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Review Article

Screening modalities for the diagnosis of Fontan-associated liver disease: evidence from the past for future development

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Abstract: Approximately 70,000 patients who have undergone the Fontan operation worldwide survive into adulthood, however the majority of these patients are faced with long-term post-operative complications due to specific hemodynamic changes. Fontan-associated liver disease (FALD) is a challenging complication characterized by various spectra. Of these, liver congestion and liver fibrosis potentially lead to cirrhosis and liver nodules. The most serious condition associated with the development of liver nodules is hepatocellular carcinoma. Various non-invasive modalities including blood tests, ultrasound scans of the upper abdomen, ultrasound elastography of the liver, computed tomography scans, magnetic resonance imaging and magnetic resonance elastography of the liver have been used as alternatives to liver biopsies for FALD assessment in post-Fontan patients. To date, a detailed understanding of the pathophysiology and natural history of these patients, and the most appropriate modality for the effective investigation of this condition is incomplete. In this comprehensive review, reports regarding the currently available screening modalities used in the detection of FALD are summarized and discussed. The findings of this review, including identification of any current knowledge gaps, can pave the way for the development of effective future strategies in the surveillance and ultimately the treatment of post-Fontan patients.

Keywords: Fontan operation, Fontan-associated liver disease, ultrasound liver elastography, computed tomography scan, magnetic resonance imaging

Introduction

The Fontan operation is a definitive palliation for patients with single ventricular physiology and can achieve a systemic venous return directly into the lungs without the need for impetus from the heart [1, 2]. The procedure abolishes intracardiac mixing of the blood and reduces volume overload on the single functional ventricle. Currently, up to 70,000 patients worldwide survive into adulthood with a 30-year survival rate of more than 80% [3-6]. Unfortunately, these patients usually continue to suffer from long-term consequences of the procedure, complications including heart failure caused by ventricular dysfunction, cardiac arrhythmia, atrioventricular valve regurgitation, pulmonary thromboembolism, and plastic bronchitis. Complications involving the liver are also common: an overall term for these conditions being Fontan-associated liver disease (FALD).

FALD involves various spectra of structural and functional alterations within the liver, which occur before the Fontan operation and persist for a long time following surgery [7]. FALD results from a specific variation in hemodynamic circulation, leading to liver congestion and liver fibrosis which have the potential to develop into cirrhosis, portal hypertension, liver nodu-

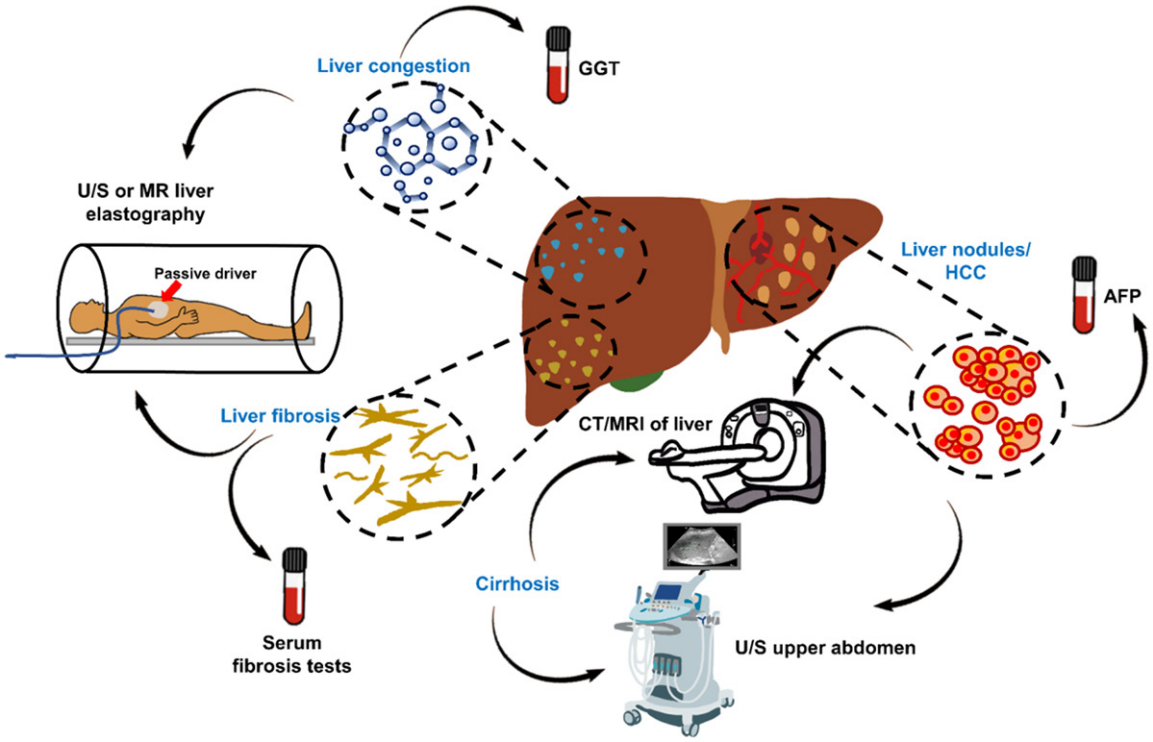

Figure 1. Multimodal approach for the evaluation of FALD at present. AFP: alpha fetoprotein; CT: computerized tomography scan; GGT: Gamma-glutamyl transferase; HCC: hepatocellular carcinoma; MRI: magnetic resonance imaging; U/S: ultrasound.

les and hepatocellular carcinoma (HCC) [8-21]. Details around FALD are still unclear since a universal definition of FALD is lacking. However, several studies have reported that the incidence of FALD was between 41 and 86% in Fontan patients [17, 22-25]. Although the gold standard for diagnosis of FALD is a liver biopsy [26], this invasive procedure can cause serious complications since most patients concomitantly use antithrombotic drugs. Currently, although many non-invasive procedures have been proposed in an attempt to diagnose FALD, due to differing degrees of efficacy, none has been accepted as a definite non-invasive method [27-29]. In addition, understanding around the pathophysiology, natural history and optimal investigation in FALD is still limited.

This review comprehensively summarizes the findings from studies reporting on various screening tests for the diagnosis of FALD including blood tests, ultrasound scanning of the upper abdomen, ultrasound elastography of the liver, computed tomography scanning, magnetic resonance imaging, and magnetic resonance elastography of the liver (**Figure 1**). Consistent and controversial findings with regard to FALD screening in Fontan patients are summarized and discussed. The aim of this review is to propose a more effective approach towards screening for FALD in the future.

Search strategy and selection criteria

The key words used to search the PubMed database were: Fontan operation; Fontan-associated liver disease; ultrasound upper abdomen; ultrasound liver elastography; cardiac catheterization; computed tomography scan; magnetic resonance imaging; and/or magnetic resonance elastography. Only research articles in the English language were selected.

