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Position Paper

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EASL-ERN position paper on liver involvement in patients with Fontan-type circulation

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Summary

Fontan-type surgery is the final step in the sequential palliative surgical treatment of infants born with a univentricular heart. The resulting long-term haemodynamic changes promote liver damage, leading to Fontan-associated liver disease (FALD), in virtually all patients with Fontan circulation. Owing to the lack of a uniform definition of FALD and the competitive risk of other complications developed by Fontan patients, the impact of FALD on the prognosis of these patients is currently debatable. However, based on the increasing number of adult Fontan patients and recent research interest, the European Association for The Study of the Liver and the European Reference Network on Rare Liver Diseases thought a position paper timely. The aims of the current paper are: (1) to provide a clear definition and description of FALD, including clinical, analytical, radiological, haemodynamic, and histological features; (2) to facilitate guidance for staging the liver disease; and (3) to provide evidence- and experience-based recommendations for the management of different clinical scenarios.

Background

Approximately 1 in 10,000 infants are born with a univentricular heart and are unlikely to survive without cardiac surgery.[1–4] Fontan-type surgery is the final step in the sequential palliative surgical treatment for these cases, and it is usually performed in infants between the ages of 2 and 4 years.[5–7] The procedure aims to restore serial circulation and avoid cyanosis at the expense of chronic high central venous pressure (CVP) and low cardiac output.[4,8–10] Those long-term maintained haemodynamic changes promote liver damage in virtually all patients. Although similarities exist in the pathophysiology of other congestive hepatopathies in adults with right-sided heart failure, Fontan-associated liver disease (FALD) is more complex and severe.

The number of persons living with Fontan-type surgery in 2020 has been estimated to be 66 per million, expected to rise to 79 per million by 2030. In 2020, this population comprised 55% adults, 17% adolescents, and 28% children, proportions which are expected to shift to 64%, 13%, and 23%, respectively, by 2030.[11–13] This increasing number of adult Fontan patients and the recent publication of several cases of hepatocellular carcinoma (HCC) in this young population have focused interest on FALD.[14,15] Due to the lack of a uniform definition of FALD and the competitive risk of other complications developed by Fontan patients, the impact of FALD on the prognosis of these patients is currently debatable. However, there is evidence suggesting that the identification of advanced FALD could identify a group of patients with a worse prognosis. Given these concerns and the increasing number of recent publications on FALD, the European Association for The Study of the Liver (EASL) and the European Reference Network on Rare Liver Diseases (ERN RARE-LIVER) decided to launch the present position document. The aims of the current paper are: (1) to provide a clear definition and description of FALD, including clinical, analytical, radiological, haemodynamic, and histological features; (2) to facilitate guidance for staging the liver disease; and (3) to provide evidence- and experience-based recommendations for the management of different clinical scenarios.

Methods

Review of evidence

This position document is based on a systematic literature search according to a PICO format (**P** Patient, Population or Problem; **I** Intervention, Prognostic Factor, or Exposure; **C** Comparison or Intervention [if appropriate]; **O** Outcome of interest), using clinical scenarios. A comprehensive literature re-

Keywords: Fontan surgery; Fontan-associated liver disease; congenital heart disease; liver fibrosis; hepatocellular carcinoma; liver nodules; portal hypertension; esophageal varices; ascites; liver transplantation; heart transplantation.
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view identified articles in English relevant to FALD care for each topic area, employing keywords proposed for each clinical scenario and topic. MEDLINE and Cochrane Library have been used. Possible exceptions (*i.e.*, data not published or analyzed explicitly for the current document) in topics with little or no direct evidence were also accepted.

Level of evidence

The guidance in this position document could not be conventionally evidence-based. As is typical for a rare disease, few large-scale prospective or randomized controlled studies have been completed for FALD. Therefore, guidance has been addressed using a method that queries a group of experts on the appropriateness and necessity of specific definitions, assessments, and interventions. This method was intended to objectify expert opinion and to make the guidance a true reflection of the views and practices of an expert panel based on their interpretation and application of the existing scientific literature.[16] Following the definitions used by the GRADE (Grading of Recommendations Assessment and Evaluation) Working Group, we adapted the level of evidence (LoE) into four categories (high: further research is very unlikely to change our confidence in the estimate of effect; moderate: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low: further research is very likely to have an important impact on our confidence in the estimate of effect and may change the estimate; and very low: any estimate of effect is very uncertain).[17]

Strength of recommendation

As a specific rare disease, few high-quality studies are available. Consequently, the strength of the recommendation has been adapted to this scenario and divided into two categories: strong and weak. The strength of recommendation was based on the quality of the evidence, consistency of studies, expert opinion, clinical relevance, cost-effectiveness, legal consequences, availability of care, and safety. Definitions and statements were not graded.

Consensus

A list of 14 Steering Committee experts contributed to this position document development. These experts covered six specialties: hepatologists, cardiologists, paediatricians, cardiac surgeons, radiologists, and pathologists. Expert selection criteria included: relevant publication experience, author's H-index, and perception as experts by their peers (authors called upon by the medical community to present their knowledge on FALD in international meetings). The Steering Committee was led by one ERN RARE-LIVER selected chair (JCGP) and one EASL representative (PER), who advised and drove the consensus. Each selected expert took responsibility and made proposals for definitions, statements, and recommendations for a specific section of the position document based on their expertise and shared the text summarizing the evidence with the working group. The consensus process for final statements and recommendations was based on unstructured methodologies (four teleconferences). All panelists discussed and approved all definitions, statements, and recommendations.

Proposed clinical scenarios and PICO questions

The panel initially established the most relevant topics to address, considering the published evidence and clinical relevance. The ten main topics that the panel included were.

a) Definition and description of the population
b) Definition of FALD
c) Clinical evaluation and staging of FALD
d) Portal hypertension considerations in FALD
e) Liver nodules and risk of HCC in FALD
f) Management of HCC in FALD
g) Heart and combined (heart-liver) transplantation in FALD
h) Other liver-related issues
i) Role of FALD surveillance programs and specialized multidisciplinary units in FALD
j) Unmet needs and future directions

Description of the population

Statements

- Fontan circulation is the result of connecting the systemic veins directly to pulmonary arteries. Thus, the pulmonary and systemic circulations are connected in series but without a sub-pulmonary ventricle, resulting in a central venous pressure higher than normal (**High LoE**).
- Fontan circulation can fail due to systolic or diastolic ventricular dysfunction, atrioventricular valve disease, elevated pulmonary vascular resistance, recurrent arrhythmia, lymphatic insufficiency, or end-organ complications. Accordingly, symptoms may be related to heart failure and hypoxemia or end-organ complications, resulting in different clinical and haemodynamic Fontan failure phenotypes (**Moderate LoE**).
- Fontan circulatory failure should be considered in patients with at least one of the following criteria: New York Heart Association (NYHA) functional class IV, NYHA functional class III for ≥12 months without sustained improvement, >2 unscheduled hospital admissions within 12 months for heart failure symptoms, and active protein losing enteropathy (PLE) or plastic bronchitis (PB) without remission for ≥6 months (**Low LoE**).

What is Fontan-type surgery?

The Fontan procedure was first described in 1971 as a palliative procedure for patients with tricuspid atresia and since then has been used for a variety of univentricular heart defects. It is mainly used in patients with congenital univentricular heart disease when a biventricular repair is not feasible.[4] In simple terms, the Fontan-type techniques create a new circulatory system (Fontan circulation) connecting the systemic venous return from both the inferior and superior vena cava and the pulmonary arteries, avoiding the right ventricle, which will passively transmit the blood through the lungs to the single ventricular chamber.

The original approach (the atriopulmonary connection or classic Fontan) was described for patients with tricuspid atresia and consisted of closing the atrial septal defect and connecting

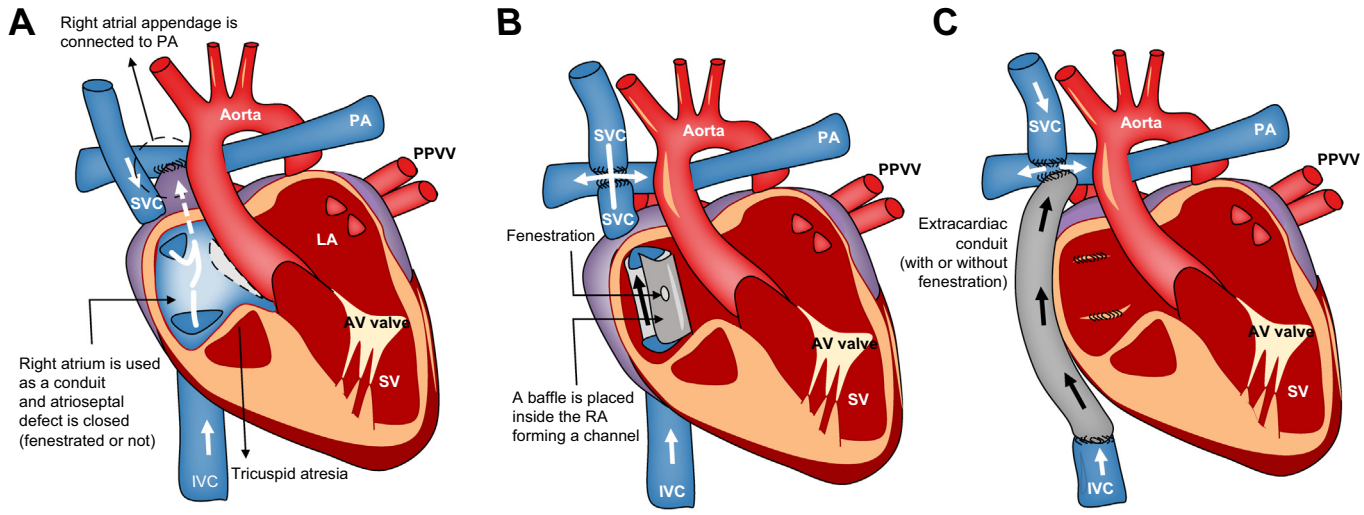

Fig. 1. The different Fontan-type procedures. (A) The atriopulmonary appendage connects the RA directly to the right PA. (B) The intracardiac total cavopulmonary connection or lateral tunnel procedure connects the SVC to the right PA. A baffle is placed inside the RA, forming a channel to direct blood from the IVC to the PA. (C) The extracardiac cavopulmonary connection consists of a direct anastomosis of the SVC to the PA and in the interposition of an extracardiac prosthesis between the IVC and the PA. AV, atrioventricular; IVC, inferior vena cava; LA, left atrium; PA, pulmonary artery; PPVV, pulmonary veins; RA, right atrium; SV, single ventricle; SVC, superior vena cava.

the right atrium directly to the right pulmonary artery. Several modifications were introduced later (Fig. 1A).[4,7,18,19] Shortly, Kreutzer *et al.* described their modified atriopulmonary connection, and Björk *et al.* reported a right atrial-right ventricular connection.[20,21] More recently, the total intracardiac cavopulmonary connection or lateral tunnel was established by De Leval in 1988.[8] This procedure connects the superior vena cava to the right pulmonary artery (classical Glenn shunt) and the inferior vena cava to the pulmonary arteries through a patch-created intracardiac tunnel in the right atrium (Fig. 1B). Finally, the most recent approach, the extracardiac cavopulmonary connection, consists of a direct anastomosis of the superior vena cava to the right pulmonary artery and the interposition of an extracardiac vascular prosthesis between the inferior vena cava and the right pulmonary artery (Fig. 1C).[22] The advantage of the latter surgical technique is that it can be performed without myocardial ischaemia, and there are fewer suture lines and no foreign material in the right atrium.

What haemodynamic changes are associated with Fontan circulation?

The pulmonary and systemic circulations are connected in series in the normal heart, and a ventricle supports each circulation. The right ventricle acts as a pump and drives the systemic venous blood into the pulmonary circulation. The tricuspid valve guards the right atrium and the systemic veins from the pressure generated in the right ventricle. Therefore, CVP remains low (<10 mmHg) while the systolic pulmonary artery pressure is higher (>15 mmHg).[23]

In the Fontan circulation, the pulmonary and systemic circulations are connected in series, like in the normal heart, but without a sub-pulmonary ventricle. The systemic venous blood is directly channeled into the pulmonary arteries from the systemic veins, and the active force of the right ventricle propelling the blood is lost. In this situation, pulmonary pressure is a result of pulmonary artery resistance and pulmonary blood flow, which is passive and dependent on central CVP. Compared to healthy individuals, the cavopulmonary connection results in an obligate higher CVP than normal (>10 mmHg) (Fig. 2).[24]

In this situation, three driving forces make possible the passage of blood flow from the systemic venous system to the left (systemic) atrium: 1) the "suction effect" of the left atrium emptying, resulting from the combination of good systolic and diastolic function of the single ventricle, atrioventricular synchrony, and the normal function of the systemic atrioventricular valve; 2) the "lung and muscle pump" resulting from the negative intrathoracic pressure created by inspiration, increased inferior vena cava return (secondary to diaphragmatic contraction and promoted by exercise), and increased recruitment of lung vessels;[25] and 3) the low resistance in the pulmonary circuit (precapillary arterioles) in the absence of mechanical stenosis in the Fontan conduit, main pulmonary arteries, and pulmonary veins.

