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ORIGINAL RESEARCH

# Liver Imaging in Fontan Patients

## How Does Ultrasound Compare to Cross-Sectional Imaging?

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## ABSTRACT

**BACKGROUND** Fontan patients frequently develop liver cirrhosis (LC); however, the diagnostic accuracy of ultrasound (US) for detecting LC and the clinical implications of such diagnoses have not been clearly established.

**OBJECTIVES** This study aims to evaluate the diagnostic performance of US for detecting LC in an adult population with Fontan circulation and to determine the correlation between LC and mortality/transplantation.

**METHODS** This was a retrospective study. Data on cross-sectional imaging, liver USs, and clinical visits that occurred within 12 months of the cross-sectional imaging were collected. Liver US diagnostic accuracy was evaluated against cross-sectional imaging. Kappa agreement between methods was assessed. Univariate Cox proportional hazards regression analysis was employed to compare mortality and transplant outcomes.

**RESULTS** Overall, 131 patients were included. Liver US and cross-sectional imaging (computed tomography 74, magnetic resonance imaging 57) was performed in all patients. Liver US reported heterogeneous parenchyma, lobar redistribution, and surface nodularity in 85.4%, 72.5%, and 65.6% of cases. Cross-sectional imaging reported these features in 60.3%, 87.0%, and 84.9% of cases, respectively. US sensitivity was greater than 0.75 for all variables, while specificity was 0.21, 0.58, and 0.85, respectively. LC was diagnosed in 78% of cases by US and in 90% by cross-sectional imaging, with a kappa agreement of 0.21 between techniques. There was no significant correlation between the presence of hepatic parenchymal changes or cirrhosis and mortality/transplantation.

**CONCLUSIONS** Liver US is effective for screening and monitoring liver cirrhotic features in the adult Fontan population. In a univariate analysis, there was no association between LC and mortality or transplantation.
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The Fontan procedure was first described in 1969 as a palliation for patients with tricuspid atresia. Since then, the procedure has had several modifications and has become the surgical technique of choice when biventricular circulation cannot be achieved. Thousands of Fontan operations are performed annually in the United States alone. Over the last few years, there has been a significant reduction in in-hospital mortality and early postoperative complications.[1] Although survival rates have

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**ABBREVIATIONS AND ACRONYMS**

**APRI** = aspartate amino transferase to Platelet Ratio Index

**CT** = computed tomography

**FALD** = Fontan-associated liver disease

**FIB-4** = Fibrosis-4

**FNH** = focal nodular hyperplasia

**HCC** = hepatocellular carcinoma

**LC** = liver cirrhosis

**MELD-XI** = Model for End-Stage Liver Disease excluding INR

**MRI** = magnetic resonance imaging

**PLE** = protein-losing enteropathy

**T1WI** = T1-weighted imaging

**US** = ultrasound

increased, these patients still have high mortality and morbidity in early adulthood from cardiac and extracardiac complications.[2] Among the extracardiac complications, liver disease is the most prevalent.

Liver anomalies in Fontan patients were first described in 1981.[3] Since then, further data have emerged, emphasizing the importance of addressing liver-related issues due to their high prevalence and association with poor prognosis.[4] A recent expert consensus defined Fontan-Associated Liver Disease (FALD) as a broad spectrum of liver disorders and their consequences linked to the specific hemodynamics of the Fontan procedure. The definition includes a range of liver fibrosis, cirrhosis, focal nodular hyperplasia (FNH), and hepatocellular carcinoma (HCC).[5] While several protocols have been published recommending different surveillance strategies for these patients,[6,7] there is no consensus on how often we should monitor the liver and what techniques should be used. While liver biopsy is the gold standard to diagnose liver cirrhosis (LC), it is not a low-risk procedure in patients with Fontan circulation and noninvasive assessment of the liver should be utilized to select patients who may benefit from a biopsy. Liver ultrasound (US) is widely available and often the technique of choice to assess the liver in these patients, but little is known about the correlation between the findings in liver US and magnetic resonance imaging (MRI)/computed tomography (CT) in patients with FALD.

At our institution, Fontan patients undergo annual liver USs, and cross-sectional imaging is primarily used to monitor patients with multiple nodules or nodules larger than 1 cm. This study seeks to evaluate the utility, accuracy, and reliability of liver US in identifying cirrhosis and liver nodules and analyze their association to outcome.

## MATERIAL AND METHODS

**STUDY POPULATION.** Patients with Fontan operation, older than 18 years of age, followed at the Toronto Adult Congenital Heart Disease Program between September 2015 and September 2022 who had both liver US and liver CT or MRI within 12 months, were included. A liver US is part of the follow-up protocol for Fontan patients in our institution and cross-sectional imaging with liver CT or MRI is requested in all patients with liver nodules >1 cm. In patients with multiple nodules or in those where the liver is not well visualized by US, cross-sectional imaging is requested at the discretion of the most responsible physician. The Institutional Review Board approved the project in January 2023.

