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REVIEW ARTICLE

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Surveillance for liver complications after the Fontan procedure

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Abstract

The physiological consequences of the Fontan circulation impose risk for hepatic dysfunction and may culminate in hepatic fibrosis, cirrhosis, and hepatocellular carcinoma. Consensus regarding appropriate surveillance modalities to diagnose liver disease in Fontan patients is lacking, in part due to the relative lack of strong evidence and prospective studies in this patient population. The goal of this paper is to critically review the current evidence and provide recommendations for the surveillance of hepatic complications in the post-Fontan patient population.

KEYWORDS
cirrhosis, Fontan

1 | INTRODUCTION

The Fontan procedure is considered the definitive palliation for patients with single-ventricle physiology.[1] The procedure, which has had many modifications over the decades, results in an anastomosis between the vena cavae or right atrium and the pulmonary arteries, whereby systemic venous blood is returned to the lungs without utilizing a pumping chamber.[1,2] The Fontan operation maintains near-normal systemic oxygenation while inducing a state of systemic venous hypertension and relatively decreased cardiac output.[2] The physiological consequences of the operation place individuals with a Fontan circulation at risk for long-term complications related to passive venous congestion of the liver.[3,4] A recent long-term follow-up study reported 10-, 20-, and 30-year survival of 74%, 61%, and 43% respectively after the Fontan procedure.[5] As more patients reach adulthood,[6,7] hepatic complications are increasingly recognized.[8] Therefore, implementation of evidence-based surveillance and management of post-Fontan hepatic complications is essential in this population. The goal of this paper is to synthesize the relevant literature and define an approach to the surveillance of hepatic complications in the post-Fontan patient population.

2 | PATHOPHYSIOLOGY OF LIVER DYSFUNCTION IN FONTAN PATIENTS

Hepatic dysfunction after the Fontan operation is multifactorial and may culminate in hepatic fibrosis and cirrhosis.[9] Recent reports of hepatocellular carcinoma in patients after Fontan operation have added further concern.[10] The hepatic changes secondary to the Fontan circulation may be divided broadly into those related to passive venous congestion; low cardiac output; and complications of portal hypertension. It should be recognized that in many patients, passive venous congestion and low cardiac output coexist.

Several of the physiologic derangements inherent to the Fontan circulation compromise the liver, including hypoxemia in the setting of chronic low cardiac output state, chronic elevation of central venous pressure, and increased mesenteric vascular resistance. It is important to note that while not all Fontan patients have low cardiac output, studies suggest that cardiac output is on average decreased in Fontan patients.[11,12] A retrospective review of catheterization data from adult and pediatric Fontan patients reported average cardiac indices of 2.7 ± 0.8 and 2.8 ± 0.7 L/min/m^2, respectively (normal range 2.5–4.0 L/min/m^2).[13] Patients may have also perioperative ischemic insults to the liver, or veno-venous connections which compound hypoxic injury to the liver.[14] Over time, "Fontan failure" may develop with further elevations in systemic venous pressure, decline in cardiac output, and multisystem dysfunction. Protein-losing enteropathy (PLE) develops in 10–15% of patients.[15] Continuous systemic venous back-pressure on the liver results in hepatic changes secondary to passive venous congestion. This passive venous congestion is continuous, in contrast to the more intermittent or pulsatile back-pressure experienced in congestive hepatopathy associated with other cardiac defects,

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TABLE 1 Hepatic changes associated with passive venous congestion, low cardiac output, and cardiac cirrhosis

	Histological changes	Biochemical abnormalities	Clinical findings
Passive venous congestion	• Zone 3 sinusoidal dilation • Hemorrhagic necrosis	• Elevated indirect bilirubin • Prolonged international normalized ratio (INR) • Mild elevation of aminotransferases (3-5 times ULN)	• Ascites • Hepatomegaly • Jaundice • Presence of hepato-jugular reflux
Low cardiac out/hepatic ischemia	• Zone 3 hepatic necrosis	Acute: • Hepatocellular pattern of aminotransferase elevation (50-250 times ULN) • Elevated LDH level Chronic: • Cholestatic pattern (bilirubin range 10-15 mg/dL) • Sustained elevated of AST, ALT, and alkaline phosphatase (3–5 times ULN)	
Cardiac cirrhosis	• Central vein to central vein bridging fibrosis • Nodule formation	• Hypoalbuminemia • APRI score >2 • FIB-4 score >3.25	• Ascites • Variceal bleeding • Hepatic encephalopathy • Jaundice

