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Hepatocellular carcinoma in Fontan-associated liver disease

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Abstract

Fontan-associated liver disease (FALD) is a significant complication in patients with Fontan palliation. The improved longevity following Fontan palliation has led to wider recognition of FALD and its association with hepatocellular carcinoma (HCC). This review examines the intricate link between FALD and HCC development, emphasizing the unique hemodynamic changes in Fontan circulation that promote hepatic congestion, fibrosis and cirrhosis, thereby facilitating carcinogenesis. The review comprehensively analyzes the existing literature, highlighting key risk factors, pathophysiological mechanisms, and diagnostic challenges in FALD-related HCC. While HCC incidence in FALD remains relatively low (1.5-5.0%), its higher mortality rate of 29.4% necessitates a thorough understanding of contributing factors and screening requirements. The management of FALD involves multidisciplinary approaches, addressing cardiac and hepatic aspects, with regular surveillance for liver disease progression and HCC using advanced imaging and biomarkers. Therapeutic considerations include interventions to manage hepatic congestion and fibrosis, although balancing these with the unique cardiac needs of Fontan circulation remains challenging. Interestingly, FALD management often mirrors that of other liver diseases, underscoring the need for tailored approaches. In severe cases, combined heart–liver transplantation offers a comprehensive solution for FALD-HCC. This review consolidates current knowledge on the epidemiology, pathogenesis and comprehensive management of HCC in the specific context of FALD, ultimately improving outcomes for this unique patient population.

Keywords Fontan-associated liver disease, cirrhosis, hepatocellular carcinoma

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Introduction

The Fontan procedure, developed in 1971 primarily for patients with tricuspid atresia, has since become a standard palliative therapy for pediatric patients with single ventricular heart disease [1-3]. Single-ventricle circulation describes a group of rare and severe congenital heart defects where the heart functions with only one working ventricle [4]. This condition affects a small percentage (10%) of individuals with congenital heart disease [4]. Hypoplastic left heart syndrome stands as the most prevalent type, but other variations exist, including defects in the heart's valves and underdevelopment of the right side of the heart [4]. The surgical intervention involves creating a shunt between the superior and inferior *vena cava* (IVC) and the pulmonary arteries, diverting blood from the subpulmonic ventricle to form a total cavopulmonary connection, thereby establishing the Fontan circulation [3]. Over 70,000 patients worldwide have undergone this procedure, underscoring its widespread adoption in managing complex congenital heart disease [3].

However, the Fontan circulation poses unique hemodynamic challenges that, over time, can contribute to Fontan-associated liver disease (FALD) [1]. The lower hepatic venous return in this circulation diminishes cardiac output, elevates cardiac pressure, and induces sinusoidal dilatation around the central veins, leading to hepatic venous congestion, hypoxia and the onset of FALD [2,3]. The long-term consequences of this circulation culminate in liver cirrhosis, hyperplastic nodules, and both benign (e.g., hepatic adenoma) and malignant (e.g., hepatocellular carcinoma [HCC] and cholangiocarcinoma) liver neoplasms [5].

The significance of exploring HCC within the context of FALD is proven by a histological analysis conducted 3 decades following the Fontan procedure. This revealed that, despite the advances in procedural techniques that have substantially

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improved the 30-year cardiac survival rate to over 80%, a considerable portion of individuals (43%) demonstrate advanced liver fibrosis post-procedure [1,2]. Furthermore, post-procedural observations reveal the occurrence of benign hepatic tumors, such as focal nodular hyperplasia (FNH) and hepatic adenoma, as well as HCC, in 1.15% of cases [1]. These findings accentuate the critical need to investigate HCC within the context of FALD, as comprehending the underlying mechanisms and risk factors associated with HCC in this population is crucial for early detection, intervention, and improving patient outcomes.

Table 1 Fontan procedure types

Procedure type	Surgical technique	Connection established
Classical Fontan	Direct connection of the right atrium to the right PA	Right atrium to right PA
Extracardiac total cavopulmonary connection	Anastomosis of SVC to the right PA with an extracardiac conduit between IVC and right PA	SVC to right PA and IVC to right PA via conduit

PA, pulmonary artery; SVC, superior vena cava; IVC, inferior vena cava

Methodology

The databases used for this comprehensive review were PubMed and Google Scholar. Primary keywords included "hepatocellular carcinoma", "HCC", "Fontan associated liver disease", "FALD", "Fontan procedure" and "congenital heart disease". The Boolean operators "AND" and "OR" were used. The search was limited to articles published in English, available as full text, and from January 2000 to the present. Articles pertaining to FALD and HCC occurrence in this population were retrieved.

Fontan procedure and liver disease

The Fontan procedure is a critical surgical intervention recommended for pediatric patients with congenital heart defects, including hypoplastic left heart syndrome, pulmonary atresia with intact ventricular septum, and tricuspid atresia [2]. The 3 surgical approaches are detailed in Table 1. The procedure aims to facilitate passive systemic venous return to the lungs for oxygenation, followed by pumping oxygenated blood to the systemic circulation by the functioning ventricle (Fig. 1) [6].