**DEMOGRAPHIC AND CLINICAL DATA.** Demographic data and baseline characteristics were extracted from the medical records, including date of birth, gender, height, weight, cardiovascular risk factors, history of previous arrhythmia, thrombotic events, or protein-losing enteropathy (PLE). Rhythm, echocardiographic data, laboratory data, and medical therapy were collected at the time of the liver US, whereas cardiopulmonary exercise test and right heart catheterization data were included when performed within a year of the liver US. Type of systemic ventricle, age at the time of Fontan completion, and type of Fontan repair were collected from surgical and medical records. Systemic ventricle systolic function and atrioventricular valve regurgitation were classified qualitatively as normal, mild, moderate, or severely impaired, and none, mild, and moderate or severe, respectively. Kidney dysfunction was considered in patients with creatinine higher than 110umol/L.

**ABDOMINAL IMAGING.** USs were performed using a Canon Aplio 500 scanner (Canon Medical Systems Corporation) equipped with a 3.5-MHz transducer. CT images were obtained using multi-detector CT machines (Aquilion, Toshiba; Ingenuity Core 128, Philips Medical Systems). The four-phase (unenhanced, arterial, portal, and delayed phase), three-phase (arterial, portal, and delayed phase), two-phase (arterial and portal phase), or single portal phase were obtained after injection of intravenous contrast material (2 mL/kg [maximum 150 mL] Ultravist 370, 370 mg iodine/mL, Bayer Healthcare). Imaging parameters were 120 kV and 80 to 440 mA with a 3.0-mm section thickness/2.4-mm interval or 5.0-mm section thickness/2.5-mm interval. MRIs were performed using either 1.5- or 3-T MRI systems (Avanto, Siemens Healthineers; Signa Excite, GE Healthcare; Skyra, Siemens Healthineers). The protocol included a nonfat-suppressed coronal single-shot fast spin echo T2-weighted imaging, fat-suppressed axial spin echo T2-weighted imaging, T1-weighted imaging (T1WI) axial in- and out-of-phase, dynamic three dimensional T1WI breath-hold fat-suppressed spoiled gradient-recalled echo sequence. For dynamic three dimensional T1WI contrast-enhanced imaging, we obtained unenhanced, late arterial phase, portal venous phase (60 seconds), late venous/transitional phase (3 minutes), and delayed phase (5 minutes) before and after dynamic administration of a gadolinium-based contrast agent. For patients who

received a liver-specific gadolinium chelate, Gd-EOB-DTPA (Primovist, Bayer Schering Pharma), hepatobiliary phase imaging was also obtained at 20 minutes post-contrast injection.

The following data were collected: the presence of surface nodularity, lobar redistribution, heterogeneous background hepatic parenchyma, liver fibrosis, varices, ascites, splenomegaly, umbilical vein recanalization and presence and number of the echogenic nodules and malignant lesions. Lobar redistribution was considered when atrophy of the posterior right hepatic lobe (segments 6/7) with concomitant hypertrophy of the left lateral segment and caudate lobe was present. Fibrosis was defined as reticulation of hepatic parenchyma by CT or MRI assessment, this feature was not reported in the US, splenomegaly was defined as a spleen larger than 13 cm, and umbilical vein recanalization when the umbilical vein was measured more than 0.3 cm in diameter. The appearance of FNH-like nodules and HCC was used as they have been described in the literature.[8] A pathological diagnosis of HCC was confirmed by biopsy in all cases. LC was defined as the presence of two or more of the following findings in the liver US: hepatic surface nodularity, lobar redistribution and/or heterogeneous parenchyma, or two or more of the following findings in the abdominal CT or MRI: hepatic surface nodularity, lobar redistribution, heterogeneous parenchyma, and/or fibrosis.

The following liver scores were calculated: Model for End-Stage Liver Disease excluding INR (MELD-XI), Fibrosis-4 (FIB-4), aspartate amino transferase to Platelet Ratio Index (APRI), and Varices, Ascites, Splenomegaly or Thrombocytopenia.[5,9]

**STATISTICAL ANALYSIS.** Continuous variables are presented as mean ± SD or median (IQR), according to data distribution. All variables were assessed for normality with the Shapiro-Wilk test. Categorical variables are presented as numbers (percentages). Comparison between groups was performed using the Student's *t*-test, Wilcoxon rank sum test, or chi-squared test, as appropriate. Univariate Cox proportional hazards regression analysis was used to compare all-cause mortality and heart or heart and liver transplant. Kaplan-Meier curves were also plotted and the log-rank test between groups was reported. For the purpose of the survival analysis, the date of the first liver imaging was used as time zero. Multivariate analysis was not performed due to the insufficient number of observations.