Despite central venous hypertension, patients are in a ventricular preload deficient state after Fontan completion. Systemic venous return must traverse the pulmonary circuit (in case of no fenestration and collaterals) before filling the single (systemic) ventricle, resulting in low end-diastolic volume and decreased stroke volume.[26] At rest, the cardiac output of a Fontan patient is at least reduced to 80% of normal. During exercise, the increase in cardiac output is even more impaired due mainly to decreased preload (augmentation of pulmonary blood flow is limited due to the lack of a sub-pulmonary ventricle) and concurrent factors like chronotropic insufficiency, decreased oxygen saturation, and reduced muscle mass (Fig. 2).[27,28]

What are the main end-organ complications of Fontan circulation?

Chronic systemic venous congestion and relatively low cardiac output form the basis for potential deleterious end-organ consequences. Several systems and organs might be affected:[29]

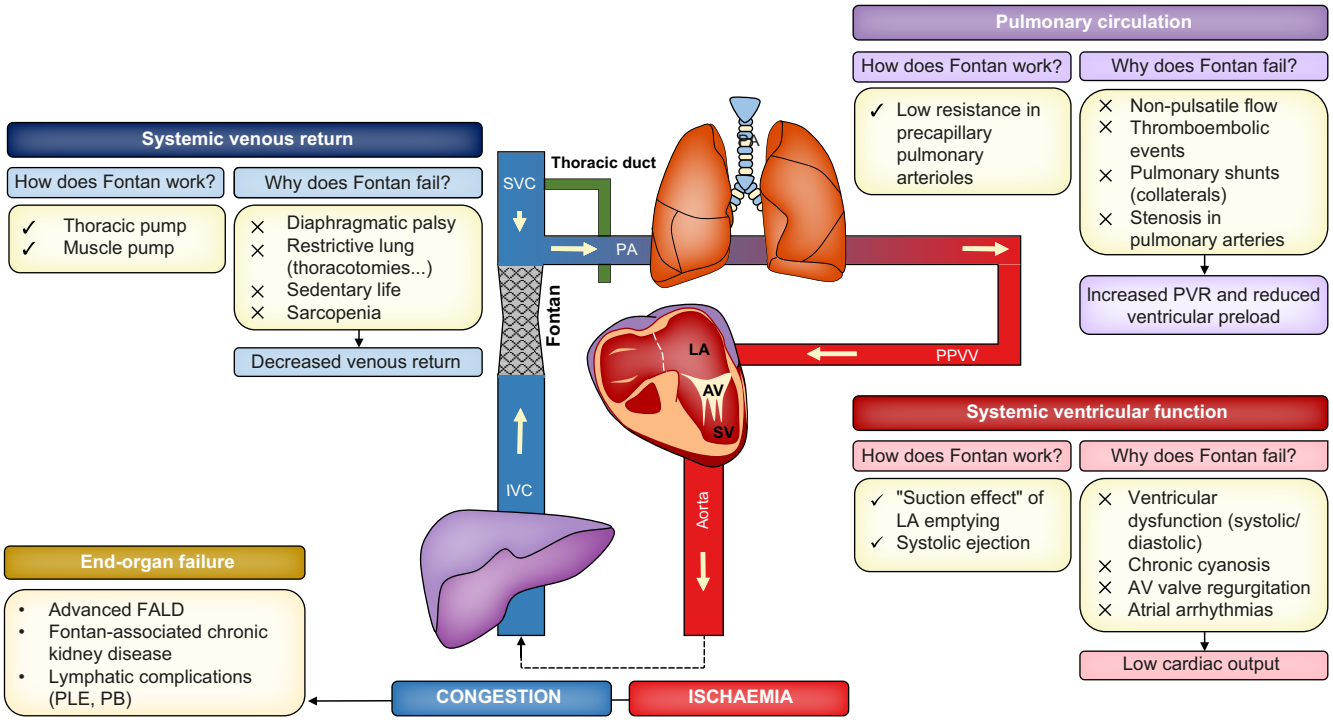

Fig. 2. How the Fontan circulation works in the absence of a sub-pulmonary pump and why the Fontan circulation fails: the three key elements. FALD, Fontan-associated liver disease; LA, left atrium; PA, pulmonary artery; PB, plastic bronchitis; PLE, protein-losing enteropathy; PPVV, pulmonary veins; PVR, pulmonary vascular resistance; SV, single ventricle.

- Heart: arrhythmias, valvulopathies, and single ventricle dysfunction.[30,31]
- Liver: FALD and HCC.[32–34]
- Kidney: Fontan-associated chronic kidney disease.[35]
- Gut: PLE.[36,37]
- Bone: bone mineral deficiency.[38]
- Lungs: pleural effusion and hypoxia due to intrapulmonary shunts.[39]
- Brain: neurocognitive disorders and behavioural deficits.[40]
- Lymphatic system: chylothorax, chylous ascites, PLE, and PB (characterized by the leakage of proteinaceous material into the airways).[34,41,42]
- Vascular system: thromboembolism, peripheral oedema, and lower extremity venous insufficiency.[43–46]

The reported prevalence of end-organ complications is 16-34% for arrhythmia,[47–49] 13-86% for FALD,[50–52] 10-50% for nephropathy,[53–56] 1-5% for PLE,[57] 50-60% for venous insufficiency,[46,58] and 1-4% for PB.[59] However, the actual prevalence of some of these disorders could be higher due to subclinical disease presentation and the lack of universal definitions.[60]

What is the Fontan circulatory failure?

A recent consensus statement proposed a standardized definition for Fontan circulatory failure as a non-specific term to describe a deteriorated clinical status affecting the patient's ability to carry out daily activities.[34] This complex syndrome can result from multiple potential aetiologies such as ventricular dysfunction, atrioventricular valve failure, increased pulmonary vascular resistance, recurrent arrhythmia, Fontan pathway obstruction, lymphatic insufficiency (PLE, PB, or chylous ascites), or other end-organ dysfunction.[61–63] Accordingly, symptoms may be related to heart failure and hypoxemia or end-organ complications (mainly PLE, PB, or advanced FALD), resulting in different clinical and haemodynamic Fontan failure phenotypes (patients with systolic ventricular dysfunction [reduced ejection fraction]; with diastolic ventricular dysfunction [preserved ejection fraction]; with systemic congestion but preserved ventricular function; and with abnormal lymphatics).[64] This clinical picture is the most frequent cause of death in this population and should be suspected in all patients meeting at least one of the following criteria: NYHA functional class IV; NYHA functional class III for ≥12 months without sustained improvement; >2 unscheduled hospital admissions within 12 months for heart failure symptoms; and active PLE or PB without remission for ≥6 months.[56,65–68] In a cohort including 683 Fontan patients aged >16 years, the probability of remaining free from Fontan circulatory failure was 93%, 77%, 62%, and 30% at ages 20, 30, 40, and 50 years, respectively.[69]

What is the prognosis of patients with Fontan circulation?

The success of Fontan-type surgery has increased in parallel with advances in surgical procedures and perioperative management.[5,70–72] While in the 1980s, only 73% of Fontan patients reached adolescence, today, this is achieved by more than 95%.[15,73,74] Nonetheless, observational studies have shown that although Fontan-type surgery is an excellent medium-term solution, it is suboptimal in the long term, and the resulting circulation cannot be maintained indefinitely.[75] Distinctively, adults with Fontan circulation have the highest

mortality ratio of any congenital heart disease, with a more than 20-fold increased risk of death compared to an age-matched population.[76] As a clarifying example, a 20-year-old Fontan patient has approximately the same 5-year risk of death as a 64-year-old individual in the general population.[75]

Definition of Fontan-associated liver disease

Statements

- FALD encompasses a broad spectrum of structural, functional, and clinical liver alterations secondary to Fontan haemodynamic changes (**Moderate LoE**).
- Some degree of FALD is universally present after Fontan-type surgery. Liver damage can start even before the Fontan procedure and is present in patients without Fontan circulatory failure (**Moderate LoE**).
- There is not a homogeneous definition of advanced FALD. A proposal is to consider advanced FALD in patients with clinical signs highly suggestive of portal hypertension (oesophageal varices, portosystemic shunts, ascites, or splenomegaly) due to liver fibrosis (**Low LoE**).
- The time elapsed from Fontan-type surgery is the main risk factor for developing advanced FALD (**High LoE**).
- Fontan patients can exhibit additional risk factors for liver damage, such as an increased prevalence of HCV or HBV infection or the use of hepatotoxic drugs (*i.e.*, amiodarone) (**High LoE**).

How is FALD defined?

In 1983, Lemmer *et al.* described, for the first time, the development of severe liver fibrosis in a patient 5 years after Fontan surgery.[77] Since then, many clinical series have employed the term FALD to name this particular liver damage, providing incidence rates ranging from 36% to 86%, depending on the diagnostic method used (signs and symptoms, imaging, liver biopsy, serological tests, or combined evaluations).[77–84] However, the true incidence of FALD is unknown and likely underrecognized, as we lack a uniformly accepted definition of the disease. Findings from elective liver biopsy indicate that all patients with Fontan circulation have some degree of liver fibrosis. Indeed, liver damage may begin even before the Fontan completion due to the numerous haemodynamic insults cumulatively developed from birth, as suggested in autopsy studies performed in patients who died very soon after the Fontan procedure.[32,85–87]

FALD encompasses a broad spectrum of structural, functional, and clinical liver alterations secondary to Fontan haemodynamic changes. These changes are secondary to the pathological haemodynamic state that exists in any kind of Fontan circulation since the first day of the surgical procedure, which means that FALD can also occur in patients without Fontan circulatory failure. This definition agrees with the recent expert consensus launched by several societies and initiatives involved in Fontan patient care.[34,88]

What is the pathophysiology of FALD?

Different mechanisms related to the vascular supply and drainage of the liver have been linked to the development of hepatic damage in Fontan patients.

- **Liver congestion**: The hepatic veins transmit systemic venous hypertension to the sinusoid, leading to sinusoidal dilatation, hyperfiltration, and perisinusoidal oedema.[32,89] In turn, sinusoidal shear stress promotes sinusoidal endothelial cell capillarization, decreases intrahepatic nitric oxide concentration, and facilitates the mechanical activation of mechanosensitive cell signaling pathways in hepatic stellate cells, resulting in liver fibrosis.[90–92] These changes also hamper the diffusion of oxygen and nutrients and promote centrilobular hepatocellular dropout and atrophy.[93] The severity of liver congestion is heterogeneous due to the technique-dependent flow characteristics of the Fontan connection in each patient, which partly explain the interindividual variability seen in liver damage.[94]
- **Hypoxia and hepatic ischaemia**: Elevated CVP may reduce the effectiveness of the hepatic arterial buffering response.[95–97] These changes put the liver at risk for hypoxemic injury during an acute event (cardiac surgeries or cardiopulmonary collapse). Moreover, in the long term, chronic reduced cardiac output and the development of aberrant intrapulmonary shunts would perpetuate liver hypoxia.[98,99]
- **Prothrombotic state**: Hepatic sinusoidal thrombosis, as evidenced by fibrin deposition, has been demonstrated both in animal models of FALD and in humans with Fontan circulation.[90,91] The anatomical and functional characteristics of the Fontan circulation and the acquired thrombophilic state (low serum levels of antithrombin III, thrombomodulin, alpha-2-antiplasmin, and C and S proteins and high levels of thrombin-antithrombin complex) could facilitate intrahepatic microthromboses.[100–105]
- **Lymphatic congestion**: Increased hepatic lymphangiogenesis and lymphatic stasis contribute to significant dilatation of hepatic sinusoids, the space of Disse, and channels passing through the limiting plate, which may contribute to collagen fiber deposition.[106,107]
- **Systemic inflammation:** It has been speculated that a state of latent microinflammation may promote end-organ fibrogenesis (*i.e.*, kidneys, liver, and myocardium).[108] Increased intestinal permeability secondary to venous and lymphatic congestion and chronic ischaemia may play a central role in the inflammatory state.[109]
- Other risk factors include an increased prevalence of hepatitis C (∼ 4% of chronic infection) and B virus infection and risk of hepatotoxic injury due to medications (*i.e.*, amiodarone).[110–112]

What is the definition of, and what are the risk factors for, advanced FALD?

There is no uniform definition of advanced FALD, and several studies have proposed arbitrary definitions based on serological biomarkers and radiological, histological, or clinical evaluations.[83,113–115] Combined clinical serological and radiological scores, such as the VAST score (VAST score >1, 1 point each for the presence of oesophageal varices, ascites, splenomegaly, or thrombocytopenia), have been proposed to diagnose advanced FALD. However, we need more data to establish these scores as a gold standard.[83] A proposal is to consider advanced FALD in those patients with clinical, endoscopic, or

radiological signs of portal hypertension (varices, portosystemic collaterals, ascites, or splenomegaly) secondary to liver fibrosis. Extrapolating the current concept from other advanced chronic liver diseases, advanced FALD can be sub-classified as compensated or decompensated. FALD would be defined as decompensated when patients have developed liver-related complications, including encephalopathy (any grade), liver-related ascites (grade >1), and (or) variceal bleeding.

