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ORIGINAL PAPER

Prevalence of hepatic dysfunction in paediatric patients with Fontan circulation

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ABSTRACT

Introduction: Hepatic dysfunction is a well-known complication and is frequently referred to as Fontan-associated liver disease. The aim of the study is to assess liver dysfunction in children and adolescents with Fontan circulation.

Material and methods: The study was an observational analytical study conducted on 30 patients who underwent Fontan operation more than 2 years before inclusion in the study and who were followed up at the Paediatric Cardiology Unit, Cairo University Children's Hospital. All patients were subjected to echocardiography, laboratory investigations, abdominal ultrasound, and liver elastography.

Results: The median patient age was 13 years (inter-quartile range [IQR] 10–16.32), and the median follow-up duration after the Fontan operation was 5 years (IQR 3.83–9). Global longitudinal strain was lower in 26 (86.7%), and the single ventricle ejection fraction was reduced in 23 (76.7%); however, no correlation was found with time interval since Fontan. None of the patients had ascites clinically or by ultrasound examination. Gamma-glutamyl transferase was elevated in 28 (93.33%), which was significantly higher in the systemic right ventricle group. Abdominal ultrasound revealed periportal enhancement in 6 (20%), which was significantly higher in the hepatitis C virus exposed group ($p = 0.006$). Superior mesenteric artery resistance index was decreased in 27 (90%), which was significantly lower in the systemic left ventricle group ($p = 0.01$). The liver stiffness values did not correlate with time interval since Fontan ($p = 0.09$).

Conclusions: Liver disease is prevalent in Fontan patients. Non-invasive measures such as laboratory tests, ultrasound, and elastography should be implemented with consideration for hepatology consultation. Fontan-associated liver disease screening is important in the monitoring of Fontan patients.

KEY WORDS:

elastography, Fontan operation, single ventricle, Fontan-associated liver disease.

INTRODUCTION

Fontan-associated liver disease (FALD) is defined as a range of abnormalities in liver structure and function induced by the abnormal circulation of the Fontan state and unrelated to another disease process [1]. These abnormalities vary from mild liver fibrosis to liver cirrhosis and hepatocellular carcinoma [2]. Although it is widely accepted that all patients after Fontan have some degree of FALD, it is unknown what proportion of patients after

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Fontan will develop clinically significant advanced liver disease [3]. The potential impact of liver abnormalities on late morbidity and mortality has been observed in numerous studies. The prevalence and severity of liver disease in Fontan patients have not been studied extensively in the past, but recent liver disease literature in Fontan patients has received increasing attention [4]. This study aimed to assess hepatic dysfunction in paediatric patients with Fontan circulation.

MATERIAL AND METHODS

This is an observational analytical study conducted on 30 patients with Fontan circulation between May 2018 and March 2020. Patients were recruited from the Paediatric Cardiology Department of Cairo University Children's Hospital and other hospitals all over Egypt, who underwent the Fontan procedure at least 2 years prior to enrolment. Patients with known hepatic problems unrelated to the Fontan circulation – except previous exposure to hepatitis C virus (HCV) infection – were excluded.

All patients were subjected to full history taking (including age, gender, age at Fontan procedure, immediate post-Fontan oxygen saturation [SpO_2%], post-Fontan complications, and time interval since the Fontan operation) and clinical examination (including weight, height, body mass index, SpO_2%, hepatomegaly, splenomegaly, ascites, signs of systemic venous congestion, and cardiac examination). Electrocardiogram, chest X-ray, and echocardiographic studies by conventional and tissue Doppler imaging were performed by a single operator according to the guidelines of the American Society of Echocardiography [5–7].

Laboratory work-up included hepatitis B surface antigen; HCV antibody and HCV RNA by polymerase chain reaction (PCR); liver functions tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, gamma-glutamyl transferase (GGT), total serum bilirubin (TSB), direct serum bilirubin (DSB), albumin, and international normalised ratio (INR); complete blood count; serum creatinine; and α-1 antitrypsin in stool (protein-losing enteropathy – PLE). Age-specific blood indices were considered [8].

Abdominal ultrasonography examinations were performed for changes in liver parenchyma (echogenicity, liver surface nodularity, and liver cirrhosis); hepatic and splenic dimensions; the presence of hepatic venous congestion; the presence of ascites; Doppler imaging to measure portal, hepatic venous flow velocity, and superior mesenteric artery resistance index (SMA-RI); and liver elastography to assess the degree of liver fibrosis [9, 10].