The diagnostic performance (sensitivity, specificity, negative predictive value, positive predictive value) of the liver US was compared with cross-sectional imaging findings as the reference standard. Agreement between the different methods was evaluated using the kappa index. A kappa value of 0 to 0.20 was considered slight agreement, 0.21 to 0.40 fair agreement, 0.41 to 0.60 moderate agreement, 0.61 to 0.80 substantial agreement, and 0.81 to 1.00 almost perfect agreement. All tests were considered significant in $P < 0.05$. Statistical analyses were performed using R-package V.4.3.1 (R Foundation for Statistical Computing).

## RESULTS

**STUDY POPULATION.** During the study period, 131 patients met the inclusion criteria, the mean age was 34.4 ± 10.1 years, and 57 (43.5%) were females. The most common type of Fontan was an extracardiac conduit, 66 patients (50.3%), followed by a lateral tunnel, 38 patients (29.0%). A classic Fontan was present in 26 patients (19.8%) while only one patient underwent Bjork modification. The median age at the time of Fontan completion was 3.3 (IQR: 2.5-6.9) years and the time elapsed since Fontan completion to the liver US was 24.8 ± 6.3 years. Most of the patients had a systemic left ventricle, 82 patients (62.5%), with most of them having preserved systolic function, 73 patients (55.7%). Atrioventricular valve regurgitation was present in 113 patients (86.0%) with only one-third having moderate-to-severe atrioventricular valve regurgitation, 36 patients (31.8%) (**Table 1**, **Central Illustration**).

**ABDOMINAL IMAGING.** Liver US was performed in all patients and liver CT was the most common cross-sectional imaging test, 74 patients (56.4%). Heterogeneous parenchyma was the most common finding in the liver US, 112 patients (85.4%), followed by lobar redistribution, 95 patients (72.5%), and surface nodularity, 86 patients (65.6%); whereas the most common finding in the cross-sectional imaging was lobar redistribution, 114 patients (87.0%), followed by surface nodularity, 110 patients (85.0%), and heterogeneous parenchyma, 79 patients (60.3%). Nodules were present in approximately two-thirds of the patients in both liver US and cross-sectional imaging, 67.9% and 65.6%, respectively. Fibrosis was present in 81 patients (61.8%) (**Table 2**). Splenomegaly was diagnosed in 60 patients (45.8%) by liver US and in 54 patients (41.2%) by cross-sectional imaging and ascites was observed in 37 patients (28.2%) by liver US and in 53 patients (40.4%) by cross-sectional imaging. Varices and umbilical vein recanalization were rarely seen by liver US, while were present in 43 patients

**TABLE 1 Baseline Characteristics**

| | |
|---|---|
| Age (y) | 34.4 ± 10.1 |
| Female | 57 (43%) |
| Age at the time of Fontan operation (y) | 3.29 (2.4-6.8) |
| Time from Fontan completion (y) | 24.8 ± 6.3 |
| History of arrhythmia | 85 (64%) |
| History of thrombotic events | 32 (24%) |
| Protein-losing enteropathy | 5 (4%) |
| Diabetes | 3 (2%) |
| Kidney dysfunction | 9 (6.8%) |
| Type of Fontan | |
| Classic Fontan | 26 (19.8%) |
| Lateral conduit | 38 (29%) |
| Extracardiac conduit | 66 (50.3%) |
| Bjork modification | 1 (0.8%) |
| Systemic right ventricle | 50 (38.1%) |
| Echocardiographic data | |
| Ventricular systolic function | |
| Normal | 73 (55.7%) |
| Mildly impaired | 40 (30.5%) |
| Moderately to severely impaired | 18 (13.7%) |
| AV valve regurgitation | |
| None | 18 (13.7%) |
| Mild | 77 (58%) |
| Moderate-to-severe | 36 (27.4%) |
| Medical therapy | |
| Loop diuretics | 56 (43%) |
| Mineralocorticoid receptor antagonists | 37 (28%) |
| Aspirin | 50 (38%) |
| Anticoagulation | 67 (52%) |
| Warfarin | 52 (77.6%) |
| NOACS | 15 (22.3%) |
| Laboratory variables | |
| Hemoglobin (g/l) | 152 ± 23 |
| Platelet (x$10^9$) | 172 ± 77 |
| Creatinine (umol/l) | 84 ± 29 |
| Albumin (mg/dl) | 45 ± 6.2 |
| AST (u/l) | 26 ± 8 |
| ALT (u/l) | 27 ± 12 |
| Bilirubin (umol/l) | 23.5 ± 15.1 |
| BNP (pg/ml) | 44.9 (17.9-114.7) |
| Alpha fetoprotein (ug/l) (n = 83) | 2.3 (1.85-4) |
| Liver scores | |
| MELD-XI | 8.72 (6.1-12.2) |
| APRI | 0.43 (0.3-0.6) |
| FIB-4 | 0.98 (0.6-1.6) |
| VAST>2 | 56 (42%) |
| Right heart catheterization (n = 61) | |
| Cardiac output (l/min) | 3.6 ± 1.2 |
| Cardiac index (l/min/$m^2$) | 2.0 ± 0.6 |
| Fontan pressure (mm Hg) | 15.3 ± 3.5 |
| Wedge pressure (mm Hg) | 10.2 ± 3.6 |
| IVC pressure (mm Hg) | 15.0 ± 3.6 |
| Hepatic pressure (mm Hg) | 15.0 ± 3.8 |
| Hepatic wedge pressure (mm Hg) | 15.8 ± 3.7 |
| Transpulmonary gradient (mm Hg) | 4.4 ± 1.68 |
| Cardiopulmonary exercise test (n = 102) | |
| Peak $VO_2$ (% of predicted) | 55.8 ± 14 |
| $VO_2$ AT (% of predicted) | 35.7 ± 9.6 |
| $VE/VCO_2$ slope | 41.7 ± 6.9 |
| Oxygen pulse (% of predicted) | 80 ± 24 |
| Peak heart rate (beats per minute) | 132 ± 30 |
| Peak $SpO_2$ (%) | 89.6 ± 5.3 |
| RER | 1.1 ± 0.1 |