The pathophysiology and natural history of FALD

The two main mechanisms proposed as being responsible for FALD include a persistent elevation of central venous pressure leading to congestive hepatopathy, and a reduction of cardiac output resulting in chronic hepatic ischemia [30-32]. These mechanisms lead to

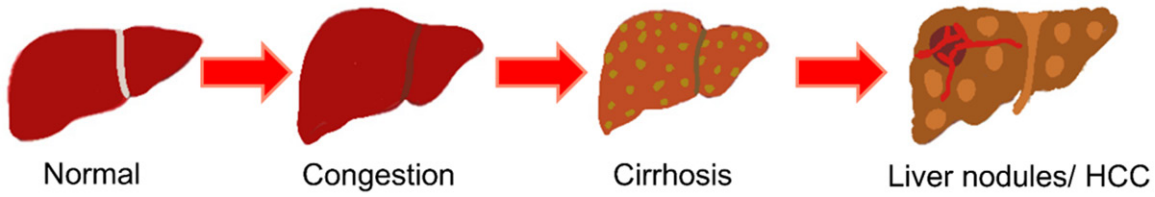

Figure 2. Natural history of FALD. HCC: hepatocellular carcinoma.

reduced blood flow into the liver via the portal vein. Fortunately, the liver has an autoregulatory response to compensate for this condition via the hepatic artery, known as "the hepatic arterial buffer response" [33]. Despite this autoregulation, the liver is still vulnerable during hemodynamically unstable periods such as exercise, hypoxia, or central venous hypertension [30].

Currently, the natural history of FALD is not well documented. However, three stages of FALD have been proposed [7] (**Figure 2**). First, congestive hepatopathy is caused by an elevation of central venous pressure. This stage develops before the Fontan operation and continues subsequently [11, 12]. The histology demonstrates a sinusoidal dilatation which correlates with the cholestatic picture of the laboratory tests including elevated indirect hyperbilirubinemia and gamma-glutamyl transferase (GGT). More than 10 years after the Fontan operation, the patients usually enter the second stage of ischemic hepatitis [7]. This results in a diminished cardiac output which can be shown in the form of a transaminitis profile. The histology reveals the presence of sinusoidal fibrosis and regenerative nodules, known to be potential precursors of HCC. The last stage usually occurs between 15 and 20 years following surgery [7]. This stage is a terminal stage that is characterized by cirrhosis and portal hypertension. In this stage, patients develop an abnormal synthetic function of the liver consisting of hypoalbuminemia and coagulopathy. Thrombocytopenia can also develop, as an indicator of portal hypertension.

Several hemodynamic evaluations using cardiac catheterization have been reported in both pediatric and adult Fontan patients. Over a period of time, patients presented with an increase in the level of pulmonary arterial wedge pressure [34], and mean pulmonary artery pressure [10, 35, 36]. Due to the persistent elevated central venous pressures [37-39] which are transmitted to the Fontan circuit, Fontan pressure rises [10, 35, 40-43], resulting in an elevation in both hepatic vein pressure [10, 36, 41, 42, 44, 45] and hepatic vein wedge pressure [10, 36, 37, 41, 42, 44, 45]. Hepatic sinusoids lack valves, therefore there is a proportionate increase in portal vein pressure and a decrease in portal venous inflow. A hepatic venous pressure of more than 5 mmHg was demonstrated as an important parameter in the confirmation of sinusoidal portal hypertension [46]. Although the optimal pressure in the Fontan circulation is 10-15 mmHg [47], physiologic right atrial pressure in adults is only 2-6 mmHg [48]. This suggests that all Fontan patients would have elevated portal pressure immediately after the operation and persistently thereafter.

The pathophysiologic changes of the Fontan connection lead to congestive hepatopathy, a common symptom of FALD. Persistent portal hypertension over a sustained period of time could reduce the preload of the heart leading to a diminished cardiac output [35, 38, 41, 42, 45]. However, several studies have demonstrated normal hemodynamic parameters 6-10 years post-Fontan operation [49, 50]. Additionally, there was no correlation between hemodynamic data and histologic changes [51, 52]. Liver changes could be detected by non-invasive imaging studies and histology in Fontan patients presenting with normal hemodynamic evaluation from biventricular physiologic data. Liver fibrosis gradually occurs and progresses to cirrhosis, portal hypertension, and liver nodules, regardless of cardiac output status.

In contrast to the studies which proposed the stages of FALD, the data currently available indicate that ischemic hepatitis is only a predisposing factor, not a stage of FALD. The pro-

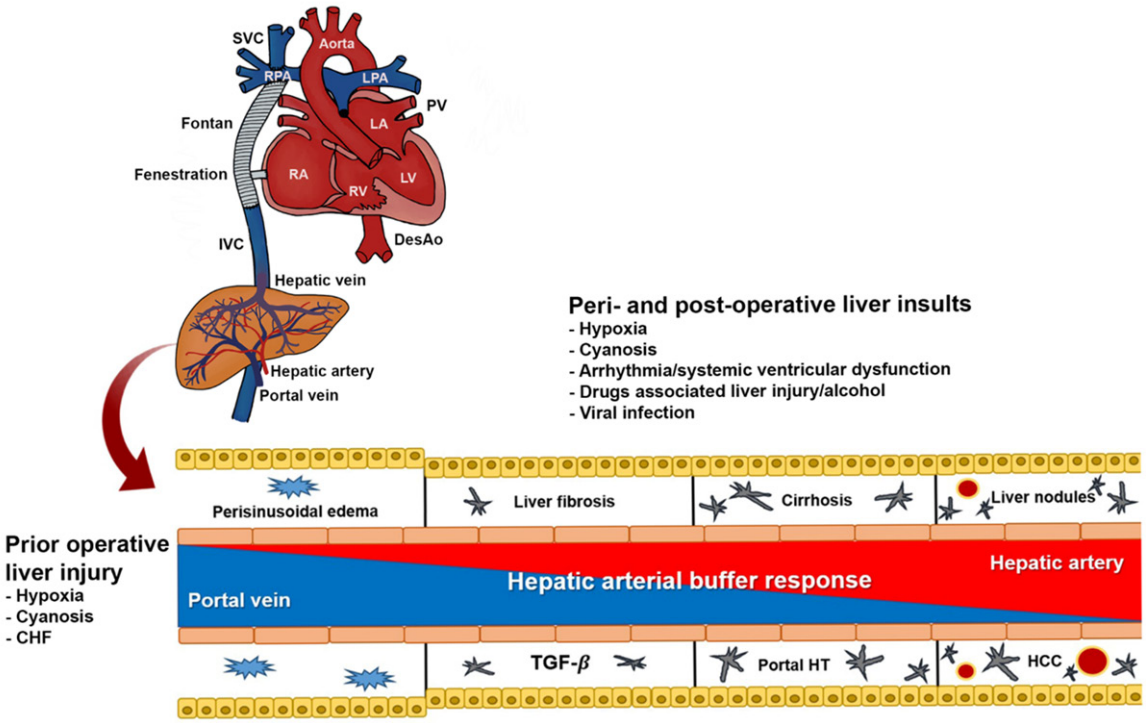

Figure 3. Continuum of FALD. The pathophysiologic change in the liver following the Fontan operation is central venous hypertension, leading to congestive hepatopathy. Liver fibrosis occurs gradually, resulting in cirrhosis, portal hypertension, liver nodules, and hepatocellular carcinoma. Autoregulation to compensate for this condition via the hepatic artery is known as the hepatic arterial buffer response. During the progression of the associated liver pathologies many factors contribute to the liver insults in each patient. CHF: congestive heart failure; DesAo: descending aorta; FALD: Fontan-associated liver disease; HCC: hepatocellular carcinoma; HT: hypertension; IVC: inferior vena cava; LA: left atrium; LPA: left pulmonary artery; LV: left ventricle; PV: pulmonary vein; RA: right atrium; RPA: right pulmonary artery; RV: right ventricle; SVC: superior vena cava; TGF-β: transforming growth factor-beta.

gression of the processes in FALD that supports this hypothesis is shown in **Figure 3**. All findings recorded from studies using cardiac catheterization in children and adult Fontan patients are shown in **Table 1**.