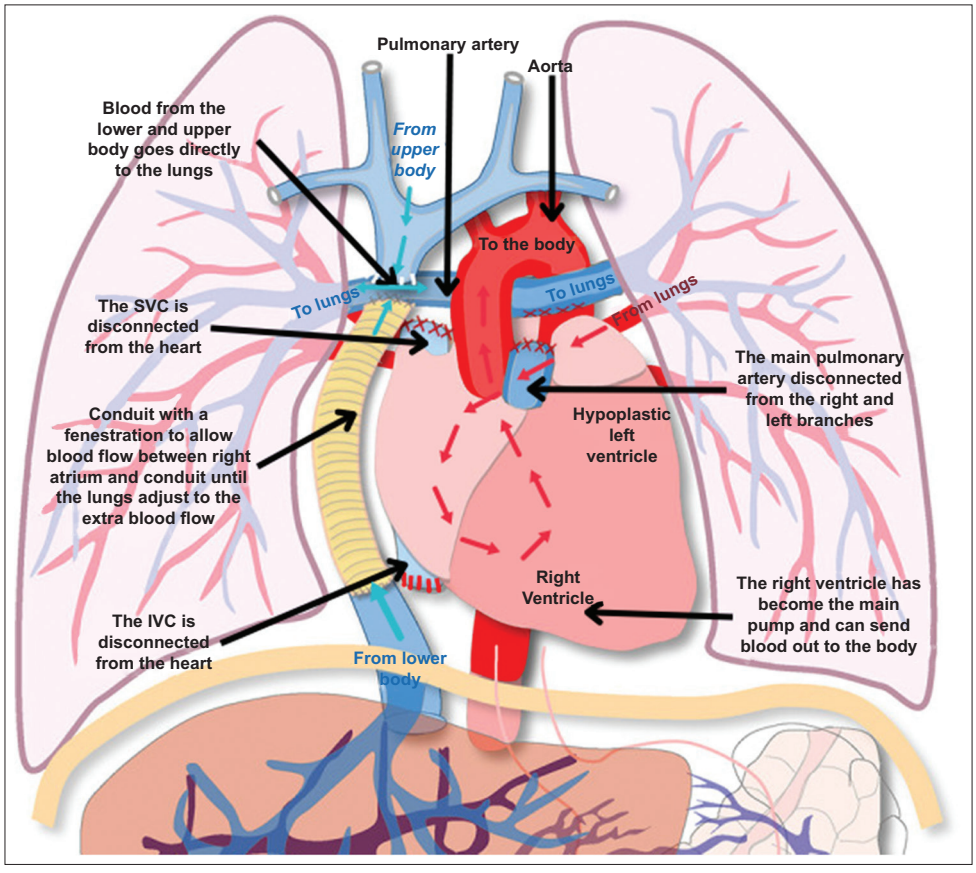

Figure 1 Adapted from De Lange C, Möller T, Hebelka H. 2023. Illustration of total cavopulmonary circulation post-Fontan procedure. Blood is rerouted directly to the lungs, bypassing the heart, with the right ventricle pumping oxygenated blood to the body [4]
SVC, superior vena cava; IVC, inferior vena cava

Modifications over time have improved outcomes, making the Fontan procedure a standard treatment for single-ventricle congenital heart disease. The modern Fontan procedure is now performed in stages. The first procedure is neonatal palliation with a Blalock Taussig shunt to ensure blood circulates to both the lungs and body [4,6]. Next, a superior cavopulmonary connection (bidirectional Glenn procedure) is established within the first few years of life so the systemic venous return from the upper body is directly connected to the pulmonary arteries via the superior *vena cava* [4,6]. Finally, a lateral tunnel or an extracardiac conduit is used to complete the inferior cavopulmonary connection within 1 to 3 years [4,6]. This results in a total cavopulmonary circuit, separating pulmonary and systemic circulation, thus increasing systemic arterial oxygen saturation and reducing volume overload on the single ventricle [6].

The Fontan procedure, while effective in managing congenital heart defects, can lead to significant liver complications due to alterations in circulation. Postoperative changes, including non-pulsatile pulmonary perfusion, systemic venous hypertension and low cardiac output, contribute to liver dysfunction [2,7]. These changes manifest as chronic injury, congestion and stiffness, with progressive liver fibrosis and cirrhosis over time [6,7]. Cardiac complications, such as arrhythmias and valve problems, are common, along with issues affecting other organs, such as plastic bronchitis, thromboembolic disease and protein-losing enteropathy [6]. With improvements in survival rates post-Fontan surgery and a growing population of adults with Fontan circulation, addressing these long-term health consequences, particularly liver-related complications, is paramount for optimizing patient care [6].

HCC in FALD

HCC typically arises within the context of chronic liver disease and can initially present with non-specific symptoms, such as abdominal pain, weight loss and fatigue. In one study, only 50% of patients were symptomatic at the time of diagnosis, presenting with symptoms including jaundice, abdominal pain, ascites, dyspnea, hematemesis, and fever [4]. This complicates early diagnosis, and makes imaging crucial for detection and staging [8]. In a study by Takaomi *et al*, liver tumors were diagnosed from single nodules with a median diameter of 47 mm (range 11-105 mm) in 8 of 12 patients who had FALD-HCC. The other 4 patients had 2 or more nodules [8]. HCC histology typically shows hepatocyte proliferation in trabecular, pseudoglandular or solid patterns [9].

FALD creates a unique context for HCC development. HCC usually occurs long after the Fontan procedure, especially in the presence of cirrhosis (1). According to a study by Sagawa *et al*, liver cirrhosis was present in a significantly higher proportion of patients with FALD who developed HCC compared to those without HCC. Specifically, cirrhosis was found in 7 out of 12 FALD-HCC patients (58.3%), while it was present in only 17.3% of non-HCC patients [10]. The causes are probably multifactorial, including genetic predisposition, underlying risk factors and the abnormal hemodynamics of chronic venous congestion [5].

