Fontan-associated liver disease and hepatocellular carcinoma in adults

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The Fontan operation creates a unique circulation, and is a palliative therapy for patients with single-ventricle congenital heart disease. Increased venous pressure and decreased cardiac output and hepatic venous drainage result in sinusoidal dilatation around the central veins. This causes congestion and hypoxia in the liver, leading to Fontan-associated liver disease (FALD). Non-invasive and invasive markers enable diagnosis and evaluation of the fibrosis status in chronic liver disease; however, these markers have not been validated in FALD. Additionally, regenerative nodules such as focal nodular hyperplasia (FNH) are frequently found. The severity of fibrosis correlates with the duration of the Fontan procedure and the central venous pressure. Cirrhosis is a risk factor for hepatocellular carcinoma (HCC), the annual risk of which is 1.5–5.0%. HCC is frequently difficult to diagnose and treat because of cardiac complications, coagulopathy, and congenital abnormalities. The mortality rate of FALD with liver cirrhosis and/or FALD-HCC was increased to ~29.4% (5/17 cases) in a nationwide survey. Although there is no consensus on the surveillance of patients with FALD, serial monitoring of the alpha fetoprotein level and imaging at 6-month intervals is required in patients with cirrhosis.

**Fontan procedures.** The procedure is typically indicated in children with tricuspid atresia, pulmonary atresia with intact ventricular septum, double-inlet left ventricle, hypoplastic left heart syndrome, double-outlet right ventricle, or complete atrioventricular septal defects23. There are three Fontan surgical techniques29. Classical Fontan was performed until around 1990, and the atropulmonary connection was made by closing the atrial-septal defect and connecting the right atrium directly to the right PA (atriopulmonary method). This operation was later modified to a lateral tunnel procedure (intra-atrial lateral tunnel). The right atrium was baffled with an intraatrial patch and the SVC was directly connected to the right PA. After 2000, an extracardiac total cavopulmonary connection, which consists of a direct anastomosis of the SVC to the right PA and the insertion of an extracardiac conduit between the inferior vena cava (IVC) and the right PA, was constructed. The lateral tunnel method is associated with better short- and medium-term outcomes, compared to the extracardiac conduit method9.

The postoperative circulatory changes result from the following: (1) single ventricle circulation, (2) nonpulsatile pulmonary perfusion, (3) systemic venous hypertension, and (4) intracardiac scarring10,11. The term "Fontan failure" is generally applied to failure of the Fontan circulation causes the composite of all-cause mortality12. In other word, many complications were observed (Table 1a). The hemodynamic consequences of FALD vary based
on the extent and stage of the liver involvement and may encompass the heart, lungs, and kidneys. Therefore, the hemodynamic status of failing Fontan should be evaluated when considering treatment for FALD (Table 1b)13,14.

Table 1. Phenotypes of patients with a failing Fontan. AV atrioventricular, EDP end-diastolic pressure, HCC hepatocellular carcinoma, FALD Fontan-associated liver disease, PLE protein-losing enteropathy.

| Condition | Incidence | Manifestations |
|-----------|-----------|----------------|
| Early failure | 3% | Low cardiac output, pleural effusions, chylothoraces, ascites, hepatomegaly |
| Late failure (lymphatic dysfunction, PLE) | 2–13% | Ascites, peripheral edema, pleural effusions, diarrhea, malabsorption of fat, hypoalbuminaemia |
| Plastic bronchitis | < 2% | Tachypnoea, cough, wheezing, expectoration of bronchial casts |
| Primary ventricular dysfunction | ~7 to 10% | Progressive exercise intolerance, AV valve insufficiency, hepatomegaly, ascites |
| Progressive increase in pulmonary resistance | Unknown | Hypoxaemia |
| Hepato-renal insufficiency | Unknown | Renal dysfunction |
| Hepatic complication | 41% (57/139)12,18 Liver cirrhosis and/or HCC: total 1.15%49, HCC: 1.5–5.0% annually in cirrhosis49 | Hepatomegaly, ascites, splenomegaly, HCC |

(b) Hemodynamic status of patients with a failing Fontan13,14

| Description | Type I (systolic heart failure) | Type II (diastolic heart failure) | Type III (non-cardiac failure) Relevant to discussion of FALD | Type IV (plastic bronchitis and PLE) Fontan failure with lymphatic abnormalities |
|-------------|-------------------------------|-------------------------------|-------------------------------------------------|-------------------------------------------------|
| Systolic function | ↓ | → | → | → |
| Ventricular EDP | ↑ or → | ↑ | → | ↓ or → |
| Cardiac output | ↓ or → | ↓ or → | → | ↓ or → |
| Systemic vascular resistance | ↑ | ↑ | ↓ or → | ↓ or → |