Abbreviation: ULN, upper limit of normal.

such as tricuspid regurgitation. Exacerbation of congestive heart failure may further exacerbate injury in the setting of hepatic congestion.[14] Chronic hepatic ischemia from low cardiac output may also instigate hepatic fibrosis.[16]

Chronic vascular shear-stress and injury in the setting of Fontan physiology instigate fibrogenic pathways that may culminate in cirrhosis. In addition, a variety of chronic liver diseases, all of which may occur in the patient with congenital heart disease including viral hepatitis, alcoholic liver disease, nonalcoholic fatty liver disease, autoimmune hepatitis, and primary biliary cholangitis, can increase the risk for cirrhosis. Less common etiologies of chronic liver disease in this patient group include biliary causes, such as biliary atresia, metabolic diseases such as Wilson disease and hemochromatosis, and hepatic venous outflow obstruction in the setting of primary vascular disorders.

It is recognized that patients with single ventricle physiology may already have hepatic damage prior to creation of the Fontan circulation. Studies report the existence of both portal and sinusoidal fibrosis in patients who died within 30 to 35 days of the Fontan procedure, suggesting that these changes existed at the time of Fontan creation.[17,18] The extent of fibrosis in these studies was attributed in part to elevated right atrial pressure, which induces sinusoidal congestion. Similarly, older age at time of Fontan operation was found to correlate with severity of hepatic fibrosis, suggesting that extended duration of single ventricle physiology induces fibrogenic changes.

Investigators have reported detection of HCV RNA (which reflects current infection) in approximately 4% of patients with congenital heart disease (CHD) who had heart surgery prior to implementation of high sensitivity tests for HCV screening in 1992.[19] HCV antibodies indicating prior exposure or infection were detected in 8% of this patient cohort, and in 5% in another cohort.[19,20] Performance of cardiac operations before 1992 has been directly related to risk of HCV infection in patients with CHD. Patients with CHD who had cardiac surgery prior to initiation of routine hepatitis C screening have a five-fold increased prevalence of HCV infection compared with the age-matched general population.[19,21,22]

2.1 | Manifestations of liver disease post-Fontan procedure

2.1.1 | Clinical features secondary to passive venous congestion of the liver

Whereas both chronic passive venous congestion and low cardiac output often coexist in post-Fontan patients, laboratory studies and physical examination may help to elucidate the contribution of each to hepatic dysfunction (Table 1). Patients with hepatic congestion may develop ascites, hepatomegaly, and jaundice. The hepato-jugular reflux is an important component of the physical examination which is suggestive of the presence of hepatic congestion. However, this physical exam finding may not be readily visualized in patients after Fontan operation due to the unique caval-pulmonary connections. Common laboratory findings include predominantly indirect hyperbilirubinemia,[23] decreased serum albumin, and prolongation of the prothrombin time (PT) out of proportion to other coagulation parameters. Aminotransferase elevation occurs in approximately one-third of patients with hepatic congestion and is generally mild, within 3 to 5 times the upper limit of normal.

2.1.2 | Clinical features secondary to low cardiac output

The pattern of laboratory abnormalities may help identify hepatic injury which is predominantly due to low cardiac output and hepatic ischemia. Acute ischemia is among the causes of a hepatocellular pattern of liver enzyme elevation, with an early and precipitous increase in aminotransferases to 50 to 250 times the upper limit of normal. This may be accompanied by an early increase in LDH levels. Acute hepatic ischemia occurs when a patient with chronic passive venous congestion of the

TABLE 2 Modalities to diagnose liver cirrhosis

Clinical	Symptoms	May be asymptomatic if compensated
		Anorexia Fatigue Weight loss
	Physical examination	Jaundice Spider nevi Palmar erythema Clubbing Gynecomastia Splenomegaly Asterixis Caput medusa
Laboratory evaluation	AST to platelet ratio index $(\text{APRI score}) = \frac{\text{AST/ULN}}{\text{Platelets } (10^9/\text{L})} \times 100$ $\text{FIB}-4 \text{ score} = \frac{\text{Age(y)} \times \text{AST/ULN} \times \text{ALT}^{1/2}}{\text{Platelets } (10^9/\text{L})}$	APRI <1.0—Cirrhosis is unlikely APRI >2.0—Suggests presence of cirrhosis FIB-4 <1.45—Cirrhosis is unlikely FIB-4 >3.25—Suggests presence of cirrhosis
Radiology	Ultrasonography	Nodular liver surface Increased echogenicity Irregular borders Splenomegaly
	Computed tomography (CT)	Reticular hepatic enhancement during portal venous phase
	Magnetic resonance elastography (MRE)	Monitors liver stiffness MRE >4.9 diagnostic of cirrhosis, but requires validation in Fontan population since hepatic congestion alone without hepatic fibrosis can increase liver stiffness.
	Shear-wave elastography	Measures liver stiffness as surrogate for fibrosis
Pathology	Liver biopsy	Gold standard to diagnose cirrhosis. Transjugular, percutaneous, or radiographically guided Generally not required if other tests described above are confirmatory of cirrhosis