Although risk factors for severe liver damage are not well-established, there is a clear relationship between the severity of liver damage and the time elapsed from Fontan-type surgery.[116,117] The risk of advanced FALD and severe fibrosis is low within the first 5 years after surgery but increases significantly after 15 years.[78,85,118–121] In a retrospective study using non-invasive tests, the authors reported 10-, 20- and 30-year freedom from cirrhosis rates of 99%, 94%, and 57%, respectively.[122] Older age at the time of Fontan-type surgery has also been related to augmented fibrosis, suggesting that prolonged univentricular circulation promotes fibrogenesis.[86,123] The atriopulmonary surgery variant has also been associated with a higher degree of liver fibrosis. However, this surgery was employed decades ago and has been replaced by total cavopulmonary techniques, so this observation is susceptible to time-dependent bias. Females have significantly higher median total fibrosis scores than males for a similar average age and Fontan circulation duration.[124] Other authors have suggested that those with an extracardiac connection may develop hepatic fibrosis faster than those with a lateral tunnel connection due to the different compliance.[125,126] Hypoplastic left ventricular syndrome, as the underlying cardiac defect, is also related to more severe liver disease in one small case series.[122] Intrapulmonary shunts and secondary chronic hypoxemia may increase the risk of advanced liver fibrosis.[127] Finally, several studies have linked the degree of liver damage (estimated by non-invasive methods) with some adverse cardiovascular events presented during follow-up: decreased ventricular function, increased pulmonary resistance, tachyarrhythmia, sinus node dysfunction, atrioventricular valve insufficiency, and Fontan conduit thrombosis or stenosis.[50,79,115,128–131]

What are the main histological characteristics that define FALD?

Histologically, FALD is typified by gross architectural distortion, massive sinusoidal dilation, and perisinusoidal fibrosis in the absence of significant parenchymal inflammation.[30,89] The most notable feature is sinusoidal dilatation, which extends from the centrilobular region (zone 3) to the portal tract (zone 1).[89]

As in other congestive liver diseases, histological changes predominantly affect the centrilobular zone instead of the portal area.[129–135] Fibrosis starts with a fine neomatrix deposited within the space of Disse and progresses, matures, and enlarges over time. The extreme long-standing congestion extends fibrosis even to the portal area, which may differentiate FALD from other congestive hepatopathies.[86,89,119,121,136–138] In FALD, cirrhosis is histologically defined by regenerative liver nodules and scar areas of bridging fibrosis, linking the central vein initially to the central vein and then the central vein to the portal tract or portal to portal tract.[121,139]

Perisinusoidal and centrilobular fibrosis is typically accompanied by centrizonal vascular alterations such as arterialization, microvessel formation, sinusoidal capillarization, and centrilobular ductular metaplasia, overall leading to loss of typical liver zonation. Centrilobular microvessel formation and sinusoidal capillarization are closely interrelated and are found in the early and late stages. The ingrowth of centrizonal arterioles could result from vascular remodelling during fibrosis progression.[140] In addition, most FALD biopsies show some degree of ductular reaction.[89]

Hepatocellular necrosis can be described in the setting of shock or respiratory failure.[132] On the other hand, portal inflammation, steatosis, ballooned hepatocytes, apoptotic bodies, ceroid-laden macrophages, and iron deposition are not hallmarks of FALD but can be observed in patients with risk factors for comorbidity.[86,138] No differences in terms of morphological substrates between paediatric and adult populations have been identified. The only key issue is the amount of collagen deposition, which correlates with the length of follow-up.[87]

Clinical evaluation and staging of Fontan-associated liver disease

Statements

- FALD is typified by gross architectural distortion, massive sinusoidal dilation, and perisinusoidal fibrosis in the absence of significant parenchymal inflammation (**High LoE**).
- In patients with FALD, liver fibrosis is nearly universal and distinctively involves both centrilobular and portal areas (**High LoE**).
- The patchy distribution of fibrosis in FALD may lead to underestimation of its stage (**Moderate LoE**).

When is a liver biopsy indicated in Fontan patients?

Recommendations

- Liver biopsy should be considered the gold standard for assessing liver fibrosis in FALD (**Moderate LoE; strong recommendation**).
- Liver biopsy is recommended in patients with Fontan circulatory failure who are candidates for heart transplantation or if another aetiology of liver disease is present or suspected (**Low LoE; strong recommendation**).

Although quantification of liver fibrosis has been proposed as one of the primary predictive tools in patients with FALD, cross-sectional and retrospective studies have demonstrated poor correlation with clinical outcomes without differences in heart transplant-free survival according to the stage of liver fibrosis.[137,141] To date, no study has prospectively compared biopsy findings with the risk of relevant clinical events. Biopsy has several limitations: high costs compared to non-invasive methods, the potential need for anaesthesia, the risk of bleeding and the risk of sampling error due to the extremely patchy nature of FALD.[138,142–144] Indeed, fibrosis grade was underestimated in 40% of liver biopsies obtained during the pretransplant evaluation of Fontan patients who underwent heart-liver transplantation.[145]

Despite these inherent limitations, most authors agree that biopsy remains the gold standard for disease staging. The need for well-designed longitudinal and prospective studies evaluating these strategies prevents us from supporting the routine performance of liver biopsy in all patients with Fontan circulation. There are two clear indications for liver biopsy: 1) in patients with Fontan circulatory failure who are candidates for cardiac transplantation, to help to decide whether combined heart-liver transplantation would be required to treat dual organ failure;[146,147] and, 2) if another aetiology of liver disease is present or suspected. Finally, some authors have suggested that biopsies systematically performed 10-15 years after completion of the Fontan procedure or when cardiac catheterization is indicated, may help to identify patients who should be referred early for medical or interventional optimization of Fontan circulation to prevent or reduce liver disease progression.[14,129,148–151]

What is the best scoring system for grading fibrosis in FALD?

Recommendations

- Simplified scoring systems integrating central zone and portal fibrosis are preferred in FALD. A combined 4-scale scoring system, such as the congestive hepatic fibrosis score, is accurate and clinically relevant and therefore suggested (**Low LoE, weak recommendation**).

Traditional staging systems of portal fibrosis, using Metavir, Ishak, and Scheuer, are helpful in identifying cirrhosis in FALD, but the intermediate stages of these scores may underestimate the severity of liver fibrosis.[14,85,120] To overcome this limitation, Kendall *et al.* used a hybrid fibrosis staging system based on gross architectural distortion (ranging from 0 to 4, modified from the Metavir system) and sinusoidal fibrosis (ranging from 0 to 3, according to the area involved).[89] Similarly, Wu *et al.* evaluated liver fibrosis in a series of 68 Fontan patients using dedicated semiquantitative scoring systems for portal fibrosis (Metavir system) and central fibrosis based on the extent of pericellular fibrosis (ranging from 0 to 4).[137] In contrast, other authors proposed using simplified scoring systems integrating centrilobular and portal fibrosis, such as the congestive hepatic fibrosis score (ranging from 0 to 4) or the modified Ishak congestive hepatic fibrosis histologic score (ranging from 0 to 6) (Table 1).[132,136] As these scores may overestimate fibrosis, Louie *et al.* adapted a 3-scale scoring system from liver explants and biopsies, with stage 3 defined as bridging fibrosis with regenerative nodules.[142] We propose considering a combined 4-scale scoring system (*i.e.*, congestive hepatic fibrosis score) as more accurate and clinically relevant, as it may reflect liver changes in FALD better (centrilobular and portal damage) and may be easier to implement for pathologists and clinicians who are familiar with 4-scale scores in other chronic liver diseases.[14,120,129,141,151] Importantly, whereas interobserver agreement has been evaluated in very few studies in the context of FALD, it is much better on portal fibrosis (>0.7) than on sinusoidal fibrosis and significantly improved after a training session.[132,141]

In parallel to semiquantitative fibrosis scoring systems, quantitative measurement of collagen deposition area through specific staining (*i.e.*, picrosirius red) using dedicated software may provide an objective global assessment of portal and centrilobular fibrosis.[85,120,141] As previously reported in chronic HCV infection, quantitative measurement of fibrosis correlated with semiquantitative staging systems.[120,141]

What are the minimum criteria for quality histological specimens for accurate fibrosis staging in FALD?

Recommendations

- Liver biopsy should be performed and evaluated in referral centres in FALD (**Low LoE; strong recommendation**).
- Routine staining for assessment of liver fibrosis may include Masson trichrome and picrosirius red. Orcein staining may provide further information on the maturity of fibrosis and the potential for reversibility (**Moderate LoE, weak recommendation**).

No studies have specifically addressed the representability of liver biopsy in FALD.[152] However, a non-fragmented specimen with a length of at least 15 mm is usually considered adequate in FALD.[120,132] Munsterman *et al.* defined adequate biopsy samples as having a length >2 cm and the presence of at least 11 portal tracts.[141] In addition to length, the width of liver biopsy, which is usually not reported, should be considered given the potential underestimation of fibrosis staging in narrow samples. Given the risk of sampling bias, we suggest performing at least two different passes.

Different staining methods, such as Masson trichrome and picrosirius red, are routinely performed to assess liver fibrosis.[85,132] Evaluation of the quality and texture of fibrosis is also essential as it reflects the chronicity of liver injury and its potential reversibility. Accordingly, orcein staining provides further information on the maturity of fibrosis and its potential for regression after Fontan circulatory failure improvement or heart transplantation.[89]

Beyond these minimum quality criteria of a liver biopsy, it is necessary to highlight that the pathologist's expertise is crucial. We recommend that dedicated pathologists interpret FALD biopsies in referral centres.

Is there any preference regarding the route of liver biopsy (transjugular or percutaneous) in Fontan patients?

Recommendations

- The diagnostic quality of liver tissue samples obtained by transjugular and percutaneous approaches is similar. Given the risk of sampling bias, performing at least two different passes is suggested (**Very low LoE; weak recommendation**).
- The transjugular approach may be preferred over the percutaneous, based on safety considerations and the possibility of performing cardiac and hepatic vein catheterization during the same procedure (**Low LoE; weak recommendation**).

Table 1. Histological grading systems integrating centrilobular and portal fibrosis employed to evaluate hepatic specimen of patients with FALD.

Congestive hepatic fibrosis score (CHFS)[134]	
0	No fibrosis
1	Central zone fibrosis
2a	Central zone and mild portal fibrosis, with accentuation at central zone
2b	At least moderate portal fibrosis and central zone fibrosis, with accentuation at portal zone
3	Bridging fibrosis
4	Cirrhosis
Modified Ishak congestive hepatic fibrosis score[131]	
0	No fibrosis (similar to CHFS 0)
1	Central zone fibrosis (similar to CHFS 1)
2a	Central zone and portal fibrosis, with accentuation of fibrosis in the central zone (similar to CHFS 2a)
2b	Portal and central zone fibrosis, with accentuation of fibrosis in the portal zone (similar to CHFS 2b)
3	Fibrous expansion of most portal areas with occasional portal to portal or portal to central bridging (similar to Ishak score 3)
4	Fibrous expansion of most portal areas with marked portal to portal or portal to central bridging (similar to Ishak score 4)
5	Marked bridging with ocassional nodules or incomplete cirrhosis (similar to Ishak score 5)
6	Cirrhosis (similar to CHFS 4 or Ishak score 6)
Modified Metavir system[91]	
0	No definite fibrosis
1	Minimal fibrosis (no septa or rare thin septum)
2	Mild fibrosis (occasional thin septa)
3	Moderate fibrosis (moderate thin septa; up to incomplete cirrhosis)
4	Cirrhosis definite or probable
3-scale scoring system for changes related to chronic congestion[144]	
0	No fibrosis
1	Pericellular fibrosis
2	Bridging fibrosis
3	Bridging fibrosis and regenerative nodules

Transjugular and percutaneous routes can be equally effective. Nevertheless, as morphological features are preferentially observed in subcapsular areas, the percutaneous route is expected to be the most informative, especially when performed with ultrasound guidance, allowing for the selection of the most abnormal regions.[142,153,154] While there have been suggestions that transjugular biopsy may introduce a sampling bias as it preferentially samples the perivascular region, which may theoretically be more affected by venous congestion, this was not confirmed by Vaikunth *et al.*, who showed that transjugular biopsy somewhat underestimated fibrosis.[145] This could be partly explained by the narrower and more prone fragment samples obtained by the transjugular route. Despite these limitations, the transjugular approach has some advantages, it provides additional liver haemodynamic data, can be performed during cardiac catheterization, and is safer. A recent cohort of percutaneous liver biopsies confirmed this population's high risk of bleeding, with a 7.1% post-procedural haemorrhage rate (minor in 5.9% and major in 1.5%, despite using tract embolization with gelatin sponge in 76%), compared to 3.2% reported with the transjugular route.[151,153]

Is hepatic venous pressure gradient a valuable measurement for staging and grading portal hypertension in FALD?