Figure 1. Hemodynamic changes after the Fontan procedure and treatment thereof. Central venous pressure frequently increases after Fontan surgery (b) compared to normal (a). ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AV, atrioventricular; Ca, calcium; CRT, cardiac resynchronization therapy; CVP, central venous pressure; ERA, endothelin receptor blocker; HOT, home oxygen therapy; MP, muscle pump; NO, nitric oxide; PA, pulmonary artery; PV, pulmonary ventricle; PDGE-5, phosphodiesterase 5 inhibitor; PGI2, prostaglandin I2; PTA, percutaneous transluminal angioplasty; RP, PA resistance.
Fontan physiology. Central venous pressure (CVP) typically increases after Fontan surgery (Fig. 1b), as compared to normal (Fig. 1a). The hepatic venous pressure and pressure load on the central vein in the hepatic lobule cause congestion of the liver\(^\text{15,16}\). Mutual buffering between the portal blood flow and the hepatic artery blood flow is known as the hepatic arterial buffer response (HABR)\(^\text{15}\) (Fig. 2). When the portal blood flow decreases, the hepatic artery is dilated to regulate the hepatic blood flow. Thus, the oxygen supply to the liver tissue is constantly maintained. Mechanical stimulation caused by dilation of the hepatic sinusoids, thrombus formation as a result of abnormal coagulation, and congestion and hepatocyte hypoxia are observed\(^\text{17}\). HABR increases the hepatic artery blood flow and hypernodular lesions may form in hypoxic areas, particularly in peripheral areas of the liver. Additionally, hypoxia and thrombosis within the sinusoids promote the activation of hepatic stellate cells (HSCs) and the production of fibronectin, leading to portal and sinusoidal fibrosis. Perisinusoidal edema and ischemic liver cause fibrosis progression without centrilobular inflammation. When fibrosis further progresses, cross-linking fibrosis mainly connecting the central zones is observed histologically, and a fibrous septum is formed, a finding of cirrhosis. Congestion causes the formation of an inverted image of the hepatic lobules (‘reverse lobulation’; an image in which the portal area is located in the center and the hepatocyte population is surrounded by a congestion zone). Postsinusoidal hepatic outflow obstruction lead to accumulation of ascites presenting a high protein level. The ascites showed a protein level of > 2.5 g/dL and the serum ascites an albumin gradient of > 1.1 g/dL\(^\text{18}\). Ascites may be caused by increased sinusoidal pressure and/or impaired lymphatic drainage\(^\text{1}\).

Prevalence and diagnosis of FALD. Baek et al. evaluated 139 patients who underwent Fontan surgery and found hepatic complications in 57 (41%)\(^\text{19}\). In the blood test, transaminase levels were typically within the normal range or mildly elevated in FALD (Table 2). The γ-glutamyltransferase (GGT) level was mildly elevated (median = 69 U/L) in 75% of patients\(^\text{20}\), but this was not correlated with histological severity. Camposilvan and colleagues reported the following complications in 34 patients (average age = 14.7 years): hepatomegaly in 53%, splenomegaly in 9%, transaminase abnormality in 30%, GGT elevation in 61%, elevated serum bilirubin in 32%, abnormal coagulation in 58%, and protein losing enteropathy (PLE) in 19%\(^\text{21}\).
### Variable | Findings | Value of estimating liver cirrhosis | Availability and warning
--- | --- | --- | ---
#### Biomarkers
- AST, ALT, GGT, T-BIL, platelet count
  - Elevated
  - Decreased
  - Not indicated the cutoff value
- Type IV collagen, hyaluronic acid, and P-III-P
  - Elevated
  - Elevated
  - Elevated
- M2BPGi
  - Elevated
- FibroSURE
  - Elevated
  - Normal
- AST/ALT ratio
  - AST, ALT
  - < 1 normal
- AST-to-platelet ratio index (APRI) score
  - AST, ALT, platelet count
  - > 2.56, > 1.5
- The MELD XI score
  - Bilirubin, creatinine
  - > 12.044
- The Fibrosis-4 (FIB-4) index
  - AST, ALT, platelet count, and age
  - > 3.2540, > 1.4544
- The Forn index
  - GGT, platelet count, age, and cholesterol
  - > 6.9133, > 4.2
- The VAST score
  - Varices, ascites, splenomegaly, thrombocytopenia
  - ≥ 24 portal hypertension
#### Ultrasound
- Abnormal parenchymal enhancement
  - Heterogeneous hyperechoic parenchymal pattern and surface nodularity
  - No nodular liver surface
  - Irregular parenchymal fatty infiltration with perivascular distribution
- Increased T2-weighted and diffusion-weighted signal intensity in the periphery of the liver
  - Increased echogenicity
  - Splenomegaly
  - Collateral circulation
- Collateral circulation
  - Ascites
  - Hepatic congestion alone can increase stiffness
- Direct comparison of types of elastography
  - Detection of cirrhosis; sensitivity 87%, specificity 92%40
#### Elastography
- HPVG
  - ≥ 5 mmHg; portal hypertension15
- Pathological findings
  - Fibrotic septa separated regenerative nodules
  - No correlation with histological findings
  - Collagen 22. Shimizu et al. suggested hyaluronic acid and GGT as markers of the progression of liver fibrosis in type IV collagen, hyaluronic acid, and type IV collagen 7S, are typically increased in the presence of liver complications and are useful for evaluating FALD.20,22 Procollagen-III-peptide (P-III-P) is more sensitive to inflammation and it is said diagnosing the stage of fibrosis is inferior than hyaluronic acid or type IV collagen 7S. Shimizu et al. suggested hyaluronic acid and GGT as markers of the progression of liver fibrosis in Fontan patients.25 While mac-2 binding protein glycan isomer (M2BPGi) is a useful marker of chronic hepatitis, the cutoff value is lacking in FALD.
particularly in patients with hepatitis C virus (HCV) infection. However, it is unlikely to rise of M2BPGi in the cases of Fontan, because FALD is not accompanied by inflammation.