Possner *et al* found that HCC can occur earlier in Fontan patients compared to the general HCC population. FALD-HCC was diagnosed in patients as young as 16 years old, with a mean of 30±9.4 years [7]. Unfortunately, the prognosis is poor, with delayed diagnosis limiting curative treatment to only 43% of the cohort and leading to a dismal 1-year survival rate of only 50% [7]. In fact, in a study by Takaomi *et al*, which compared FALD-HCC patients with non-HCC FALD patients, the survival rate after 25 years was 68.6% vs. 97.9%, respectively. In this study, 3 patients were not amenable to treatment and thus died from heart and/or liver failure, and 1 patient died after treatment from transplantation. Recurrence of the tumor occurred either intra-hepatically (median time: 221 days; n=5 patients) or as lung metastasis (median time: 2.7 years; n=3 patients) [10].

Epidemiology of HCC in Fontan patients

The epidemiological profile of HCC in Fontan patients reveals concerning trends within a growing and unique population. While the number of individuals with Fontan circulation steadily increases (estimated at 66 per million in 2020), so too does the risk of FALD and its most severe complication, HCC [4]. This trend is particularly worrisome given the relatively young age at which FALD and HCC can manifest in this population.

A recent retrospective analysis found that 9.7% of FALD patients developed HCC within 2 decades of their Fontan procedure [1]. This was further corroborated by a prevalence of HCC of 9.8% in another cohort of FALD patients studied by Takaomi *et al* [10]. The incidence appears to increase over time, with estimates of 0.8%, 2.9% and 13.3% at 10, 20 and 30 years post-Fontan, respectively [1]. A study by Kim *et al* found that length of exposure to the Fontan physiology is not the main driver of HCC, and that HCC cases more commonly had advanced FALD and cardiac comorbidities [11]. The annual HCC incidence in FALD patients with cirrhosis is 1.5-5.0% [2]. Cirrhosis is a significant risk factor, but not a prerequisite for HCC development in FALD patients [2]. This highlights the need for long-term vigilance, even decades after the initial surgery.

Alarmingly, cirrhosis, a major HCC risk factor, can develop in Fontan patients younger than 25 years of age, often within 11-15 years of the procedure [12]. A study by Inuzuka *et al* found that the incidence of fibrosis, FNH-like lesions and HCC increases over time to a cumulative incidence of 27.3% at 15 years after the Fontan operation [6]. Evidence from histological analysis found advanced liver fibrosis in 43% of patients 30 years after the Fontan procedure [10]. In contrast, guidelines from the European Association for the Study of the Liver (EASL) state that the average age of people with metabolic associated steatohepatitis (MASH) is 40-50 years, while the average age for MASH-associated cirrhosis is 50-60 years [13].

The median age of HCC diagnosis in this population is between 30-32.5 years, with a median of 21-22 years between the Fontan operation and HCC development [2,4]. These findings differ from those for the general population, where HCC typically arises in older individuals with a median age that ranges from 49-68 years old in patients with MASH over different retrospective studies [14-16]. Moreover, while comprehensive data are still needed, a study by Takaomi *et al* suggested a higher incidence of FALD-HCC in males (7/12, 58.3%) [10]. Unfortunately, the prognosis remains poor, with a 1-year survival rate of approximately 50% [4,17].

Pathophysiological mechanisms

The development of HCC in FALD arises from a multifaceted interplay of pathophysiological pathways triggered by the chronically altered hemodynamics of the Fontan circulation [7]. While the precise mechanisms remain under investigation, key contributors include the effects of chronic hepatic congestion, cellular-level changes, and ultimately the progression of fibrosis and cirrhosis [7]. Understanding this intricate cascade is crucial for developing targeted FALD-HCC prevention and treatment strategies (Fig. 2).

The hemodynamic abnormalities observed in FALD present a unique pathophysiological challenge. After the Fontan procedure, patients exhibit a paradox: elevated portal and central venous pressures, yet a low hepatic venous pressure gradient (HVPG) [7]. This pattern classifies FALD as post-sinusoidal portal hypertension, where complications such as varices, ascites and splenomegaly can appear despite the low HVPG [18]. The root of this paradox lies in the elevated central venous pressure, which reduces the pressure gradient driving portal venous inflow [17]. Compounding this effect is the often-present low cardiac output in Fontan patients [17]. The liver partially compensates via the hepatic arterial buffer response (HBAR), which dilates the hepatic artery to increase blood supply to the liver [4]. However, the HBAR is limited in its effectiveness, especially when portal pressures exceed 20 mmHg [4]. Above this threshold, arterial inflow can decrease, contributing to hepatic ischemia alongside the ongoing challenges of portal hypertension [4].

This complex mechanism results in the chronic passive hepatic congestion unique to the Fontan patient, since the liver is continuously exposed to non-pulsatile elevated pressure [6]. Passive congestion leads to sinusoidal dilatation, perisinusoidal edema with sinusoidal stretch, and atrophy of hepatocytes near the central hepatic veins [6]. The sinusoidal dilatation causes mechanical stimulation and damage to liver sinusoidal endothelial cells (LSEC) and the inter-hepatocytic tight junctions that separate the extravascular space from the bile canaliculus [1,19]. The resulting stagnant flow leads to thrombus formation within sinusoids, hepatic venules and portal tracts, and results in