Values are mean ± SD, n (%), or median (IQR).

ALT = alanine aminotransferase; APRI = aspartate aminotransferase to platelet ratio index; AST = aspartate aminotransferase; AV = atrioventricular; BNP = B-type natriuretic peptide; FIB-4 = Fibrosis 4; MELD = Model for End-Stage Liver Disease; MELD-XI = Model for End-stage Liver Disease excluding INR; NOACs = non-vitamin K antagonist oral anticoagulants; RER = respiratory exchange ratio; $SpO_2$ = oxygen saturation; VAST = Varices, Ascites, Splenomegaly or Thrombocytopenia score; $VE/VCO_2$ = minute ventilation/carbon dioxide production; $VO_2$ = oxygen consumption; $VO_2$ AT = oxygen consumption at anaerobic threshold.

(32.8%) and 24 patients (18.3%), respectively, by cross-sectional imaging (Table 2).

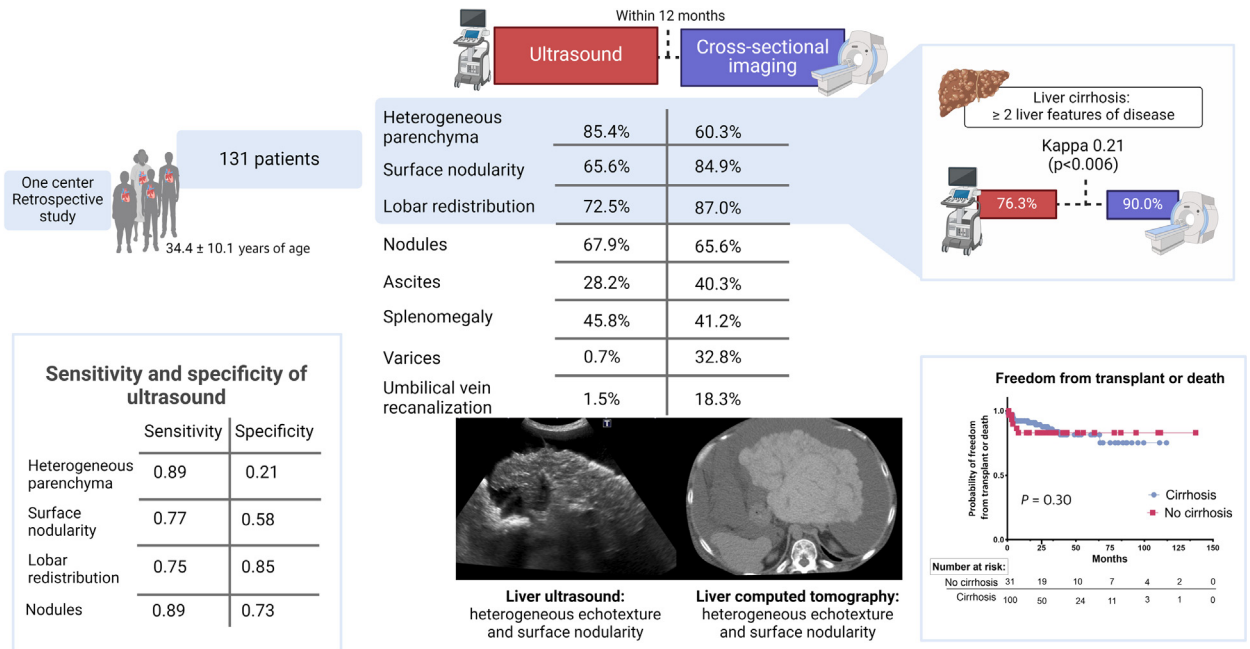
The diagnosis of LC by imaging was made in three-quarters of patients by liver US, 100 patients (76.3%) and in almost all the patients by cross-sectional imaging 118 patients (90.0%).