In the imaging, the liver may appear normal on radiological examination or slightly hypoechoic on ultrasound at the early stage of congestive hepatopathy. As fibrosis develops, a coarse heterogeneous hypoechoic parenchymal pattern and surface nodularity become evident. The liver is often enlarged with caudate lobe hypertrophy, similar to Budd-Chiari syndrome. Irregular parenchymal fatty infiltration of a perivascular distribution can be seen on ultrasound. Contrast-enhanced ultrasound (CEUS) shows heterogeneous and decreased enhancement of the liver in the portal venous phase. Hepatic vein waveforms assessed by doppler ultrasound change in accordance with liver fibrosis progression.

In computed tomography (CT), hepatic fibrosis may be seen as reticular pattern on delayed-phase CT (i.e., peripheral diffuse patchy enhancement). Zonal enhancement (i.e., altered enhancement of the liver periphery) is correlated with lower hepatic vein pressure and a lower likelihood of cardiac cirrhosis. On magnetic resonance imaging (MRI), there are areas of increased T2-weighted and diffusion-weighted signals with reduced T1-weighted signal intensity in the periphery of the liver, corresponding to areas of abnormal contrast enhancement. Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced MRI (Gd-EOB-MRI) revealed a characteristic reticular or mosaic pattern of diminished enhancement (i.e., ‘frog spawn’ appearance). The apparent diffusion coefficient (ADC) calculated by diffusion-weighted imaging (DWI) enables estimation of the degree of hepatic fibrosis.

Assessment of liver stiffness by transient elastography (TE), acoustic radiation force impulse (ARFI) elastography, and magnetic resonance elastography (MRE) enables evaluation of hepatic fibrosis. However, it was not correlated with the histopathologic findings at a single time point. ARFI and TE might be useful for monitoring liver stiffness in patients with Fontan physiology. The mean shear wave propagation velocity in liver tissue by ARFI elastography in Fontan patients was 1.86 ± 0.5 m/s. Of that, 76% of patients had a value over the cirrhosis threshold of 1.55 m/s. In contrast, the mean shear wave propagation velocity was significantly lower in patients who had undergone heart transplant. However, TE/shear-wave elastography (SWE) cannot distinguish hepatic congestion from fibrosis. While MRE reportedly enables evaluation of liver fibrosis, its utility in FALD needs to be evaluated.

The gross appearance of the liver is termed ‘nutmeg liver’ in patients with FALD. The pathological findings showed liver sinus fibrosis in 76%, centrilobular necrosis in 33%, pericentral fibrosis in 79%, and portal vein fibrosis in 52% of cases. FALD showed dilatation and fibrosis of hepatic sinusoids, fibrosis of the portal area, and no inflammation. Pathological evaluation of the liver via percutaneous or transvenous biopsy is the gold standard for assessing the degree of fibrosis; however, obtaining liver samples is difficult and there is a risk of bleeding. Also, the role and timing of the initial and follow-up liver biopsies in this population are unclear.

**Diagnosis of liver cirrhosis by invasive and non-invasive biomarkers in FALD.** Cardiac cirrhosis results from prolonged passive liver venous congestion secondary to right-sided congestive heart failure and is defined as stage-4 fibrosis on liver biopsy. At this stage, obtaining liver samples is hampered by the risk of bleeding and ascites accumulation. As another invasive examination, transjugular measurement of the hepatic vein waveforms assessed by doppler ultrasound change in accordance with liver fibrosis progression.

The apparent diffusion coefficient (ADC) calculated by diffusion-weighted imaging (DWI) enables estimation of the degree of hepatic fibrosis. Assessment of liver stiffness by transient elastography (TE), acoustic radiation force impulse (ARFI) elastography, and magnetic resonance elastography (MRE) enables evaluation of hepatic fibrosis.

