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FULL RESEARCH PAPER
Congenital heart disease

Morbidity and mortality in adults with a Fontan circulation beyond the fourth decade of life

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Aims To evaluate the late outcomes of adults (above 35 years) with a Fontan-type circulation, for whom current data on morbidity and mortality are lacking.

Methods and results Data were collected retrospectively on consecutive patients with Fontan circulation above the age of 35 years followed in three European specialist centres. Overall, 115 Fontan patients were included [median age 35 (range 35–48) years, 47.8% female]. The most common underlying congenital heart disease diagnosis was tricuspid atresia ($n = 58$, 50.4%), and the age at first Fontan completion was 9.1 (interquartile range 5.0–15.8) years. Almost two-thirds (61.7%) of patients had undergone an atriopulmonary Fontan, and 23.5% had received a total cavopulmonary connection. One-third required repeat surgery or intervention. Most patients (55.9%) were in New York Heart Association functional class II or class I (30.6%), 76 (66.1%) patients had experienced at least one arrhythmia, and eight (7.0%) protein-losing enteropathy. At a median follow-up of 5.0 (2.4–10.3) years, 15 (13.0%) patients were referred for transplantation assessment and 19 (16.5%) patients died, mainly from heart failure (84.2%). Univariable predictors of death or transplantation included lower serum albumin level [hazard ratio (HR) 1.09 per g/L decrease, 95% confidence interval (CI): 1.04–1.15, $P = 0.0009$], prior heart failure admission (HR 4.28, 95% CI:1.75–10.44, $P = 0.001$), prior atrial tachycardia or flutter (HR 3.02, 95% CI: 1.23–7.38, $P = 0.02$), and baseline pulmonary vasodilator therapy (HR 8.59, 95% CI:1.05–70.13, $P = 0.04$). Lower serum albumin and prior atrial tachycardia or flutter remained significant on bivariable analysis.

Conclusion Our study highlights the significant morbidity and mortality in older adults with a Fontan-type circulation, emphasizing the need for lifelong specialist surveillance with frequent risk stratification, close monitoring, and early consideration for transplantation assessment.

Lay summary This study sheds light on the complex medical journey of adults living with the outcomes of Fontan surgery—a procedure performed in early childhood. These individuals have reached the milestone of their forties and beyond, yet they confront an array of significant health challenges that necessitate lifelong, individualized congenital heart disease care. The key findings are as follows:

- While adults with Fontan circulation are living longer, they are at high risk of death, mainly due to heart failure. They also face a host of other health issues, including the need for additional surgeries or interventions. Nearly two-thirds have experienced some form of heart rhythm problem, and a substantial number eventually require evaluation for a heart transplant.

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- Heart transplants within this group were rare, which may be linked to the various barriers to transplantation in the Fontan population. Moreover, those with multiple indicators of advanced disease have a heightened risk of life-threatening events, reinforcing the critical need for personalized and continuous specialist care designed to meet their distinct health requirements.

Keywords Fontan • Single ventricle • Congenital heart disease • Observational study • Outcome

Introduction

Congenital heart disease (CHD) affects ~1% of live births, while a smaller proportion, around 1 in 3000 infants, are born with a functionally single ventricle.[1] The Fontan procedure has become the operative strategy of choice for patients with this condition. Initially performed in 1968 as an atriopulmonary (AP) connection, Fontan-type surgeries have undergone substantial modifications, now involving a total cavopulmonary connection (TCPC).

Advances in surgical techniques, and especially for patients with single-ventricle physiology, have resulted in a growing population of adults with complex CHD.[2] In a recent US study, 81.4% of individuals with any CHD survived to 35 years of age, though only 21.5% of those with hypoplastic left heart syndrome and 53.5% with other single-ventricle defects survived to this age. Long-term follow-up studies focusing on adult survivors with a Fontan-type circulation have reported a survival of 80–90% at 30 years of age.[3–5] The likelihood of being free from morbidity over time, however, remains quite low: Heart failure, thromboembolism, arrhythmias, liver disease, and protein-losing enteropathy (PLE) are common complications in these patients and may contribute to premature death.[6,7]

Improved survival following the Fontan procedure has prompted interest in long-term outcomes, yet the outcome of this population over the age of 35 years remains unclear. To address this knowledge gap, we conducted a retrospective study on adult Fontan patients from three European centres entering the fourth decade of life. Our primary objective was to evaluate morbidity and mortality in this specific age group.

Methods

Data were collected retrospectively on consecutive patients with Fontan-type circulation ≥35 years under specialist follow-up at one of three specialist adult CHD centres (Royal Brompton Hospital in London, Southampton General Hospital, IRCCS Policlinico San Donato, Milan) over the past 15 years. Patients for whom survival status was unknown were excluded. The study was approved by the UK Health Research Authority and the Ethics Committee of the Policlinico San Donato. This was a retrospective analysis based on anonymized data collected for routine clinical care and administrative purposes; hence, individual informed consent was waived.

Baseline demographic and clinical characteristics of patients who turned 35 years old from 2005 onwards were collected from dedicated clinical databases and including type of Fontan connection, New York Heart Association (NYHA) functional class, physical examination, blood tests, medications, history of pregnancy, previous history of arrhythmias, heart failure, thromboembolic, Fontan-associated liver disease (FALD), PLE, and plastic bronchitis. Kawashima procedure was defined as a bilateral, bidirectional superior cavopulmonary connection in the context of left atrial isomerism with interruption of the inferior vena cava with azygous continuation. Patients were classified as having FALD based on liver ultrasound or other non-invasive imaging when there was evidence of cirrhosis and/or portal hypertension, splenomegaly, or ascites. Systemic ventricular function on echocardiography was reported in a semi-quantitative fashion as normal, mild, moderate, and severe systolic impairment and systemic atrioventricular valve regurgitation (as absent, mild, moderate, and severe). Information from cardiopulmonary exercise testing (CPET) was also collated from studies performed as part of routine clinical evaluation. Data from the test closest to the date of the patient's 35th birthday and the latest follow-up were included.