Blood tests used for the diagnosis of FALD

Many studies reported a correlation between serum biomarkers and the stages of FALD. In both pediatric and adult Fontan patients, the changes in the serum biomarker pattern were similar. The type of Fontan operation did not show a direct correlation with blood test abnormalities (**Tables 2**, **3**). The most common blood test abnormality was an increase in GGT level, a recognized hallmark of cholestasis. GGT could be elevated while other blood tests were unchanged [17, 35, 37, 40, 44, 53-55]. Interestingly, hyperbilirubinemia was rarely observed and most commonly associated with advanced liver dysfunction [51, 56], therefore, bilirubin was not considered a sensitive blood test for the early detection of FALD. During long-term follow-up, the elevation of aspartate transaminase (AST) and/or alanine transaminase (ALT) were also reported [15, 38, 49, 51, 57]. These findings support the proposed concept that liver injury occurs after the congestive stage of FALD. Several studies reported that liver fibrosis showed a correlation with an increase in AST-to-platelet ratio index (APRI) score [41, 49, 51, 56, 57], Forn's index [57, 58], FibroSure [44, 59] and model for end-stage liver disease (MELD-XI) score [60]. The length of time after the Fontan operation was also associated with these fibrosis scores [44, 51, 59]. However, many studies reported that all laboratory tests were still normal a considerable length of time post-Fontan surgery [36, 42, 43, 45, 52, 55, 56, 59, 61]. There are 2 possible explanations for these inconsistent findings. First, the current blood tests including the fibrosis scores are not sensitive enough to

Table 1. Cardiac catheterization for the diagnosis of FALD in children and adults

Average age at Fontan operation (year)/ Number of patients	Type of Fontan (%)	Duration after Fontan operation (year)	Major Findings								FALD	Interpretations	References
			HVWP	HVP	Fontan pressure	CVP	mPAP	PAWP/ TPG	SVEDP	CI			
Children													
NA/16	LT (54), EC (46)	11 ± 6*						↑/-	↑	↔	↑ Liver stiffness by US-SWE system	- PAWP and SVEDP were correlated with liver stiffness.	[34]
5.4/64	EC (76.6), LT (12.5), KS (9.4), AP (1.5)	12.1				↑		-/↔	↔	↓	↑ Liver stiffness by ARFI	- CVP was associated with liver stiffness by ARFI.	[38]
2 (1-16)†/40	EC (62.5), LT (37.5)	6.5			↔							- Fontan pressure was normal in Fontan patients at mid-term follow-up.	[50]
13.7 (5.9-16.8)†/22	-	9.6 (1.0-12.9)†			↔				↔			- Fontan pressure and SVEDP were still normal in some patients for a long time after Fontan operation.	[49]
Adults													
NA/57	EC (56), AP (44)	12.9 (4.4-23.3)†	↑			↑	↔			↔	↑ Liver stiffness by MRE	- CVP was associated with liver stiffness by MRE of the liver.	[37]
NA/30	NA	20.2 (8-29)†				↑					HCC confirmed by liver biopsy	- CVP was increased in HCC higher than FNH-like nodules in post-Fontan patients.	[39]
2.9 (1.3-40.7)†/45	LT (82), AP (8), EC (8)	9.9 (0.1-32.5)†			↑		↑	↔/-		↓	↑ Liver stiffness	- Elevated Fontan pressure and decreased CI correlated with liver stiffness.	[35]
4 (2-9)†/30	AP (40), LT (34)	22 (16-26)†	↑	↑	↑			↔/-	↔	↓	↑ Liver biopsy-derived total fibrosis score and stiffness	- Elevated Fontan pressure and decreased CI correlated with liver biopsy-derived total fibrosis score and liver stiffness.	[41]
3.5/86	EC (75.2), LT (15.2), Other (9.7)	10.3	↑	↑			↔	↔	↔		↑ Liver stiffness by Fibroscan	- Hepatic vein wedge pressure correlated strongly with liver stiffness measured by Fibroscan.	[44]
NA/12	EC (100)	14.1 (6.9-26.4)†	↑	↑	↑		↑		↔		↑ Liver fibrosis by liver biopsy	- Cirrhosis correlated with hepatic vein pressure and hepatic vein wedge pressure.	[10]
NA/67	LT (60), EC (36)	14.9 ± 4.5*			↔						↑ Liver fibrosis by % collagen deposit	- Liver fibrosis was found in Fontan patients but was not associated with Fontan pressure.	[52]
13 (10-35)†/26	NA	10.5 (4-17)†	↑	↑			↑	↔	↔		↑ Liver cirrhosis by CT upper abdomen	- mPAP was associated with liver cirrhosis detected by CT upper abdomen.	[36]

5 (3-6)†/22	AP (46)	-			↑	-/↑	↔	↔	↔	↑ Liver stiffness by MRE of liver	- Elevated PVR index correlated with liver stiffness by MRE of the liver.	[43]
5.2 (1.3-39)†/12	AP (56), LT (44)	20.4 (12.0-31.3)†	↑	↑	↔	↔/-	↔		↓	Modified METAVIR score by histology	- Liver histology was associated with hepatic vein pressure and hepatic vein wedge pressure.	[45]
5 (0.7-39)†/68	LT (50), AP (38.2), EC (5.9)	18.1 (1.2-32.7)†	↑	↑	↑		↑		↓	METAVIR fibrosis staging by histology	- Hemodynamic data showed no correlation with histology grading of liver biopsy.	[42]
NA/66	EC (64.5), AP (27) LT (8.5)	18.3			↑	↔			↔	Liver nodules by CT or MRI of the upper abdomen	- Hemodynamic data were not correlated with liver nodules detected by CT or MRI of the upper abdomen.	[40]
2 (0.9-11.7)†/67	LT (60.8), EC (33.8)	14.9 (3.1-25.3)†			↔					CHF score by histology	- Histologic changes of liver were detected while Fontan pressure was normal.	[51]

*Mean ± SD, †Median (IQR). Abbreviations: AP, atriopulmonary; ARFI, acoustic radiation force impulse; CHF, congestive hepatic fibrosis; CI, cardiac index; CT, computerized tomography; CVP, central venous pressure; EC, extracardiac conduit; FALD, Fontan-associated liver disease; FNH, focal nodular hyperplasia; HCC, hepatocellular carcinoma; HVP, hepatic vein pressure; HVWP, hepatic vein wedge pressure; IVC, inferior vena cava; LT, lateral tunnel; LS, liver stiffness; mPAP, mean pulmonary artery pressure; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; SVEDP, single ventricular end-diastolic pressure; SWE, shear wave elastography; TPG, transpulmonary gradient; US, ultrasound.