Instead of these invasive examinations, typical imaging findings of the liver, formation of esophageal and gastric varices, ascites accumulation, and splenomegaly can facilitate diagnosis of liver cirrhosis. Moreover, several scores are used to assess patients with end-stage liver disease. The model for end stage liver disease (MELD) XI score, which is based on the serum bilirubin and serum creatinine levels, may be predictive of the outcomes of Fontan patients. A recent retrospective review revealed a positive correlation between the MELD-XI score and hepatic fibrosis scores on pathology (correlation coefficient = 0.4; \( p = 0.003 \)). Although, a receiver operator characteristic analysis did not identify a score cutoff with adequate sensitivity and specificity, patients with a MELD-XI score of ≥ 19 had a higher mortality rate.

Proprietary tests such as FibroSURE, which includes assessment of multiple serum markers, have been validated only in patients with HCV and rely on inflammatory markers that are unlikely to be relevant in FALD. FibroSure for identifying evolving or established cirrhosis when compared to liver biopsy had a positive predictive value (PPV) of 33.3% and a negative predictive value (NPV) of 52.6%. A hyaluronic acid level of > 46 ng/mL is indicative of liver cirrhosis and the PPV and NPV were 33.3% and 38.5%, respectively.

Besides, the aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio, AST-to-platelet ratio index (APRI) score, Forns index, and fibrosis-4 (FIB-4) score are reported as markers of fibrosis in FALD. While the FIB-4 index includes age and has lower predictive utility among young adults with other liver disease. In contrast, the VAST score is used to evaluate portal hypertension according to the liver-related complications. A VAST score of ≥ 2 was reported to be significantly related to major adverse events (odds ratio = 9.8, 95% confidence interval [CI] = 2.9–32.7). Treatment for FALD. Medical therapies specific for FALD are not available. Nevertheless, preventive, medical, surgical, and transplant strategies beneficial for similar disease processes may be applicable in FALD. Prior to initiating a treatment strategy, it is important to improve cardiac output and/or raise the Fontan pressure (Fig. 1b). Regarding treatments for liver cirrhosis, ursodeoxycholic acid (UDCA), lactulose, kanamycin, and heart–lung transplantation were used in a nationwide study. Generally, UDCA treatment decreased the elevation of liver enzymes; however, the long-term benefit for FALD was uncertain. A branched-chain amino acid (BCAA),
### Table 3. Characteristics of liver nodules in FALD.  

| Modality                  | Ultrasound (n = 152) | CT/MRI (n = 152) |
|---------------------------|----------------------|------------------|
| **Hepatic nodules**       |                      |                  |
|                           | 3/49 (6.1%)          | 14/44 (31.8%), MRI: 19/48 (39.6%) |
|                           | 45/152 (29.6%)       | CT (n = 37)/MRI (n = 93): 62/130 (47.7%) |
| Medium size of nodules    | 11 (6–18) mm         | 9 (6–12) mm      |
| **Number of nodules**     |                      |                  |
| (1/2/3/more)              | 15 (33.3%)/11 (24.4%)/10 (22.2%)/4 (8.8%) | 30 (23.1%)/15 (11.5%)/6 (4.6%)/11 (8.4%) |
| Nodular parenchyma with countless micronodules | 5 (11.1%) | 143 (92.3%)/11 (7.1%) |
| **Shape**                 |                      |                  |
| Round                     | 85 (83.3%)           | 140 (90.3%)      |
| Ellipsoidal               | 7 (6.8%)             | 6 (3.9%)         |
| Irregular                 | 5 (4.9%)             | 9 (5.8%)         |
| Periphery location        | 68 (66.6%)           | 116 (74.8%)      |
| Other characteristics     |                      |                  |
| <Echogenicity>            |                      |                  |
| Hyperechoic 78 (76.5%)    | <CT> Liver imaging reporting and data system 1:10 (6.4%), 2:24 (15.5%), 3:92 (59.4%), 4:6 (3.9%), 5:5 (3.2%), Unclassified: 18 (11.6%) |
| Isoechoic 15 (14.7%)      | <MRI> T1-weighted MRI isointense 76 (71.7%) |
| T2-weighted MRI isointense 85 (80.2%) |
| Arterial-phase enhancement/wash out | 143 (92.3%)/11 (7.1%) |                  |