Variables of interest during the period of follow-up included new-onset arrhythmias, thromboembolic events, new diagnosis of FALD, Fontan failure, need for cardiac surgery, transplantation, or referral for transplantation assessment. Fontan failure was defined in accordance with previously published criteria,[8] if any of the following were present: referral for transplantation (including heart), Fontan revision, conversion or takedown, PLE, plastic bronchitis, or NYHA functional class III or IV. 'Fontan conversion' referred to patients with a classic AP connection who were converted to a TCPC in one of the following patterns: lateral tunnel (LT) or extra-cardiac conduit (ECC). The term 'Fontan revision' referred to surgical procedures aimed at optimizing the Fontan circuit and improving symptomatology, e.g. enlargement of the pulmonary arteries, removal of intra-atrial thrombus, and/or conduit replacement.

Statistical analysis

Statistical analyses were performed using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are presented as mean ± standard deviation or median [interquartile range (IQR)], unless stated otherwise, and categorical variables are presented as number (percentage). For continuous variables with a normal distribution, paired and unpaired Student's *t*-test was used. For variables not normally distributed, the Wilcoxon signed-rank test for paired samples and the Mann–Whitney *U* test for independent samples were used. Categorical variables for two independent groups were compared using the χ^2 test or Fisher's exact test, according to sample size. Univariable logistic regression analysis was performed to assess the relation between baseline demographic and clinical variables and the occurrence of arrhythmia during follow-up. For survival analysis, rates of freedom from death or heart transplantation (receipt) were estimated using Kaplan–Meier cumulative event curves. Patients were censored if they were lost to follow-up (>3 years between last clinic attendance and date of data collection). Univariable and bivariable Cox regression analysis was used to identify predictors of the combined endpoint of death or transplantation. A two-sided *P*-value of <0.05 was considered indicative of statistical significance.

Results

In total, 115 Fontan patients who turned 35 years old during the study period were included [median age 35 (range 35–48) years, 47.8% female]. Baseline characteristics of the cohort are shown in *Table 1*. The most common underlying CHD diagnosis was tricuspid atresia ($n = 58$, 50.4%), followed by double inlet left ventricle ($n = 27$, 23.5%) and double outlet right ventricle ($n = 11$, 9.6%). Median age at first Fontan procedure was 9.1 (IQR 5.0–15.8) years: 73 (63.5%) had undergone an AP Fontan, 26 (22.6%) received a TCPC (LT in 12%, ECC in 10%), 12 (10.4%) had undergone a Björk–Fontan procedure, and 4 (3.5%) a Kawashima procedure. Repeat surgical or interventional procedures had been required in 59 (51.3%) patients with the following being performed: Fontan revision (11, 9.6%), Fontan conversion (28, 24.3%), fenestration closure (7, 6.1%), branch pulmonary artery stenting (3, 2.6%), embolization of collateral vessels (3, 2.6%), aortic valve and root replacement (2, 1.8%), atrioventricular valve intervention

Table 1 Baseline characteristics of adults with a Fontan-type circulation age 35 years and above

Characteristic	All, $n = 115$	AP, $n = 50$	TCPC, $n = 53$	Björk–Fontan and Kawashima procedure, $n = 12$	P value[a]
Male sex	60 (52.2)	26 (52)	32 (60.4)	2 (16.7)	0.15
Ventricular morphology					0.09
Left	94 (81.7)	49(98)	39 (73.6)	6 (50)	
Right	11 (9.6)	1 (2)	8 (15.1)	2 (16.7)	
Biventricular	10 (8.7)	0 (0)	6 (11.3)	4 (33.3)	
BMI, kg/m^2	23.9 ± 5.4	24.4 ± 7.1	23.8 ± 3.6	22.3 ± 4.7	0.54
Resting oxygen saturation, %	93 [88.2–96]	92 [88–95]	94 [90.8–96]	95 [89–96.5]	0.3
Pre-Fontan surgery	74 (64.3)	33 (66)	35 (66)	6 (50)	0.88
Arterial shunt (Blalock–Taussig)	40 (34.8)	18 (36)	19 (35.8)	3 (25)	0.98
Pulmonary arterial banding	18 (15.7)	8 (16)	10 (18.9)	0 (0)	0.54
Central shunt (Waterston)	14 (12.2)	6 (12)	6 (11.3)	2 (16.7)	0.99
Other pre-Fontan surgeries	4 (3.5)	0 (0)	4 (7.5)	0 (0)	0.09
Age at Fontan procedure, years	10 [5.6–16.4]	9.3 [6.1–13.6]	9.8 [5.4–18.6]	11.9 [3.7–16.8]	0.58
Fontan type at first completion					**<0.0001**
AP	74 (64.3)	50 (100)	24 (45.3)	0 (0)	
LT	13 (11.3)	0 (0)	13 (24.5)	0 (0)	
ECC	12 (10.4)	0 (0)	12 (22.6)	0 (0)	
Other (Björk, Kawashima)	16 (13.9)	0 (0)	4 (7.5)	12 (100)	
Fenestration at completion	23 (20.5)	5 (10.6)	16 (30.2)	2 (16.7)	**0.03**
NYHA functional class					**0.03**
I	34 (30.6)	16 (33.3)	14 (27.5)	4 (33.3)	
II	62 (55.9)	23 (47.9)	34 (66.7)	5 (41.7)	
III	14 (12.6)	9 (18.8)	2 (3.9)	3 (25)	
IV	1 (0.9)	0 (0)	1 (2)	0 (0)	
Anticoagulant therapy	92 (81.4)	44 (88)	37 (72.5)	11 (91.7)	0.05
Antiplatelet therapy	17 (15.2)	4 (8.2)	12 (23.1)	1 (9.1)	0.06
Antiarrhythmic therapy					0.62
Amiodarone	26 (23.2)	13 (26)	10 (20)	3 (25)	0.96
Sotalol	8 (7.1)	3 (6)	3 (6)	2 (16.7)	0.57
Flecainide	2 (1.8)	2 (4)	0 (0)	0 (0)	
'Heart failure' therapy					
ACE-I or ARB	44 (38.6)	18 (36)	22 (42.3)	4 (33.3)	0.58
Beta-blocker	44 (38.6)	19 (38)	21 (40.4)	4 (33.3)	0.87
MRA	27 (23.7)	13 (26)	11 (21.2)	3 (25)	0.72
Loop diuretic	45 (39.5)	20 (40)	21 (40.4)	4 (33.3)	0.99
Pulmonary vasodilator	2 (1.8)	1 (2)	1 (1.9)	0 (0)	0.99