Scoring systems were used to assess liver disease in Fontan patients, but it should be noted that they are not designed for patients after Fontan procedure:

1. MELD-XI (model for end-stage liver disease excluding INR) = 5.11 Ln (serum bilirubin) + 11.76 Ln (serum creatinine) + 9.44. The MELD-XI cut-off points were: low (≤ 10.5); low-intermediate (10.6–12.6); intermediate-high (12.7–16.4); and high (> 16.4) [11].
2. Fibrosis-4(FIB-4) values were calculated by the formula: age (years) × AST [U/l]/(platelets [10^9/l] × (ALT [U/l])$^{1/2}$). FIB-4 index < 1.45 was considered as no or moderate fibrosis; > 3.25 was considered extensive fibrosis or cirrhosis [12].
3. Aspartate aminotransferase-to-platelet ratio index (APRI) score: AST [U/l]/AST upper limit of normal [U/l] × 100)/platelet count (× 10^9/l). APRI values of ≤ 1 rule out significant fibrosis and cirrhosis, and ≥ 2 indicates significant fibrosis [2].

STATISTICAL ANALYSIS

Data were described as the mean ± standard deviation, median and inter-quartile range (IQR), or frequencies (number of cases) and percentages. Numerical data were tested for the normal assumption using the Kolmogorov-Smirnov test. Correlation between various variables was done using the Spearman rank correlation equation. Data were compared using Student's *t*-test, the Mann-Whitney *U* test, and χ^2, according to the data type. Two-sided *p*-values less than 0.05 were considered statistically significant. All statistical calculations were done using IBM SPSS (Statistical Package for the Social Sciences; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.

RESULTS

The total number of patients included was 30, of whom 17 were male (56.7%). The ages ranged 5–18 years (median = 13; IQR 10–16.32). Weight Z-score ranged from –3.98 to +2.42 (median = –1.10; IQR from –1.82 to +0.24), and height Z-score ranged from –5.08 to +1.71 (median = –1.36; IQR –2.02 to –0.56). Body mass index Z-score ranged from –2.93 to +4.10 (median = –0.13; IQR from –0.82 to +0.75).

FONTAN OPERATION

The age at the time of Fontan completion ranged 3–16 years (median = 6.84 years; IQR 5–8). SpO_2 post-Fontan ranged 85–98% (mean = 93.53 ±3.05). All patients underwent extracardiac Fontan completion with Gore-Tex conduits (18–20 mm).

Most of our patients were using salicylate (73.3 %); warfarin was used in 60% of the cases.

Post-operative Fontan complications included pleural effusion in 5 patients (16.7%), HCV positive conversion in 4 patients, chest infections in 2 patients (6.7%), wound infections in 2 patients (6.7 %), reversible bradycardia in one patient (3.3%), chylothorax in one patient (3.3%), and systemic venous congestion in one patient (3.3%).

Post-Fontan clinical evaluation: the duration since Fontan procedure ranged 2–12 years (median = 5 years; IQR 3.83 to 9); SpO_2 ranged 83–98% (mean = 93.97 ±3.37). Hepatomegaly was present in 2 patients (median liver size at mid-clavicular line was 6 cm, and median liver size at the subcostal line was 4 cm), but no evidence of systemic venous congestion was detected in any of the patients. Electrocardiogram findings are listed in Table 1. On chest X-ray, cardiomegaly was found in 20 patients (66.66%). Post-Fontan echocardiography parameters for the patients are shown in Table 2.

TABLE 1. Electrocardiogram findings

ECG findings	*n* (%)
Normal sinus rhythm	27 (90)
Sinus tachycardia	1 (3.3)
Junctional rhythm	1 (3.3)
Second degree heart block	1 (3.3)

ECG – electrocardiogram

TABLE 2. Echocardiography findings

Echocardiography findings	*N* = 30 (%)
Tricuspid atresia	10 (33.3)
Double inlet left ventricle	9 (30)
Double outlet right ventricle	7 (23.3)
Complete AVSD Rastelli type C*	1 (3.3)
Complete AVSD Rastelli type A*	1 (3.3)
TGA, VSD, PS	2 (6.7)
Left ventricle	21 (70)
Right ventricle	9 (30)
Ventricular dimension (EDD) [cm], median (IQR)	4.25 (3.50–4.73)
Ventricular dimension (EDD) Z-score, median (IQR)	–0.18 (–2.23 to 2.53)
EF (%), median (IQR)	64 (59.75–67)
FS (%), median (IQR)	34 (31–36.25)
Valvular regurgitation	
Trivial	11 (36.7)
Mild	10 (33.3)
Mild to moderate	3 (10)