Prevalence, characteristics, and diagnosis of HCC. The prevalence of liver nodules is reportedly 29.6% (95% CI 23–37%) on ultrasound and 47.7% (95% CI 39–56%) on CT/MRI. Nodules were usually hyper-echoic (76.5%), round-shaped (> 80%), hyperenhancing in the arterial phase (92%) and located in the liver periphery (75%) (Table 3). In a study based on nationwide surveys of FALD-HCC, 31 HCC cases (1.15%) were detected among 2,700 cases who had undergone the Fontan procedure. In multicenter case studies, 33 HCC cases (1.3%) were observed among 2,470 patients who had undergone the Fontan operation. The estimated annual incidence is 1.5–5.0% in patients with liver cirrhosis. Case reports of FALD-HCC are listed in Table 4. In our cohort, HCC was diagnosed in 12 cases (9.8%) at a median age of 32.5 years (range: 20.6–46.1 years), and the median interval between the Fontan procedure and diagnosis was 21.3 years (range: 3.7–31.2 years), an incidence of 2.9%. Liver nodules are missed on ultrasound in 30% of cases. Contrast-enhanced CT and Gd-EOB-MRI enable detection of FALD-related HCC, however, 14% of FNH cases show portal/delayed washout, which is also present in patients with HCC. The sensitivity of positron emission tomography (PET)-CT scan is only 55% for diagnosis of HCC. Wells et al. demonstrated that mosaic architecture and an elevated alpha fetoprotein (AFP) level are associated with HCC, especially an AFP level of ≥ 400 ng/mL. Some HCC cases are difficult to diagnose because of the lack of an increased AFP level. Again, a large proportion of the patients were treated with warfarin potassium and obtaining a tumor biopsy sample for diagnosis was problematic. Also, it affected the level of des-gamma-carboxy prothrombin (DCP), a marker of HCC. Therefore, a new marker for FALD-HCC is needed.

There are no reports of the misdiagnosed rate of patients with FALD-HCC. Almost all investigations have been case reports, and large studies are limited. In our 124 cases, we detected 77 (62.1%) cases with hyperchoic lesions on ultrasound. Twelve patients were diagnosed with HCC. An increase in AFP was observed in seven cases. Five cases were finally diagnosed with HCC by imaging and the clinical course. We experienced several HCC cases that were difficult to distinguish from FNH. Case 1: A 37-year-old female had a complicated hypervascular tumor periphery on CT (Fig. 3a). The nodules were increasing in size, ultrasound could not detect the nodule, and MRI could not be performed because of a pacemaker. Although preoperatively diagnosed as HCC by CT, the pathological findings of the surgically removed tumor indicated FNH (Fig. 3b). A non-cancerous liver specimen showed sinusoidal dilatation and mild fibrosis. Case 2: A 30-year-old male was detected with a hypervascular tumor on CT of the late arterial phase (Fig. 3c). The tumor was positive by PET-CT (Fig. 3e) and surgically removed, because TACE and PBT were ineffective. It was diagnosed as confluent-multinodular-type...
| Case                      | Gender | Age at HCC detection (years) | Post Fontan (years) | Complications                  | AFP (ng/mL) | Treatment                  | Pathological diagnosis | Prognosis/cause of death                        |
|--------------------------|--------|-----------------------------|---------------------|--------------------------------|-------------|----------------------------|------------------------|------------------------------------------------|
| Ghaferi and Hutchins5    | Male   | 24                          | 18                  | ASD, VSD, cirrhosis            | ND          | –                          | +                      | Died, ruptured HCC                                |
| Ewe8                     | Male   | 29                          | 19                  | ASD, VSD, cirrhosis            | 4674        | Oral chemotherapy          | –                      | Alive                                          |
| Saliba et al.85          | Female | 27                          | 23                  |                                | 162.7       | Chemotherapy               | –                      | Died after 1 year                                |
| Female                   | 28     | 18                          |                     |                                | 788.9       | Sorafenib                 | –                      | Died after 1 year                                |
| Rosenbaum et al.84       | Female | 13                          | 2                   |                                | 3340 (ug/L) | TACE                       | –                      | Waiting for CHLT                                  |
| Asrani et al.8           | Female | 32                          | –                   | Cirrhosis                      | 700         | TACE                       | –                      | Waiting for CHLT                                  |
| Male                     | 24     | –                           | PVTT, ascites, gastric varices | 5000                          | –           | Well-differentiated        | Died, metastasis  | Died, hepatic artery pseudoaneurysm ruptured     |
| Female                   | 33     | –                           |                     | 630                            |             | Radioembolization          | –                      | Died, hepatic artery pseudoaneurysm ruptured     |
| Female                   | 42     | –                           | HCV, advanced fibrosis | 106                            |             | TACE                       | –                      | Waiting for CHLT                                  |
| Elder et al.87           | Male   | 51                          | 28                  | Atrial arrhythmias, ascites, pleural effusions | Normal | Local ablation             | –                      | Heart transplantation Cancer free                 |
| Wallihan et al.88        | Male   | 15                          | 11                  |                                |             | –                          | –                      | Fibrolamellar HCC –                                |
| Rajoriya et al.92        | Female | 41                          | 22                  | Situs invers                   |             | –                          | –                      | Died                                            |
| Weyker et al.93          | Female | 23                          | 22                  |                                |             | –                          | –                      | Alive                                           |
| Yamada et al.91          | Male   | 15                          | 14                  |                                | 2           | TACE                       | –                      | Died after 2 years                                |
| Kwon et al.92            | Male   | 32                          | 23                  | Tachycardia                    | 13 (μg/L) | Liver resection            | Fibrolamellar HCC – | Cancer free                                      |
| Female                   | 16     | 14                          | Sinus bradycardia     | 211,580                        |             | Chemotherapy               | –                      | Lung metastasis Died after 2 months due to hematemesis |
| Takuma et al.94          | Female | 29                          | 19                  | Situs inversus                 | 117.1       | Liver resection            | Poorly differentiated | Alive, cancer free                                |
| Male                     | 30     | 18                          | ASD, VSD             | 20,740 (μg/L)                  | BSC         | –                          | Died                           | Metastasis to Lungs                               |
| Female                   | 42     | 32                          | ASD, VSD, early cirrhosis | 2996 (μg/L)                  | Liver resection + RFA | + | Alive                           |
| Female                   | 48     | 34                          | ASD, VSD, cirrhosis   | 865 (μg/L)                     | BSC         | –                          | Died                                           |
| Lo et al.95              | Female | 24                          | 23                  | Atrial tachycardia, cirrhosis  | 50,000 (ng/dL) | Liver resection TACE | Moderately differentiated | Died after 6 months, HCC recurrence |
| Female                   | 28     | 18                          | 8                   | Sorafenib                      |             | Moderately differentiated, HCC with vascular infiltration | Alive                           |
| Mazzarelli et al.96      | Female | 20                          | 18                  |                                | 12,000      | TACE                       | –                      | Alive                                           |
| Male                     | 21     | 17                          | VSD                 | 4                               | TACE        | –                          | Waiting for CHLT                                   |
| Angelico et al.94        | Female | 33                          | 6                   |                                | 3005        | Laparoscopic liver resection | Sorafenib treatment combined with TACE. After downsizing, CHLT was performed |
| Ogasawara et al.97 / Sagawa et al.98 | Female | 27                          | 21                  | Polysplenia, heterotaxy        | 1622        | PBT                        | –                      | No recurrence                                     |
| Continued                |        |                             |                     |                                |             |                            |                                      |                                                 |
poorly differentiated-HCC based on liver cirrhosis (Fig. 3d). Two cases (2.6%) including case 1 were diagnosed as FNH by surgery. Therefore, the false-positive misdiagnosed rate was 2.6% (2 of 77 cases with nodules). It is difficult to take samples from the peripheral type of nodule. In one case, we performed a tumor biopsy just before transcatheter arterial chemoembolization (TACE) therapy to prevent bleeding. It is a method to diagnose HCC; however, it might increase the bleeding risk in patients in the margin. Therefore, new diagnostic method or marker for FALD-HCC is needed.