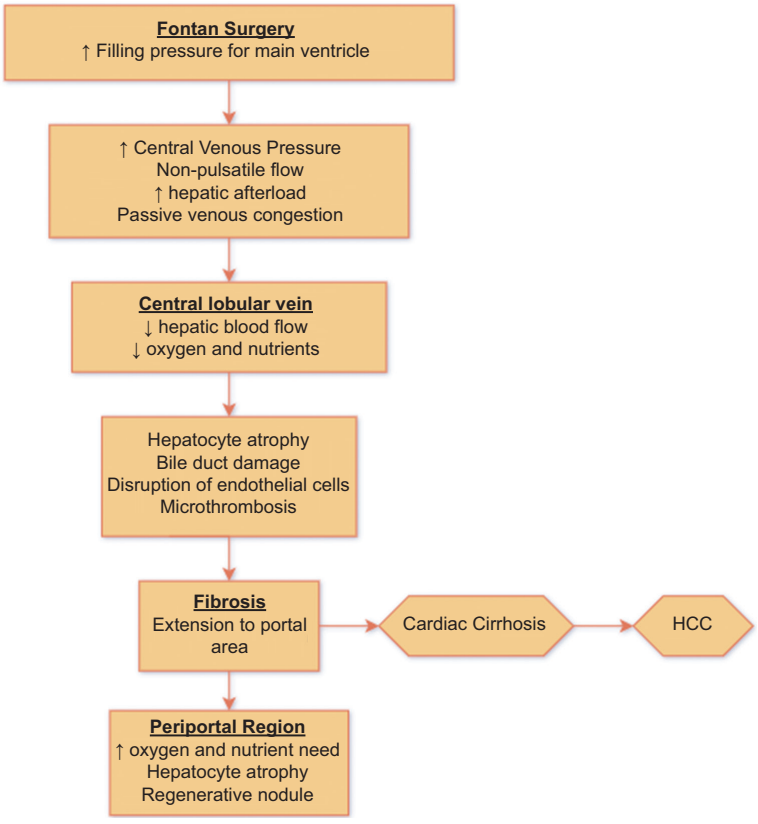

Figure 2 Pathophysiology of congestive hepatopathies after Fontan surgery
HCC, hepatocellular carcinoma

hepatocyte hypoxia [1,19]. Additionally, the impaired LSEC function decreases intrahepatic nitric oxide, hampering oxygen and nutrient diffusion while promoting hepatocyte death. LSECs may also secrete cytokines that promote platelet aggregation and microvascular thrombosis [4]. The disrupted endothelial cells also allow exudation of a protein-rich fluid and extravasation of red blood cells, eventually leading to exudative ascites and reddened areas within the hepatic parenchyma, respectively [19].

These changes activate the hepatic stellate cells, which secrete fibronectin and cause extracellular matrix assembly and thus portal and sinusoidal fibrosis [1,4,8]. Starting in the centrolobular zone, fibrosis gradually spreads to the portal region in varying degrees [19]. Damage eventually causes broad fibrous septa to form, bridging central hepatic veins [6]. This pattern of fibrosis is known as centrilobular fibrosis, and differs from the periportal or perisinusoidal fibrosis that is usually found in other types of liver disease, such as chronic viral hepatitis [6]. However, because of the multifactorial sources of liver injury, the other fibrotic patterns may also be visible [6]. In this process, hepatocyte death occurs through atrophy and apoptosis, and thus fibrosis progresses without widespread centrilobular inflammation and necrosis, as in other liver diseases [2,18,19]. Consequently, most patients remain asymptomatic from a hepatic perspective, with preserved liver function until at least the third decade after Fontan completion [18].

Hypoxic areas in the liver as a result of failure of the HABR are mostly located in the periphery, and they are susceptible to the development of hypervascular, hyperechoic lesions [1,2]. Hepatic masses, including benign tumors such as hepatic adenomas and FNH-like nodules, as well as malignant lesions such as intrahepatic cholangiocarcinoma (ICC) and HCC, can arise in this situation [20].

Histologically, typical cirrhotic features, such as portal inflammation, fibrosis, steatosis, apoptosis/Mallory bodies, ceroid-laden macrophages and iron deposition, are absent in Fontan patients [5].

While cardiac function can impact liver health, studies suggest no direct correlation between specific cardiac pathologies and HCC development within the Fontan population [1].

The development of HCC in FALD stems from a complex interplay of molecular and cellular changes driven by the unique pathophysiology of the Fontan circulation (Fig. 3 and Table 2).

Genetic alterations and aberrant signaling pathways play a significant role. Studies have identified fibroblast growth factor receptor 3 (FGFR3) copy number alterations and mutations in FALD-HCC and ICC, suggesting a potentially distinct role for FGFR3 in the Fontan microenvironment [5]. While FGFR3 generally promotes tumor progression but protects against liver necrosis and fibrosis, the loss of an allele in FGFR3 in FALD-HCC and ICC raises the possibility that it could contribute to cirrhosis development [5]. Mutations in the *CTNNB1* and *NRAS* genes, known to be involved in HCC pathogenesis, have also been observed in FALD-HCC cases [5]. Furthermore, a unique DNAJB1-PRKACA fusion transcript, found exclusively in fibrolamellar carcinomas within the FALD cohort, highlights the distinct molecular profile of liver tumors arising in this setting [5]. Notably, mutations commonly seen in other HCCs, such as those in the TERT promoter, *TP53*, *CDKN2A/B*, *KRAS*, *ARID1A* and *IDH1* genes, were absent in the FALD-HCC/ICC cases studied, suggesting a potentially unique carcinogenic pathway [5].