liver develops hypotension resulting in hepatic infarction. Chronic ischemia in the setting of depressed cardiac output may induce a more cholestatic pattern of liver enzyme abnormalities, with bilirubin levels ranging from 10 to 15 mg/dL and sustained elevation of AST, ALT, and alkaline phosphatase to three to five times the upper limit of normal.

2.1.3 | Clinical features secondary to cirrhosis

The clinical manifestations of cirrhosis are variable and correlate with severity of disease. Patients with compensated cirrhosis may be asymptomatic or may present with nonspecific symptoms such as anorexia, fatigue, or weight loss. Patients are defined as having decompensated cirrhosis if they develop any of the complications of ascites, hepatic encephalopathy, jaundice, or variceal bleeding. Physical examination findings suggestive of cirrhosis include spider nevi, palmar erythema, clubbing, gynecomastia, splenomegaly, asterixis, and caput medusa, all of which are seen predominantly in patients with decompensated cirrhosis.

2.1.3.1 | Diagnosis of cirrhosis

The diagnosis of cirrhosis relies on a combination of clinical, laboratory, and radiologic findings (Table 2). This diagnosis requires a greater index of suspicion in patients with compensated cirrhosis who may not manifest characteristic physical or laboratory findings. Several laboratory-based scoring systems have been devised which can supplement radiologic and clinical evidence in the diagnosis of cirrhosis in adults, although these scores and their "cutoffs" have yet to be validated in the Fontan population. The AST to platelet ratio index (APRI) score was devised to predict significant fibrosis and cirrhosis in patients with chronic hepatitis C and has subsequently been applied more broadly.[24] This score is calculated by dividing AST elevation by the platelet count and multiplying by a factor of 100. An APRI score <1 has a negative predictive value of 98% while an APRI score >2 has a positive predictive value of approximately 60% in diagnosing cirrhosis. The FIB-4 model is another scoring system which incorporates age, AST elevation, ALT elevation, and platelet count.[25] A FIB-4 score <1.45 has a negative predictive value of 94.7% to exclude a diagnosis of cirrhosis, while a score >3.25 has a positive predictive value of 82.1% to confirm the existence of significant fibrosis.[26] Baek et al.[27] compared various non-invasive hepatic fibrosis markers in a cross-sectional study of 204 patients who had undergone the Fontan procedure, 25.9% of whom had hepatic complications. Scores of liver fibrosis examined included the Forns index, APRI score, AST/ALT ratio, cirrhosis discriminant score, and Pohl score. Of these, the Forns index, which incorporates platelet count, GGT, age, and cholesterol, performed best with an area under the receiver operator curve (AUROC) of 0.786. The Model for

End Stage Liver Disease Excluding INR (MELD-XI) score was devised to predict short-term survival in patients with cirrhosis whose INR is artificially elevated by anticoagulation[28] and has subsequently been used to predict mortality after cardiac transplantation.[29,30] A recent retrospective review of Fontan patients who underwent transvenous hepatic biopsy at the time of routine cardiac catheterization revealed a positive correlation between MELD-XI and hepatic fibrosis scores on pathology (correlation coefficient = 0.4; $P = .003$), although receiver operator characteristic analysis did not identify a score cutoff with adequate sensitivity and specificity.[31] These scores appear to be promising, but the specific cutoffs to diagnose or rule out cirrhosis in the Fontan population need to be validated.