Table 2. Blood tests for the diagnosis of FALD in adults

Average age at Fontan operation (year)/Number of patients	Type of Fontan (%)	Duration after Fontan operation (year)	CBC		LFT			Fibrosis score	Interpretations	References
			Hb/Plt	Alb	AST/ALT	ALP/GGT	TB	APRI/Forn's index/Fibrosure		
3.5/65	EC (75.2), LT (15.2), Other (9.7)	10.3			↔/↔	-/↑	↔	-/-/↔	- GGT was increased in Fontan patients after long-term follow-up. - Fibrosure was increased in association with duration after Fontan operation.	[44]
5 (3-6.3)†/38	EC (40), AP (37), LT (18)	21.4 ± 5.5*	-/↔	↔	↔/↔	↔/↑	↔		- GGT was increased in Fontan patients after very long-term follow-up.	[53]
2.9 (1.3-40.7)†/45	LT (82), AP (8), EC (8)	9.9 (0.1-32.5)†	-/↔	↔	↔/↔	-/↑	↔	↔/-/-	- GGT was not elevated in Fontan patients, while platelet count, liver function, and APRI were unchanged.	[35]
NA/57	EC (56), AP (44)	12.9 (4.4-23.3)†	-/↔			-/↑		↔/-/-	- Elevated GGT was found in Fontan patients after long-term follow-up.	[37]

NA/152	EC (64.5), AP (27), LT (8.5)	18.3	-/↔	↔	↔/↔	↔/↑	↔		- GGT was increased in Fontan patients after very long-term follow-up.	[40]
2 (0.9-11.7)†/74	LT (60.8), EC (33.8)	14.9 (3.1-25.3)†	↔/↔	↔	↔/↔	↔/↑	↔		- Elevated GGT was found in Fontan patients after long-term follow-up.	[17]
6 (3-9)†/37	AP (43), EC (30), LT (27)	22 (19-28)†	↔/↔	↔	↔/↔	-/↑	↔		- GGT was increased in Fontan patients after very long-term follow-up.	[54]
8 (4-13)†/57	AP (66.7), BJ (22.7), EC (5.3), LT (5.3)	17 (15-22)†	-/↔	↔	↔/↔	-/↑	↔	-/↑/-	- GGT and Forn's index were increased in adult patients after Fontan operation.	[58]
5 (0.1-40.7)†/241	LT (53), AP (37), EC (2)	20.3 (5.4-34.5)†	-/↓			-/↑			- Thrombocytopenia and elevated GGT were found in Fontan patients after very long-term follow-up.	[23]
4 (1-16)†/59	EC (93), AP (7)	18 (11-34)†	-/↓		↑/-	-/↑		↑/↑/-	- Thrombocytopenia, elevated AST and GGT were found in adult Fontan patients, in association with an increase in APRI and Forn's index.	[57]
4.2 ± 4.1*/139	LT (71), AP (35), EC (33)	0	↔/↔		↔/↔		↔	↔/↔/↔	- During long-term follow-up, Fontan patients developed thrombocytopenia, as well as increased AST and TB.	[51]
		11.5 ± 4.7*	-/↓		↑/-		↑	↑/↑/-	- APRI and Forn's index were associated with the duration after Fontan operation.	
4 (2-9)†/50	AP (40), LT (34)	22 (16-26)†	↔/↓	↔	↔/↔	↑/↑	↔	↑/-/-	- Thrombocytopenia, elevated ALP and GGT were associated with an increase in APRI after long-term follow-up.	[41]
6.4 (2.3-28.1)†/8		0	↔/↔			↔/↔	↔	↔/↔/↔	- Hemoconcentration, thrombocytopenia, and cholestasis were found in patients after very long-term Fontan surgery.	[56]
	EC (37.5), LT (37.5)									
		21.1 ± 4*	↑/↓			↑/↑	↑	↑/-/-	- APRI was associated with the duration after Fontan surgery.	
5.2 (1.3-39)†/27	AP (56), LT (44)	20.4 (12-31.3)†	↔/↔	↔	↔/↔	↔/↔	↔	-/-/↔	- Blood tests and Fibrosure were normal in adult Fontan patients after very long-term follow-up.	[45]

NA/67	LT (60), EC (36)	14.9 ± 4.5*	↔/↔	↔	↔/↔	↔/↔	↔		- Liver function, hemoglobin, and platelet count were unchanged in Fontan patients after long-term follow-up.	[52]
NA/14	NA	24.7 ± 6.2*			↔/↔			-/-/↔	- Liver enzymes and Fibrosure were unchanged in patients very long-term after Fontan operation.	[61]
5 (0.7-39)†/68	LT (50), AP (38.2), EC (5.9)	18.1 (1.2-32.7)†			↔/↔	↔/↔	↔		- Liver function test was normal in adult Fontan patients.	[42]
3.6 (1-29)†/26	NA	10.5 (4-17)†	↔/↔		↔/↔	-/↔	↔		- Liver function, hemoglobin, and platelet count were unchanged in Fontan patients after long-term follow-up.	[36]
5 (3-6)†/22	AP (46)	Baseline	-/↔	↔	↔/↔	↔/↔	↔	↔/-/-	- Liver function, platelet count, and APRI score were unchanged in adult Fontan patients.	[43]
		Post-op								
		2 yrs from baseline	-/↔	↔	↔/↔	↔/↔	↔	↔/-/-		

*Mean ± SD, †Median (IQR). Abbreviations: Alb, albumin; ALP, Alkaline phosphatase; ALT, alanine aminotransferase; AP, atriopulmonary; APRI, AST to Platelet Ratio Index; AST, aspartate aminotransferase; BJ, Bjork operation; CBC, complete blood count; EC, extracardiac conduit; GGT, gamma-glutamyl transferase; Hb, hemoglobin; LFT, liver function test; LT, lateral tunnel; Plt, platelet count; TB, total bilirubin.

Table 3. Blood tests for the diagnosis of FALD in children

Average age at Fontan operation (years)/ Number of patients	Type of Fontan (%)	Duration after Fontan operation (year)	CBC	LFT				Fibrosis score	Interpretations	References
			Hb/ Plt	Alb	AST/ALT	ALP/ GGT	TB	APRI/Forn's index/Fibrosure		
5.0 ± 5.7*/46	EC (54.4), LT (30.4), AP (15.2)	13.5 ± 5*	-/↔	↔	↔/↔		↑	↔/-/-	- Total bilirubin was increased in Fontan patients after long-term follow-up.	[66]
3.5/80	EC (75.2), LT (15.2), Other (9.7)	10.3			↔/↔	-/↑	↔	-/-/↑	- GGT was increased in Fontan patients after long-term follow-up. - FibroSure was increased in association with the duration of the Fontan operation.	[44]
4.9 (1.2-15.8)†/51	LT (73), EC (27)	4.6 ± 2.3*	↔/↔	↔	↔/↔	↔/↔	↔		- AST, ALT, and GGT were elevated after long-term Fontan operation.	[15]
		11.2 ± 3.2*	↔/↔	↔	↑/↑	-/↑	↔			
5.4 (1.3-29.3)†/64	EC (76.6), LT (12.5), KS (9.4), AP (1.5)	12.1 (2.8-20.9)†	↔/↔		↑/↑	-/↑			- Liver enzymes and GGT were elevated after long-term Fontan surgery.	[38]
13.7 (5.9-16.8)†/22	NA	9.6 (1.0-12.9)†	-/↓	↓	↑/↑	-/↑		↑/-/-	- Thrombocytopenia, liver dysfunction, and increased APRI were found in patients after Fontan operation.	[49]
NA/39	LT (95), EC (5)	0	↔/↔	↔	↔/↔	↔/↔	↔	-/-/-	- FibroTest was increased in association with length of time after Fontan surgery.	[59]
		5.7 ± 3.4*	↔/↔	↔	↔/↔	↔/↔	↔	-/-/↑		
2.9 (0.6-19)†/55	EC (85), LT (15)	10.1 (0-17.4)†		↔	↔/↔		↔		- Liver function test was unchanged in Fontan patients after long-term follow-up	[55]
3.1 (1.9-3.8)†/19	EC (68), LT (16)	5.4 ± 4.1*	↔/↔	↔	↔/↔	↔/↔	↔		- Blood tests were still normal after mid-term follow-up in Fontan patients.	[56]