Treatment and outcomes of HCC. The treatment of HCC is dependent on liver function and the number and size of tumors, establishing the various guidelines. In addition to volumetry of HCC and residual liver, MELD-XI score and indocyanine green retention rate at 15 min (ICG-R15) may assist evaluation of liver function before surgery. In patients with FALD, cardiac function should be considered when selecting a treatment for HCC. There is limited evidence to suggest the optimal treatment strategy for FALD-HCC.

Liver resection increases the CVP if the IVC clumping is applied, and so was regarded as unsuitable for patients with FALD. Nemoto et al. performed surgery in the reverse Trendelenburg position without IVC clamping. This procedure reduced the CVP from 12 to 10 mmHg without decreasing the systemic blood pressure resulting in reduced blood loss. Moreover, laparoscopic hepatectomy was reported as safe procedure in the FALD setting. The laparoscopic hepatectomy was safely performed keeping the pneumoperitoneum pressure at less than 6–10 mmHg and adequate fluid infusion was given to maintain cardiac preload. Central venous pressure was monitored (11–21 mmHg) and end-tidal carbon dioxide tension was shifted to 36–40 mmHg. The Pringle maneuver was applied during liver resection.

In contrast, the utility of radiofrequency ablation (RFA) is limited in the patients with a pacemaker, accumulation of ascites, and coagulopathy or anticoagulant therapy.