AVSD – atrioventricular septal defect, EDD – end-diastolic diameter, EF – ejection fraction, FS – fractional shortening, IQR – interquartile range, PS – pulmonary stenosis, TGA – transposition of great arteries, VSD – ventricular septal defect
** These 2 patients underwent univentricular repair because of associated straddling atrioventricular valve.*

LABORATORY INVESTIGATIONS

Mild anaemia was found in 3 patients (10%). Mild and moderate leucopaenia were found in 3.33% and 6.66% of patients, respectively. Mild thrombocytosis was found in one patient (3.33 %). Liver function tests are shown in Table 3. Stool α-1 antitrypsin was elevated in one patient.

APRI and FIB-4 were calculated for all included subjects, and values were normal in all patients. MELD-XI was mildly elevated in 2 patients (6.66 %).

Patients were classified according to HCV exposure into the following groups:

1. HCV group (n = 6): patients who were exposed to HCV (HCV antibody positive), all patients underwent spontaneous remission and were negative for HCV RNA by PCR.
2. Non-HCV group (n = 24).

ABDOMINAL ULTRASOUND

The most common sonographic findings were congestion of the hepatic veins in 16 patients (53.3%), peri-portal enhancement in 6 patients (20%), hepatomegaly in 5 patients (16.7 %), with mild enlargement and splenomegaly in 3 (10 %) patients. The spleen size ranged 6.6–15.4 cm with a median of 9.20 cm (IQR 7.70–10.47).

Doppler ultrasound was performed for all patients, showing that all patients had hepatic venous flow velocity less than 25 cm/s (normal: 25–40 cm/s). In 29 patients (96.66%), the portal venous flow velocity was less than 16 cm/s (normal: 16–40 cm/s). Superior mesenteric artery resistance index was decreased in 27 patients (90%).

TABLE 3. Liver function tests

Parameters (normal value)	Median (IQR)	Abnormal	*N* (%)
AST (up to 50 U/l)	32.5 (26.5–47.5)	High	6 (20)
ALT (up to 40 U/l)	30.5 (24.75–42.50)	High	7 (23.33)
GGT (3-22 U/l)	50.50 (40–100.50)	High	28 (93.33)
ALP (up to 640 U/l)	182 (161–296)		0
TSB (up to 1.2 mg/dl)	0.4 (0.3–0.65)		0
DSB (≤ 0.2 mg/dl)	0.1 (0.1–0.2)		0
Albumin (3.5–5.2 g/dl)	4.3 (4–4.83)	Low	1 (3.33)
INR	1.23 (1.1–1.3)	High	20 (66.6)

ALP – alkaline phosphatase, ALT – alanine aminotransferase, AST – aspartate aminotransferase, DSB – direct serum bilirubin, GGT – gamma-glutamyl transferase, INR – international normalised ratio, IQR – interquartile range, TSB – total serum bilirubin

Liver elastography*:* using liver elastography to assess the degree of hepatic fibrosis, none of the patients was F0, 7 patients (23.3%) were F1, 8 were F2 (26.7%), 1 (3.33%) was F3, and 14 (46.7 %) were F4.

There was one mortality as a result of Fontan failing with PLE. The cardiac diagnosis was transposition of great arteries, ventricular septal defect, and pulmonary stenosis. The patient was exposed to HCV (HCV antibody positive) and underwent spontaneous remission; faecal α-1-antitrypsin was elevated, and he was the only patient with hypoalbuminaemia.

CORRELATIONS

No correlation was found between echocardiography findings and time interval since Fontan. Of all laboratory investigations, there was a significant negative correlation between AST and time interval since Fontan ($r = -0.46$, $p = 0.01$). Of all the sonographic findings, only the splenic size was positive correlated with the time interval since Fontan ($r = 0.45$, $p = 0.01$).

We compared all studied parameters between the group of 6 patients who were exposed to HCV and the rest of the studied group ($n = 24$).

No statistically significant differences were found in blood count parameters, liver function tests, fibrosis scoring systems, ultrasound findings, Doppler findings, liver elastography values, and tissue Doppler echocardiography findings. The only difference observed between both groups was the periportal enhancement by ultrasound, which was significantly higher in the HCV-exposed group ($p = 0.006$).