Abdominal ultrasonography frequently is employed in the evaluation and diagnosis of liver disease and has been reported to have a sensitivity of 91% and specificity of 94% in diagnosing cirrhosis.[32] A nodular liver surface with increased echogenicity and irregular borders is suggestive of cirrhosis, but may be seen in Fontan patients even without cirrhosis. The radiologic appearance of the liver on CT may help define the extent of liver injury and likelihood of cirrhosis.[33] Reticular enhancement describes peripheral heterogenous enhancement during portal venous phase imaging and has been associated with more extensive fibrosis on histologic examination. In contrast, zonal enhancement suggests preservation of peri-hilar vascularity and is associated with a lower likelihood of cardiac cirrhosis.[33] Radiologic assessment of liver stiffness is increasingly employed in the staging of fibrosis. Hepatic stiffness which is a surrogate for hepatic fibrosis may be measured either by ultrasound based shear wave elastography or by magnetic resonance based elastography. In patients post Fontan, increased hepatic stiffness on ultrasound shear wave elastography was associated with high hepatic afterload and hepatic fibrosis.[34]

Recent studies indicate that magnetic resonance elastography (MRE) may also be an effective tool to monitor liver stiffness as a surrogate of fibrosis.[35] MRE has been effective in detecting imaging features of cirrhosis and hypervascular liver nodules.[36] MRE of the liver may also be added on to the cardiac MRI examination that many of these patients undergo. Liver stiffness values obtained via MRE are higher in Fontan patients when compared with control patients or patients with CHD who did not undergo a Fontan procedure.[37] Diagnosis of cirrhosis on the basis of increased stiffness requires caution since elevated central venous pressure can induce hepatic congestion, which also elevates liver stiffness.[35] A retrospective review of radiologic, laboratory, hemodynamic, and histopathologic data from 50 Fontan patients undergoing evaluation for liver disease revealed that increased liver stiffness on MRE correlated with APRI score, MELD score, time from Fontan, and Fontan pressures, suggesting that this index may constitute an effective means of screening Fontan patients for cirrhosis in the setting of hepatic congestion.[38] While adequate liver biopsy specimens were available in only 16% of the cohort studied, liver stiffness significantly correlated with histologic grade of fibrosis ($R = 0.74$, $P = .02$). However, more studies are needed to accurately correlate liver stiffness scores on MRE in patients with hepatic congestion with histologic change. Therefore, elevated liver stiffness on MRE should be correlated with laboratory studies, physical examination, and cardiac catheterization data to differentiate elevation due to hepatic congestion from elevation due to fibrosis; liver biopsy may be required if diagnosis of cirrhosis is still uncertain.

Liver biopsy may be pursued from a transjugular or percutaneous radiographically guided approach. Whereas liver biopsy is considered the gold standard in diagnosing cirrhosis, there are several inherent limitations including cost, sampling error, and potential complications such as pain and bleeding. Biopsy is generally not required to confirm a diagnosis in decompensated cirrhosis. Rychik et al. have published a prospective protocol for clinical evaluation of the liver in Fontan patients, with a recommendation of liver biopsy in all patients 10 years after Fontan.[14] It remains unclear if such an approach will result in actionable data for the clinical management of the patient, and whether such an approach will appeal to patients and their families.

2.1.3.2 | Complications of cirrhosis

Complications of cirrhosis include portal hypertension, jaundice, and hepatocellular carcinoma (HCC). Manifestations of portal hypertension include ascites, variceal bleeding, and hepatic encephalopathy. Onset of these clinical features marks the development of decompensated cirrhosis, although ascites frequently occurs in Fontan patients in the absence of cirrhosis. Hepatic encephalopathy is a rare complication of Fontan-related cirrhosis; a retrospective review of 40 Fontan patients diagnosed with cirrhosis identified hepatic encephalopathy in only one patient.[8] The reported incidence of varices in patients who have undergone the Fontan procedure ranges from 9.3% to 38%,[33,39,40] although reports of variceal bleeding are rare. In addition, splenomegaly and hypersplenism occur with the initial laboratory manifestation being thrombocytopenia. If ascites develops, the serum albumin ascites gradient (SAAG) and ascites total protein should be measured to determine if the ascites is of cardiac or hepatic origin.[41] In the absence of renal failure, when the cause of ascites is unclear, levels of BNP above 500 pg/mL suggest the ascites is more likely of cardiac origin. However, in post-Fontan patients who have both cardiac and hepatic dysfunction, the level of plasma BNP may be unreliable in differentiating ascites of hepatic origin from ascites of cardiac origin. In such situations, transjugular measurement of hepatic venous pressure gradient (HVPG) and liver biopsy may be undertaken to further elucidate the etiology of the ascites. The HVPG measures the difference between the wedged hepatic vein pressure (representing portal vein pressure) and the free hepatic vein pressure (representing IVC pressure). Catheterization of the hepatic vein (HV) to obtain HVPG generally is feasible in Fontan anatomy from either a jugular or femoral approach. The normal HVPG is <5 mm Hg; portal hypertension is diagnosed if the HVPG is ≥ 6 mm Hg. In patients with Fontan circulation but without cirrhosis both the free and wedged HV pressure are elevated, but the HVPG is <5 mm Hg. HVPG >6 mm Hg implies intrinsic liver disease in addition. As Fontan physiology imposes postsinusoidal obstruction, the hepatic venous pressure gradient (HPVG), which reflects hepatic sinusoidal pressure, may not always accurately reflect portal vein pressure.[33,39,42] Cannulation of the portal vein constitutes the most accurate assessment of portal pressures, but usually is not carried out because it adds on