In previous studies, several cases were treated with transcatheter arterial chemo-embolization (TACE) or hepatic arterial infusion chemotherapy (HAIC) based on the greater hypervascularity of FALD-HCC (Table 4). The efficacy of TACE is limited in some cases of abnormal vasculature. We reported proton beam therapy (PBT) as a treatment option for patients with FALD-HCC. PBT is potentially more beneficial in sparing organs-at risk. For liver tumors, the tolerance of surrounding normal liver, biliary tracts, and gastrointestinal structures is the main limiting factor for dose escalation. Therefore, PBT has a dosimetric advantage compared to X-ray therapy. We treated four patients with HCC; no serious adverse event was observed.

| Case | Gender | Age at HCC detection (years) | Post Fontan (years) | Complications | AFP (ng/mL) | Treatment | Pathological diagnosis | Prognosis/cause of death |
|------|--------|-----------------------------|---------------------|---------------|-------------|------------|-----------------------|-------------------------|
| Sagawa et al. | Male | 31 | 21 | Cerebral infarction | 4 | BSC | Well differentiated | Died due to heart failure |
| | Female | 36 | 30 | HCV | 5520 | BSC | – | Died due to liver and heart failure |
| Male | 46 | 21 | HCV, post MVR | 743 | BSC | – | Died due to heart failure |
| Female | 23 | 19 | PVTT | 14,867 | Hepatic arterial infusion chemotherapy | – | Died due to liver failure and HCC |
| Male | 22 | 4 | SSS | 7 | TACE | – | No recurrence |
| Male | 34 | 30 | – | 7 | Liver resection | Poorly differentiated | Unknown |
| Male | 42 | 29 | SSS | 7 | PBT | – | Died due to bleeding of metastatic HCC in the chest cavity |
| Female | 33 | 27 | SSS | 8786 | PBT | – | Lung metastasis |
| Male | 20 | 15 | PLE, polysplenia | 5 | PBT | Well differentiated | Intrahepatic recurrence |
| Male | 27 | 30 | 22 | 25 | 78 | TACE | Well differentiated | Intrahepatic recurrence |
| | | | | | 3901 | PBT, liver resection | Poorly differentiated | PBT and liver resection were undertaken for recurrence |
| Nemoto et al. | Female | 36 | 31 | Polysplenia | 81,663 | Liver resection | Poorly differentiated | Lung metastasis |
| | Yokota et al. | Male | 18 | 6 | – | Laparoscopic liver resection | Well differentiated | Alive |

Table 4. Characteristics of patients with Fontan-associated liver disease-hepatocellular carcinoma (FALD-HCC). AFP, alpha fetoprotein; ASD, atrial septal defect; BSC, best supportive care; CHLT, combined heart-liver transplant; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MVR, mitral valve replacement, ND, not detected; PBT, proton beam therapy; PLE, protein-losing enteropathy; PVTT, portal vein tumor thrombosis; RFA, radiofrequency ablation; SSS, sick sinus syndrome; TACE, transcatheter arterial chemoembolization; TAE, transcatheter arterial embolization; VSD, ventricular septal defect.
In addition to intrahepatic metastasis, most extrahepatic metastases are to the lungs. We experienced three cases of lung metastases among 12 FALD-HCC (Table 4). We speculated that the increase in pulmonary vascular resistance may reduce the blood flow speed, facilitating adhesion of cancer cells. This might promote the metastasis of HCC to the lungs.

Risk factors for FALD and FALD-HCC. The severity of fibrosis correlated with the duration of the Fontan procedure and the CVP13,69 (Fig. 4). In one case series, 43% of patients had advanced fibrosis 30 years after Fontan operation51. Additionally, aging, underlying hepatitis B or C infection, alcohol intake, and hepatotoxic drug use were associated with FALD development (Fig. 4). Timing of diagnosis, type of Fontan, cardiac complications, comorbid systemic disease and obesity may influence the clinical picture in ways that are poorly understood14.

Notably, cirrhosis is a strong risk factor for FALD-HCC59. The annual risk of HCC in cirrhotic patients with FALD was estimated to be 1.5–5.0%60. CVP has been reported to be 16.4 ± 6.1 mmHg in patients with liver cirrhosis after the Fontan procedure and 11.3 ± 2 mmHg in non-cirrhotic cases13. Although cirrhosis is a risk factor of HCC, it does not predict the prognosis. Ohuchi et al. reported that a high CVP and low arterial oxygen saturation strongly predict clinical events in children (p < 0.001), whereas these prognostic factors were marginal in adults71. Instead of CVP, renal dysfunction and metabolic abnormalities predicted clinical events in adults (p < 0.05). Therefore, medication and fenestration that lowers right atrial pressure are effective for decreasing CVP and might inhibit the progression of FALD; however, it may be insufficient to prevent FALD-HCC. The liver stiffness values on ARFI elastography were significantly higher in patients with hepatic nodules31. In our cohort, complications of polysplenia (HR 44.257, 95% CI 1.309–1495.862, p = 0.035) and higher FIB-4 index (HR 4.008, 95% CI 1.304–12.317, p = 0.015) were risk factors for FALD-HCC56.