The HVPG facilitates the differential diagnosis of portal hypertension: high hepatic vein pressures (free and wedged) with a normal HVPG suggest a post-hepatic origin, the most frequent finding in advanced FALD.[155] In FALD, five studies assessed HVPG in 248 patients. In those studies, the median HVPG never exceeded 2 mmHg. In a recent large study including 56 Fontan patients, HVPG was not associated with the severity of liver dysfunction or the presence of signs of portal hypertension, nor with heart transplant-free survival.[156] As expected, HVPG did not correlate with liver stiffness or fibrosis severity.[136,156,157] Three studies evaluated the correlation between HVPG and cardiac haemodynamic features, concluding that HVPG was only poorly associated with a higher Fontan conduit, end-diastolic, and pulmonary arterial pressures.[118,156,158] Moreover, the increased prevalence of intrahepatic veno-venous collaterals and intense hepatic vein dilatation may compromise the accuracy of HVPG measurement.[15,88] Consequently, HVPG measurement has limited, if any, usefulness for staging the severity of FALD and does not have prognostic significance. The significance of absolute values of free and wedged pressures should be studied in the future.

Statements

- The hepatic haemodynamic profile of FALD is characterized by high hepatic vein pressures (free and wedged) with a normal hepatic venous pressure gradient (HVPG), *i.e.* post-sinusoidal portal hypertension (**High LoE**).
- HVPG has no value in assessing the presence of advanced fibrosis or the severity of portal hypertension and does not have prognostic significance in Fontan patients (**Moderate LoE**).

What are the typical symptoms and signs of FALD?

FALD is often clinically silent and diagnosed through invasive and non-invasive liver tests. Due to the distension of the Glisson capsule, some patients report discomfort in the upper right quadrant of the abdomen. The liver edge is easily palpable, hard, smooth, and tender in these cases. Hepatojugular reflux could also be easily identified after applying compression over the liver. In adolescent Fontan patients, hepatomegaly is associated with poor cardiovascular outcomes.[159] Mild jaundice is common, yet deeper jaundice is rare, though it may occur at the end of an episode of hypoxic hepatitis. Finally, signs of portal hypertension may appear in the later stages of FALD.

What are the typical laboratory abnormalities of FALD? Are serum biomarkers useful for the diagnosis and staging of FALD?

Statements

- A mild increase in serum gamma-glutamyltransferase is the most common and early laboratory liver abnormality in Fontan patients. Slight elevations of serum bilirubin may also be present (**High LoE**).
- Most scores (*i.e.*, model for end-stage liver disease [MELD], MELD-Na, and Child-Pugh classification) may not be accurate to stage liver disease severity in this population (**Moderate LoE**).

Recommendations

- Serological and combined serum-clinical tests used in other liver aetiologies (aspartate aminotransferase-to-platelet ratio index [APRI], ELF, FIB-4, Forns index, and FibroTest®) have a modest discriminatory power in identifying patients with severe fibrosis and cannot be routinely recommended for staging the liver disease (**Low LoE, strong recommendation**).

A mild increase in serum gamma-glutamyltransferase is the most common and early laboratory liver abnormality, present in >85% of adult Fontan patients.[79,119,160] However, markers of cholestasis are not clearly associated with worse cardiac function, more severe liver fibrosis or impairment of other liver function parameters.[141,161–163] Mild unconjugated hyperbilirubinemia is also frequently observed in FALD. Hyperbilirubinemia can be multifactorial and results from a combination of liver impairment and passive congestion or, less frequently, due to ischaemic biliary damage, haemolysis, or medications.[154,164] In the non-cirrhotic phase of FALD, passive congestion is associated with elevated prothrombin time and prolonged international normalized ratio (INR). Still, only one case series of 74 patients with FALD showed a relationship between elevated INR and the severity of fibrosis.[120] Aminotransferases are rarely elevated in stable Fontan patients, but they can increase in acute cardiac events (*i.e.*, after cardiac surgeries or a cardiovascular collapse), reflecting hypoxic injury and hepatocellular necrosis.[154] Low serum albumin levels may be secondary to PLE, nephropathy, malnutrition, or chronic wasting.[57,109,165,166] However, in advanced FALD, the liver's synthetic protein function may also fail and albumin levels decrease.

Addressing liver function is challenging since most commonly employed scores (*i.e.*, MELD and Child-Pugh classification) are based on creatinine, INR, albumin, and bilirubin, which may reflect liver function poorly in this population.[35,167] MELD score excluding the international normalized ratio (MELD-XI) can be employed to overcome the increased INR due to warfarin therapy.[118] MELD-XI has demonstrated a significant correlation with histologically proven liver fibrosis, though a specific MELD-XI cut-off value for severe liver fibrosis has not been identified. Other reports did not observe this correlation.[141] Retrospective studies suggest that the MELD-XI score correlates with systolic ventricular dysfunction and decreased oxygen saturation.[168] In a single-centre experience, MELD-Na was highly elevated in patients with bridging fibrosis who died.[161] Progressive thrombocytopenia is frequently found in FALD and may be associated with more advanced fibrosis, reflecting hypersplenism due to portal hypertension.[83,150,161]

Most serological tests used to estimate liver fibrosis in other chronic liver diseases (ELF score, APRI, FIB-4, FibroTest®, and Forns index) have been evaluated in FALD in several studies. However, these studies generally lacked histology as the gold standard and demonstrated a modest discriminatory power in identifying patients with severe fibrosis in FALD.[78,81,129,169–174] A single-centre study comparing patients with histologically proven mild and severe liver fibrosis did not find differences in ELF score, APRI, and FIB-4 values between the two groups.[141] Although APRI and FIB-4 were significantly higher in patients with severe fibrosis in a larger cohort; these tests had a modest discriminatory power in identifying patients with advanced FALD.[161] Novel approaches should be clinically evaluated in the future.[175]

What are the typical radiological abnormalities of FALD? Are radiological findings useful for diagnosing and staging FALD?

Recommendations

- In abdominal imaging, typical findings of FALD are bulging liver contours, hepatomegaly, dilated hepatic veins, atrophy of the right lobe, hypertrophy of the caudate and left lobes, patchy and heterogenous parenchyma patterns, and multiple peripheral small nodules. These changes are more apparent with increased Fontan circulation duration and can be secondary to liver congestion, fibrosis, or both. Thus, abdominal imaging alone cannot be recommended for staging liver disease severity (**Low LoE, strong recommendation**).

In abdominal imaging, typical findings of FALD are bulging liver contours, hepatomegaly, atrophy of the right lobe, and hypertrophy of the caudate and left lobes, which become more apparent as the duration of the Fontan circulation increases.[176,177] Notably, the vascular origin of liver damage results in a patchy and heterogeneous distribution of fibrosis, which is also represented by multiple peripheral nodules of different sizes and peripheral irregular regions of poor enhancement after contrast administration. In advanced fibrosis and cirrhosis, the liver becomes less compliant, and dilated hepatic veins within the liver may not be observed.[88]

Abdominal Doppler ultrasound: The most frequent ultrasound findings are heterogeneous echogenicity (16-92%), a nodular liver surface, and small-sized hyperechoic nodules.[30,50,178–182] Heterogeneous echogenicity is not specific to congestion and can also be related to fibrosis, cirrhosis, or steatosis. Veno-venous shunts between hepatic veins can be seen in states of severe congestion.[88] Doppler changes in Fontan patients may show the same patterns as in patients with chronic liver disease, but the lack of three-phase blood flow of hepatic veins may be secondary to the loss of the atrial beat.[181–183]

CT and MRI: Hepatic MRI is preferable but not always possible due to contraindications such as incompatible cardiac devices, in which CT of the liver is recommended. The most common finding in CT and MRI is a heterogeneous parenchymal enhancement (68-98%) with mosaic or reticular liver patterns.[80,82,119,182,184] On MRI, the T2-weighted images frequently exhibit diffusely increased liver signal intensity that might reflect the degree of congestion.[180,185] This is contrary to hepatic fibrosis in non-congestive chronic liver disease, revealing typical changes such as peripheral reticular increased T2-weighted and decreased T1-weighted signal intensity.[186] The vascular contrast enhancement pattern on CT and MRI of the liver in a patient with Fontan circulation demonstrates a distinct peripheral, reticular, and patchy enhancement pattern during the late arterial and portal venous phases, which equilibrates during the delayed phase.[187] This configuration is probably due to delayed wash-in of contrast material into the

congested liver. Using hepatocyte-specific contrast agents, the heterogeneous enhancement of the liver parenchyma is most prominent during the portal venous phase and may equilibrate in the equilibrium or delayed phase.[186] A heterogeneous hypoenhancement in the hepatobiliary phase MRI using a hepatocyte-specific contrast agent may reflect decreased hepatic function.[188] Liver extracellular volume fraction, derived from MRI T1 relaxometry, is increased in Fontan patients, which suggests fibrotic remodelling and/or congestion in the liver, but its prognostic significance remains to be determined.[189–191]

In summary, most patients with Fontan circulation show radiological changes in the liver parenchyma, which may be related to congestion, fibrosis, or both. Only a few studies have compared the significance of these alterations to liver biopsy. They agree that conventional radiological changes highly suggestive of severe fibrosis in non-congestive aetiologies (*i.e.*, nodular liver contours, heterogeneous parenchyma, and segmental atrophy) are frequently present in Fontan patients even with absent, mild, or moderate fibrosis.[141,161] Consequently, the prognostic significance of radiological changes remains to be determined. One of the primary uses of CT and MRI in FALD stems from their accurate diagnosis and characterization of liver nodules.[145,179]

Is liver stiffness helpful for staging liver fibrosis in FALD?

Different elastography techniques have studied the role of liver stiffness measurement (LSM) in Fontan patients: point shear-wave elastography, also called point radiation force impulse; two-dimensional shear-wave elastography imaging; transient elastography (TE) (Fibroscan®); and MR elastography (MRE). Their use in Fontan patients is challenging, as systemic venous congestion can increase LSM.[192,193] Compared to healthy controls, children and adults with Fontan-type surgery universally show increased values of LSM, mostly reaching values corresponding to advanced disease stages for non-congestive aetiologies.[194–200]

Studies using elastography have reported difficulties in staging fibrosis in children and adults with Fontan circulation. Only one study found a correlation between LSM estimated by ultrasound elastography and fibrosis grade on biopsy, and another work observed an association between LSM, ventricular pressure, and veno-venous collaterals.[195,201] However, other series displayed different results.[202] A few studies using TE have compared LSM to histology, but no strong correlation to fibrosis grade was found.[141,157,203–205] Other studies found a relationship between some parameters of liver impairment (MELD-XI, serum albumin, and platelets) and LSM estimated by TE, suggesting that in the later stages, fibrosis may contribute to LSM.[118,170,182] There is still little evidence of MRE's role in staging fibrosis. However, two small cohorts of adult Fontan patients revealed a strong correlation of LSM with histology and duration of Fontan circulation.[129,199,206] Elastography deserves prospective studies that might determine appropriate "normal" LSM values for Fontan patients and to evaluate if different cut-offs of LSM for ruling in and ruling out severe liver fibrosis could be established.

Is LSM valuable for predicting clinical outcomes?

The relationship between LSM and strong liver-related outcomes has been scarcely studied.[118,170,182,200,206–209] Some studies have demonstrated that patients with clinical signs of portal hypertension showed higher LSM than patients without portal hypertension, but no cut-offs have been established.[162,182,203,204,210,211] One small single-centre study showed that LSM was significantly higher in patients with liver nodules, but these results have not been replicated.[179,212] Unfortunately, no study has specifically evaluated the usefulness of elastography for risk stratification of HCC in this population. In one retrospective and longitudinal study including 22 patients, progression of LSM estimated by MRE correlated with clinical deterioration as measured by worsening liver disease severity scores (MELD and MELD-XI) and the occurrence of adverse events (death, heart-liver transplant listing, palliative care, hospitalization, and need for paracentesis).[213] Longitudinal and prospective studies are required to determine the specific role of elastography in predicting strong clinical outcomes.

The correlation between LSM and the risk of Fontan circulatory failure is debatable. In a study with MRE, haemodynamic signs of Fontan failure showed a weak correlation to LSM in adults, which was not reproduced in a paediatric cohort.[211,214] Other studies found moderate associations between LSM and decreased systolic and diastolic function.[113,195,215] Simultaneously, a correlation between LSM and CVP has been found in several studies.[129,157,195,196] In a large cohort of 129 Fontan patients evaluated by a non-invasive comprehensive hepatic assessment, the authors created the FALD score based on laboratory, hepatic ultrasound, and TE results.[50] The resulting score significantly correlated with impaired Fontan haemodynamics (increased end-diastolic ventricular, arterial pulmonary, and CVP) and showed high diagnostic accuracy in detecting Fontan circulatory failure. Finally, in a case-control study, patients with PLE had increased values of LSM by TE compared to Fontan patients without bowel impairment.[109] These results suggest a possible role of elastography and other non-invasive parameters as valuable biomarkers for predicting non-liver-related clinical outcomes.[50]

Is spleen stiffness measurement valuable for staging FALD?