complexity to what is otherwise a relatively easy procedure.9,16 Moreover, the additional information gained does not usually impact management. In patients with failing Fontan and cirrhosis both the wedged and free HV pressure are elevated and the HVPG is >6 mm Hg. In adults with HCV or alcoholic cirrhosis HVPG >10 mm Hg is considered clinically significant portal hypertension, with HVPG >12 mm Hg being associated with risk of variceal bleeding; such degrees of elevation in HVPG are uncommon in Fontan patients. Measurement of the HVPG is most helpful in determining whether ascites is of cardiac origin (normal HVPG) or hepatic origin (elevated HVPG). A HVPG above 12 mm Hg suggests significant portal hypertension and we suggest in such patients that if cardiac transplantation be required, the procedure be combined with a liver transplant.

Recent evidence suggests that patients after Fontan operation with portal hypertension may be at increased risk for adverse outcomes. A study of 73 Fontan patients with 17 years of follow up found that clinical features of portal hypertension included in the VAST (varices, ascites, splenomegaly, thrombocytopenia) score were significantly associated with major adverse events (death, need for heart transplant, or hepatocellular carcinoma) (OR = 9.8, 95% CI [2.9–32.7]).[42] Patients with portal hypertension may benefit from regular evaluation by a hepatologist.

2.1.3.3 | Screening for esophageal varices

Patients with cirrhosis are at risk for development of esophageal varices and variceal hemorrhage. Because mortality associated with an episode of variceal bleeding in patients with cirrhosis and without underlying cardiac disease is as high as 15–20%, it is important that measures be taken to decrease bleeding risk. All patients with cirrhosis therefore require screening for esophageal varices.[43] Upper gastrointestinal endoscopy is the only modality recommended for screening. If on endoscopy large varices are noted, prophylaxis to prevent variceal bleeding should be initiated with either nonselective beta-blockers or endoscopic variceal ligation to obliterate the varices. If small varices are noted, repeat endoscopy is carried out in 1–2 years. If no varices are noted, repeat endoscopy is carried out in 2–3 years.

2.1.3.4 | Hepatocellular carcinoma

Hepatocellular carcinoma is recognized increasingly as a late complication of the Fontan procedure,[10,44–46] usually in the setting of cirrhosis. HCC has also been reported as a rare complication of prolonged congestion of the liver in the setting of Budd-Chiari syndrome,[47] constrictive pericarditis,[48] and heart failure after corrective surgery for transposition of the great arteries,[49] As post-Fontan survival increases, the incidence of HCC is expected to increase in this population. Given the high case-fatality rate of HCC after the onset of symptoms, early diagnosis through screening of all patients with cirrhosis may improve patient survival.

3 | SUGGESTED LONG-TERM EVALUATION FOR LIVER DISEASE OF THE PATIENT POST FONTAN PROCEDURE

Thus far, consensus regarding appropriate surveillance modalities to diagnose liver disease in Fontan patients is lacking. This is due to the relative lack of strong evidence as studies of post-Fontan complications consist largely of retrospective cohort studies. Thus, our recommendations are primarily based on expert opinion rather than evidence.

It is uncertain when surveillance for liver disease should be initiated, and whether surveillance should be restricted to selected patients. Hepatic complications post-Fontan procedures have been correlated with the duration of the Fontan circulation.[9,27,33,50] The extent of hepatic fibrosis significantly correlates with hepatic vein pressures ($r = 0.83$, $P = .003$) and Fontan duration ($r = 0.75$, $P = .013$).[33] Hepatic complications have also been associated with decreased ventricular function ($P = .02$), sinus node dysfunction ($P = .034$), and arrhythmia ($P < .001$).[27] Therefore, it is logical to conclude that patients with long duration of Fontan circulation, ventricular dysfunction, and elevated central pressures may constitute a high-risk subgroup requiring more intensive monitoring for liver disease.