Categorical variables displayed as n (%). Numeric variables shown as mean ± SD (if normally distributed) or median [IQR] (non-normally distributed). $P < 0.05$ indicates statistical significance (shown in bold font).
ACE-I, angiotensin-converting enzyme inhibitor; AP, atriopulmonary; ARB, angiotensin receptor blocker; BMI, body mass index; ECC, extra-cardiac conduit; LT, lateral tunnel; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.
[a]P value for comparison between TCPC and non-TCPC Fontan.

(2, 1.8%), conduit dilatation (1, 0.9%), left superior vena cava ligation (1, 0.9%), and failed Fontan conversion (1, 0.9%).

Clinical status of Fontan patients beyond 35 years of age

At the first assessment beyond the age of 35, most patients were symptomatic in NYHA functional class II (62, 55.9%), with 34 (30.6%) in functional class I and 14 (12.6%) in functional class III. Most patients (92, 81.4%) were being prescribed anticoagulation (97% warfarin, 1% dabigatran), while 17 (15.2%) were on antiplatelet therapy with aspirin, clopidogrel, or both. Antiarrhythmic medication was prescribed to 42 (37.5%) patients. Angiotensin-converting enzyme inhibition or angiotensin receptor blockade was used in 44 (38.6%) patients, 44 (38.6%) were prescribed beta-blockers, and 27 (23.7%) were on a mineralocorticoid receptor antagonist. A total of 45 (39.5%) patients were on loop diuretics. Results of blood testing, echocardiography, and cardiopulmonary exercise testing are shown in *Table 2*.

At baseline, many patients had a history of adverse clinical events (*Table 3*). A total of 76 (66.1%) patients had experienced at least one arrhythmia at a median age of 29.0 (25.0–35.2) years, with atrial tachycardia/flutter being the most common (42, 55.3%), followed by atrial

Table 2 Results of baseline investigations of Fontan patients at 35 years of age

Investigation result	All, $n = 115$	AP, $n = 50$	TCPC, $n = 53$	Björk–Fontan and Kawashima procedure, $n = 12$	P value[a]
Haemoglobin, g/L	151 ± 21	152 ± 21	152 ± 21	146 ± 29	0.74
MCV, fL	90.6 [86.2–93]	91 [88–95]	90 [86.8–92]	87 [80.3–94]	0.42
Urea, mmol/L	5.8 [4.4–9]	6.4 [4.4–8.3]	5.7 [4.2–10.2]	5.8 [4.7–6]	0.96
Creatinine, μmol/L	78 [63.4–88]	76.1 [62.8–87.3]	79.6 [66.3–88.5]	78 [59–84]	0.36
eGFR, mL/min/1.73 m^2	99.6 [83.4–118.1]	99.6 [75.6–116.3]	107.6 [88.6–121.3]	94.4 [78.5–102.3]	0.22
Bilirubin, μmol/L	18 [14–26]	19 [12.5–24]	18 [14–27]	19 [14.5–31.8]	0.81
ALP, IU/L	81 [58.5–114]	81 [62–113.8]	81 [56–98]	100.5 [70.5–138.8]	0.14
ALT, IU/L	27 [20.5–32.5]	25 [22–40]	26 [20–31.3]	27 [22–29]	0.46
Albumin, g/L	42 [38–46]	42 [36.3–44.8]	44 [40–47]	41 [40.3–45]	0.08
Serum iron, μmol/L	15.5 ± 7.3	15.1 ± 7.1	17.1 ± 7.7	11.4 ± 5.9	0.24
TIBC, μmol/L	70 [64.5–75]	70 [68–75]	65 [58–73]	73 [69.3–73]	0.14
Peak VO_2, mL/kg/min	19.1 ± 6.6	20.9 ± 6.6	17.6 ± 6.7	18.4 ± 6	0.24
VE/VCO_2 slope	36 [30.6–44]	35 [30.6–40]	40.5 [30.5–47.6]	37.5 [32.5–43]	0.5
Peak heart rate, b.p.m.	141.8 ± 32.4	142.3 ± 33.8	137.7 ± 33.9	153.6 ± 21.3	0.3
Systemic ventricular function					0.99
Normal	79 (69.9)	36 (72)	36 (70.6)	7 (58.3)	
Mild	23 (20.4)	9 (18)	10 (19.6)	4 (33.3)	
Moderate	6 (5.3)	3 (6)	3 (5.9)	0 (0)	
Severe	5 (4.4)	2 (4)	2 (3.9)	1 (8.3)	
Moderate/severe systemic AV valve regurgitation	15 (13.5)	7 (14.3)	4 (8)	4 (33.3)	0.21

