type III procollagen-N-peptide
Qp	Pulmonary blood flow
Qs	Systemic blood flow ratio
ROI	Region of interest
ROC	Receiver operating characteristics
RTE	Real-time Tissue Elastography
SaO_2	Arterial oxygen saturation
SE	Strain elastography
SVR	Systemic vascular resistance
SWE	Shear wave elastography
SWM	Shear Wave Measurement
TBA	Total bile acid
T-Bil	Total bilirubin
TE	Transient elastography
TSH	Thyroid-stimulating hormone
US	Ultrasonography
Vs	Shear wave velocity

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-025-03965-1.

Supplementary Material 1.

Acknowledgements
We would like to thank Enago (www.enago.jp) for the English language review.

Authors' contributions
K.I., G.T. and M.T. contributed to the conception and design of this study. Y.A., T.H., T.A., H.N., A.N., T.K. and A.I. acquired, analyzed, and interpreted the data. The first draft of the manuscript was written by K.I, and M.T. K.Y., I.S. K.A. and Y.O assisted in the preparation of the manuscript and critically reviewed the manuscript. Y.O. supervised the work. All authors have read and approved the final version of the manuscript.

Funding
This work was supported in part by the Smoking Research Foundation (2024Y011), JSPS KAKENHI (Grant Numbers: JP22 K16021, JP22 K07963, JP22 K07987, JP23 K19591, JP24 K18977), and AMED (JP24fk0210102).

Data availability
The data used to support the findings of this study are included in the article.

Declarations

Ethics approval and consent to participate
The study was conducted following the Declaration of Helsinki and authorized by Institutional Review Board for Clinical Research of Kyushu University Hospital and Medical Institutions as a retrospective study (approval number: 23202–01), with information disclosed in an opt-out format. Therefore, written informed consent was waived by Institutional Review Board for Clinical Research of Kyushu University Hospital and Medical Institutions.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-Ku, Fukuoka 812-8582, Japan. [2]Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-Ku, Fukuoka 812-8582, Japan. [3]Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-Ku, Fukuoka 812-8582, Japan.

Received: 28 October 2024 Accepted: 2 May 2025
Published online: 08 May 2025

References

1. Rychik J, Atz AM, Celermajer DS, et al. Evaluation and management of the child and adult with Fontan circulation: a scientific statement from the American heart association. Circulation. 2019;140:e234–84.
2. Ohuchi H. Adult patients with Fontan circulation: what we know and how to manage adults with Fontan circulation? J Cardiol. 2016;68:181–9.
3. Hilscher MB, Wells ML, Venkatesh SK, et al. Fontan-associated liver disease. Hepatology (Baltimore, MD). 2022;75:1300–21.
4. Surrey LF, Russo P, Rychik J, et al. Prevalence and characterization of fibrosis in surveillance liver biopsies of patients with Fontan circulation. Hum Pathol. 2016;57:106–15.
5. Goldberg DJ, Surrey LF, Glatz AC, et al. Hepatic fibrosis is universal following Fontan operation, and severity is associated with time from surgery: a liver biopsy and hemodynamic study. Journal of the American Heart Association. 2017;6:6.
6. Wu FM, Kogon B, Earing MG, et al. Liver health in adults with Fontan circulation: a multicenter cross-sectional study. J Thorac Cardiovasc Surg. 2017;153:656–64.
7. Kuwabara M, Niwa K, Toyoda T, et al. Liver cirrhosis and/or hepatocellular carcinoma occurring late after the Fontan procedure - a nationwide survey in Japan. Circ J. 2018;82:1155–60.
8. Emamaullee J, Khan S, Weaver C, et al. Non-invasive biomarkers of Fontan-associated liver disease. JHEP Reports: innovation in hepatology. 2021;3: 100362.
9. Nii M, Inuzuka R, Inai K, et al. Incidence and expected probability of liver cirrhosis and hepatocellular carcinoma after Fontan operation. Circulation. 2021;144:2043–5.
10. Inuzuka R, Nii M, Inai K, et al. Predictors of liver cirrhosis and hepatocellular carcinoma among perioperative survivors of the Fontan operation. Heart (British Cardiac Society). 2023;109:276–82.
11. Gordon-Walker TT, Bove K, Veldtman G. Fontan-associated liver disease: a review. J Cardiol. 2019;74:223–32.
12. Sagawa T, Kogiso T, Sugiyama H, et al. Characteristics of hepatocellular carcinoma arising from Fontan-associated liver disease. Hepatology research: the official journal of the Japan Society of Hepatology. 2020;50:853–62.
13. Shiraishi J, Itoh S, Tomino T, et al. Surgical treatment of hepatocellular carcinoma after Fontan operation: three case reports and review of the literature. Clin J Gastroenterol. 2023;16:559–66.
14. Sharma S, Khalili K, Nguyen GC. Non-invasive diagnosis of advanced fibrosis and cirrhosis. World J Gastroenterol. 2014;20:16820–30.
15. Vaikunth SS, Higgins JP, Concepcion W, et al. Does liver biopsy accurately measure fibrosis in Fontan-associated liver disease? A comparison of liver biopsy pre-combined heart and liver transplant and liver explant post-transplant. Clin Transplant. 2020;34: e14120. https://doi.org/10.1111/ctr.14120.
16. Berzigotti A, Tsochatzis E, Boursier J, et al. EASL clinical practice guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. J Hepatol. 2021;2021(75):659–89.
17. Munsterman ID, Duijnhouwer AL, Kendall TJ, et al. The clinical spectrum of Fontan-associated liver disease: results from a prospective multimodality screening cohort. Eur Heart J. 2019;40:1057–68.
18. Schachter JL, Patel M, Horton SR, et al. FibroSURE and elastography poorly predict the severity of liver fibrosis in Fontan-associated liver disease. Congenit Heart Dis. 2018;13:764–70.
19. Shimizu M, Miyamoto K, Nishihara Y, et al. Risk factors and serological markers of liver cirrhosis after Fontan procedure. Heart Vessels. 2016;31:1514–21.