*Mean ± SD, †Median (IQR). Abbreviations: Alb, albumin; ALP, Alkaline phosphatase; ALT, alanine aminotransferase; AP, atriopulmonary; APRI, AST to Platelet Ratio Index; AST, aspartate aminotransferase; CBC, complete blood count; EC, extracardiac conduit; FALD, Fontan-associated liver disease; GGT, gamma-glutamyl transferase; Hb, hemoglobin; KS, Kawashima operation; LFT, liver function test; LT, lateral tunnel; Plt, platelet count; TB, total bilirubin.

detect the potential subtle changes associated with FALD. Second, FALD is multifactorial. The effects of duration after Fontan operation on FALD could be modified by other factors. Possibilities include the pressure in the Fontan circuit, the severity of underlying cardiac diseases and ischemic liver insults from cyanosis prior to the Fontan operation or decompensation of the hepatic arterial buffer response. According to the available data, no specific time course of FALD could be characterized. A summary of these findings in both pediatric and adult Fontan patients is shown in **Tables 2**, **3**.

Imaging for the screening of FALD

Ultrasound of the upper abdomen

Ultrasound of the upper abdomen has been used as a screening modality for the diagnosis of FALD (**Tables 4**, **5**). The most ominous presentation is the presence of heterogeneous parenchyma (16-92%), which was the most common finding in Fontan patients [29, 36, 40, 44, 55]. Other findings consist of signs of portal hypertension, cirrhosis and liver nodules [15, 40, 45, 56]. Some studies showed that heterogeneous parenchyma and cirrhosis, as detected by ultrasound of the liver, were associated with the duration of Fontan operation [50, 55]. It has also been shown that this modality could detect FALD earlier than the serum biomarkers [27, 62]. However, the weakness of this screening modality is that the interpretations can be somewhat subjective and rely on the experience of the radiologists. In addition, this procedure can be difficult to perform in obese patients. Although reports currently available suggest that ultrasound scans of the upper abdomen are a particularly useful modality for the tentative screening of Fontan patients, it still lacks the delineated, detailed findings that are necessary for the establishment of the timescale of the progression of the disease, and thus it is not sufficiently reliable for use as an early diagnostic tool.

Computerized tomography (CT) scans or magnetic resonance imaging (MRI) of the upper abdomen for the diagnosis of FALD

The use of CT scans or MRI of the upper abdomen are non-invasive modalities capable of the detection of liver diseases, and the findings can be more delineating and detailed than those from ultrasound. However, due to the risk from exposure to the x-ray beams and contrast media, CT scans are not frequently used in children. The most common finding in CT scans or MRI of the upper abdomen in both children and adult Fontan patients is parenchymal enhancement (68-98%) which corresponds to mosaic, reticular, or nutmeg-liver patterns [10, 23, 24, 36, 53-55]. The other common findings are cirrhosis (26-73%) and portal hypertension (18-40%) [23, 24, 36, 41, 51, 53-55]. Interestingly, liver nodules have been frequently discovered in Fontan patients [10, 24, 39-41, 51, 53-55, 63]. Liver nodules present as multiple, regenerative arterial hyper-enhanced masses located in the periphery. A number of studies reported that CT scans or MRI of the upper abdomen could potentially detect the presence of liver nodules [10, 24, 53, 54, 63]. Liver nodules were detected in 6.1% of cases using ultrasound, while 31.8% and 39.6% were detected by CT scans and MRI, respectively [43]. In addition, it has been shown that the nodules detected by CT scans or MRI of the upper abdomen were associated with the time elapsed after Fontan surgery [10, 40, 51], and show a strong correlation with abnormal liver histology [10, 41].

In some studies, however, inconsistent findings have been reported. In adult Fontan patients, it has been shown that liver abnormalities detected by CT scans or MRI of the upper abdomen did not show a correlation with the presence of liver fibrosis evidenced by histology [23]. Additionally, the benign nodules in post-Fontan patients could be demonstrated by MRI as washed-out lesions, presenting in a similar fashion to HCC features [39]. The reports pertinent to the CT scans and MRI of the upper abdomen in children and adult Fontan patients are summarized in **Table 6**.

Although CT scans or MRI of the upper abdomen could be essential tools for the diagnosis of cirrhosis, liver nodules and HCC, a liver biopsy should always be performed in the case of suspected HCC. The imaging studies cannot be substitutes for liver biopsy because of the radiographic findings of liver nodules, which sometimes mimic HCC. Furthermore, conven-

Table 4. Ultrasound and ultrasound liver elastography for the diagnosis of FALD in adults

Average age at Fontan operation (year)/Number of patients	Type of Fontan (%)	Duration after Fontan operation (year)	U/S upper abdomen				Ultrasound liver elastography		Histology	Interpretations	References
			Heterogeneous parenchyma (%)	Portal HT (%)	Cirrhosis (%)	Liver nodule (%)	Type (Machine)	Liver stiffness			
2.9 (1.3-40.7)†/45	LT (82), AP (8), EC (8)	9.9 (0.1-32.5)†					TE (Echosens)	21.4 ± 10.8‡	↑ Centrilobular fibrosis	- Liver stiffness measured by TE was associated with centrilobular fibrosis.	[35]
3.6 (1-29)†/26	NA	10.5 (4-17)†	+ (92)				TE (Echosens)	18.2 ± 3.3‡		- Liver ultrasound demonstrated heterogeneous parenchyma. - Liver stiffness was increased, but was not correlated with the duration of surgery.	[36]
6.4 (2.3-28.1)†/5	EC (37.5), LT (37.5)	21.1 ± 4*	+ (40)	+ (20)		+ (60)	Fibroscan (Echosens)	22.4 (17.3-36.3)‡		- Heterogeneous parenchyma and liver nodules were detected by ultrasound in about half of Fontan patients. - Liver stiffness was associated with the duration of the Fontan operation.	[56]
5 (3-6.3)†/38	EC (40), AP (37), LT (18)	21.4 ± 5.5*	+ (16)				TE (Fibroscan 502)	22.5 (8.8-45.7)‡	↑ collagen proportionate area	- Heterogeneous parenchyma was associated with collagen deposition in the liver. - Liver stiffness was not correlated with the histology.	[53]
11.3 ± 5.1*/49	EC (61.2), LT (26.5), AP (8.2)	14.8 ± 7.1*				-	ARFI (Siemen Acuson)	2.64 ± 0.81‡‡		- Liver ultrasound was not sufficiently sensitive to detect liver nodules. - Liver stiffness was increased in Fontan patients.	[63]
4 (1-16)†/59	EC (93), AP (7)	18 (11-34)†					SWE (Philips iU22)	9.1 (3.9-18.5)‡ (METAVIR)		- Liver stiffness was correlated with the duration of the Fontan operation.	[57]
NA/14	NA	24.7 ± 6.2*					SWE (GE LOGIQ E9)	13.58 ± 1.82‡	Not correlated with CHF score	- Liver stiffness was not correlated with the histology.	[61]
2 (0.9-11.7)†/74	LT (61), EC (34)	14.9 (3.1-25.3)†	+ (50)						↑ High-grade CHF score	- Heterogeneous parenchyma on liver ultrasound was associated with a high-grade CHF score.	[17]