**HEPATOCELLULAR CARCINOMA.** Four patients were diagnosed with HCC, the mean age at diagnosis was 43.7 ± 14.8 years, and 50% were female. Patients with HCC were older, mean age 50.0 ± 12.8 years vs 34.1 ± 9.7 years ($P = 0.009$) and more cyanotic, oxygen saturations 88.8% ± 9.7 vs 92.5% ± 4.0 ($P = 0.03$). The time from Fontan completion to the diagnosis of HCC was 31.5 ± 6.6 years. There were no differences on the liver scores between patients with and without diagnosis of HCC.

All patients with HCC showed lobar redistribution and surface nodularity in the liver US and cross-sectional imaging. Heterogeneous parenchyma was present in all patients by liver US but only in 3 patients by cross-sectional imaging and only one patient showed liver fibrosis. LC was diagnosed in all patients with HCC. The medium size of the lesions was 2.4 (IQR: 1.8-3.1) cm.

**DIAGNOSIS OF THE LIVER US.** The sensitivity and specificity of the liver US were high for surface nodularity (sensitivity 75%, specificity 85%) and echogenic nodules (sensitivity 89%, specificity 73%), including nodules < 1 cm (sensitivity 83%, specificity 75%). Heterogeneous parenchyma and lobar redistribution had high sensitivity, 89% and 77%, respectively, but low specificity, 21% and 58%, respectively, although lobar redistribution had a high positive

**CENTRAL ILLUSTRATION** **Liver Imaging in Fontan Patients: How Does Ultrasound Compare to Cross-Sectional Imaging? Single-Center Study Showing Liver Ultrasound as Effective for Screening and Monitoring Liver Cirrhotic Features in the Adult Fontan Population When Comparing to Cross-Sectional Imaging**

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There was no evidence linking liver cirrhosis to mortality or transplantation in this population.

predictive value, 0.92. Abdominal US had high specificity to diagnose ascites (specificity 0.89) and high sensitivity for splenomegaly (specificity 0.79, sensitivity 0.81) (Table 3). The agreement analysis between liver US and cross-sectional imaging showed substantial agreement for nodules (kappa 0.64, $P < 0.001$), moderate agreement for surface nodularity (kappa 0.42, $P < 0.001$), mild agreement for lobar redistribution (kappa 0.24, $P = 0.001$), and slight agreement for heterogeneous parenchyma (kappa 0.12, $P = 0.07$) (Table 2). There was also moderate agreement for splenomegaly (kappa 0.59, $P < 0.001$) and ascites (kappa 0.46, $P < 0.001$) and fair agreement in the diagnosis of cirrhosis (kappa 0.21, $P = 0.006$) (Table 2).

**OUTCOMES.** Over a median follow-up of 31.1 (IQR: 15.1-50.5) months, 16 patients (12.2%) died, and 2 patients (1.5%) were transplanted, one underwent heart alone and one combined heart and liver transplant. History of thrombotic events, history of arrhythmia, presence of renal dysfunction and having PLE were the strongest unadjusted univariate predictors of outcome (Table 4).

The presence of heterogeneous parenchyma, lobar redistribution, surface nodularity, varices, umbilical vein recanalization, and splenomegaly showed no significant association with mortality or heart transplant. The presence of HCC (HR: 5.9; 95% CI: 1.35-26.00, $P$ 0.01) and ascites (HR: 6.7; 95% CI: 1.24-8.41,