Categorical variables displayed as n (%). Numeric variables shown as mean ± SD (if normally distributed) or median [IQR] (non-normally distributed). $P < 0.05$ indicates statistical significance.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AP, atriopulmonary; AV, atrioventricular; eGFR, estimated glomerular filtration rate; MCV, mean corpuscular volume; TCPC, total cavopulmonary connection; TIBC, total iron-binding capacity; VE/VCO_2, minute ventilation/carbon dioxide production; VO_2, oxygen uptake.
[a]P value for comparison between TCPC and non-TCPC Fontan.

fibrillation (14, 18.4%). Patients with an AP Fontan or its modifications were more likely to have experienced an arrhythmia by the age of 35 years than those with a TCPC (76.1% vs. 33.3%, $P = 0.0001$). Ablation procedures had been carried out in 41 (35.7%) patients, with 12 (10.4%) patients having had 2 and 2 (1.7%) patients having had 3 procedures. Prior to the age of 35 years, 4 (3.5%) patients had been diagnosed with an atrial thrombus. Only two patients had a history of a thromboembolic event: one stroke and one pulmonary embolism. Protein-losing enteropathy had been diagnosed in 8 (7.0%) patients.

Outcomes from 35 years onwards

Overall, 113/115 (98.3%) patients were included in the survival analysis. The median follow-up period after the age of 35 was 5.0 (2.4–10.3) years. Results of Fontan investigations and complications at follow-up are shown in *Table 4*. Freedom from death or transplantation is shown in *Figure 1A*. Transplant-free survival at 40 years was 85% for AP vs. 92.6% for TCPC (log-rank $P = 0.16$, *Figure 1B*). At 45 years, survival was 69% for AP vs. 84.6% for TCPC. Overall, 19 (16.5%) patients died. The cause of death was ascertained in 16 (84.2%) patients: Heart failure was the commonest cause of death (10, 62.5%), with each of the following causing one patient death: hepatocellular carcinoma on a background of FALD, sepsis secondary to an implantable cardioverter defibrillator lead infection, pulmonary embolism, and malignancy not related to the cardiac condition. No patient in our cohort died suddenly. Overall, 15 (13.0%) patients were referred for heart transplantation, of whom 2 (13.3%) patients died on the transplant list and only 3 (20.0%) patients underwent a successful orthotopic heart transplant.

Atrial arrhythmia in the follow-up period occurred in 47 (40.9%) patients. On univariable logistic analysis, Fontan type was predictive of arrhythmias after the age of 35 years [OR 2.31 for non-TCPC, 95% confidence interval (CI): 1.08–5.07, $P = 0.03$]. At least 1 new ablation procedure was undertaken in 21 (18.3%) patients after the age of 35. New device (pacemaker) implantation occurred in 5 (4.3%) patients.

On univariable analysis for the combined endpoint of death or transplantation ($n = 22$), lower serum albumin level [hazard ratio (HR) 1.09 per unit decrease, 95% CI:1.04–1.15, $P = 0.0009$], prior heart failure admission (HR 4.28, 95% CI: 1.75–10.44, $P = 0.001$), prior atrial tachycardia or flutter (HR 3.02, 95% CI: 1.23–7.38, $P = 0.02$), and pulmonary vasodilator therapy at baseline (HR 8.59, 95% CI: 1.05–70.13, $P = 0.04$) were associated with death or heart transplantation. Age at first Fontan (HR 0.94, 95% CI: 0.89–1, $P = 0.06$) and a lower iron level (HR 1.08 per unit decrease, 95% CI: 0.98–1.19, $P = 0.12$) were not related to outcome. Right ventricular morphology was also not associated with the primary endpoint. On bivariable analysis, lower serum albumin and prior atrial tachycardia or flutter remained significant predictors of adverse outcome. When using univariable predictors in an additive fashion, a significantly poorer outcome was observed in patients with two or more risk factors (*Figure 1C* and *D*).

Discussion

An increasing number of Fontan patients are surviving to the fourth decade of life and beyond, despite significant morbidity and mortality from a young age.[5,9] Older patients with a Fontan-type circulation have a substantial mortality, with heart failure being the most common

Table 3 Complications prior to study inclusion in adults with a Fontan-type circulation

Complication	All, $n = 115$	AP, $n = 50$	TCPC, $n = 53$	Björk–Fontan and Kawashima procedure, $n = 12$	P value[a]
History of atrial arrhythmia	76 (66.1)	39 (78)	29 (54.7)	8 (66.7)	**0.03**
Atrial tachycardia/flutter	42 (36.5)	19 (38)	18 (34)	5 (41.7)	0.74
Atrial fibrillation	15 (13)	10 (20)	3 (5.7)	2 (16.7)	0.06
Catheter ablation for arrhythmia	41 (35.7)	23 (46)	14 (26.4)	4 (33.3)	0.09
Pacemaker implantation	41 (35.7)	15 (30)	24 (45.3)	2 (16.7)	0.07
Any re-intervention or re-operation	59 (51.3)	18 (36)	36 (67.9)	5 (41.7)	**0.002**
Fontan revision	11 (9.6)	6 (12)	0 (0)	5 (41.7)	**0.004**
Fontan conversion to TCPC	28 (24.3)	0 (0)	28 (52.8)	0 (0)	**<0.0001**
Fenestration closure	7 (6.1)	4 (8)	3 (5.7)	0 (0)	0.99
Thromboembolism/atrial thrombus	6 (5.2)	5 (10)	1 (1.9)	0 (0)	0.29
PLE	8 (7)	5 (10)	2 (3.8)	1 (8.3)	0.38
FALD	22 (19.3)	10 (20)	8 (15.4)	4 (33.3)	0.46
Previous admission for HF therapy	15 (13.2)	10 (20)	4 (7.7)	1 (8.3)	0.19

Categorical variables displayed as n (%). $P < 0.05$ indicates statistical significance (shown in bold font).
AP, atriopulmonary; FALD, Fontan-associated liver disease; HF, heart failure; PLE, protein-losing enteropathy; TCPC, total cavopulmonary connection.
[a]P value for comparison between TCPC and non-TCPC Fontan.

cause of death. Despite the high prevalence of arrhythmias in this age group, death directly related to arrhythmia was not observed in our cohort. Only a small fraction of Fontan patients with heart failure were referred for heart transplantation, and only three individuals were transplanted. Patients with two or more markers of advanced disease, including previous heart failure admissions, low albumin, atrial arrhythmia, or pulmonary arterial hypertension (PAH) therapy, had the highest risk of adverse events. Our results underscore the importance of close monitoring and individualized management strategies in a specialist service for adults with Fontan circulation.