*Mean ± SD, †Median (IQR). ‡Liver stiffness in kPa, ‡‡Liver stiffness in m/s. Abbreviations: AP, atriopulmonary; ARFI, acoustic radiation force impulse; CD, collagen deposit; CHF, congestive hepatic fibrosis; EC, extracardiac conduit; HT, hypertension; kPa, kilopascal; LT, lateral tunnel; SWE, shear wave elastography; TE, transient elastography; U/S, ultrasound.

Table 5. Ultrasound and ultrasound liver elastography for the diagnosis of FALD in children

Average age at Fontan operation (year)/Number of patients	Type of Fontan (%)	Duration after Fontan operation (year)	U/S upper abdomen				Ultrasound liver elastography		Histology	Interpretations	References
			Heterogeneous parenchyma (%)	Portal HT (%)	Cirrhosis (%)	Liver nodules (%)	Type (machine)	Liver stiffness			
3.1 (1.9-3.8)†/11	EC (68), LT (16)	5.4 ± 4.1*	+ (27)	+ (18)			Fibroscan (Echosens)	14.6 (7.1-24.2)‡		- Less than one-third of Fontan patients had ultrasonographic changes. - Liver stiffness measured by Fibroscan was associated with the duration of Fontan operation.	[56]
3.5/117	EC (75.2), LT (15.2), Other (9.7)	10.3	+ (71)	+ (33)	+ (15)		Fibroscan (Echosens)	28‡		- Heterogeneous parenchyma is the most common finding detected by liver ultrasound. - Liver stiffness measured by Fibroscan was associated with the duration of Fontan operation.	[44]
NA/152	EC (64.5), AP (27) LT (8.5)	18.3	+ (70)		+ (54)	+ (30)	Fibroscan (Echosens)	26.2‡		- Heterogeneous parenchyma and cirrhosis were common features in FALD. - Liver stiffness measured by Fibroscan was increased after very long-term follow-up in Fontan patients.	[40]
NA/39	LT (95), EC (5)	5.7 ± 3.4*					Fibroscan (Echosens)	2.9 ± 1.0‡‡		- Liver stiffness measured by Fibroscan was increased after mid-term follow-up.	[59]
13.7 (5.9-16.8)†/22	NA	9.6 (1.0-12.9)†					TE (Echosens)	18.6‡		- Liver stiffness measured by TE was increased in Fontan patients but was not correlated with age at Fontan or duration of surgery.	[49]
5.04 ± 5.74*/46	EC (54.4), LT (30.4), AP (15.2)	13.5 ± 5*					TE (Echosens)	21.1 ± 8.0‡		- Liver stiffness measured by TE was increased in Fontan patients and correlated with age at Fontan operation.	[66]
2 (1-16)†/40	EC (62.5), LT (37.5)	1-5 5-10 >10	+ (6) + (22) + (50)		+ (6) - + (29)		ARFI (Siemens-Acuson)	2.1 ± 0.2‡‡ 2.1 ± 0.3‡‡ 2.2 ± 0.7‡‡		- Heterogeneous parenchyma and cirrhosis detected by liver ultrasound were increased in association with the duration of Fontan operation. - ARFI was elevated in all Fontan patients and was not correlated with the duration of surgery.	[50]
5.4/64	EC (76.6), LT (12.5), KS (9.4), AP (1.5)	12.1					ARFI (Siemens-Acuson)	1.95‡‡		- Liver stiffness measured by ARFI was increased in Fontan patients.	[38]

33.5 (18-52)†/18	NA	- 24-72 hr - prior D/C - 6 mo					SWE (Siemens-Acuson)	2.28 ± 0.31‡‡ 2.22 ± 0.38‡‡ 2.08 ± 0.24‡‡		- Liver stiffness measured by SWE was increased immediately after Fontan operation and persisted for at least 6 months.	[67]
NA/41	NA	11 ± 6*					SWE (US-SWE system)	15.6‡	Cirrhosis (20%), Liver fibrosis (70%)	- Liver stiffness measured by SWE was associated with cirrhosis and liver fibrosis examined by histology but was not correlated with the duration of Fontan surgery.	[34]
4.9 (1.2-15.8)†/51	LT (73), EC (27)	4.6 ± 2.3* 12.5 ± 3.1*	+ (51)	+ (44)	+ (77)					- In the majority of Fontan patients with long-term follow-up, the liver ultrasound showed heterogeneous parenchyma and cirrhosis.	[15]
2.9 (0.6-19)†/55	EC (85), LT (15)	0-5 5-10 10-15 >15	+ (17) + (60) + (65) + (75)		+ (8) + (20) + (55) + (63)	- + (27) + (60) + (38)				- Heterogeneous parenchyma and cirrhosis detected by liver ultrasound were associated with the duration of Fontan operation.	[55]

*Mean ± SD, †Median (IQR). ‡Liver stiffness in kPa, ‡‡Liver stiffness in m/s. Abbreviations: AP, atropulmonary; ARFI, acoustic radiation force impulse; D/C, discharge; EC, extracardiac conduit; HT, hypertension; kPa, kilopascal; LT, lateral tunnel; SWE, shear wave elastography; TE, transient elastography; U/S, ultrasound.