The risk of hepatic complications and fibrosis increases with duration post-Fontan; increases in risk of hepatic complications have been noted 10 years following creation of the Fontan circulation.[27] However, severe hepatic fibrosis has been reported as early as 5 years post-Fontan in a patient with elevated right atrial pressure,[51] and studies suggest that fibrosis may exist at the time of Fontan creation in patients with high right atrial pressures.[18,52] Consequently, we think it is reasonable to initiate screening for hepatic dysfunction even before Fontan creation irrespective of age. Screening should include liver biochemistry, calculation of the APRI, FIB-4, Forns index, or MELD-XI scores, and ultrasound of the liver with shear-wave elastography if available.

Current guidelines from the American College of Cardiology and American Heart Association recommend a minimum of annual clinical evaluation with a cardiologist experienced in the management of complex CHD.[53] At these evaluations, the history and physical examination should aim to detect complications or failure of the Fontan circulation, where increased central venous pressure may promote hepatic congestion and dysfunction. Signs and symptoms potentially suggestive of hepatic congestion include right upper quadrant discomfort, anorexia, nausea, hepatomegaly, and ascites.[50] However, many Fontan patients with biopsy-proven advanced liver disease may be largely asymptomatic from their liver disease,[50] thereby rendering the clinical history and physical examination alone an insensitive evaluation for the existence of hepatic involvement.

3.1 | Laboratory monitoring post Fontan

Abnormalities in liver enzymes have long been recognized in post-Fontan patients.[54–56] A cholestatic pattern of liver enzyme elevation, with mild elevation of alkaline phosphatase and total and direct bilirubin, is common, although the most prevalent abnormality is elevation of gamma-glutamyl transferase (GGT).[57–59] In the absence of PLE, serum albumin is preserved until the onset of decompensated cirrhosis.[33] Liver biochemical tests may be monitored every 2 to 3 years after Fontan completion with calculation of the APRI score, FIB-4 score, or Forns index to detect fibrosis. The pattern of liver

enzyme elevation should guide further diagnostic testing. For example, isolated indirect hyperbilirubinemia is suggestive of passive congestion whereas a hepatocellular pattern of injury with elevation of serum aminotransferases may be secondary to hepatic ischemia. APRI score, FIB-4 score, or Forns index suggestive of advanced hepatic fibrosis warrants liver elastography and perhaps a liver biopsy for confirmation of cirrhosis.

3.2 | Radiological imaging

There is no current consensus on the optimal time to initiate liver imaging in the post-Fontan population, and studies indicate that the timing and modality of liver imaging varies widely in clinical practice.[60] In a study of 60 adult Fontan patients who had undergone the Fontan procedure during childhood, 53 (88%) underwent hepatic imaging on average 18 years post-Fontan. Twenty-nine patients (54%) were noted to have significant hepatic derangements on imaging, including evidence of congestion, cirrhosis, and liver nodules. Those patients who underwent serial imaging demonstrated progression of hepatic derangements over time.[60] This finding, in combination with the known escalation of cirrhosis and neoplasm risk with time post-Fontan, suggests that earlier imaging with frequent surveillance is prudent to monitor for cirrhosis and liver masses.[9,33,46] We suggest liver ultrasound with shear–wave elastography 5 years (if available) post-Fontan to screen for liver disease., followed by and starting 10 years after Fontan, annual imaging with liver ultrasound. However, it is reasonable to start earlier in those patients with failing Fontan circulation characterized by elevated systemic venous pressures, given the known correlation between elevated mean right atrial pressures and cardiac cirrhosis.[46] Many patients can undergo hepatic MRE at the end of their cardiac MRI (as the MRE adds on only a few minutes to the procedure). If hepatic stiffness on MRE is elevated >4 kPa, annual hepatic imaging may be recommended; if hepatic stiffness is <4kPa, less frequent hepatic imaging may be reasonable. Hepatic stiffness >5 kPa may suggest advanced hepatic fibrosis and a liver biopsy may be required to confirm the diagnosis of cirrhosis.