A few small studies have been published correlating spleen stiffness measurement (SSM) with liver fibrosis, but no firm conclusions can be made.[206,216–220] One prospective study reported that SSM was higher in children with Fontan circulation than in healthy controls.[221] In a cohort of 50 patients (biopsy was available in 10), MRE-SSM correlated with the histologic degree of liver fibrosis and was related to spleen volume and the presence of oesophageal varices.[206] On the other hand, a retrospective study found SWE-SSM comparable to healthy controls.[222] No studies using the spleen-specific probe of TE are available.

Should LSM be recommended for FALD surveillance?

Recommendations

- Longitudinal assessment of LSM during follow-up could help monitor patients and predict clinical outcomes. Thus, in surveillance programmes for FALD, LSM can be considered and easily performed when available as an adjunct to a liver ultrasound or MR examination (**Very low LoE, weak recommendation**).

The variable results of elastography studies are explained by the complex interplay between LSM, degree of liver fibrosis, Fontan pathway pressure, and risk of Fontan circulatory failure. However, it is essential to highlight that increased LSM measured with elastography in the individual patient may signal the need to further evaluate the Fontan circulation and advanced FALD. Conversely, a reduction in LSM could indicate an improvement in the Fontan circulation in the short term and liver fibrosis in the long term.[88] Consequently, different surveillance strategies have been proposed in children and adults where elastography has been added as a part of liver disease screening or follow-up.[30,143,154,223] MRE is still not widely available but it is recommended if available and when performing MRI during follow-up from adolescence onwards.

Portal hypertension considerations and management of complications

What is the risk of oesophageal varices and variceal bleeding in FALD?

The risk of oesophageal or gastric varices in the Fontan population has been poorly evaluated and predominantly assessed at imaging.[83,119,224] Accordingly, the prevalence of varices in adult Fontan patients ranges from 19% to 43%, while it is lower in children (~9%), which suggests that its development is a late complication.[118]

The presence of oesophageal varices at endoscopy deserves special consideration, as they can appear in FALD even in the absence of severe liver fibrosis or cirrhosis. In the context of elevated superior vena cava and pulmonary pressures, venovenous communications and diffuse dilatation of the upper venous plexus can be present. These venous communications can lead to oesophageal varices more likely to be located in the upper oesophagus (also known as "downhill varices") rather than lower varices reflecting true portal hypertension. Consequently, if upper gastrointestinal endoscopy is performed, a detailed description of varices (size, presence of red wale marks, and location) should be reported.

The incidence of haemorrhage related to portal hypertension following the Fontan operation appears to be lower than in non-cardiac cirrhosis and is a rare cause of death.[60,130,225,226] In a retrospective study, oesophageal varices were documented in 43% and portal hypertensive gastropathy in 39% of adults with Fontan-type surgery, but gastrointestinal bleeding was only observed in 6% of them.[52]

Is primary and secondary prophylaxis of variceal bleeding indicated in FALD?

Recommendations

- Gastro-oesophageal varices in FALD are usually small, and the risk of bleeding is very low. Primary prophylaxis cannot be systematically suggested (**Very low LoE, weak recommendation**).
- Treatment of acute variceal bleeding and secondary prophylaxis can follow the current recommendations for patients with cirrhosis (**Very low LoE, weak recommendation**).

The impact of non-selective beta-blockers (NSBBs) on portal pressure has yet to be addressed in Fontan patients. However, from a pathophysiological point of view, NSBBs could be less effective or ineffective in the FALD model of portal hypertension, characterized by hypodynamic circulation. Alternatively, sedated endoscopic variceal band ligation can be employed as primary or secondary prophylaxis, but the risk of deep sedation should be considered. Thus, considering the low incidence and risk of bleeding in this population, a discussion regarding primary prophylaxis should be had with a cardiologist, considering the risk and benefits of NSBBs and interventional endoscopy, and primary prophylaxis cannot be systematically recommended. Without evidence on FALD, secondary prophylaxis can follow current recommendations for patients with cirrhosis (NSBBs plus variceal band ligation). Still, this treatment should be individualized, as NSBB use or sedation is contraindicated in some Fontan patients.

Is variceal screening recommended in patients with FALD?

Recommendations

- "Downhill oesophageal varices" secondary to diffuse dilatation of the upper venous plexus or systemic-to-pulmonary venous communications and real portal hypertension-derived gastro-oesophageal varices can coexist in FALD. Thus, a detailed description of varices (size, presence of red wale marks, and location) should always be reported (**Low LoE, strong recommendation**).
- The presence of gastro-oesophageal varices is related to worse outcomes in FALD, and screening for gastro-oesophageal varices is suggested for staging purposes (**Low LoE, weak recommendation**).

In the VAST study, comprising a retrospective cohort of 73 Fontan patients, the presence of oesophageal varices, along with other manifestations of portal hypertension, was associated with an increased risk of death, heart transplantation, and HCC.[83,118] Consequently, screening for oesophageal varices may be advisable for staging purposes. Because of the poor association between the severity of FALD and LSM, the Baveno VII recommendation to avoid endoscopy cannot be applied in this population.[155,227] Although varices may be incidentally noted on cross-sectional imaging; endoscopy is the only modality recommended for screening. Some groups propose that upper gastrointestinal endoscopy may be systematically performed after 10 years of Fontan-type surgery and then every 2 years during follow-up and prior to listing in all candidates for heart transplantation.[15] However, based on current evidence, a strong recommendation about the optimal timing of upper endoscopy cannot be made.

How should variceal haemorrhage be managed in FALD?

Recommendations

- TIPS is not indicated in FALD, but it may be considered in highly selected cases of severe uncontrolled variceal bleeding (**Very low LoE, weak recommendation**).

Without specific studies on FALD, acute episodes of variceal haemorrhage should be managed with vasoactive drugs, endoscopic band ligation, and prophylactic antibiotics.[155] The preemptive transjugular intrahepatic portosystemic shunt (TIPS) strategy cannot be recommended in these patients, and there is not enough evidence to suggest TIPS in all cases of recurrent bleeding. The sudden decompression of the splanchnic circulation induces a blood volume shift into the systemic vascular bed, resulting in increased pulmonary preload, which may precipitate cardiac failure in case of poor ventricular function. Hence, TIPS use should be restricted to highly selected cases of severe uncontrolled bleeding when ventricular and valvular functions are estimated to be sufficient to serve increased cardiac output demands.[150,228]

What is the minimum diagnostic workup indicated in patients with Fontan circulation who develop ascites?

Recommendations

- The minimum workup recommended in patients developing ascites shall include performing heart catheterization, addressing stenosis or thrombosis across the Fontan pathway, and excluding PLE (**Low LoE, strong recommendation**).

Ascites is present in 4% to 58% of Fontan patients and may have a multifactorial origin.[80,120,141,170,207,224,229] Diagnostic paracentesis can be recommended in patients with new-onset grade 2 or 3 ascites. To determine the hepatic or cardiac origin, the serum albumin ascites gradient (SAAG) and heart catheterization may be helpful.[154,230] A SAAG >1.1 g/dl indicates that portal hypertension is involved in ascites formation but a SAAG >1.1 g/dl can also be present in heart failure.[231,232] A high ascitic fluid protein concentration (>2.5 g/dl) supports a cardiac origin.[233,234] An ascitic concentration of triglycerides >200 mg/dl suggests chylous ascites. Although serum brain natriuretic peptide >364 pg/ml has a sensitivity of 98% and specificity of 99% in diagnosing cardiac ascites, this cut-off has yet to be specifically evaluated in patients with Fontan circulation who have both cardiac and hepatic impairment.[235] Measuring HVPG has also been proposed for the differential diagnosis. However, the HVPG value is typically within the normal range in FALD and cannot differentiate between ascites of hepatic or cardiac origin. Notably, evaluating new-onset or worsening ascites should address residual stenosis or thrombosis across the Fontan pathway. Finally, ascites can directly result from decreased oncotic pressure due to hypoalbuminemia secondary to PLE. Thus, in patients with ascites and low serum proteins, PLE should be ruled out, and a determination of alpha-1 antitrypsin clearance is recommended, even in the absence of diarrhoea.[37]

How should ascites be managed in patients with Fontan circulation?

Recommendations

- The initial treatment of ascites should include optimizing cardiac function, loop diuretics, and anti-aldosterone drugs. In some cases, heart transplantation and other therapies directed towards the aetiologies of ascites may be needed (**Moderate LoE, strong recommendation**).
- TIPS is not indicated in patients with recurrent or refractory ascites, and repeated paracentesis is recommended (**Very low LoE, strong recommendation**).

Given the multifactorial origin of ascites (PLE, lymphatic abnormalities, sinusoidal portal hypertension, Fontan pathway obstructions or Fontan circulatory failure), holistic management is desirable. Generally, ascites is usually manageable by optimizing cardiac function and nutrition, loop diuretics, and anti-aldosterone drugs.[154,236–238] In patients with ascites and Fontan circuit obstruction, a transcatheter treatment (stenting or dilatation) should be performed, even in patients without a measurable pressure gradient.[239] Those cases with Fontan circulatory failure and no pathway obstruction should be evaluated for heart transplantation. In patients with ascites and PLE, some options may be considered: angiotensin-converting enzyme (ACE) inhibitors, pulmonary vasodilators, oral glucocorticoids, heparin therapy, albumin, fresh frozen plasma, and immunoglobulin infusions; transcatheter direct embolization of liver lymphatic channels into the duodenum and interventional thoracic duct decompression; or heart transplantation as a last resort.[240–242]

Although infrequently needed, large-volume paracentesis is the rescue treatment in patients with tense ascites and may even improve systemic haemodynamics.[243] Repeated paracentesis is useful in patients with recurrent ascites. Alfapump ensured a significant reduction of the number of paracentesis procedures required in non-FALD patients with cirrhosis and refractory ascites, but at the expense of a high risk of infection. Anecdotally, intraperitoneal corticosteroid injection has shown some efficacy in patients with recurrent ascites and low SAAG.[244] Given the high risk of heart failure, TIPS is not a good option in Fontan patients with refractory ascites, and no case reports have been published.

Is hepatic encephalopathy a frequent complication of FALD?

Hepatic encephalopathy is a rare complication of FALD, which can be explained by preserved liver function, even in patients with severe fibrosis. Only a few cases have been described in the literature.[122,148,245] However, the actual incidence and prevalence might be underestimated by the retrospective nature of most series and the frequent presence of other neurological complications in the Fontan population (*i.e.*, anoxic encephalopathy, cardioembolic stroke, and cognitive impairment).[15,246,247] In a retrospective review of 10 patients who received vasoconstrictor therapy for Fontan failure, Miike *et al.* reported hyperammonemia in nine patients and overt hepatic encephalopathy (with severe symptoms of drowsiness and seizures) in five patients. In this study, hepatic encephalopathy strongly predicted mortality.[248]

Is portal vein thrombosis a frequent complication of FALD?

Despite the high inherent risk of thrombosis and thromboembolism in almost all variants of Fontan circulation, portal vein thrombosis has not obviously been described in the context of FALD, and only one case has been documented.[249–251] Based on the currently available data, there is no evidence to support specific screening or preventive measures for portal vein thrombosis in FALD.

Liver nodule characterization and hepatocellular carcinoma surveillance and diagnosis in Fontan patients

Statement

- Nodular hepatocellular lesions of different sizes are common in FALD and are mostly benign (**Low LoE**).

Recommendations

- Compared with the age-matched population, the incidence of HCC in Fontan patients is increased, and a surveillance programme is recommended (**Low LoE, strong recommendation**).
- HCC surveillance should be initiated 10 years after Fontan-type surgery and strongly considered earlier in case of Fontan circulatory failure (**Low LoE, strong recommendation**).
- Surveillance should be performed by experienced personnel using abdominal ultrasound examination every 6 months. This should be complemented by cross-sectional contrast-enhanced imaging every 1-2 years (**Very low LoE, strong recommendation**).
- Patients developing liver nodules should be referred to centres experienced in managing FALD (**Very low LoE, strong recommendation**).
- Contrast-enhanced cross-sectional imaging (CT and MRI) is preferred over ultrasound examination to characterize liver nodules. The use of hepatobiliary MR contrast agents, if available, may facilitate better characterization (**Low LoE, strong recommendation**).
- The semi-annual determination of alpha-fetoprotein (AFP) can be used for HCC surveillance. Elevated AFP levels (≥10 ng/ml) might be considered suspicious of malignancy (**Very low LoE, weak recommendation**).
- A biopsy of all radiologically suspicious nodules >1 cm (see Table 2) is always required for a more definitive diagnosis of a malign or benign lesion. The optimal management of nodules <1 cm showing typical HCC patterns should be discussed in multidisciplinary teams (**Moderate LoE, strong recommendation**).
- Diagnosis of HCC in FALD should be confirmed by pathology (**Low evidence, strong recommendation**).
- Repeated sampling is recommended in cases of inconclusive histological or discordant findings or cases of growth or change in enhancement pattern during follow-up (**Low evidence, strong recommendation**).