Sphingosine 1-phosphate (S1P) signaling appears to be another crucial contributor to FALD-HCC development. Studies in mice models indicate that chronic liver congestion, a hallmark of FALD, promotes the growth of both diethylnitrosamine-induced and metastatic liver cancer (21). This effect is linked to elevated levels of liver and plasma endothelin (ET-1) and angiopoietin 2 (ANGP-2) produced by LSEC [21]. Congestion induces LSEC capillarization and upregulation of SphK1 (the S1P-synthesizing enzyme) [21]. Subsequent S1P/SPR2-mediated signaling appears to contribute to liver fibrosis and ultimately

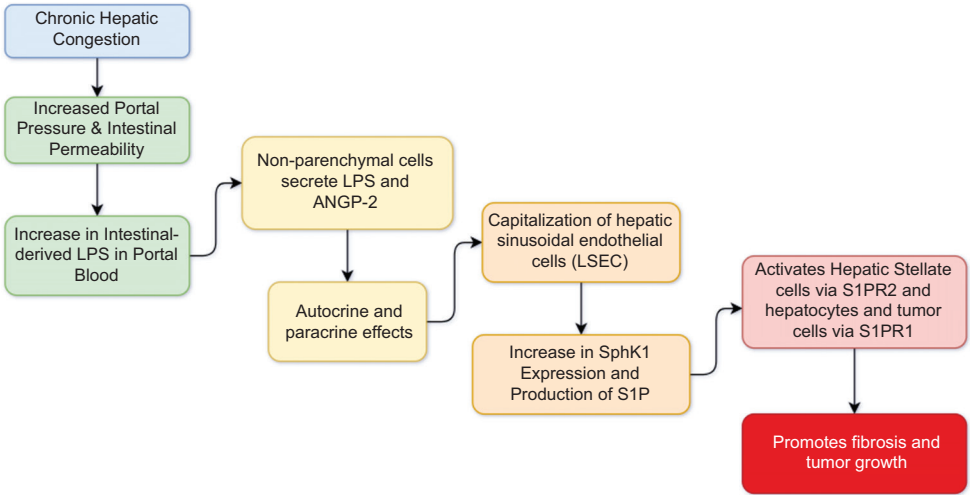

Figure 3 A flow chart of the assumed mechanism of congestive liver fibrosis and tumor growth
LSEC, liver sinusoidal endothelial cells; SphK1, sphingosine-1-phosphate-synthesizing enzyme; S1PR1, sphingosine-1-phosphate receptor 1; S1PR2, sphingosine-1-phosphate receptor 2; LPS, lipopolysaccharide; S1P, sphingosine 1-phosphate

Table 2 Liver injury mechanisms

Perioperative/prenatal vascular factors and cellular factors	Postoperative hemodynamic vascular factors and additional factors
Systemic hypotension Increased CVP Hypoxia	Elevated CVP (non-pulsatile) Congestion Portal hypertension Decreased arterial flow
Cellular factors	
Activation of mechanosensitive receptors Liver sinusoidal endothelial cells Hepatic stellate cells	Decreased cardiac output Hypoxia
	Increased lymphatic angiogenesis?
Inflammatory cytokine activation	
(C-X-C motif) ligand (CXCL) 1 interleukin 6, TNF-alpha and others Microvascular thrombosis	Visceral congestion – ischemia? Intestinal microbiome
Neurohormonal activation Renin, angiotensin, aldosterone	Abnormal hepatic venous circulation Venovenous shunts
	Additional factors Hepatotoxins Alcohol, obesity Virus Metabolic factors

CVP, central venous pressure; TNF, tumor necrosis factor

tumor development [21]. Intriguingly, intestinal toxin lipopolysaccharide may further exacerbate these processes by promoting LSEC capillarization [21].

Serum biomarkers provide valuable insights into FALD-HCC progression. Elevated levels of aspartate aminotransferase, alanine transaminase, gamma-glutamyl transferase (GGT), and direct bilirubin are observed in 34%, 14%, 69% and 20% of FALD patients, respectively [1]. GGT increase can be an early sign of FALD, even with normal aminotransferases and bilirubin levels [5]. Elevated total bilirubin above 2.2 mg/dL, in particular, might indicate advancing fibrosis and increased HCC risk [1]. Alpha-fetoprotein (AFP) is elevated in some FALD-HCC cases, particularly in those with conventional HCC [10]. The link between AFP and HCC is especially significant when AFP levels are ≥400 ng/mL [2]. Additionally, higher hyaluronic acid levels (>55.5 ng/mL) are associated with FALD-HCC and could serve as a sensitive and specific biomarker [1].

Studies reveal systemic inflammation, neurohormonal activation, and multi-organ fibrosis as additional factors in FALD-HCC. FALD patients exhibit elevated inflammatory biomarkers, complement factors, and cytokines such as interleukin 6, growth derived factor-15 (GDF-15), tumor necrosis factor-α and β2-macroglobulin [4,6]. GDF-15, a stress-responsive cytokine, correlates with increasing adverse clinical events within 1 year in stable FALD patients and could play a long-term role in pathogenesis [6]. The renin–angiotensin system is also dysregulated, with elevated serum renin, aldosterone and angiotensin observed [11,13]. Angiotensin 2 may promote collagen synthesis and fibrosis; in fact, collagen IV levels increase with worsening hepatic dysfunction (4,6). A reduction in platelet count was noted in 20% of cases; however, as with other thrombosis markers (vWF-A2) the results were not statistically significant [1,6]. Fibrosis can extend beyond the liver, affecting the kidneys and myocardium, and is associated with elevated fibrogenic serum biomarkers such as matrix metalloproteinases [4].