3.3 | Evaluation of liver nodules in patients post Fontan procedure

Hypervascular nodules on arterial phase imaging of the liver frequently are detected in patients with high Fontan pressures.[33] These hypervascular nodules may be most commonly benign focal nodular hyperplasia (FNH) of the liver.[61] Detection of hypervascular nodules on imaging necessitates further evaluation, particularly in the setting of cirrhosis due to risk of HCC.[9,10,33] Masses smaller than one centimeter in diameter should be monitored with repeat liver ultrasound imaging in 3 months' time (Figure 1). Larger lesions require further evaluation with contrast-enhanced CT or MRI (in patients who do not have implanted defibrillators or pacemakers) and directed biopsy of the masses for nondiagnostic studies.[62] Growth of a mass within 3 months is more suggestive of HCC than FNH. The classic diagnostic features of HCC on hepatic imaging include enhancement during the hepatic arterial phase and "washout" during the portal vein phase. The "triple-phase" CT or MRI scan describes characteristics of the liver during the hepatic arterial phase 30–45 s after intravenous contrast injection in a peripheral systemic vein); portal vein phase 75–90 s after contrast injection); and the delayed phase (>5 min after contrast injection). The normal hepatic parenchyma shows contrast enhancement during the portal vein phase since the hepatic parenchyma receives blood from the portal vein. However, HCC derive blood almost exclusively from the hepatic artery and show enhancement before the rest of the hepatic parenchyma during the arterial phase. When the rest of the liver is showing enhancement during the portal vein phase, HCC no longer show enhancement because the tumors are not getting contrast enriched portal vein blood. The HCC appears darker than the rest of the liver. This phenomenon is termed "early washout". The normal hepatic parenchyma washes out contrast only after 5–10 min. In the presence of arterial enhancement "early washout" is diagnostic of HCC. In fact, HCC is the only tumor where a biopsy (because of observer variation and difficulty in differentiating from regenerative nodules) is inferior to imaging in making a diagnosis. Moreover, needle biopsy is associated with a small risk of seeding the needle track with tumor cells. The imaging characteristics of HCC may not always apply to patients post-Fontan since the high systemic venous pressure and low cardiac output may alter the typical contrast enhancement and washout imaging characteristics. Therefore, elevation of the tumor marker alpha-fetoprotein (AFP) may be important in making the diagnosis of HCC. An AFP >200 ng/mL in the setting of a hepatic mass is considered diagnostic of HCC. When the diagnosis is still in doubt a directed biopsy of the mass may be necessary. A negative biopsy does not rule out malignancy and follow up imaging is recommended in 3 months.

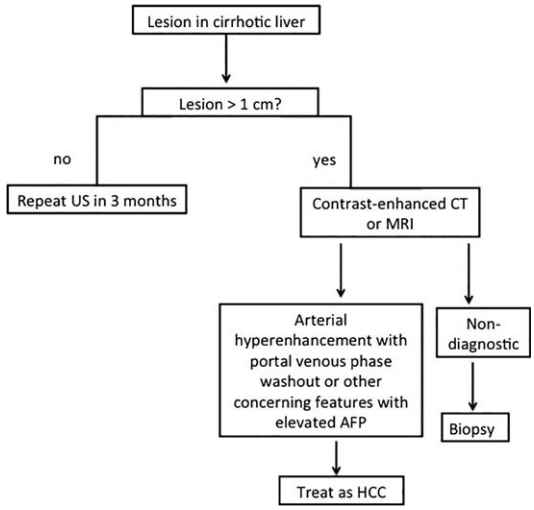

FIGURE 1 Recommended evaluation of liver nodules

We recommend implementation of HCC surveillance with twice annual ultrasonography and measurement of AFP in post-Fontan