Are liver nodules frequent in Fontan patients?

Liver nodules are frequent in children and adult Fontan patients, and the prevalence varies across studies, ranging from 20-35% in retrospective series to 48% in a large prospective and multicentric cohort.[119,176,178–180,206,252–255] These differences may be due to the diagnostic method employed.[179] Liver nodules may correspond to benign regenerative lesions and malignant neoplasms (*i.e.*, HCC).[139,179,186] The main risk factors for nodule development are elevated systemic pressure and longer duration of Fontan circulation.[179,254,256]

What are the histological features of liver nodules in FALD?

The most common focal lesions in FALD are benign nodules, and the histological diagnosis relies on the classic morphological features initially described in patients without FALD.[121,257,258] In FALD, typical benign nodules may show overlapping features between large regenerative nodules and focal nodular hyperplasia (FNH) and have been called FNH-like nodules. FNH-like nodules are characterized by the proliferation of normal hepatocytes without a prominent central scar, lobulated by thin fibrous septa with a more or less apparent ductular reaction. These lesions have been linked to a hyperplastic response to impaired hepatic venous outflow, which leads to atrophy and hypoxia-induced damage, followed by a compensatory arterialization of liver parenchyma and regenerative changes.[176,254]

Hepatocellular adenomas are less frequent, and all subtypes may be described theoretically.[121,139,258–260] However, they

Table 2. Radiological features of liver nodules in FALD.

Benign nodules	Nodules suspicious of malignancy
• Small (<1 cm), well-defined, multiple, and peripheral • CT/MR Hyperenhancing in arterial phase that turn isodense/isointense in the portal venous phase compared to surrounding parenchyma • Homogeneous in attenuation on all MR sequences • Mild MR T1 and T2 iso-/hypo-/hyperintensity • MR iso- to hyperintense compared to the surrounding parenchyma in the late hepatocyte phase • Stable in size during follow-up	• Large (>1 cm) and irregular • CT/MR Hyperenhancing in arterial phase with portal venous or delayed phase washout of contrast • MR High T1 weighted signal intensity with signal drop on T1 opposed phase and hypointense or heterogeneous signal on T2 weighted images • MR hypointensity compared to the surrounding parenchyma in the hepatobiliary phase (using a hepatobiliary MR contrast agent) • Presence of threshold growth during follow-up (50% in less than six months or 100% in more than six months)

could be underdiagnosed as their radiological and histological appearance may overlap with regenerative nodules. Finally, patients with FALD are prone to develop dysplastic nodules and HCC.[261] Differentiating regenerative, dysplastic, and neoplastic nodules is challenging, and it should be based on a panel of cytological and architectural criteria and additional immunomarkers associated with malignancy.[262]

What are the radiological features of "typical benign" and "suspicious of malignancy" liver nodules in FALD?

"Typical" imaging features of a "benign nodule" in FALD

On ultrasound, benign lesions are usually detected as small (<5 mm), multiple, rounded, and hyper- or isoechogenic nodules located in peripheral areas of the liver.[139,179,180] These characteristics make them difficult to visualize within heterogeneous coarse parenchyma, which explains the low sensitivity of ultrasound for detecting liver nodules compared to cross-sectional imaging.[179,253,263]

On CT and MRI, benign nodules are typically identified in the arterial contrast phase as small, hyperenhancing, and rounded lesions that turn isodense/isointense to the surrounding parenchyma in the portal venous phase.[139,179,252,254] Notably, the finding of washout in the delayed phase can also be seen in benign FNH-like nodules. On MRI, FNH-like nodules are commonly homogeneous in attenuation on all series, with mild T2 iso-to hyperintensity, isointensity to slightly isointensity in the T1 signal, and mild or no restricted diffusion.[186,254] After injection of a hepatocyte-specific contrast agent (*i.e.*, gadoxetic acid), FNH-like nodules are typically iso-to hyperintense compared to the surrounding parenchyma in the late hepatocyte phase.[176,180,186,199,253,255] They generally remain stable in size during follow-up and rarely disappear.[264]

"Suspicious of malignancy" imaging features of liver nodules in FALD

Liver nodules above 10 mm diameter, irregular contours, or rapid growth (50% in less than 6 months or 100% in more than 6 months) detected on ultrasound examination should be evaluated with CT or, preferably, with MRI with a hepatocyte-specific contrast agent for better characterization.[154,179,199] The "worrisome features" of a liver nodule on contrast-enhanced CT and MRI are: i) portal venous and delayed phase washout of contrast; ii) capsule appearance (smooth, uniform, sharp, enhancing or non-enhancing border around liver nodule that can represent a true pathological capsule or a pseudocapsule); iii) restricted diffusion; iv) high T1-weighted signal intensity with signal dropout on opposed phase imaging (suggesting lipid content) and decreased or heterogeneous signal on T2-weighted images; and v) hypointensity compared to the liver parenchyma in the hepatobiliary phase using a hepatobiliary MR contrast agent. However, interpreting these "worrisome features" may be difficult due to the intense congestive changes, even using hepatocyte-specific contrast agents.[199] Similarly, adding diffusion-weighted sequences has not enabled further characterization of nodules.[185] Several studies have demonstrated that LI-RADS (Liver Imaging Reporting and Data System) could overestimate the probability of malignancy in FALD, compared to biopsy, as portal venous and delayed phase washout in contrast-enhanced CT and MRI can also be seen in benign nodules, and cannot be applied in FALD and other vascular liver diseases.[139,179,180,186,199,252,265–268] This could be explained by the delayed liver wash-in and -out in FALD secondary to the inherent congestion. Consequently, all suspicious nodules should undergo biopsy and be evaluated in referral centres.[141,179,265,269] (Table 2). Finally, the optimal management for nodules <1 cm showing typical HCC patterns has yet to be clarified in non-FALD patients. A multidisciplinary board discussion to review such tiny and apparently typical lesions is recommended.

What are the epidemiological peculiarities of HCC in FALD?

The risk of HCC is increased in patients with Fontan circulation and may appear at younger ages than in other liver diseases.[265,270,271] In a prospective cohort of 103 patients with FALD, the cumulative incidence rates of HCC at 10, 20, and 30 years postoperatively were 0.8, 2.9, and 13.3%, respectively.[272] Similarly, 10 of 339 consecutive Fontan patients had HCC after a median follow-up of 2.9 years (annual incidence of 0.89%).[273] These rates are markedly increased compared to the low annual incidence of HCC in the general European populations aged 25 to 34 years (0.11 to 0.95 per 100,000 people).[274] Of note, these frequencies are based on cohorts of patients treated at the beginning of Fontan-type surgery (*i.e.*, with the initial types of surgery and mostly performed at a later age). Consequently, the impact of changes in surgical techniques and perioperative management on the risk of HCC should be addressed in prospective studies.

Distinctively, 44-50% of HCC cases in FALD are diagnosed in the absence of cirrhosis, which is in contrast to only 20% of patients who develop HCC in the context of non-cirrhotic livers in other aetiologies.[82,139,265,269,270,275,276] Finally, up to 40% of HCC cases in FALD are diagnosed in the advanced stages of the neoplastic disease, which explains the reported poor survival outcomes (12- and 24-month survival rates of 50-60% and 37-40%, respectively).[265,269,273,277]

Is HCC surveillance justified in FALD?

As in other scenarios, in FALD, the diagnosis of HCC in pre-symptomatic stages offers a clear survival benefit (1-year mortality rates of 60% *vs.* 30% in the symptomatic and asymptomatic phases, respectively).[270,273] The advantage of an early diagnosis could be higher in FALD given the younger age of patients at HCC diagnosis (~30 years in FALD *vs.* ~70 years in non-FALD liver disease), which implies a more substantial effect on years of life lost.[265] Cost-effectiveness studies addressing surveillance strategies for HCC in patients with non-FALD chronic liver disease indicate that an incidence of 1.5% per year or greater in patients with cirrhosis and at least 0.2% per year in those without cirrhosis would justify HCC surveillance.[278–282] These numbers are similar to those reported in FALD, with a cumulative incidence of 5% during a median follow-up of 3 years (1.3% per year) in the only prospective study focused on HCC diagnosis.[82] Finally, the cumulative HCC incidence in FALD is close to that previously reported in patients with Budd-Chiari syndrome (4% after 5 years of follow-up), where HCC surveillance is highly recommended.[283,284] These data and our expert opinion support the HCC screening recommendation in FALD.

What is the best surveillance strategy for HCC in FALD?

Even though it is impossible to establish evidence-based guidelines, there is a comprehensive agreement on the need to perform liver imaging follow-up for early detection of possible malignancy.[30,143,154,223,285] Only one study has assessed the benefit of HCC surveillance imaging in FALD. However, the study's retrospective design and the heterogeneous follow-up precluded the authors from recommending specific methods and intervals for surveillance.[3]

In a recent systematic review, HCC was very unlikely within the first 10 years after Fontan-type surgery (only one case of HCC was diagnosed before this time point), with an exponential increase in risk over time.[265,273] Other suggested predictive factors of new-onset HCC are higher body mass index, worse NYHA functional class, poorer results on serological biomarkers of liver fibrosis (FIB-4 and APRI score), early Fontan circulatory failure, MELD-XI scores ≥19, and high levels of serum AFP.[116,130,265,273,286]

The rate of tumour growth should dictate the ideal surveillance interval up to the limit of its detectability. The mean HCC volume doubling time has yet to be addressed in FALD, but extrapolating the knowledge from HCC in other aetiologies, a

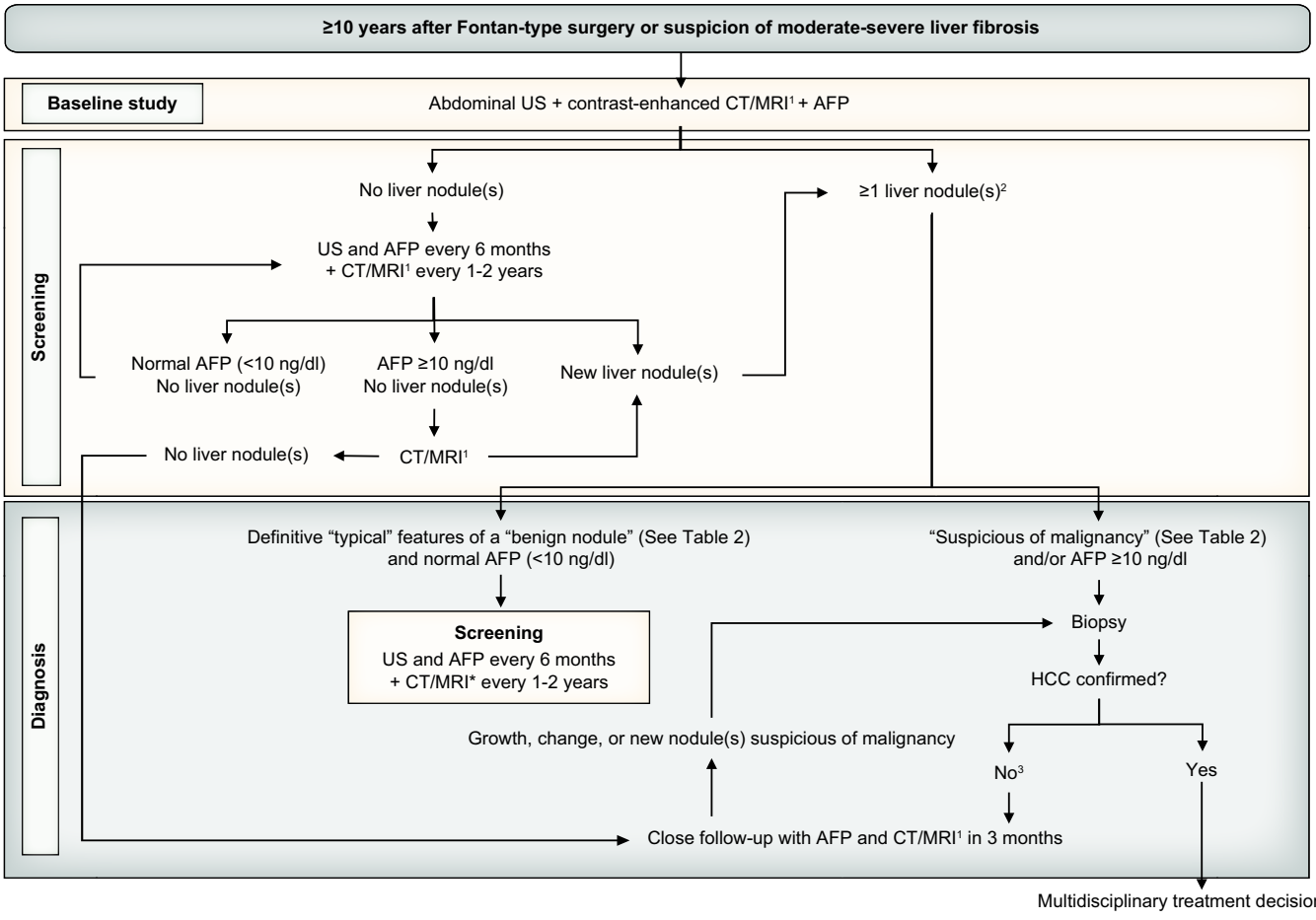

Fig. 3. Flow diagram for evaluation of liver nodules and HCC surveillance and diagnosis in FALD. (1) Multiphasic contrast-enhaced CT/multiphasic contrast-enhaced MRI, or (preferable) gadoxetic-enhaced MRI; (2) The optimal management for nodules <1 cm showing typical HCC patterns has yet to be clarified, and a multidisciplinary board discussion is recommended; (3) Consider re-biopsy. AFP, alpha-fetoprotein; FALD, Fontan-associated liver disease; HCC, hepatocellular carcinoma; US, ultrasound.