20. Evans WN, Winn BJ, Yumiaco NS, et al. Transvenous hepatic biopsy in stable Fontan patients undergoing cardiac catheterization. Pediatr Cardiol. 2014;35:1273–8.
21. Jarasvaraparn C, Thoe J, Rodenbarger A, et al. Biomarkers of fibrosis and portal hypertension in Fontan-associated liver disease in children and adults. Dig Liver Dis. 2024;56:1335–42.
22. Bulut OP, Bailey SS, Bhat DP. Accuracy of elastography versus biopsy in assessing severity of liver fibrosis in young Fontan patients. Cardiol Young. 2024;34:1990–96.
23. Ozturk A, Olson MC, Samir AE, et al. Liver fibrosis assessment: MR and US elastography. Abdom Radiol (NY). 2022;47:3037–50.
24. Wallihan DB, Podberesky DJ, Marino BS, et al. Relationship of MR elastography determined liver stiffness with cardiac function after Fontan palliation. Journal of magnetic resonance imaging: JMRI. 2014;40:1328–35.
25. Serai SD, Wallihan DB, Venkatesh SK, et al. Magnetic resonance elastography of the liver in patients status-post Fontan procedure: feasibility and preliminary results. Congenit Heart Dis. 2014;9:7–14. https://doi.org/10.1111/chd.12144.
26. Poterucha JT, Johnson JN, Qureshi MY, et al. Magnetic resonance elastography: a novel technique for the detection of hepatic fibrosis and hepatocellular carcinoma after the Fontan operation. Mayo Clin Proc. 2015;90:882–94.
27. Sugimoto M, Oka H, Kajihama A, et al. Non-invasive assessment of liver fibrosis by magnetic resonance elastography in patients with congenital heart disease undergoing the Fontan procedure and intracardiac repair. J Cardiol. 2016;68:202–8.
28. Egbe A, Miranda WR, Connolly HM, et al. Temporal changes in liver stiffness after Fontan operation: results of serial magnetic resonance elastography. Int J Cardiol. 2018;258:299–304.
29. Alsaied T, Possner M, Lubert AM, et al. Relation of magnetic resonance elastography to fontan failure and portal hypertension. Am J Cardiol. 2019;124:1454–9.
30. Martin de Miguel I, Kamath PS, Egbe AC, et al. Haemodynamic and prognostic associations of liver fibrosis scores in Fontan-associated liver disease. Heart (British Cardiac Society). 2023;109:619–25.
31. Miranda WR, Kamath PS, Jain CC, et al. Liver fibrosis scores are associated with resting and exercise Fontan and pulmonary artery wedge pressures: insights into FALD. Can J Cardiol. 2023;39:1349–57.
32. Friedrich-Rust M, Koch C, Rentzsch A, et al. Noninvasive assessment of liver fibrosis in patients with Fontan circulation using transient elastography and biochemical fibrosis markers. J Thorac Cardiovasc Surg. 2008;135:560–7.
33. Wu FM, Opotowsky AR, Raza R, et al. Transient elastography may identify Fontan patients with unfavorable hemodynamics and advanced hepatic fibrosis. Congenit Heart Dis. 2014;9:438–47. https://doi.org/10.1111/chd.12159.
34. Yoo BW, Choi JY, Eun LY, et al. Congestive hepatopathy after Fontan operation and related factors assessed by transient elastography. J Thorac Cardiovasc Surg. 2014;148:1498–505.
35. Chen B, Schreiber RA, Human DG, et al. Assessment of liver stiffness in pediatric Fontan patients using transient elastography. Can J Gastroenterol Hepatol. 2016;2016:7125193.