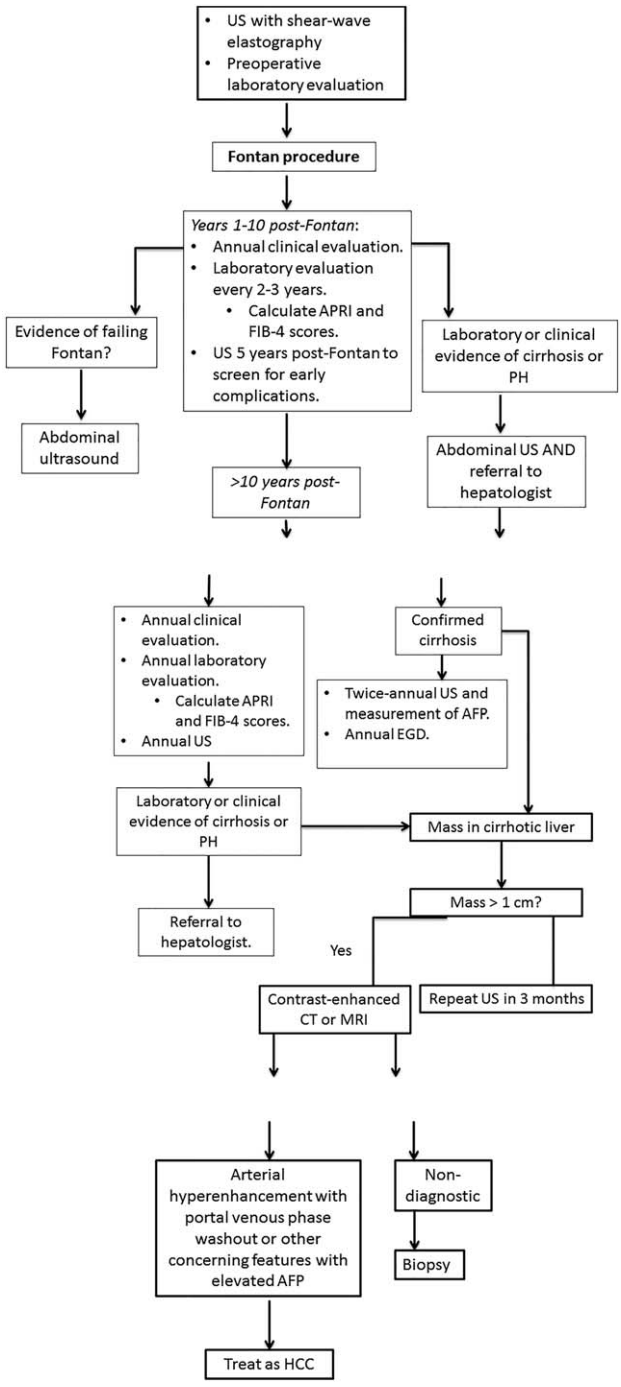

FIGURE 2 Liver surveillance before and after the Fontan procedure

patients with cirrhosis.[9,33] If a hepatic nodule is detected on ultrasound imaging, either a contrast enhanced CT or MRI scan should be carried out. If the diagnosis is still uncertain both a CT and MRI may need to be carried out. The presence of a cardiac pacemaker or implantable defibrillator may make MR imaging more challenging. Patients who have hepatic nodules with characteristic features on either CT or MR imaging (arterial hyperenhancement and portal venous washout), or hepatic masses with concomitant AFP levels >200 ng/mL should be considered to have HCC.

4 | SUMMARY RECOMMENDATIONS FOR LONG-TERM EVALUATION FOR LIVER DISEASE OF THE PATIENT POST FONTAN PROCEDURE

As survival after the Fontan procedure improves, hepatic complications of the Fontan physiology will become more evident. Optimal surveillance for liver complications in post-Fontan patients has not been identified in part due to lack of prospective trials in this patient population. Based on the available evidence, we recommend that post-Fontan patients undergo regular laboratory and clinical evaluation (Figure 2). This should include testing of total and direct bilirubin, aminotransaminases (AST, ALT), alkaline phosphatase, gamma-glutamyl transferase, albumin, INR, and complete blood count to screen for early hepatic complications. Laboratory evaluation with calculation of the APRI score, FIB-4 score, or Forns index may be repeated every 2–3 years after Fontan completion and then monitored annually starting 10 years post-Fontan. Annual liver ultrasonography should be initiated 10 years post-Fontan or earlier if there is evidence of failure of the Fontan circulation. Failure of the Fontan circulation may manifest in a variety of cardiac and extra-cardiac complications, including declining functional status, onset of arrhythmias, symptoms of heart failure, or protein-losing enteropathy.[63] Down-trending platelets, elevated liver biochemical tests, or evidence of ascites on ultrasound should prompt MRE or shear-wave elastography to assess for liver fibrosis or cirrhosis. Post-Fontan patients with a confirmed diagnosis of cirrhosis require more rigorous screening for complications and should be referred to a hepatologist with experience in caring for Fontan patients. Follow-up in these patients with cirrhosis should include HCC surveillance with twice annual ultrasound (US) and AFP measurement; and esophagogastroduodenoscopy (EGD) to screen for esophageal varices as described earlier. Immunization against hepatitis A, hepatitis B, pneumococcal pneumonia, and influenza is also recommended.

Detection of nodules on US requires close monitoring due to risk of HCC as per the algorithm in Figure 2. Even though such monitoring may detect cirrhosis and HCC at an early stage, the impact of such measures in improving survival in this unfortunate group of young adults needs to be proven.

DISCLOSURES

The authors of this manuscript have no conflicts of interest to disclose as described by the journal *Congenital Heart Disease*.

AUTHOR CONTRIBUTIONS

MBH: Concept/design. Drafting of article

JNJ, PSK: Concept/design. Critical revision of article. Approval of article.

FC, DJD, JJP, WS, HMC: Critical revision of article.

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