6-month interval seems a reasonable choice.[287–289] A longer interval of 12 months is probably more cost-effective, but would result in fewer early-stage diagnoses.[290]

Based on the current evidence and our expert opinion, active HCC surveillance might be initiated at least 10 years after completion of the Fontan procedure and strongly considered earlier in case of Fontan circulatory failure, even in the absence of cirrhosis. As detailed before, the sensitivity of liver ultrasound for diagnosing liver nodules in FALD is low, and contrast-enhanced modalities may be more suitable for this population to identify the full spectrum of nodules. In a prospective and multicentre cohort comparing ultrasound to MRI/CT, 2/8 patients with suspected malignant nodules were not identified by ultrasound, though none of these nodules were finally HCC at biopsy.[179] On the other hand, in a systematic review, HCC nodules were visible on ultrasound in 9 of 10 patients with reported findings.[259] Consequently, ultrasound could be useful as an HCC screening tool and has important advantages, such as low costs and low side effect rates.

A practical option could be to combine serial ultrasound (every 6 months) by experienced personnel with contrast-enhanced imaging at baseline (10 years after surgery) and periodically during follow-up to identify the whole spectrum of liver nodules. MRI is generally preferred over CT as hepatobiliary contrast agents offer some advantages in diagnostic accuracy and it is non-irradiating. However, a significant drawback is that MRI is contraindicated in many Fontan patients with old cardiac devices.[291] Although we lack robust evidence, performing an MRI at least every 1-2 years could be a practical and reasonable approach (see algorithm in Fig. 3). Importantly, this expert opinion-based recommendation is founded on HCC incidences from patients treated with Fontan-type surgeries decades ago. The surgical and perioperative improvements may decrease the HCC risk in the future, and this recommendation could be modified.

Is AFP determination useful for screening proposes?

Serum AFP is a valuable complementary biomarker for diagnosing HCC in FALD, as it is above the standard upper limit in 74-80% of patients diagnosed with HCC.[265,269] These rates are not equal in non-FALD aetiologies, with a very small proportion of patients (10-20%) presenting abnormal AFP levels at diagnosis of HCC.[292] In contrast, in a large prospective series with a high prevalence of non-neoplastic nodules (48%), no patient with Fontan-type surgery without HCC showed elevated AFP (defined as >7 ng/dl).[179] This is not the rule in viral or alcohol-related chronic liver diseases, where fluctuating levels of AFP might reflect flares or inflammatory-mediated exacerbations of underlying disease.[293] Results from a large cohort of stable Fontan patients identified that the likelihood of HCC was 26 times higher in patients with AFP levels ≥10 ng/dl. Interestingly, patients who did not develop HCC had a substantially lower value of AFP (median: 2.9 ng/dl), which supports its role in predicting new-onset HCC in this population.[273] Consequently, elevated AFP levels in patients with FALD should always prompt suspicion of HCC.

Management of hepatocellular carcinoma in Fontan patients

Recommendations

- The management of HCC in FALD should follow current clinical practice guidelines in HCC and should be discussed in multidisciplinary teams in centres that are highly experienced in FALD (**Very low LoE, strong recommendation**).
- Local ablation (radiofrequency or microwave) should be considered the first-line therapy for solitary HCC ≤2 cm over surgery. Beyond this size, solitary HCC can be treated with surgical resection, especially in patients with preserved liver and cardiac function. Although local ablation in HCC >2 cm may be less effective, it can be employed alone or combined with transarterial therapies in selected patients with high surgical risk (**Very low LoE, strong recommendation**).
- Transarterial therapies are indicated in patients with unresectable HCC who are not candidates for local ablation. As portosystemic, extrahepatic, and right-to-left cardiac shunts are frequent in FALD, the risk of adverse events with these treatments may be considered (**Very low LoE, weak recommendation**).
- Systemic therapy is indicated in patients with preserved liver function, good performance status, and advanced or metastatic tumours. It can be employed in progressing tumours or those which are unsuitable for loco-regional therapies. A careful evaluation of cardiac function is suggested before using potentially cardiotoxic drugs (**Very low LoE, weak recommendation**).
- Although liver transplantation has been considered the first-line option for HCC within Milan criteria unsuitable for resection or local curative treatment, no specific recommendations can be made in FALD. The indication of liver transplantation should be made on a case-by-case basis in highly experienced centres (**Very low LoE, strong recommendation**).

What are the specific considerations for HCC treatment in FALD?

Treatment modalities used in Fontan patients with HCC have been very heterogeneous. In a systematic review, treatment was reported in 62 out of 65 patients, and transarterial chemoembolization (TACE) was the most common therapy (28.6%), followed by surgical resection (19%). Best supportive care alone was offered in up to 20% of cases, highlighting the high rate of

late HCC diagnosis in Fontan patients.[265] In general, the management of HCC in FALD should follow current clinical practice guidelines updated in 2022.[278,294] However, Fontan patients have unique anatomical and functional abnormalities that should be considered when tailoring treatment. This document mainly focuses on these specific considerations.

Surgical resection: The rate of surgical complications and long-term survival of Fontan patients treated with tumour resection is unknown, but the significant risk of cardiac comorbidity may burden results. In general, liver resection can be performed by open surgery (laparotomy) or minimally invasive operations (laparoscopic). Open abdominal surgeries are associated with a high risk of bleeding and cardiac decompensation in the Fontan population.[295] The laparoscopic approach appears safer, with fewer postoperative complications and a potentially non-significant impact on liver function. Still, pneumoperitoneum can modify abdominal and intrathoracic pressures, hindering cardiac preload during surgery.[296] The choice between open or laparoscopic surgery depends on the tumour size, the number of satellite lesions, the location, and the surgical team's preference or expertise.[297] As the risk of massive bleeding secondary to high CVP is the major concern in this population, extraordinary surgical maneuvers (Pringle maneuver, reverse Trendelenburg position, veno-venous bypassing, or inflow plus outflow ligation) could be needed.[297–301] Thus, specialized anaesthesia and perioperative management, including cardiac and nutritional optimization, is crucial in this fragile population. The anaesthetic goal is the preservation of an adequate CVP, avoiding systemic hypotension, and ensuring proper flow through the pulmonary circulation.[297] A central venous catheter and trans-oesophageal echocardiogram should continuously monitor CVP and cardiac contractility. Consequently, these hepatic surgeries should be performed in highly specialized centres.

Local ablation: Local ablation (mainly radiofrequency or microwave) should be considered the standard of care for Fontan patients with HCC ≤2 cm, given the presumably lower risk of complications and it conferring the same survival benefit as surgical resection in other hepatopathies.[302] Although local ablation beyond this size is less effective, it can be employed alone or combined with transarterial therapies in selected patients in whom surgery is not appropriate. Importantly, the frequent use of pacemakers and other cardiac devices in Fontan patients may limit the applicability of radiofrequency. Ethanol injection, laser ablation, or cryoablation could be suitable options in those cases where thermal ablation is not technically possible, but there is no reported data in FALD.

Transarterial therapies: Although TACE has been the most common therapy employed in Fontan patients, as a unique treatment or a bridge to transplant, evidence regarding its effectiveness and safety is scarce.[270,273,303,304] Classically, patients with bilirubin >2-3 mg/dl or slight fluid retention requiring diuretics are considered at high risk of adverse events and suboptimal survival after TACE. These considerations may not be accurate in Fontan patients, as slight bilirubin elevations are persistent and do not always reflect liver impairment, and mild ascites could be due to other non-liver-related complications. Notably, portosystemic, extrahepatic and right-to-left cardiac shunts are frequent in this population and may increase the risk of adverse events of TACE, as shown by the reported cases of unexpected retinal artery embolism,[305] depositions of radiopaque substance in the brain,[306] and development of posterior reversible leukoencephalopathy following TACE (personal data). Transarterial radioembolization using yttrium-90 microspheres has been employed in Fontan patients with HCC, with results comparable to TACE in unresectable tumours.[232] One of the advantages of transarterial radioembolization is that it can be used in patients with compromised portal inflow.

External radiation therapy: The role of external radiation therapy has been scarcely evaluated in Fontan patients.[270,307] The current evidence of external radiotherapy in HCC without FALD is also controversial, and most series have focused on its combination with local treatments (*i.e.*, TACE). There are only five case reports of patients with Fontan circulation who have been satisfactorily treated with proton beam therapy without side effects or recurrence.[277,308]

Systemic therapy: As a unique or combined treatment, systemic therapy has been documented in 11 Fontan patients with unresectable HCC. Recently, the increasing number of systemic therapies with demonstrated evidence of efficacy in HCC has changed the landscape of cancer management. According to current clinical practice guidelines, three different treatments can be used as first-line: i) tyrosine-kinase inhibitors (sorafenib and lenvatinib); ii) the combination of antiangiogenic drugs and immunotherapy (atezolizumab-bevacizumab); and iii) combinations of different immunotherapies (tremelimumab-durvalumab).[294,309] Unfortunately, the evidence for using these agents in Fontan patients is minimal and mainly restricted to sorafenib, due to the relatively short period of time that the aforementioned combinations have been clinically available compared to long-term experience with sorafenib. The safety of systemic therapy in this scenario has not been established, but we should be aware of potential cardiotoxicity, particularly with tyrosine-kinase inhibitors. Lately, several case reports have suggested using cisplatin-based regimens though the results in FALD have been poor. Cisplatin-based regimens are not recommended in EASL current guidelines; thus, we recommend against their use in FALD.[270,310,311]

Liver and combined heart-liver transplantation: Although liver transplantation is the first-line option for HCC within Milan criteria (three nodules, each <3 cm in size) and unsuitable for resection/ablation, the major limitation in the Fontan population is the reasonable doubt about if isolated liver transplantation is safe and valuable. Only one successful case of living-donor isolated liver transplantation and no cases of combined heart-liver transplantation have been reported in patients with FALD and HCC.[312] If these patients should be evaluated for combined heart-liver transplantation is a matter of debate since current policies in most centres contemplate the presence of solid malignancy within the past 5 years as an absolute contraindication for heart transplantation.[313] Until more evidence is available, we cannot make any recommendations.

Palliative and best supportive care: Patients with terminal HCC with a life expectancy of less than 3-4 months should receive palliative care focused on pain, nutrition, and psychological support.[278] The clinical picture of Fontan patients with terminal HCC is particularly complex, resulting from symptoms deriving from their liver and cardiac disease, along with the effect of tumour bulk. Palliative care in Fontan patients is an unmet need that reference centres should urgently address to

include practitioners specialized in supporting this young, frail, and unfortunate population.

In summary, while current general recommendations on HCC are based on robust scientific evidence, the particular features of Fontan patients highlight the complexity of management at the individual level and the need to personalize decisions at the tumour board level based on stage of liver disease, cardiac function, and performance status. Multiparametric evaluation should be integrated into highly proficient multidisciplinary boards where hepatologists, oncologists, cardiologists, anaesthesiologists, interventional radiologists, nurses, and nutritional experts are actively involved.

Other liver-related issues

Recommendations

- All Fontan patients should be screened for HCV and HBV infection. Vaccination against HBV and HAV is universally recommended (**Moderate LoE, strong recommendation**).
- Sarcopenia and malnutrition should be identified early and treated in patients with Fontan circulatory failure and/or advanced FALD (**Low LoE, strong recommendation**).
- In patients with advanced FALD and an established indication, antithrombotic treatment should not be discouraged (**Very low LoE, strong recommendation**).

Which other measures can be implemented for liver care in Fontan patients?

Patients who had cardiac surgery in childhood before the implementation of blood donor screening have a five-fold increased prevalence of HCV infection compared with the age-matched general population.[314,315] Therefore, all Fontan patients should be screened for HCV and HBV infection. Vaccinations against HAV and HBV and follow-up serologies to confirm the presence (and maintenance) of protective antibodies are recommended. Revaccination is advised if a protective antibody response is absent.[88,150,204]

A co-existing liver disorder should be excluded and treated, including metabolic, viral, and autoimmune diseases. Patients should be counseled on lifestyle measures to prevent obesity, promote regular physical activity and a healthy diet, and avoid alcohol and drug use. Weight control is particularly relevant as weight gain in adulthood is associated with a higher risk of developing HCC in FALD.[14,273,316] On the other side, sarcopenia and malnutrition are ominous landmarks in patients with Fontan circulatory failure and advanced liver disease.[317–319] Thus, their early identification and treatment should be a priority.