Table 6. Computerized tomography (CT) scan or magnetic resonance imaging (MRI) of upper abdomen for the diagnosis of FALD in children and adults

Average age at Fontan operation (year)/Number of patients	Type of Fontan (%)	Duration after Fontan operation (year)	Modality (N)	Major Findings				Histology	Interpretations	References
				Parenchymal enhancement (%)	Cirrhosis (%)	Portal HT (%)	Liver nodules (%)			
Children										
2.9 (0.6-19)†/55	EC (85), LT (15)	10.1 (0-17.4)†	CT (17), MRI (3)	+ (74)	+ (26)		+ (21)		- Parenchymal enhancement in the portal phase was found in most Fontan patients after long-term follow-up.	[55]
Adults										
4 (2-9)†/50	AP (40), LT (34)	22 (16-26)†	MRI (50)		+ (68)	+ (32)	+ (26)	HCC by liver biopsy	- MRI of the upper abdomen could detect HCC features that correlated with liver biopsy.	[41]
NA/30	NA	20 (8-29)†	MRI (30)				+ washout (97)	HCC by liver biopsy (atypical nodules: HCC 50%)	- Benign nodules in post-Fontan patients could show HCC features in MRI.	[39]
6 (3-9)†/37	AP (43), EC (30), LT (27)	22 (19-28)†	CT (21), MRI (16)	+ (86)	+ (73)	+ (30)	+ (46)		- CT or MRI of the upper abdomen was a sensitive tool for the detection of liver abnormalities in Fontan patients.	[54]

NA/130	EC (64), AP (28) LT (8)	18.3	MRI (93), CT (37)				+ (47.7)	HCC by liver biopsy (28.5% of hypervascular wash out lesion in CT or MRI)	- CT or MRI of the upper abdomen could detect liver nodules which were associated with time post-Fontan operation >10 years. - Liver nodules which are highly suspicious of HCC should be investigated by a liver biopsy.	[40]
4 (2-6.8)†/145	NA	19 (17-23)†	CT (11), MRI (19)	+	+	+	+		- CT or MRI of the upper abdomen could potentially detect Fontan-associated liver disease.	[24]
5 (0.1-40.7)†/241	LT (53), AP (37), EC (2)	20.3 (5.4-34.5)†	CT (45), MRI (9)	+ (98)	+ (50)	+ (40)		Not correlated with imaging	- There was no correlation between liver abnormalities on CT/MRI and liver fibrosis by histology.	[23]
5 (3-6.3)†/38	EC (40), AP (37)	21.4 ± 5.5*	CT (8), MRI (30)	+ (87)	+	+ (18)	+ (24)		- Parenchymal enhancement on CT of the upper abdomen was the most common liver abnormality in Fontan patients.	[53]
11.3 ± 5.1*/49	EC (61.2), LT (26.5), AP (8.2)	14.8 ± 7.1*	CT (44), MRI (48)				+ (31.8)		- In one-third of Fontan patients, liver nodules were detected by CT scan.	[63]
13 (10-35)†/26	NA	10.5 (4-17)†	CT (19)	+ (68)	+ (32)				- After long-term follow-up, CT of the upper abdomen showed liver parenchyma enhancement or cirrhosis in most Fontan patients.	[36]
4.2 ± 4.1*/139	LT (71), AP (35), EC (33)	0 11.5 ± 4.7*	CT (139)		- + (25.9)		- + (2.9)		- Cirrhosis and liver nodules detected by CT of the upper abdomen were associated with the duration of Fontan operation.	[51]
NA/12	EC (100)	14.1 (6.9-26.4)†	CT (12)	+ (67)		+ (17)		Liver fibrosis and cirrhosis by liver biopsy	- All hypervascular nodules detected by CT of the upper abdomen were associated with cirrhosis. - Liver fibrosis and cirrhosis were associated with the duration of Fontan operation.	[10]

*Mean ± SD, †Median (IQR). Abbreviations: AP, atriopulmonary; CT, computerized tomography; EC, extracardiac conduit; HCC, hepatocellular carcinoma; HT, hypertension; IVC, inferior vena cava; LT, lateral tunnel; MRI, magnetic resonance imaging.

tional CT scans and MRI, as well as ultrasound, of the upper abdomen could detect liver diseases only when the anatomical changes have already occurred. These imaging studies may not be ideal screening tools for detection of the early phase of FALD.

Modalities to assess liver fibrosis in FALD

Ultrasound liver elastography

Recently, ultrasound liver elastography has been introduced as a new modality for early screening. It is used to measure liver stiffness in order to detect fibrosis in cases of chronic liver disease [34, 64, 65]. A number of studies demonstrated that an increase in liver stiffness detected by Fibroscan [40, 59, 66] or shear wave elastography [38, 63, 67, 68] was an indicator of FALD in both children and adult Fontan patients. In addition, many studies reported that liver stiffness was associated with the duration of the Fontan operation [38, 40, 44, 56, 57, 59, 63, 66, 67], and a strong correlation was shown between the progression of liver fibrosis in children [34] and adults following Fontan surgery [35]. However, a number of studies reported otherwise. The inconsistent findings showed that liver stiffness measured by ultrasound elastography was not associated with the time after Fontan surgery and liver fibrosis [34, 36, 49, 50]. A summary of findings from these reports are shown in **Tables 4**, **5**.

Since both congestion and fibrosis affect liver stiffness, it is unavoidable that both factors are assessed by ultrasound liver elastography. Unlike other chronic liver diseases, congestive hepatopathy is concomitant with FALD. Liver stiffness increases immediately after Fontan operation due to liver congestion [67]. In addition, liver congestion might deteriorate when a patient develops heart failure. So theoretically, ultrasound liver elastography is not applicable for the screening of FALD and in addition there are currently no cut off values in this area for FALD.

Magnetic resonance elastography (MRE) of the liver

Magnetic resonance elastography (MRE) has been proposed as a novel modality that could be implemented as a highly sensitive tool for the early screening and evaluation of FALD [37, 69]. It offers a higher reliability than ultrasound as regards liver elastography in obese and ascites patients [70, 71]. The use of MRE in adult Fontan patients has demonstrated that elevated liver stiffness is associated with GGT, creatinine level, MELD score, and MELD-XI score [41]. In addition, studies have found that liver stiffness shows a correlation with central venous hypertension, increased Fontan pressure, pulmonary vascular resistance, and a reduction in cardiac output [37, 41, 43]. MRE has also been shown to be associated with length of time after the Fontan operation [18, 37, 41, 72]. A summary of reports on the MRE of the liver in Fontan patients is shown in **Table 7**.

Despite those promising reports, it is still not possible to distinguish clearly between liver congestion and liver fibrosis in the liver stiffness measured by MRE [69, 73]. Currently, there is only one study which showed a correlation between liver stiffness and histological changes by total fibrosis score [41]. Further studies to confirm the usefulness of MRE are still needed. In addition, cost and availability issues are practical concerns in the implementation of its use as a screening tool in post-Fontan patients.

Hepatocellular carcinoma in patients with FALD

The most serious complication of FALD is liver malignancy. In 2018, the prevalence of HCC in patients with FALD worldwide was discovered to be about 1.3% [74]. The study demonstrated that patients who were asymptomatic when HCC was detected appeared to have a better prognosis than those who were symptomatic [29]. So, all Fontan patients with severe liver fibrosis or cirrhosis should be recruited onto HCC surveillance programs and monitored for development of the disease. Unfortunately, the hallmark features of HCC from a CT scan which include arterial contrast-enhancing lesions and washout appearance in portal venous and delay phases could also indicate regenerative nodular hyperplasia, benign liver nodules. In these cases, MRI with hepatocyte-specific contrast media could differentiate HCC from benign lesions.