Elevated model for end-stage liver disease (excluding international normalized ratio) (MELD-XI) scores may serve as an early indicator of HCC risk in FALD patients [1]. A MELD-XI score of >18.7 is noted to be significant [1]. A high fibrosis-4 index is a risk factor for HCC, although this has a low predictive value [10].

Notably, FALD-HCC patients had a higher frequency of hypersplenism and esophageal varices, and of protein-losing enteropathy [7,10]. However, in a study done by Paola Francalanci *et al*, interestingly, none of the patients developed esophageal varices [5].

These findings shed light on the intricate molecular landscape driving HCC in FALDs and emphasize the need for further research to unravel the underlying mechanisms and develop targeted therapeutic strategies for improved patient outcomes [5].

Diagnosis and surveillance

FALD and the Fontan circulation's unique physiology complicate HCC diagnosis [4]. FALD lacks a standardized definition, potentially underestimating its true prevalence [4]. It presents as a spectrum of liver dysfunction, often subclinical initially [4].

Diagnostic tools have limitations: liver function tests can be unreliable because of cardiac dysfunction and medications [4]; noninvasive fibrosis scores (Child-Pugh score, MELD score, LI-RADS) may not be accurate in FALD because of the anticoagulation therapy [4,7,17,18]. Imaging is crucial, with ultrasound (US) being accessible, but limited in detecting early fibrosis or characterizing nodules [2,4,18]. Doppler US and contrast-enhanced US (CEUS) can provide additional vascular information [2]. CEUS has a high specificity of 93%, albeit low sensitivity (40%), for detecting HCC [22]. Computed tomography (CT) is faster and more accessible than magnetic resonance imaging (MRI), but is undesirable because of the radiation exposure. MRI offers better tissue characterization, but may be incompatible with cardiac devices [2,4]. It has been shown that annual non-contrast abbreviated MRI is superior to twice yearly US in detecting early HCC. Alternating 6 monthly US with annual non-contrast abbreviated MRI is superior to twice yearly US [23].

MR elastography (MRE) offers noninvasive assessment of liver stiffness, potentially reflecting fibrosis [4]. US

elastography is less useful than MRE, since it only displays a small region of the right liver lobe, which might not be representative of a patchy disease [2,4]. Evolving techniques, such as shear wave dispersion, US attenuation imaging, MR fat fraction, and relaxometry, hold potential, but require further research and validation in the FALD population [4]. Liver biopsy, the gold standard, carries risks in Fontan patients because of potential complications [4,10,17,18]. Moreover, FALD's patchy fibrosis distribution can lead to sampling errors that affect accuracy [4,17,18].

On cross-sectional imaging, HCC commonly exhibits contrast washout during the portal venous and delayed phases, along with restricted diffusion. The capsule is generally smooth and consistent. On hepatobiliary phase imaging with hepatocyte-specific contrast agents, the nodules appear hypointense. T2-weighted images typically show reduced or heterogeneous signal intensity, while T1-weighted images reveal high signal intensity with signal dropout on opposed-phase imaging, indicative of high lipid content [2,4].

Some of the remaining challenges include differentiating HCC from other nodules (benign focal nodular hyperplasia, hepatocellular adenoma and cholangiocarcinoma), assessing liver stiffness, and having a standardized surveillance system [2,4,17,18]. A comprehensive approach combining routine surveillance and multimodal assessment is essential to tackle the challenges presented [10,17,19]. The combination of assessing liver function tests, especially a high AFP level, and MRI features, including portal/delayed phase washout and a large and expanding nodule, makes it more likely that a nodule is malignant [4,10,18,19]. New evolving techniques such as 18F-fluorocholine and 18F-fluorodeoxyglucose PET/CT show promise, but require further research and validation in the FALD population [4,19].

Evidence regarding the most effective screening approach for HCC in FALD is sparse. To date, only one study has explored the utility of surveillance imaging for HCC in this context. However, its retrospective nature and inconsistent follow-up periods limited the ability to establish definitive recommendations for surveillance protocols. Available data indicate that HCC is uncommon during the first 10 years after the Fontan procedure. As a result, current surveillance practices are largely informed by this finding and expert opinion [22].

The risk of HCC occurring 10 years post-Fontan is extremely low (0%, 95% confidence interval 0.00-0.01) and thus screening in this population can be avoided [24]. A recent meta-analysis shows that the annual incidence 10-20 years after Fontan is between 0% and 0.2% and thus screening cannot be definitely recommended [24]. Since HCC risk increases approximately 20 years post-Fontan, initiating surveillance around 10 years post-procedure or on suspicion of moderate-severe liver fibrosis is often suggested [2,10,22]. The 2019 American Heart Association statement recommends liver function tests every 1-3 years for Fontan teenagers and every 1-2 years for adults, including AFP levels [2,18]. Imaging every 6 months is advised by the International Hepatology Guidelines for patients with known cirrhosis [18]. The EASL- European Reference Network on Rare Liver Diseases (ERN) advises the combination of serial US (every 6 months) and contrast-enhanced imaging with CT or MRI starting at baseline (i.e., 10 years after surgery) and periodically during follow up, at least every 1-2 years [22,24]. Suspicious nodules requiring further investigation (e.g., biopsy) may include those >10 mm with irregular contours, capsules or rapid growth (50% in less than 6 months or 100% in more than 6 months), atypical contrast enhancement patterns, or an atypical signal on basic MRI sequences [4]. A biopsy can be necessary in cases with ambiguous imaging findings, though confirmation rates for malignancy can be low [18]. Several surveillance strategies emerge in the available texts. Fig. 4 shows a strategy proposed by the EASL-ERN paper [22]. However, further research is needed to establish the most effective method [18].