Can antithrombotic therapy be used in patients with advanced FALD?

Thrombosis is a significant complication after Fontan-type surgery, associated with an increased risk of advanced FALD and death.[100,320] Many authors support that anticoagulation is indicated in the presence or history of atrial thrombus, atrial arrhythmias, previous thromboembolic events, or with a patent fenestration.[321,322] However, the use of anticoagulants in patients with advanced FALD is a matter of debate. Recent data suggest a protective effect of warfarin on FALD, reducing the risk of HCC.[272] Moreover, in an animal model of FALD, fibrosis regression was observed after warfarin administration.[90] Consequently, we can conclude that advanced FALD is not a contraindication for anticoagulation, and its potential beneficial clinical effects need to be examined in the future.

Aspirin is an alternative to anticoagulation in Fontan patients.[323] Although recent evidence supports that regular use of aspirin reduces the risk of HCC, liver-related complications, and death in chronic liver disease, we lack specific studies on FALD.[324] Hence, we cannot systematically recommend aspirin use in FALD, but it should not be discouraged in patients with an established indication.

Despite the extensive use of direct oral anticoagulants (DOACs) in patients at risk of thrombotic complications, experience in adult Fontan patients is limited.[325] Indeed, there is a recommendation from the American Heart Association against using DOACs in this population due to the scarce safety and efficacy data, along with concerns regarding abnormal coagulation secondary to FALD.[326,327] While not well studied in Fontan patients specifically, based on the pharmacokinetic and pharmacodynamic proprieties and safety profile of DOACs in patients with chronic liver diseases, DOACs may be employed in patients with FALD with preserved liver function.[328] DOAC treatment in children is still evolving, and no recommendations can be made for this population.

Are angiotensin-converting enzyme inhibitors indicated to ameliorate FALD progression?

ACE inhibitors are often indicated for ventricular systolic or diastolic dysfunction, atrioventricular valve regurgitation, preservation of normal ventricular function, and arterial hypertension in Fontan patients.[329,330] Theoretically, they may downregulate angiotensin II receptors on activating hepatic stellate cells, which are responsible for cell proliferation, contraction, and collagen secretion.[331–335] However, this antifibrotic effect has not been evaluated in FALD. In addition, a recent prospective study showed no improvement in exercise capacity or ventricular function after short-term ACE inhibition in paediatric Fontan patients with moderate-good systolic function.[336] Thus, there is no evidence to recommend the systematic use of ACE inhibitors as a specific therapy for FALD.

Should pulmonary vasodilators be routinely indicated in advanced FALD to ameliorate liver damage?

Pulmonary vasodilators improve systemic venous return and exercise capacity in Fontan patients.[337–341] Whether this improvement may diminish liver congestion is debatable. A retrospective cross-sectional study found a correlation between the severity of FALD and pulmonary artery and ventricular end-diastolic pressures. In contrast, the transpulmonary gradient did not increase significantly in patients with advanced FALD, suggesting a minor role of increased pulmonary resistance in FALD progression.[113] Therefore, pulmonary vasodilators cannot be routinely recommended to decrease liver damage and should only be considered if pulmonary vascular resistance is increased.[342–344]

Heart and heart-liver transplantation in FALD

Recommendations

- Advanced FALD *per se* cannot be considered as an indication for heart transplantation, but FALD progression might indicate haemodynamic deterioration and, subsequently, the need for heart transplantation (**Low LoE, weak recommendation**).
- In patients with an indication for heart transplantation (Fontan circulatory failure, severe ventricular dysfunction or refractory PLE or PB) and compensated advanced FALD with preserved liver function, liver transplantation cannot be systematically recommended. These patients should be evaluated for isolated heart transplantation (**Low LoE, strong recommendation**).
- Liver transplantation alone is not generally recommended in Fontan patients. Fontan patients with an indication for liver transplantation due to liver insufficiency or HCC should be evaluated for combined heart-liver transplantation (**Low LoE, strong recommendation**).
- Although hepatic fibrosis regression and resolution of liver-related clinical complications are possible after isolated heart transplantation in patients with advanced FALD, post-transplant liver surveillance may be maintained (**Low LoE, weak recommendation**).

What are the current indications for heart transplantation in Fontan patients?

Heart transplantation is the only definitive curative treatment option for patients with Fontan circulatory failure.[345] However, the decision to transplant is frequently empirical. Among paediatric patients, ventricular systolic dysfunction is the most common indication for heart transplantation.[346–348] However, this primary indication is less frequent in adulthood, and most patients referred for transplant have circulatory failure but preserved ventricular function.[146,349] Mechanical problems of Fontan circulation can usually be surgically or interventionally solved, and pathway obstruction is rarely the only reason for cardiac transplantation.[350] PLE refractory to medical and interventional treatment is another classical indication for heart transplantation, present in 36% of transplanted patients.[351] Due to the promising results of lymphatic interventions, PB has become a rarer indication, reported in only 7% of waitlisted patients in the contemporary era, compared to 15% in the past.[352]

Is advanced FALD an indication *per se* for heart transplantation?

There is no evidence that advanced FALD *per se* is an indication for cardiac transplantation. However, as monitoring of FALD is mandatory in all Fontan patients, detection of liver damage progression might indicate haemodynamic deterioration and, subsequently, the need for cardiac transplantation. Therefore, a detailed haemodynamic assessment, including echocardiography, cardiac catheterization, and MRI, should be performed when FALD progression is observed. As heart transplant alone in the setting of advanced FALD can lead to a reduction in FALD progression, with an improvement of liver-related signs and symptoms, early consideration for heart transplant alone should be given to avoid combined heart-liver transplantation in the setting of an overall shortage of donor organs.[353]

When should combined heart-liver transplantation be considered?

Liver transplantation alone is not generally recommended in Fontan patients due to the challenging management of systemic pressures during the anhepatic and reperfusion stages of surgery.[14] Currently, guidelines concerning the indication and timing of combined cardiac and liver transplantation in Fontan patients are missing.[354] It is well-known that multi-organ dysfunction is associated with poor outcomes after heart transplantation. Particularly, some studies have determined that MELD-XI, which evaluates kidney and liver function, is a good predictor of early and late mortality after heart transplantation in Fontan patients.[146,355–359] Combined with the protective effect of combined liver-heart transplantation on cellular rejection, these findings have led some authors to consider combined transplantation in patients with Fontan circulatory failure and severe liver fibrosis (grade 3 or 4), with favourable results.[360–363] However, other studies have shown no differences in survival between cirrhotic and non-cirrhotic Fontan patients who undergo heart transplantation,

Box 1. Unmet needs in FALD research and future directions.

- Impact of FALD on global and heart transplant-free survival of Fontan patients.
- Impact of improvements in the surgical and perioperative management of patients with a univentricular heart on FALD progression and HCC risk.
- Role of FALD surveillance programmes based on liver biopsy and on non-invasive methods.
- Role of lymphography in diagnosing and staging FALD.
- Evaluation of different cut-offs of elastography for ruling in and ruling out severe fibrosis.
- Role of elastography in predicting strong clinical outcomes (risk of liver decompensation, unfavourable cardiac outcomes, need for transplantation, and death).
- Role of spleen elastography in FALD.
- A better understanding of hepatic haemodynamics. Evaluation of the significance of absolute values of hepatic free and wedged pressures.
- Potential beneficial clinical effects of anticoagulation in advanced FALD.
- Sensitivity and specificity of ultrasound for detection of HCC.
- Prospective validation of HCC surveillance algorithms and implementation of screening programmes to identify at-risk candidate populations.
- Effectiveness and safety of treatment options for HCC in FALD.
- Palliative care focused on the unique characteristics of Fontan patients.

FALD, Fontan-associated liver disease; HCC, hepatocellular carcinoma.

concluding that severe fibrosis, while cirrhosis is compensated, should not be a contraindication for isolated heart transplantation.[364–366] Additionally, a remarkable hepatic remodelling may follow cardiac transplantation in advanced FALD.[367] Consequently, there is no evidence to systematically indicate combined transplantation in all failing Fontan patients with compensated severe liver fibrosis. This option should probably be reserved for those cases with liver insufficiency, which is very rare in FALD, or severe liver-related complications.[149] Nonetheless, each transplant programme should determine its specific thresholds based on institutional experience, preferences, and recent transplant outcomes.[353]

Should liver surveillance be maintained after heart transplantation in Fontan patients?

The effect of isolated heart transplantation on the course of FALD post-transplantation is not well understood and is probably heterogeneous.[368,369] A small case series, including mostly patients with histologically proven cirrhosis, has demonstrated no progression of FALD, resolution of ascites, and freedom from HCC in the mid-term after heart transplantation.[353] A sequential strategy of liver transplantation following heart transplantation may be an option in case of liver disease progression. However, only a few cases of patients with congenital cardiac disease have been documented, with a high mortality rate on the waiting list, and further studies in FALD are needed.[363,370] The small number of patients included and the short follow-up preclude us from recommending stopping liver monitoring after heart transplantation. We suggest that long-term liver surveillance is mandatory.

Role of specialized units in FALD

Recommendations

- The FALD surveillance programme should be considered one of the most critical parts of lifelong specialized care, and a multidisciplinary approach is mandatory (**Low LoE, strong recommendation**).
- A FALD surveillance programme should be recommended to detect liver disease progression at a stage early enough to consider interventions to optimize Fontan circulation and prevent advanced liver fibrosis (**Low LoE, strong recommendation**).
- A FALD surveillance programme for FALD may include an initial screening at baseline (before Fontan-type surgery), followed by a 2-3 yearly screening in children and adolescents consisting of clinical assessment by expert hepatologists, biochemical evaluation, and liver Doppler ultrasound (with or without LSM) (**Very low evidence, weak recommendation**).

How should Fontan patients with FALD be managed in multidisciplinary units?

All Fontan patients require lifelong specialized multidisciplinary care in a tertiary centre.[30] Beyond comprehensive cardiologic follow-up by specialists in congenital heart disease, several specialties might be needed during long-term follow-up: cardiac surgery, hepatology, gastroenterology, nephrology, radiology, pathology, psychology, endocrinology, specialized nursery, and social workers, among others. Optimizing haemodynamics is the central therapeutic principle in managing Fontan patients.[69] Then, cardiologic examinations will generally account for the greatest share of follow-up diagnostics, especially in younger Fontan patients.[371,372] The ultimate aim of surveillance is to detect FALD progression at a sufficiently early stage to consider interventions to optimize the Fontan circulation in due time and to prevent advanced fibrosis.[95] Therefore, installing a minimally invasive FALD screening protocol in children and adolescents seems advisable to facilitate the early detection of advanced FALD and eventually initiate treatment optimization.[181,207] A consensus on assessment content, timing, and frequency has to be established. However, there is growing evidence that an initial screening at baseline (before Fontan creation) followed by 2-3 yearly FALD screening in children and adolescents consisting of clinical examination, biochemical evaluation, and liver Doppler ultrasound (with or without liver stiffness assessment) might be beneficial and allow for early FALD detection in the individual patient.[204,207,372,373]

Unmet needs and future directions

What are the research priorities in FALD?

FALD is an emerging liver disease that represents a significant clinical challenge. The characteristics of the Fontan population make this unique entity different. The need for robust evidence in management has been the most significant barrier to implementing the current evidence-based position paper. Multi-institutional collaborative registries and prospective studies are imperative. However, as in most orphan diseases, the lack of funding sources for research represents a clear drawback for augmenting knowledge in FALD. The panel suggests that increasing public funds for research in FALD should be a priority. Box 1 summarizes the study's goals for the future.

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Abbreviations

ACE, angiotensin-converting enzyme; AFP, alpha-fetoprotein; APRI, aspartate aminotransferase-to-platelet ratio index; CVP, central venous pressure; DOACs, direct oral anticoagulants; EASL, European Association for the Study of the Liver; ERN RARE-LIVER, European Reference Network on Rare Liver Diseases; FALD, Fontan-associated liver disease; FNH, focal nodular hyperplasia; HCC, hepatocellular carcinoma; HVPG, hepatic venous pressure gradient; INR, international normalized ratio; LoE, level of evidence; LSM, liver stiffness measurement; MELD, model for end-stage liver disease; MELD-XI, MELD excluding the international normalized ratio; MRE, magnetic resonance elastography; NSBBs, non-selective beta-blockers; NYHA, New York Heart Association; PB, plastic bronchitis; PLE, protein-losing enteropathy; SAAG, serum albumin ascites gradient; SSM, spleen stiffness measurement; TACE, transarterial chemoembolization; TE, transient elastography; TIPS, transjugular intrahepatic portosystemic shunt.

Conflict of interest

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

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Disclaimer

This position document reflects the current state of knowledge at the time of publication, and clinical consensus judgments when knowledge is lacking. The expected changes in the state of scientific information mandate that periodic review and updating will be needed. The recommendations included in this document do not apply to all patients, and each must be adapted and tailored to each individual patient.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2023.07.013.

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