36. Fidai A, Dallaire F, Alvarez N, et al. Non-invasive investigations for the diagnosis of Fontan-associated liver disease in pediatric and adult Fontan patients. Frontiers in cardiovascular medicine. 2017;4: 15.
37. Song J, Kim K, Huh J, et al. Imaging assessment of hepatic changes after Fontan surgery. Int Heart J. 2018;59:1008–14.
38. Schleiger A, Salzmann M, Kramer P, et al. Severity of Fontan-associated liver disease correlates with Fontan hemodynamics. Pediatr Cardiol. 2020;41:736–46.
39. Chemello L, Padalino M, Zanon C, et al. Role of transient elastography to stage Fontan-Associated Liver Disease (FALD) in adults with single ventricle congenital heart disease correction. J Cardiovasc Dev Dis. 2021;8:117.
40. Cho Y, Kabata D, Ehara E, et al. Assessing liver stiffness with conventional cut-off values overestimates liver fibrosis staging in patients who received the Fontan procedure. Hepatology research: the official journal of the Japan Society of Hepatology. 2021;51:593–602.
41. Shin YR, Kim SU, Lee S, et al. Noninvasive surrogates are poor predictors of liver fibrosis in patients with Fontan circulation. J Thorac Cardiovasc Surg. 2022;164:1176-85.e3.
42. Meyer Z, Haas N, Mühlberg R, et al. Transient liver elastography in the follow-up of Fontan patients: results of a nation wide survey in Germany. Front Pediatr. 2023;11: 1194641.
43. Kutty SS, Peng Q, Danford DA, et al. Increased hepatic stiffness as consequence of high hepatic afterload in the Fontan circulation: a vascular Doppler and elastography study. Hepatology (Baltimore, MD). 2014;59:251–60.
44. Evans WN, Acherman RJ, Ciccolo ML, et al. A composite noninvasive index correlates with liver fibrosis scores in post-Fontan patients: preliminary findings. Congenit Heart Dis. 2018;13:38–45.
45. Smaś-Suska M, Skubera M, Wilkosz T, et al. Noninvasive assessment of liver status in adult patients after the Fontan procedure. Polish archives of internal medicine. 2019;129:181–8.
46. Mueller S, Sandrin L. Liver stiffness: a novel parameter for the diagnosis of liver disease. Hepatic medicine: evidence and research. 2010;2:49–67.
47. Hopper I, Kemp W, Porapakkham P, et al. Impact of heart failure and changes to volume status on liver stiffness: non-invasive assessment using transient elastography. Eur J Heart Fail. 2012;14:621–7.
48. Wang HK, Lai YC, Tseng HS, et al. Hepatic venous congestion after living donor liver transplantation: quantitative assessment of liver stiffness using shear wave elastography–a case report. Transpl Proc. 2012;44:814–6.
49. Taniguchi T, Sakata Y, Ohtani T, et al. Usefulness of transient elastography for noninvasive and reliable estimation of right-sided filling pressure in heart failure. Am J Cardiol. 2014;113:552–8.
50. Fenstad ER, Dzyubak B, Oh JK, et al. Evaluation of liver stiffness with magnetic resonance elastography in patients with constrictive pericarditis: preliminary findings. Journal of magnetic resonance imaging: JMRI. 2016;44:81–8.
51. Yoshitani T, Asakawa N, Sakakibara M, et al. Value of virtual touch quantification elastography for assessing liver congestion in patients with heart failure. Circ J. 2016;80:1187–95.