**TABLE 2** **Abdominal Findings and Agreement Between Ultrasound and Cross-Sectional Imaging**

| | Abdominal Ultrasound (n = 131) | Cross-Sectional Imaging (n = 131) | Kappa |
|---|---|---|---|
| Heterogeneous parenchyma | 112 (85.4%) | 79 (60.3%) | 0.12 ($P = 0.07$) |
| Lobar redistribution | 95 (72.5%) | 114 (87.0%) | 0.24 ($P = 0.001$) |
| Surface nodularity | 86 (65.6%) | 110 (84.9%) | 0.42 ($P < 0.001$) |
| Fibrosis | - | 81 (61.8%) | - |
| Nodules | 89 (67.9%) | 86 (65.6%) | 0.64 ($P < 0.001$) |
| Nodules <1 cm | 62 (69.6%) | 53 (61.6%) | 0.61 ($P < 0.001$) |
| Ascites | 37 (28.2%) | 53 (40.4%) | 0.46 ($P < 0.01$) |
| Splenomegaly | 60 (45.8%) | 54 (41.2%) | 0.59 ($P < 0.01$) |
| Umbilical vein recanalization | 2 (1.5%) | 24 (18.3%) | 0.05 ($P = 0.24$) |
| Varices | 1 (0.7%) | 43 (32.8%) | 0.03 ($P = 0.15$) |

Values are n (%).

**TABLE 3 Diagnostic Accuracy of Ultrasound for Fontan Liver Attributes**

| | Sensitivity (%) | Specificity (%) | Positive Predictive Value (%) | Negative Predictive Value (%) |
|---|---|---|---|---|
| Heterogeneous parenchyma | 89% | 21% | 63% | 57% |
| Lobar redistribution | 77% | 58% | 92% | 27% |
| Surface nodularity | 75% | 85% | 96% | 41% |
| Nodules | 89% | 73% | 86% | 78% |
| Nodules <1 cm | 83% | 75% | 70% | 92% |
| Nodules >1 cm | 75% | 83% | 92% | 69% |
| Ascites | 54% | 89% | 78% | 74% |
| Splenomegaly | 81% | 79% | 73% | 85% |

$P = <0.001$) were predictors of outcome, whereas the diagnosis of LC by imaging was not related mortality and/or transplant (HR: 0.8; 95% CI: 0.29-3.32, $P = 0.71$) (Figure 1). The MELD-XI, APRI, and FIB-4 scores were also related to outcome (Table 4).

## DISCUSSION

This study shows for the first time that the liver US has good diagnostic accuracy in determining surface nodularity, lobar redistribution, and heterogeneous parenchyma in adult patients with FALD. Additionally, there is a notable agreement between liver US and liver CT/MRI when evaluating the liver in these patients.

Assessing the liver in patients with Fontan circulation poses significant challenges. While numerous studies have revealed structural changes, the synthetic function of the liver is typically preserved.[10] Hepatic changes in patients with FALD can be categorized into three phases: 1) hepatic congestion and sinusoidal dilatation: present even before the completion of Fontan circulation, this phase is characterized by high pressure in the centrilobular vein of the hepatocyte (zone 3); 2) liver fibrosis without portal hypertension: this phase is generally seen 5 to 10 years after Fontan completion due to persistent edema in the Disse space, leading to centrilobular/perisinusoidal fibrosis; and 3) liver fibrosis with portal hypertension as seen in patients with advanced primary liver disease.[11] As liver fibrosis advances, the liver becomes more heterogeneous, and the liver surface becomes nodular. This progression results in lobar redistribution, determined by right lobe atrophy and caudate lobe