Surveillance of FALD and HCC. A recent long-term follow-up study reported 10-, 20-, and 30-year survival rates of 74%, 61%, and 43%, respectively, among 1,052 patients after the Fontan procedure32. However, a recent systemic review of 65 FALD-HCC cases, which reported that 1-year survival is 50%72. Only four patients (6.2%) were under liver imaging surveillance for FALD-HCC, suggesting that HCC surveillance is necessary.
There is no consensus on the surveillance of HCC in patients with FALD and the optimum screening method and interval are unclear. In the presence of cirrhosis, serial monitoring by AFP and imaging every 6 months should be recommended similar to patients with HCV. We think we could also follow the patients by this algorism to surveillance for FALD-HCC (Fig. 5). We experienced 12 cases of FALD-HCC, for an incidence of 0.8%, 2.9%, and 13.3% after 10, 20, and 30 years, respectively; these values are lower than those for HCV-related

**Figure 4.** Development of fibrosis after Fontan surgery. Hemodynamic changes, complications of Fontan, viral infection, and metabolic factors are associated with the development of fibrosis. FALD, Fontan-associated liver disease; HCC, hepatocellular carcinoma.

**Figure 5.** The algorithm for FALD-HCC surveillance. AFP, alpha fetoprotein, APRI, aspartate aminotransferase-to-platelet ratio index; CT, computed tomography; FIB-4, Fibrosis-4; FALD, Fontan-associated liver disease; GI, gastrointestinal; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; MRI, magnetic resonance imaging, VAST score, varices, ascites, splenomegaly, thrombocytopenia.
HCC\(^7\). The mortality rate of liver-related death among FALD is 0.19% (5/2,700 cases) and increased by \(\sim 29.4\%\) (5/17 cases) in only those with liver cirrhosis and/or FALD-HCC (Overall, 25 year-survival rates after Fontan procedure were 68.6% and 97.9% in FALD-HCC and non-FALD-HCC, respectively, \(p < 0.01\))\(^8\). HCC must be diagnosed as at an early stage as possible to facilitate timely treatment. The incidence increases approximately 20 years after the operation. Therefore, we recommend that HCC surveillance should begin 10 years after the Fontan procedure\(^9,10,11\).

Mental health care and transitional care of FALD in adults. People with a Fontan circulation have a higher rate of lifetime psychiatric diagnosis (65%) than their healthy peers (22%), particularly for anxiety and behavioral disorders\(^77\). Therefore, there needs to be a low threshold for the provision of mental health care. Also, a higher rate of lifetime psychiatric diagnosis (65%) than their healthy peers (22%) particularly for anxiety and behavioral disorders. Transitioning from child to adult care, including clinical and social care, is necessary for patients with FALD. FALD must be followed-up continuously for the lifetime of the patient.

Conclusion and future perspective

The prevalence of FALD is increasing worldwide and the frequency of liver complications is rising because of improvement of cardiac survival. Evaluation of Fontan is different in children and adults, so further studies to identify non-invasive markers of fibrosis and FALD-HCC criteria are needed.

Ethical approval. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent. Informed consent was obtained from the patient for the publication of our study.

Received: 2 October 2020; Accepted: 20 November 2020

Published online: 10 December 2020

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Scientific Reports | (2020) 10:21742 | https://doi.org/10.1038/s41598-020-78840-y
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We would like to express our gratitude to Professor Hisashi Sugiyama and Dr. Tokuko Shinohara of the Pediatric Cardiology and adult congenital cardiac, TWMU for supervising the follow-up. We also thank Dr. Etsuko Hashimoto of Seibu Railway Company Health Support Center for supervision; We also thank Professor Masakazu Yamamoto, Dr. Shunichi Ariizumi, and Dr. Yoshihito Kotera of the Institute of Gastroenterology, Department of Surgery, TWMU for surgical treatment of liver tumors.

Acknowledgements
We would like to express our gratitude to Professor Hisashi Sugiyama and Dr. Tokuko Shinohara of the Pediatric Cardiology and adult congenital cardiac, TWMU for supervising the follow-up. We also thank Dr. Etsuko Hashimoto of Seibu Railway Company Health Support Center for supervision; We also thank Professor Masakazu Yamamoto, Dr. Shunichi Ariizumi, and Dr. Yoshihito Kotera of the Institute of Gastroenterology, Department of Surgery, TWMU for surgical treatment of liver tumors.

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Conception, and design: T.K. Drafting of the manuscript: T.K. and K.T.
Competing interests
KT has received research funding from Sumitomo Dainippon Pharma Co., Ltd., Astellas Pharma Inc., Eisai Co., Ltd., Taiho Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Pharmaceutical Co., Ltd., AbbVie GK, Takeda Pharmaceutical Co. Ltd., Asahi Kasei Corporation, Ajinomoto Co., Inc., and Otsuka Pharmaceutical Co., Ltd. TK; Nothing to declare.

Additional information
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