Table 7. Magnetic resonance elastography (MRE) of the liver for the diagnosis of FALD in adults

Average age at Fontan operation (year)/ Number of patients	Type of Fontan (%)	Duration after Fontan operation (year)	Liver stiffness (kPa)	Correlated with	Interpretations	References
NA/16	AP (44), LT (56)	19 (5-26)†	5.1 (3.4-8.2)†	↑ duration of Fontan operation	- Liver stiffness measured was elevated in association with the duration of Fontan operation.	[18]
4 (2-9)†/50	AP (40), LT (34)	22 (16-26)†	5.5 ± 1.4*	↑ total fibrosis score ↑ time since Fontan operation ↑ Fontan pressure ↑ PVR ↑ malignant nodules ↑ varices ↑ GGT, creatinine, MELD score ↓ fenestration ↓ cardiac index	- Liver stiffness was associated with total fibrosis score, duration of Fontan operation, Fontan pressure, PVR, malignant nodules, varices, GGT, creatinine, and MELD score. - Liver stiffness measured showed an inverse correlation with fenestration and cardiac index.	[41]
NA/57	EC (56), AP (44)	12.9 (4.4-23.3)†	5.6	↑ CVP ↑ duration of Fontan operation	- Liver stiffness measured was elevated in association with CVP and duration of Fontan operation.	[37]
5 (3-6)†/22	AP (46)	Baseline	5.4 ± 1.1*	↑ MELD-XI score ↑ PVR ↑ NT-pro BNP	- Liver stiffness measured was elevated in association with PVR, MELD-XI score, and NT-pro BNP.	[43]
		2 yrs from baseline	5.8 ± 0.9*			
NA/14	LT (60), EC (27), AP (13)	16.5 (6.9-32.9)†	4 (3.4-6.2)†	↑ duration of Fontan operation ↓ cardiac index	- Liver stiffness measured was inversely correlation to cardiac index and was elevated in association with the duration of Fontan operation.	[72]

*Mean ± SD, †Median (IQR). Abbreviations: AP, atriopulmonary; CVP, central venous pressure; EC, extracardiac conduit; GGT, gamma-glutamyl transferase; HCC, hepatocellular carcinoma; HT, hypertension; IVC, inferior vena cava; LT, lateral tunnel; MELD, Model for End-stage Liver Disease; MELD-XI, Model for End-stage Liver Disease excluding INR; NT-pro BNP, N-terminal pro B-type natriuretic peptide; PVR, pulmonary vascular resistance.

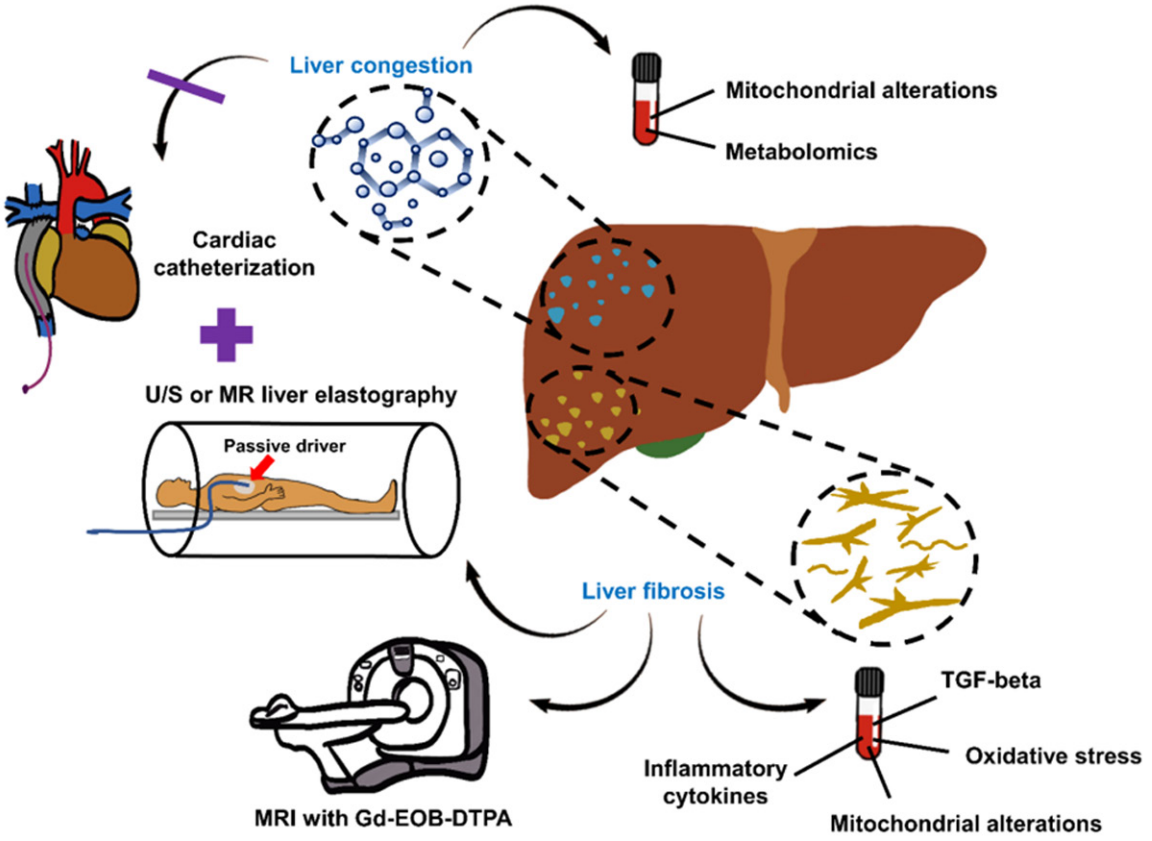

Figure 4. Proposed multimodal approach for the evaluation of FALD in the future. Gd-EOB-DTPA: gadolinium ethoxybenzyl-diethylenetriaminepentaacetic acid; MRI: magnetic resonance imaging; TGF-β: transforming growth factor-beta; U/S: ultrasound.

Gaps in current knowledge and future direction for FALD screening methods

FALD is a challenging issue that impacts both mortality rate and quality of life in Fontan patients. Currently, there is no single non-invasive modality that can detect all the conditions associated with FALD. Moreover, liver biopsies are not routinely carried out in Fontan patients, especially in children. Therefore, a multimodal approach is essential for the evaluation and diagnosis of FALD (**Figure 4**). Identification of novel molecular biomarkers that could detect early fibrosis of the liver or determine the prognosis of FALD are essential. These biomarkers may include transforming growth factor-β (TGF-β), and oxidative stress markers and inflammatory cytokines. Understanding of any relationships between mitochondrial and metabolomic changes could also be crucial in understanding the progress of these conditions and should be explored in future studies. With regard to the knowledge around Fontan pathophysiology, novel non-invasive imaging studies which could directly measure fibrosis, but not congestion, in the liver would be extremely beneficial. These potential modalities may include MRI with gadolinium ethoxybenzyl-diethylenetriaminepentaacetic acid (Gd-EOB-DTPA) [75], and ultrasound elastography or MRE adjusted with Fontan pressure.

Conclusion

Due to the effectiveness of the Fontan operation, there is an increasing chance of those patients surviving into adulthood. However, many patients develop liver complications in the long-term follow-up, ranging from liver fibrosis, liver cirrhosis, and liver cancer. FALD is still a challenging complication worldwide, and investigations to allow us to understand the unique pathophysiology and natural history of FALD are crucial. Currently, no single non-inva-

sive modality effectively evaluates FALD, and an invasive liver biopsy remains the imperfect gold standard for diagnosis. Longitudinal studies initiated prior to the Fontan operation with long-term follow-up with a multimodality approach by a multidisciplinary team could elucidate the natural history of FALD and improve the management of these Fontan patients.

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None.

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