**TABLE 4 Univariate Analysis of Clinical and Imaging Factors Associated With Mortality and Transplant**

| | No (n = 113) | Yes (n = 18) | HR (95% CI) | *P* Value |
|---|---|---|---|---|
| Age (y) | 33.1 ± 9.5 | 43.1 ± 9.9 | 1.1 (1.0-1.1) | <0.001 |
| Female | 50 (44%) | 7 (38%) | 1.1 (0.4-2.8) | 0.85 |
| Age at the time of Fontan operation (y) | 5.2 ± 5.8 | 8.9 ± 5.4 | 1.1 (1.0-1.1) | 0.01 |
| Time from Fontan completion (y) | 24.5 ± 6.0 | 26.8 ± 7.5 | 1.1 (0.9-1.1) | 0.08 |
| History of arrhythmia | 68 (60%) | 17 (89%) | 9.4 (1.3-71.1) | 0.02 |
| History of thrombotic events | 19 (16%) | 13 (68%) | 10.3 (3.6-29.6) | <0.001 |
| PLE | 3 (2.6%) | 2 (10%) | 4.5 (1.0-19.8) | 0.048 |
| Baseline $SpO_2$ (%) | 93 ± 3.3 | 88 ± 5.3 | 0.8 (0.8-0.9) | <0.001 |
| Renal dysfunction | 5 (4.4%) | 4 (18%) | 4.5 (1.4-13.8) | 0.007 |
| Albumin (mg/dL) | 45.9 ± 6.2 | 38.9 ± 6.8 | 0.9 (0.9-0.97) | 0.001 |
| Type of Fontan | | | | |
| Extracardiac Fontan | 60 (53.0%) | 6 (33.3%) | 0.5 (0.2-1.2) | 0.13 |
| Systemic right ventricle | 42 (37.1) | 8 (44.4%) | 0.8 (0.3-1.9) | 0.55 |
| Echocardiographic data | | | | |
| Moderate to severe ventricular dysfunction | 15 (13.2%) | 3 (16.6%) | 1.2 (0.3-4.3) | 0.7 |
| Moderate to severe AV valve regurgitation | 33 (29.2%) | 3 (16.6%) | 0.5 (0.6-1.8) | 0.31 |
| Liver scores | | | | |
| MELD-XI | 8.6 (6.0-11.5) | 11.8 (8.3-15.1) | 1.2 (1.1-1.3) | 0.003 |
| APRI | 0.4 (0.3-0.6) | 0.6 (0.3-1.5) | 1.7 (1.3-2.2) | <0.001 |
| FIB-4 | 0.9 (0.6-1.5) | 2.6 (0.7-4.8) | 1.1 (1.1-1.2) | <0.001 |
| Ultrasound findings | | | | |
| Ascites | 25 (22%) | 12 (66%) | 6.7 (1.2-8.4) | <0.001 |
| Splenomegaly | 52 (46%) | 8 (44%) | 0.89 (0.4-2.3) | 0.81 |
| Cirrhosis | 87 (77%) | 13 (72%) | 0.8 (0.3-2.3) | 0.71 |

Values are mean ± SD, n (%), or median (IQR) unless otherwise indicated.
PLE = protein-losing enteropathy; other abbreviations as in Table 1.

hypertrophy. In our study, both liver US and liver CT/MRI demonstrated high sensitivity in identifying surface nodularity and lobar redistribution. However, liver US exhibited low specificity in diagnosing lobar redistribution, likely due to suboptimal acoustic windows in some of these patients, sometimes limiting visualization of the caudate lobe of the liver.

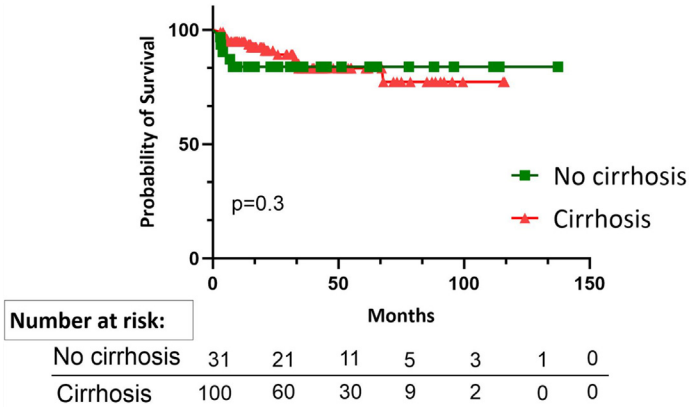
**DIAGNOSTIC OF LIVER CIRRHOSIS.** In our study, most of the patients had LC, which is expected to be due to the age of the population.

Liver fibrosis is a common finding in patients with FALD as fibrosis progresses, central-to-central vein or central-to-portal vein bridging occurs. Liver cirrhosis is defined as fibrosis encircling nodules with regeneration of hepatocytes. Compensated LC may be asymptomatic with preserved hepatic synthetic function, but decompensation typically ensues as liver disease progresses. Liver biopsy is the gold standard technique to diagnose liver fibrosis; however, this is not a low-risk procedure in patients with Fontan circulation and considering that the heterogeneous distribution of fibrosis in patients with FALD increases the risk of false negative biopsies it is important to select the patients who may benefit from this procedure. Noninvasive imaging modalities such as US, MRI, and CT can identify features of cirrhosis and hepatic nodules but may not accurately predict the degree of fibrosis compared with histological findings. CT and MRI are better techniques to diagnose LC in non-Fontan patients[8] and our study confirmed that the same applies to patients with FALD. Interestingly, heterogeneous parenchyma was common in the liver US but not in the liver CT or MRI. We assumed this could be related to the standardized liver US report template used in our center, identifying and describing the echotexture of the liver parenchyma in the US.

**NODULES AND HEPATOCELLULAR CARCINOMA.** The presence of arterialized nodules is common in patients with FALD, and the incidence correlates with the time since the Fontan operation. These nodules are often multiple, and localized in the periphery of the liver, and the most common histological finding is FNH-like nodules. Liver US is a well-established tool for monitoring nodules in individuals with chronic non-FALD liver disease.[8] In our study, liver US demonstrated high sensitivity and specificity in visualizing liver nodules, even those smaller than 1 cm, in patients with FALD, making it an excellent screening technique in this population.