52. Nishi H, Toda K, Miyagawa S, et al. Novel method of evaluating liver stiffness using transient elastography to evaluate perioperative status in severe heart failure. Circ J. 2015;79:391–7.
53. Saito Y, Kato M, Nagashima K, et al. Prognostic relevance of liver stiffness assessed by transient elastography in patients with acute decompensated heart failure. Circulation. 2018;82:1822-9. d.
54. Terashi E, Kodama Y, Kuraoka A, et al. Usefulness of liver stiffness on ultrasound shear-wave elastography for the evaluation of central venous pressure in children with heart diseases. Circ J. 2019;83:1338–41.
55. Deorsola L, Aidala E, Cascarano MT, et al. Liver stiffness modifications shortly after total cavopulmonary connection. Interact Cardiovasc Thorac Surg. 2016;23:513–8.
56. DiPaola FW, Schumacher KR, Goldberg CS, et al. Effect of Fontan operation on liver stiffness in children with single ventricle physiology. Eur Radiol. 2017;27:2434–42.
57. Yada N, Sakurai T, Minami T, et al. Influence of liver inflammation on liver stiffness measurement in patients with autoimmune hepatitis evaluation by combinational elastography. Oncology. 2017;92 Suppl 1:10–5.
58. Hirooka M, Koizumi Y, Hiasa Y, et al. Hepatic elasticity in patients with ascites: evaluation with real-time tissue elastography. AJR Am J Roentgenol. 2011;196:W766–71.
59. Sakamoto T, Ito S, Endo A, et al. Combinational elastography. Int Heart J. 2022;63:271–7.
60. Jianping D, Xi C, Guangwen C, et al. Dual elastography to discriminate adjacent stages of fibrosis and inflammation in chronic hepatitis B: a prospective multicenter study. Hepatology (Baltimore, MD). 2024;79:438–50.
61. Elder RW, McCabe NM, Hebson C, et al. Features of portal hypertension are associated with major adverse events in Fontan patients: the VAST study. Int J Cardiol. 2013;168:3764–9.
62. Elder RW, McCabe NM, Veledar E, et al. Risk factors for major adverse events late after Fontan palliation. Congenit Heart Dis. 2015;10:159–68.
63. Téllez L, Payancé A, Tjwa E, et al. EASL-ERN position paper on liver involvement in patients with Fontan-type circulation. J Hepatol. 2023;79:1270–301.
64. Tatsumi C, Kudo M, Ueshima K, et al. Non-invasive evaluation of hepatic fibrosis for type C chronic hepatitis. Intervirology. 2010;53:76–81.
65. Fujimoto K, Kato M, Kudo M, et al. Novel image analysis method using ultrasound elastography for noninvasive evaluation of hepatic fibrosis in patients with chronic hepatitis C. Oncology. 2013;84(Suppl 1):3–12.

66. Koizumi Y, Hirooka M, Tanaka T, et al. Noninvasive ultrasound technique for assessment of liver fibrosis and cardiac function in Fontan-associated liver disease: diagnosis based on elastography and hepatic vein waveform type. J Med Ultrason (2021). 2001;48:235–44.
67. Nakatsuka T, Soroida Y, Nakagawa H, et al. Identification of liver fibrosis using the hepatic vein waveform in patients with Fontan circulation. Hepatology research : the official journal of the Japan Society of Hepatology. 2019;49:304–13.
68. de Franchis R. Expanding consensus in portal hypertension: report of the Baveno VI consensus workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol. 2015;63:743–52.

Publisher's Note