Although there have been significant improvements in the survival of patients who have undergone a Fontan operation,[10] mortality is high after the age of 35 years, with ~1 in 10 patients dying within 5 years and 1 in 5 patients dying within 10 years. Patients with a Fontan-type circulation are only now reaching the fourth and fifth decades of life, and data on outcomes beyond this age are very limited. Moreover, most of the patients were operated in the early surgical experience with Fontan surgery and when Fontan surgery was itself evolving. Atriopulmonary Fontan procedures have now been abandoned due to the high long-term morbidity and mortality,[4,11] and the patients described in this study are the long-term survivors of this population, who are likely at the best end of the spectrum, both in terms of pre-Fontan anatomy (allowing late Fontan completion) and Fontan haemodynamics. Still, mortality and morbidity are high in this population, and the predictors of outcome identified can assist specialist services in their management.[12] It is likely that, as patients with more modern versions of the Fontan circulation (i.e. TCPC) who were operated on earlier reach this age, their outcomes may differ. However, patients with more complex forms of single-ventricle physiology, e.g. systemic right ventricle (who were a small minority in our population) or hypoplastic left heart syndrome, are benefitting from Fontan-type surgery, and these patients are entering adulthood with a high burden of morbidity and healthcare resource utilization.[13–15]

In our study, heart failure was the most prevalent cause of death.[5] The term Fontan failure is currently used to describe Fontan patients with a chronically low cardiac output state and systemic venous congestion, who typically develop multiorgan involvement. In our study population, one in eight patients had a previous admission for heart failure therapy. Furthermore, heart failure was the single commonest cause of death in Fontan patients beyond the age of 35, complementing the findings in younger Fontan cohorts.[6] Multiple clinical variables act as physiological drivers of a failing Fontan circulation: inefficiencies or obstructions within the Fontan circuit, diastolic (and less commonly systolic) systemic ventricular dysfunction, ventricular myocardial fibrosis, atrioventricular valve dysfunction, chronotropic incompetence, and neurohormonal activation can result in worsening systemic venous hypertension and a drop in cardiac output, fluid overload, cyanosis, and exercise intolerance.[16–18] This is compounded by insidious, extracardiac organ dysfunction, including FALD, renal, and pulmonary vascular disease. The assessment of adults with a Fontan-type circulation therefore requires regular, routine surveillance in specialist centres by clinicians with significant expertise in managing these patients. Close collaboration between specialties (e.g. in joint clinics and involvement in multidisciplinary team meetings) is required in cases of progressive extra-cardiac organ dysfunction, with early consideration of referral for transplantation assessment in patients with a failing Fontan circulation. Indeed, even though transplantation is advocated in patients with a failing Fontan, few patients in our cohort underwent heart transplantation. Multiple barriers to transplantation exist, including multiorgan involvement (particularly of the liver), high levels of anti-human leukocyte antigen (HLA) antibodies in patients who have undergone multiple previous surgeries, extensive aortopulmonary collateral arteries that carry a high risk of bleeding, or the difficulty in identifying the right timing for referral.

Previous atrial tachycardia or flutter was also a strong predictor of death or transplantation, though a history of arrhythmia did not identify patients at a higher risk of new arrhythmic events, suggesting that in this older Fontan population, most patients have a propensity for atrial arrhythmia. Organized arrhythmias are common in these patients and only later degenerate into atrial fibrillation.[4,19,20] These arrhythmias are more common in patients with an AP Fontan and large right atria and reflect long-standing severely raised pressures in the Fontan circulation.[20,21] This adverse haemodynamics status is also related with a higher risk of heart failure and thromboembolic events, which can be catastrophic in a Fontan patient. Most centres currently prefer establishing patients with an AP Fontan on full-dose thromboprophylaxis.[22]