Treatment approaches

The optimal treatment strategy for HCC arising in the context of FALD remains challenging because of the limited data and the unique pathophysiological complexities of Fontan circulation. While guidelines exist for HCC treatment in the general population, their direct applicability in FALD patients requires careful adaptation. Medically, over half of failing Fontan patients who received pulmonary vasodilators and bosentan were found to have lower post-exercise heart rate and improved NYHA class and 6-min walk test outcomes [25].

Local-regional therapies such as radiofrequency ablation (RFA) and transarterial chemoembolization (TACE) may be used with curative intent in those with early-stage disease or as palliation [26]. However, they could be limited by the existence of cardiac pacemakers, extrahepatic shunts limiting radioembolization, and abnormal vasculature [12,26]. TACE is useful based on the greater hypervascularity of FALD-HCC compared with HCC of other etiologies; however, in a study by Takaomi *et al*, 2 of 3 patients treated with TACE developed metastases after the treatment [10]. However, there is a lack of robust data regarding the effectiveness and safety of TACE in FALD patients [22].

Patients with congenital heart disease are known to have an elevated risk of infective endocarditis, particularly following vascular interventions [26]. However, the authors were unable to identify any published cases in the literature specifically linking TACE to infective endocarditis in patients with FALD. Proton beam therapy (PBT) is better at sparing at risk organs, since it is not related to cardiac function and does not require infrahepatic IVC clamping. It was reported that, of the 4 patients who underwent PBT, 2 (50%) had recurrences in the lung or liver [2,10]. Ogasawara *et al* present another case that was successfully treated with PBT with no recurrence so far [27].

In FALD patients, surgical removal of the carcinoma might be constrained by cirrhosis, cardiac failure and portal hypertension [2,12,26]. In a study by Takaomi *et al*, 2 surgically treated patients with FALD-HCC had massive bleeding from the hepatic vein intra-operatively [10]. Additionally, severe cardiac dysfunction can result from postoperative liver decompensation [19]. These 2 risks have been minimized by a laparoscopic approach [2,12,19].

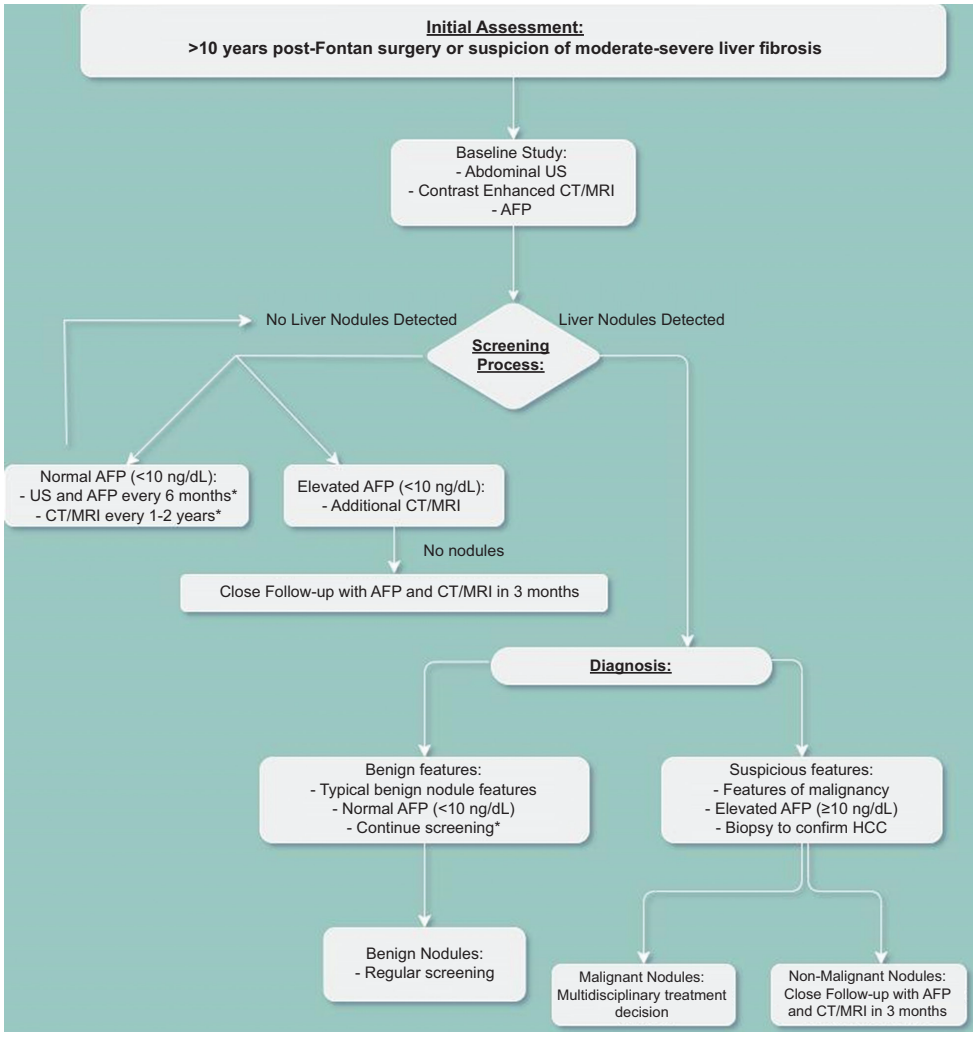

Figure 4 Surveillance strategy for hepatocellular carcinoma in Fontan-associated liver disease
US, ultrasound; CT, computed tomography; MRI, magnetic resonance imaging; AFP, alpha-fetoprotein

Liver transplantation alone is generally not recommended in FALD-HCC, because of persisting cardiac dysfunction and the associated high right atrial pressures, pulmonary hypertension and hypoxia, which compromise graft survival [4,12,26,28]. Cardiac transplantation alone may be considered for select patients with severe disease but without cirrhosis [2]. Additionally, there is evidence suggesting comparable survival after heart transplantation in Fontan patients with and without compensated cirrhosis [4]. The potential for liver regeneration after heart transplantation remains an area of investigation, but one study reported a higher regenerative capacity than expected when compared to those of other reversible liver diseases [4].