We also compared the group of patients with systemic right ventricle (RV) ($n = 9$) to those with systemic left ventricle (LV) ($n = 21$), and no significant differences were found as regards the following: blood count parameters, liver function tests EXCEPT for GGT which was significantly higher in those with systemic RV ($p = 0.004$), fibrosis scoring systems, abdominal ultrasound findings, Doppler findings EXCEPT for SMA-RI, which was significantly lower in the systemic LV group ($p = 0.01$), liver elastography values, and tissue Doppler echocardiography findings EXCEPT for early diastolic inflow velocity, which was significantly higher in the systemic RV group ($p = 0.01$).

DISCUSSION

We studied the hepatic involvement in 30 Fontan patients, ranging 5–18 years. The median age at Fontan operation was 3–16 years (median 6.84 years), which is generally older than reported in other studies [13]. However, some centres perform the Fontan procedure at a similar age range [14–19] or even older in adulthood [4].

Our cases were exclusively extracardiac Fontan, similar to the regular practice. We studied the cases for FALD at a median of 5 years following the Fontan procedure. Other studies reporting on FALD performed their analysis after a comparable duration since Fontan [15–17, 19], while Ackerman *et al.* [4] studied their Fontan patients for FALD after a longer median duration (median 19.7 years; IQR 14.5–21.4).

As regards liver function tests, TSB and DSB were normal in all our study populations. These findings were in agreement with those reported by Arya *et al.* [18], unlike other studies that reported elevation in TSB and DSB in 31% and 50%, respectively. This could be explained by the fact that individuals with hepatic congestion are frequently asymptomatic, and the presence of abnormally high TSB and DSB levels was accidentally discovered during routine investigations [4].

In our cohort, 23.33% had elevated ALT and 20% had elevated AST. Other studies reported comparable results [4, 17, 19]. No correlation was found between ALT elevation and time interval since Fontan, while a significant negative correlation was found between AST elevation and time interval since Fontan ($r = -0.64$, $p = 0.01$). These findings were in agreement with those reported by Rathgeber *et al.* [16] ($r = -0.55$, $p < 0.01$).

Elevations of ALT and AST are uncommon in Fontan patients, mostly because these parameters probably do not reflect congestion-induced changes, but inflammation [4].

One of our main findings in liver function tests was the elevation of GGT levels in 93.9%; which was significantly higher in those with systemic RV compared to those with systemic LV (101.1 ±59.8 vs. 52.2 ±27.4, $p = 0.004$). Other studies reported nearly similar findings [4, 17, 20]. Moreover, a significant rise of GGT was reported 3 to 6 months after Fontan completion as compared to the pre-Fontan values [21].

We could not find a correlation between GGT elevation and time interval since Fontan as reported by Ackerman *et al.* [4] and Rathgeber *et al.* [16]. However, in serial evaluation, Kaulitz *et al.* [22] were able to observe a significant increase in GGT levels with time since Fontan. This could be explained by the fact that GGT is an enzyme located on the external surface of cellular membranes, and in these patients the low cardiac output and chronic venous congestion may diminish vascular supply of intrahepatic bile ducts, leading to endothelial injury and release of GGT [17].

Two-thirds of our patients had prolonged INR; however, no correlation was found with time interval to Fontan. Ackerman *et al.* [4] and Surrey *et al.* [20] reported prolonged INR in 48% and 46%, respectively.

One of our patients (3.33%) had low serum albumin. Ackerman *et al.* [4] reported low serum albumin in 14%, while Arya *et al.* [18] reported normal albumin in all their patients. No correlation was found with time interval since Fontan ($r = 0.31$, $p = 0.10$). This finding was in agreement with that reported by Rathgeber *et al.* [16] ($r = -0.03$, $p = 0.8$).

We investigated our patients for PLE using faecal α-1-antitrypsin. It was elevated in one patient (3.33%), who was the only patient with low serum albumin in our cohort (2.5 gm/dl). Ackerman *et al.* [4] reported elevated faecal α-1 antitrypsin in 22% of cases.

In our cohort, 6 patients (20%) were positive for HCV antibodies and were negative by PCR for HCV RNA, which means that they were exposed to HCV infection (4 of them as a post-operative complication), but luckily all of them had spontaneous clearance of their HCV infection. Because of the endemicity of HCV infection in Egypt, we did not exclude these patients from the study, particularly because they cleared their infection. This is unlike other studies that excluded HCV-positive patients from their studied population [17, 19].