Table 4 Results of Fontan investigations and complications at follow-up

Type of first Fontan procedure	All, $n = 115$	AP, $n = 50$	TCPC, $n = 53$	Björk–Fontan and Kawashima procedure, $n = 12$	P value[a]
Haemoglobin, g/L	147.3 ± 21.2	145.2 ± 18.5	146 ± 19.9	161 ± 32	0.92
MCV, fL	91.1 [88.8–96]	90.5 [88.8–97]	91.1 [89–95]	93 [87–96.5]	0.64
Urea, mmol/L	5.5 [4.1–7.6]	5.5 [4.3–8.1]	5.3 [3.9–6.9]	5.5 [4.7–6.6]	0.3
Creatinine, µmol/L	76 [61–94.5]	76 [62.5–99]	79.3 [61.8–88.4]	61.5 [58.8–74.3]	0.89
eGFR, mL/min/1.73 m^2	98.6 [78.3–121.3]	95 [74–108.2]	104.7 [85.1–132.6]	95.9 [91.2–101.8]	0.1
Bilirubin, µmol/L	19 [12.8–27]	19.5 [15–25.8]	17.6 [12–24]	20.5 [13.8–30.8]	0.64
ALP, IU/L	93.5 [76–138.2]	94 [74–144]	90 [75–118]	111 [87.8–180]	0.39
ALT, IU/L	28 [21.2–36]	25 [21.5–34]	29 [20–40]	29 [22.8–35.3]	0.33
Albumin, g/L	43 [38.5–46]	41.5 [37.8–45]	43 [39–47]	44 [43.3–46.5]	0.36
Serum iron, µmol/L	16.5 ± 7.4	14.4 ± 5.7	19.1 ± 8.7	15.8 ± 7.1	0.07
TIBC, µmol/L	68 [60–73]	70 [65–73]	65 [53–73.5]	69 [63.3–73.5]	0.15
Peak VO_2, mL/kg/min	18.8 ± 6.6	19.4 ± 6.2	16.7 ± 5.9	21.4 ± 8.4	0.21
VE/VCO_2 slope	35 [30.9–47.8]	33.5 [30.8–35.5]	36 [30.5–48.3]	45 [40.3–52]	0.82
Peak heart rate, b.p.m.	128.7 ± 36.9	121.8 ± 42.7	125.9 ± 32.5	144.3 ± 34.2	0.9
Systemic ventricular function					0.8
Normal	64 (55.7)	27 (54)	29 (54.7)	8 (66.7)	
Mild	27 (23.5)	12 (24)	12 (22.6)	3 (25)	
Moderate	5 (4.3)	2 (4)	3 (5.7)	0 (0)	
Severe	1 (0.9)	0 (0)	1 (1.9)	0 (0)	
At least moderate systemic AV valve regurgitation	22 (22.9)	9 (22.5)	9 (20)	4 (36.4)	0.69
New episode of atrial arrhythmia	47 (40.9)	25 (50)	16 (30.2)	6 (50)	0.05
New episode of Thromboembolism/atrial thrombus	7 (6.5)	4 (8.7)	3 (6.1)	0 (0)	0.99
New diagnosis of PLE	7 (6.5)	6 (13)	0 (0)	1 (8.3)	**0.03**
New diagnosis of FALD	40 (37.4)	18 (39.1)	17 (34.7)	5 (41.7)	0.74

Categorical variables displayed as n (%). Numeric variables shown as mean ± SD (if normally distributed) or median [IQR] (non-normally distributed). $P < 0.05$ indicates statistical significance (shown in bold font).

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AP, atriopulmonary; AV, atrioventricular; eGFR, estimated glomerular filtration rate; FALD, Fontan-associated liver disease; MCV, mean corpuscular volume; PLE, protein-losing enteropathy; TCPC, total cavopulmonary connection; TIBC, total iron-binding capacity; VE/VCO_2, minute ventilation/carbon dioxide production; VO_2, oxygen uptake.

[a]P value for comparison between TCPC and non-TCPC Fontan.

Recurrent atrial tachycardia or atrial fibrillation has been an indication for Fontan conversion,[23] although this practice is rarely adopted nowadays because of the significant peri-operative risk. Catheter ablation is increasingly used in this population, but requires high levels of expertise, and often needs to be repeated due to recurrence.[24] In our population, even though arrhythmic events were not uncommon, they were never a direct cause of death but were more likely to reflect the underlying anatomy and haemodynamics.

A raised pulmonary vascular resistance is one of the many ways in which the Fontan circulation may fail and has been a treatment target for patients with a Fontan circulation. Unfortunately, results from trials have been mixed, and consensus is lacking regarding the role of PAH therapies in the Fontan population.[25–30] Even though studies have mainly focused on stable patients, most experts use PAH therapies in this context in patients with advanced disease and evidence of Fontan failure.[8] In our paper, the association between PAH therapies and outcome was likely to reflect the use of these therapies in patients with advanced disease where other therapies have failed, as well as the impact of pulmonary vascular disease on the Fontan circulation, which relies on a low pulmonary artery pressure to sustain transpulmonary flow and cardiac output.

Study limitations

Our study, while offering key insights into Fontan patients aged over 35 years, has limitations, including its retrospective nature. The patients included in the study were, by definition, survivors reflecting the experience of specialist centres. Despite a sizable cohort, smaller subgroups, especially those with Björk–Fontan or Kawashima procedures, limit the ability to draw conclusions about these patients. Despite a significant event rate, the small sample size did not allow full multivariable modelling and adequately powered subgroup survival analysis, e.g. by type of Fontan or ventricular morphology. Indeed, larger registries have explored the differences in prognosis of various types of Fontan circulation.[5] Additionally, even with bivariable analysis, residual confounding due to unavailable variables such as genetic factors, imaging data, and neurohormonal markers is a possibility. Finally, even though using the four univariable variables in an additive fashion identified a group of patients at very high risk of adverse outcomes, full multivariable analysis could not be performed due to the limited number of events. Moreover, validation of our model is required before recommending its broad clinical utilization. Despite these limitations, our study provides valuable data for future studies aimed at improving the outcomes of these patients.