While some patients with FALD may develop HCC, the incidence of HCC is lower in patient with FALD 0.6% to 1.8%[12,13] than in patients with LC from other causes 1% to 6%.[14] In our study, the incidence of HCC (3%) was higher than the incidence reported in the literature but since we are a referral transplant center this is likely a referral bias. In our study, all patients with HCC had LC but LC was not a predictor of HCC, which correlates with previous studies.[12]

**FIGURE 1** Freedom From Heart Transplant or Death




Kaplan-Meier survival of fontan patients with fontan circulation diagnosed with and without cirrhosis. No difference in mortality or heart transplantation observed.

**OUTCOMES.** A history of thrombotic events, arrhythmia, low oxygen saturation, renal dysfunction or PLE emerged as unadjusted univariate predictors of the composite outcome in our study population. This aligns with previous publications where PLE and thromboembolic events were identified as leading causes of morbidity and mortality in Fontan patients.[15] In addition, arrhythmias and low oxygen saturations are common complications in patients with Fontan circulation [16] and both are recognized risk factors for thrombotic events.[17,18] Kidney dysfunction is highly prevalent in adult congenital heart disease patients mainly in those with complex congenital heart disease. Dimopoulos et al showed in a cohort of 1,102 patients with CHD that mortality is 3-fold higher than normal in the 1 in 11 patients who have moderate or severe glomerular filtration rate reduction.

In our study, the presence of ascites was found to be associated with the outcome, while the presence of cirrhosis or cirrhotic features in US, CT, or MRI scans was not. In patients with Fontan circulation, ascites may result from increased sinusoidal pressure and impaired lymphatic drainage, as observed in patients with PLE, and it is not always indicative of LC.[19]

Therefore, identifying new ascites without acute decompensation should prompt a referral for consideration of advanced therapies.

Splenomegaly is often considered a sign of portal hypertension in patients with chronic non-FALD liver disease; however, this is not always the case in patients with Fontan circulation where mild increases in spleen size may be seen even without cirrhosis. In our study, the presence of splenomegaly was not related to outcome.

In our study, noninvasive fibrosis scores, such as MELD-XI, APRI, and FIB-4 score, were related to outcome. Although this was also seen in other publications,[10,20] it is important to emphasize that these scores are not validated in patients with FALD and should be interpreted with caution in this population. In addition, low platelet count is a common finding in patients with cyanosis and it is not necessarily related to liver disease.

**STUDY LIMITATIONS.** This study was limited by its retrospective nature and the unavailability of liver biopsy. The inclusion criteria were based on cross-sectional imaging requests linked to liver US made by the most responsible physician. It is important to note that the suspicion of advanced liver disease likely prompted these imaging requests. Consequently, it is not appropriate to extrapolate the observed frequency of cirrhosis to the entire Fontan population.

Our institution is a tertiary-level hospital with a large caseload of patients in the liver imaging service, being the largest liver transplant unit in the country. This high level of expertise in assessing the liver should be considered.

Additionally, our center does not perform contrast-enhanced US routinely when screening patients, which could have provided more detailed information. Contrast-enhanced US was only performed when a nodule remained indeterminate after US, CT, and MRI were performed.

Finally, since the univariate analysis was unadjusted, the results may be skewed due to the potential influence of confounding factors.

## CONCLUSIONS

Liver US has a strong ability to identify LC in adult patients with Fontan circulation, it also demonstrates reliably identifies hepatic nodules, therefore is an effective tool for continuous surveillance of those low-risk lesions, including those less than 1 cm.

While we observed associations between advanced age, low oxygen saturation, history of arrhythmia, thrombosis, PLE, and elevated liver scores, there was no direct correlation found between liver features indicative of advanced disease or LC and poor outcomes in this population.

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## PERSPECTIVES

**COMPETENCY IN PATIENT CARE:** The findings of this study highlight the importance of liver ultrasound as a vital tool for monitoring liver cirrhosis and hepatic nodules in adult patients with Fontan circulation. Its robust ability to identify cirrhosis and reliably detect nodules, even those smaller than one centimeter, establishes liver ultrasound as an effective, noninvasive surveillance option for this vulnerable population. Although certain clinical factors, such as age and low oxygen saturation, are associated with liver scores, the lack of a direct correlation between advanced liver features and poor clinical outcomes suggests a complex understanding of disease progression in these patients.

**TRANSLATIONAL OUTLOOK:** Future research should aim to uncover the underlying mechanisms of liver disease in Fontan patients and investigate how routine liver ultrasound can be integrated into comprehensive care strategies. This could potentially guide interventions to reduce the risk of liver-related complications in this cohort.

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