We compared all studied parameters between the group members who were exposed to HCV (HCV antibody positive) and underwent spontaneous remission (negative HCV RNA by PCR) and the rest of the studied group. The only difference observed between both groups was the periportal enhancement by ultrasound, which was significantly higher in the HCV-exposed group ($p = 0.006$)

On Doppler ultrasound, all patients had low hepatic venous flow velocity and 96.66% had low portal venous flow velocity. DiPaola *et al.* [13] reported that hepatic and portal venous flow velocities were normal in all their studied patients. The decreased hepatic venous flow is thought to result from chronic venous congestion; however, Mori *et al.* [23] reported that the reduction of hepatic venous flow velocity is associated with major clinical adverse outcomes in Fontan patients, while the reduction in portal venous flow velocity might reflect impaired portal perfusion and suggest portal hypertension [22].

A decreased SMA-RI was reported in 90% of our cases, with no correlation with time interval since Fontan. Similar findings were reported by Kutty *et al.* [14]. In other studies, SMA-RI was found to be correlated with the Fontan interval, with a longer Fontan interval resulting in a lower SMA-RI [4].

Importantly, in our study, we found that patients with systemic LV had significantly lower SMA-RI compared to those with systemic RV (0.47 ±0.12 vs. 0.61 ±0.13 $p = 0.01$). Conversely, other studies reported no significant differences in SMA-RI and ventricular morphology [24].

We measured liver stiffness (LS) by elastography to assess the degree of hepatic fibrosis in our patients. The median LS was 11.65 kPa (IQR 7.77–17.53); however, no correlation was found with time interval since Fontan ($r = 0.31$, $p = 0.10$). Other studies reported that LS values were significantly higher in Fontan patients compared with controls with no correlation with time interval since Fontan [13, 14]. Also, Arya *et al.* [18] reported similar findings. However, other studies demonstrated a positive correlation between LS and time interval since Fontan [17, 16]. Hepatic venous congestion alone may increase the LS, yielding an elevated score, even in the absence of fibrosis. This has important implications regarding the interpretation of LS values in Fontan patients.

Most of our patients (96.6%) had normal platelet count. Thrombocytopaenia was reported in other studies [17, 19]. Decreased platelet count seems to be associated with many other forms of progressive hepatic fibrosis with the concomitant development of portal hypertension [19].

In our cohort, the APRI score was normal in all patients. Most of the other studies reported similar findings [4, 9]. However, other studies reported an elevated APRI score of 11.1%, with no correlation to time interval since Fontan [19]. In addition, FIB-4 score was normal in all patients, similarly to the report by Ackerman *et al.* [4].

On post-Fontan echocardiography, the group of patients with systemic RV demonstrated significantly higher early diastolic inflow velocity vs. those with systemic LV (0.08 ±0.04 vs. 0.07 ±0.04, $p = 0.01$). Margossian *et al.* [25] reported similar findings.

Among our studied group, 86.7% had reduced global longitudinal strain (GLS) and 76.7% had reduced single ventricle (SV) ejection fraction; however, no correlation was found with time interval since Fontan. Other studies demonstrated that the GLS significantly reduced with preserved ejection fraction [26, 27].

In our study, we found no difference in GLS and SV ejection fraction comparing those with systemic RV to those with systemic LV. However, other studies reported that patients with systemic RV had significantly lower GLS compared to those with systemic LV. This is unclear because there have been conflicting reports regarding the influence of ventricular morphology on outcomes after Fontan palliation [24].

CONCLUSIONS

Our patients demonstrated differences between those with systemic RV and those with systemic LV. Doppler ultrasound showed decreased SMA-RI in 27 patients (90%), and SMA-RI was significantly lower in those with systemic LV ($p = 0.01$). In addition, GGT was elevated in 28 patients (93.33%), and it was significantly higher in those with systemic RV ($p = 0.004$). Patients with previous exposure to HCV infection had more significant periportal enhancement by abdominal ultrasound ($p = 0.006$) as compared to those who were not exposed to HCV.

DISCLOSURES

1. The Ethical Committee of Kasr Alainy Medical School, Cairo University, approved the study protocol. All procedures complied with the principles of the Declaration of Helsinki and other applicable ethical statements.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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