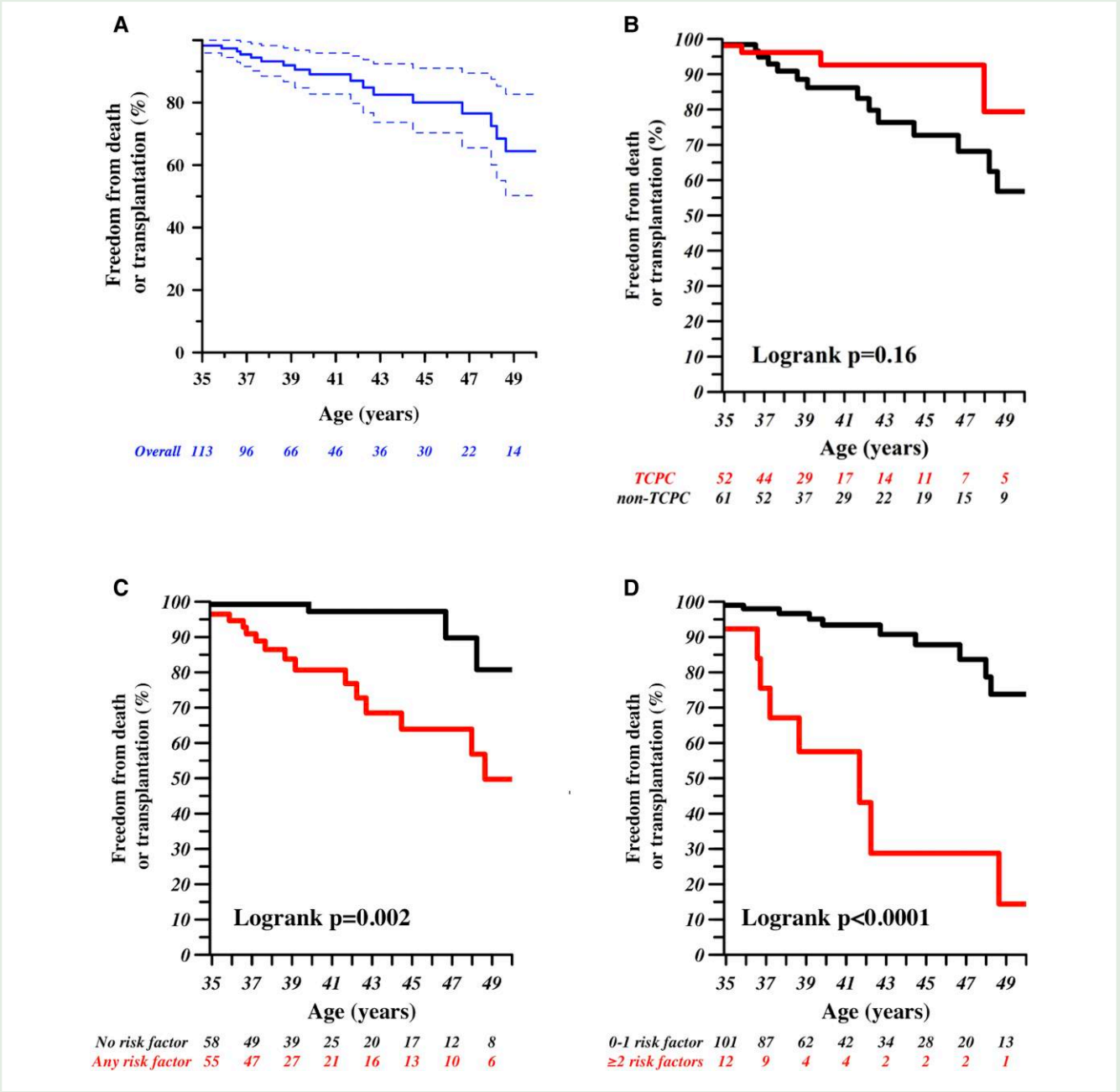

Figure 1 Freedom from death or transplantation in older adults with a Fontan-type circulation in (*A*) the overall cohort and for (*B*) patients with a total cavopulmonary connection at age 35 years vs. other forms of repair. In (*C*) and (*D*), the impact of the presence of at least 1 and ≥2 risk factors on transplant-free survival is shown. TCPC, total cavopulmonary connection.

Conclusions

In conclusion, our study highlights the significant morbidity and mortality experienced by older adult patients with Fontan circulation. It emphasizes the importance of specialized, lifelong follow-up of these patients and provides valuable insights into potential risk factors for poor outcomes. As the management of patients with univentricular heart disease evolves, with earlier surgical intervention and optimal paediatric and adult care, more patients will be reaching the fourth decade of life and beyond and require accurate risk stratification, close monitoring, and early consideration for transplantation.

Author contributions

A.C., E.G., K.D., and I.R. conceptualized the study. E.G., G.C., P.M., P.F., and A.C. performed data curation. A.C. and K.D. performed formal analysis and data visualization. A.C., K.D., and I.R. wrote the original draft, which was critically reviewed and edited by all remaining authors. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Data availability

To minimize the possibility of unintentionally sharing information that can be used to re-identify private information, in line with the conditions of the ethical approval, patient-level data are not available for use outside of this study.