Many centers proceed with combined heart and liver transplantation because of the virtually universal presence of advanced liver fibrosis [4]. Although there is limited experience with heart–liver transplantation, it should also be considered as a favorable outcome, as 83% 10-year survival is reported [2,12,25]. Notably, in combined heart and liver transplantation, the longer-term cardiac graft rejection occurs at a significantly lower rate than with heart transplant only [26]. Despite its high risk, this approach appears most suitable for patients with portal hypertensive complications or HCC, where liver disease prognosis is a significant concern and resolution of congestive stress may not lead to complete recovery. However, the potential benefits of combined heart–liver transplantation for individuals with compensated cirrhosis or lesser degrees of fibrosis remain unclear from both clinical and immunological perspectives [18].

Because of the limited evidence, transplant indications and patient selection vary between institutions [4]. European recommendations state that combined heart–liver transplantation is usually reserved for patients who are in liver failure or have HCC within the Milan criteria. Patients who fulfil cardiac transplant criteria (Fontan circulatory failure, significant ventricular dysfunction, or refractory protein-losing enteropathy or plastic bronchitis) but have compensated advanced liver fibrosis without fibrosis, should undergo isolated heart transplantation [4]. A collaborative approach

involving congenital cardiologists, hepatologists, transplant surgeons, and anesthesiologists is crucial for case-specific decision-making in the management of FALD-HCC [4,18,19].

Prognosis and outcomes

Reviewing the available evidence on the prognosis of HCC in Fontan patients, significantly concerning findings emerge. Firstly, studies consistently demonstrate a poor prognosis for FALD, with 1- and 5-year survival rates of 57% and 35%, respectively (18). Studies reported that the 1-year survival rate after diagnosis in patients with FALD-HCC was less than 50% [1,2,4,17]. Nationwide surveys have revealed a stark reality, with a mortality rate of approximately 29.4% (5/17 cases) among FALD patients presenting with liver cirrhosis and/or FALD-HCC, underscoring the challenging outcomes faced by this cohort [2].

Several factors appear to negatively influence the prognosis. A recent meta-analysis found a strong link between post-Fontan mortality and liver disease severity, especially if clinical symptoms are present at diagnosis and if tumors are >4 cm in size [4,17,25]. Late referrals and markers of failing Fontan physiology, such as poor functional status, varicosities and venovenous collaterals, were associated with higher post-transplant mortality, while liver fibrosis did not predict transplant-free or overall survival [25]. High levels of total bilirubin (>2.2 mg/dL) and AFP (≥400 ng/mL), and higher MELD-XI scores are associated with both a greater HCC risk and a poorer prognosis in FALD patients [1,2]. Bridging fibrosis and portal hypertension also indicated worse outcomes [26].

These findings underscore the importance of early detection through rigorous surveillance protocols, the development of FALD-HCC specific treatment strategies, and reliable risk stratification methods to guide targeted interventions for this vulnerable patient population.

Future directions and research gaps

Despite ongoing investigations, significant gaps remain in our current understanding of HCC arising in FALD. Addressing these gaps through focused research is crucial for advancing knowledge and ultimately improving patient outcomes. One key area warranting further exploration is the specific mechanisms of hepatocarcinogenesis in FALD. While chronic hepatic congestion plays a role, the exact molecular pathways driving malignant transformation in this unique patient population remain poorly understood. Research aimed at identifying FALD-specific molecular signatures could potentially lead to the development of novel therapeutic targets.

Additionally, there is a lack of consensus on the most effective surveillance protocols for early HCC detection in Fontan patients. Studies should evaluate the sensitivity, specificity, and cost-effectiveness of various imaging modalities (US, MRI, CT), biomarkers (including novel noninvasive markers), and their combinations specifically in the FALD population [5,17]. The ability to reliably stratify FALD patients based on their risk of HCC development would enable tailored surveillance and early intervention. Studies should investigate the predictive value of clinical, biochemical and potentially genetic factors in identifying high-risk individuals [29].

Currently, FALD-HCC treatment strategies are largely extrapolated from those used in the general population. Research specifically focused on evaluating the efficacy and safety of locoregional therapies (TACE, RFA, PBT), surgical resection, and various transplant modalities within the context of Fontan physiology is urgently needed [12,18,29]. Finally, given the complex nature of managing FALD-HCC, a greater understanding of long-term outcomes and the impact of various treatment strategies on the quality of life in Fontan patients is essential.

Concluding remarks

The importance of early HCC detection in FALD cannot be overstated. The lack of standardized surveillance and management protocols highlights the need for collaborative studies evaluating the efficacy of different imaging and treatment modalities in this specific population [11,18]. Moreover, research into the molecular mechanisms of FALD-HCC could uncover novel targets for therapy, while studies focused on risk stratification would facilitate targeted surveillance for high-risk individuals [5]. The complex and evolving nature of FALD-HCC management underscores the importance of interdisciplinary collaboration and ongoing research to optimize patient care.

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