References

1. Khairy P, Poirier N, Mercier L-A. Univentricular heart. *Circulation* 2007;**115**:800–812.
2. Marelli AJ, Ionescu-Ittu R, Mackie AS, Guo L, Dendukuri N, Kaouache M. Lifetime prevalence of congenital heart disease in the general population from 2000 to 2010. *Circulation* 2014;**130**:749–756.
3. Greutmann M, Tobler D, Kovacs AH, Greutmann-Yantiri M, Haile SR, Held L, *et al.* Increasing mortality burden among adults with complex congenital heart disease. *Congenit Heart Dis* 2015;**10**:117–127.
4. Pundi KN, Johnson JN, Dearani JA, Pundi KN, Li Z, Hinck CA, *et al.* 40-year follow-up after the Fontan operation: long-term outcomes of 1,052 patients. *J Am Coll Cardiol* 2015;**66**:1700–1710.
5. Dennis M, Zannino D, du Plessis K, Bullock A, Disney PJS, Radford DJ, *et al.* Clinical outcomes in adolescents and adults after the Fontan procedure. *J Am Coll Cardiol* 2018;**71**:1009–1017.
6. Poh CL, d'Udekem Y. Life after surviving Fontan surgery: a meta-analysis of the incidence and predictors of late death. *Heart Lung Circ* 2018;**27**:552–559.
7. Schwartz I, McCracken CE, Petit CJ, Sachdeva R. Late outcomes after the Fontan procedure in patients with single ventricle: a meta-analysis. *Heart* 2018;**104**:1508–1514.
8. Constantine A, Dimopoulos K, Jenkins P, Tulloh RMR, Condliffe R, Jansen K, *et al.* Use of pulmonary arterial hypertension therapies in patients with a Fontan circulation: current practice across the United Kingdom. *J Am Heart Assoc* 2022;**11**:e023035.
9. Downing KF, Nembhard WN, Rose CE, Andrews JG, Goudie A, Klewer SE, *et al.* Survival from birth until young adulthood among individuals with congenital heart defects: CH STRONG. *Circulation* 2023;**148**:575–588.
10. Khairy P, Fernandes SM, Mayer JE Jr, Triedman JK, Walsh EP, Lock JE, *et al.* Long-term survival, modes of death, and predictors of mortality in patients with Fontan surgery. *Circulation* 2008;**117**:85–92.
11. Plappert L, Edwards S, Senatore A, De Martini A. The epidemiology of persons living with Fontan in 2020 and projections for 2030: development of an epidemiology model providing multinational estimates. *Adv Ther* 2022;**39**:1004–1015.
12. Egbe AC, Miranda WR, Devara J, Shaik L, Iftikhar M, Goda Sakr A, *et al.* Recurrent sustained atrial arrhythmias and thromboembolism in Fontan patients with total cavopulmonary connection. *Int J Cardiol Heart Vasc* 2021;**33**:100754.
13. Erikssen G, Liestøl K, Aboulhosn J, Wik G, Holmstrøm H, Døhlen G, *et al.* Preoperative versus postoperative survival in patients with univentricular heart: a nationwide, retrospective study of patients born in 1990–2015. *BMJ Open* 2023;**13**:e069531.
14. Well A, Dawson C, Johnson G, Patt H, Fraser CD, Mery CM, *et al.* Hospitalisations of children and adults with Hypoplastic Left Heart Syndrome in Texas from 2009 to 2019. *Cardiol Young* 2022;**33**:1819–1827.
15. Schilling C, Dalziel K, Nunn R, Du Plessis K, Shi WY, Celermajer D, *et al.* The Fontan epidemic: population projections from the Australia and new Zealand Fontan registry. *Int J Cardiol* 2016;**219**:14–19.
16. Penny DJ, Rigby ML, Redington AN. Abnormal patterns of intraventricular flow and diastolic filling after the Fontan operation: evidence for incoordinate ventricular wall motion. *BR Heart J* 1991;**66**:375–378.
17. Rathod RH, Prakash A, Powell AJ, Geva T. Myocardial fibrosis identified by cardiac magnetic resonance late gadolinium enhancement is associated with adverse ventricular mechanics and ventricular tachycardia late after Fontan operation. *J Am Coll Cardiol* 2010;**55**:1721–1728.
18. Cheung YF, Penny DJ, Redington AN. Serial assessment of left ventricular diastolic function after Fontan procedure. *Heart* 2000;**83**:420–424.
19. Weipert J, Noebauer C, Schreiber C, Kostolny M, Zrenner B, Wacker A, *et al.* Occurrence and management of atrial arrhythmia after long-term Fontan circulation. *J Thorac Cardiovasc Surg* 2004;**127**:457–464.
20. Giannakoulas G, Dimopoulos K, Yuksel S, Inuzuka R, Pijuan-Domenech A, Hussain W, *et al.* Atrial tachyarrhythmias late after Fontan operation are related to increase in mortality and hospitalization. *Int J Cardiol* 2012;**157**:221–226.
21. Takeuchi D, Uto K, Inai K, Nagashima Y, Shinkawa T. Prominent atrial fibrosis and its correlation with atrial tachyarrhythmia and dilated atrium long after classic Fontan surgery. *J Cardiol* 2022;**79**:671–677.
22. Van den Eynde J, Possner M, Alahdab F, Veldtman G, Goldstein BH, Rathod RH, *et al.* Thromboprophylaxis in patients with Fontan circulation. *J Am Coll Cardiol* 2023;**81**:374–389.
23. Mavroudis C, Deal BJ, Backer CL. The beneficial effects of total cavopulmonary conversion and arrhythmia surgery for the failed Fontan. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu* 2002;**5**:12–24.
24. Kamp A, Moore JP, Khairy P. How to perform catheter ablation of atrial tachyarrhythmia after the Fontan operation. *Heart Rhythm* 2023;**20**:1048–1054.
25. Goldberg DJ, French B, McBride MG, Marino BS, Mirarchi N, Hanna BD, *et al.* Impact of oral sildenafil on exercise performance in children and young adults after the Fontan operation: a randomized, double-blind, placebo-controlled, crossover trial. *Circulation* 2011;**123**:1185–1193.
26. Goldberg DJ, Zak V, Goldstein BH, Schumacher KR, Rhodes J, Penny DJ, *et al.* Results of the Fontan Udenafil Exercise Longitudinal (FUEL) trial. *Circulation* 2020;**141**:641–651.
27. Hebert A, Mikkelsen UR, Thilen U, Idorn L, Jensen AS, Nagy E, *et al.* Bosentan improves exercise capacity in adolescents and adults after Fontan operation: the TEMPO (Treatment With Endothelin Receptor Antagonist in Fontan Patients, a Randomized, Placebo-Controlled. Double-Blind Study Measuring Peak Oxygen Consumption) study. *Circulation* 2014;**130**:2021–2030.
28. Giardini A, Balducci A, Specchia S, Gargiulo G, Bonvicini M, Picchio FM. *et al.* Effect of sildenafil on haemodynamic response to exercise and exercise capacity in Fontan patients. *Eur Heart J* 2008;**29**:1681–1687.
29. Rhodes J, Ubeda-Tikkanen A, Clair M, Fernandes SM, Graham DA, Milliren CE, *et al.* Effect of inhaled iloprost on the exercise function of Fontan patients: a demonstration of concept. *Int J Cardiol* 2013;**168**:2435–2440.
30. Cedars AM, Saef J, Peterson LR, Coggan AR, Novak EL, Kemp D, *et al.* Effect of ambrisentan on exercise capacity in adult patients after the Fontan procedure. *Am J Cardiol* 2016;**117**:1524–1532.