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Outcomes after initial heart failure consultation in Fontan patients

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Abstract

Background: Patients with Fontan failure are high-risk candidates for heart transplantation and other advanced therapies. Understanding the outcomes following initial heart failure consultation can help define appropriate timing of referral for advanced heart failure care. *Methods:* This is a survey study of heart failure providers seeing any Fontan patient for initial heart failure care. Part 1 of the survey captured data on clinical characteristics at the time of heart failure consultation, and Part 2, completed 30 days later, captured outcomes (death, transplant evaluation outcome, and other interventions). Patients were classified as "too late" (death or declined for transplant due to being too sick) and/or "care escalation" (ventricular assist device implanted, inotrope initiated, and/or listed for transplant), within 30 days. "Late referral" was defined as those referred too late and/or had care escalation. *Results:* Between 7/2020 and 7/2022, 77 Fontan patients (52% inpatient) had an initial heart failure consultation. Ten per cent were referred too late (6 were too sick for heart transplantation with one subsequent death, and two others died without heart transplantation evaluation, within 30 days), and 36% had care escalation (21 listed ± 5 ventricular assist device implanted ± 6 inotrope initiated). Overall, 42% were late referrals. Heart failure consultation < 1 year after Fontan surgery was strongly associated with late referral (OR 6.2, 95% CI 1.8–21.5, p=0.004). *Conclusions:* Over 40% of Fontan patients seen for an initial heart failure consultation were late referrals, with 10% dying or being declined for transplant within a month of consultation. Earlier referral, particularly for those with heart failure soon after Fontan surgery, should be encouraged.

Individuals with a Fontan palliation will likely require advanced heart failure care during their lifetime, with many needing heart, and some heart-liver, transplantation. Survival after transplantation for Fontan patients has improved significantly over the years and is currently comparable to transplantation for others with CHD.[1,2] However, post-transplant mortality is increased for those with compromised end-organ function at the time of transplant.[3] Given limited donor availability and often long transplant wait times, especially when compared to patients with cardiomyopathy,[4] more Fontan patients are requiring advanced cardiac therapies, such as continuous intravenous inotropes or ventricular assist device support, while on the wait list.[5,6]

Guidelines on indications for referral for formal heart failure consultation in Fontan patients are limited and only recently emerging.[7] As a result of this, as well as a paucity of reliable data on the topic, there is significant practice heterogeneity both between and among heart failure providers and non-heart failure providers with respect to the indications for and timing of referral.[8] Excessive delays in referral can result in irreversible end-organ damage or clinical instability, with a resultant increase in the risks of both ventricular assist device implant and transplant. In serving as stewards for a limited donor pool, and to minimise negative regulatory performance reviews, transplant programmes may decide not to list individuals who are too sick or too high risk for transplant. Defining the status of Fontan patients referred for advanced heart failure consultation, and outcomes after referral may help in the development of

recommendations for when Fontan patients should be referred for formal heart failure consultation.

The aims of this study were to (1) characterise Fontan patients referred for advanced heart failure care; (2) describe outcomes after initial consultation for advanced heart failure care; and 3) identify risk factors for late referral. The overall goal is to improve timely referral for advanced heart failure care, which in turn may lead to better ventricular assist device and transplant outcomes in Fontan patients.

Methods

Centres involved in the Advanced Cardiac Therapies Improving Outcomes Network registry were invited to participate in a web-based survey study. Advanced Cardiac Therapies Improving Outcomes Network is an international learning network of paediatric heart failure and heart transplantation teams from over 50 centers.[9] Each Advanced Cardiac Therapies Improving Outcomes Network centre obtains approval to participate in the registry from their respective Institutional Review Boards, with many sites utilising the central Institutional Review Board at Cincinnati Children's Hospital Medical Center (Cincinnati, OH). Informed consent and assent were waived by the central Institutional Review Board for the retrospective arm of the Advanced Cardiac Therapies Improving Outcomes Network registry. Patients in the registry are assigned unique Advanced Cardiac Therapies Improving Outcomes Network identification numbers. This survey study was conducted with approval from the leadership committee of Advanced Cardiac Therapies Improving Outcomes Network.

A link to a web-based survey (based in RedCap) was provided to heart failure and transplant team members at participating centres. The survey had two parts, as detailed in Supplemental Table S1. Providers completed the first part of the survey within 5 days of consultation on any patient with Fontan physiology who was newly being seen for heart failure and/or transplant evaluation. Fontan patients of any age, either inpatient or outpatient, were included; patients who had not been discharged from the hospital after Fontan surgery were excluded. The first part of the survey captured data on clinical characteristics of Fontan patients seen for an initial heart failure consultation. The second part of the survey was sent electronically to the provider 30 days after the first survey was completed and captured data on patient outcomes (such as interventions, transplant evaluation outcomes, and death) following the initial consultation. At the time of completing the first survey, the outcome of the heart failure consultation would not have been known. Survey data were de-identified, with the two parts of the survey linked by the Advanced Cardiac Therapies Improving Outcomes Network registry identification number.

The survey data included qualitative assessment of systemic ventricular function and atrioventricular valve regurgitation from last echocardiogram, magnetic resonance imaging, or cardiac catheterisation prior to heart failure consultation, as well as hemodynamic data from cardiac catheterisation within two years of heart failure consultation. Free text was used to capture specific reasons for referral if provided. Patients referred for consultation by a provider within the same centre as the heart failure team were defined as internal referrals, whereas an external referral was defined as a referral by a provider not within the same centre as the heart failure team. Survey questions capturing other clinical characteristics at time of heart failure consultation are shown in Supplemental Figure S1.

Patients were classified as having been referred TOO LATE if, within a month (30±5 days) of initial consultation, they had died or were declined for transplant listing due to being too sick. Patients were classified as receiving CARE ESCALATION if, within a month of initial consultation, they underwent ventricular assist device implant, were listed for heart (or heart-liver) transplantation, and/or had new continuous inotrope therapy initiated. Patients who were already on inotropes at the time of initial heart failure consultation were not included in care escalation. Patients could be classified as both too late and care escalation (i.e. someone who was started on inotropes and also determined to be too sick for transplant). The primary outcome of LATE REFERRAL was the presence of TOO LATE and/or CARE ESCALATION (Fig. 1/ Supplemental Table S2).

Clinical characteristics captured on the first survey, at the time of initial consultation, were compared between the various classifications (too late versus not too late, care escalation versus without care escalation, and late referral versus not late referral), using Wilcoxon rank sum and chi-squared analyses. Descriptive data are presented as median (25^{th}, 75^{th} percentiles) or frequency (%). Univariate logistic regression was used to identify risk factors associated with being too late, having care escalation, and being a late referral. The overall sample size and event rates did not allow for multi-variable analysis.

Results

From July 2020 to July 2022, 13 Advanced Cardiac Therapies Improving Outcomes Network centres participated and contributed data on 77 Fontan patients seen for an initial heart failure consultation. Exact dates of both referral and consultation were available for 56 (73%) patients. For these patients, the median time between referral date and consultation date was 5 (0, 30) days. All inpatient consultations were seen within 30 days of referral, at a median of 1 (0, 3) days.

Table 1 shows the characteristics at time of initial consultation. Forty (52%) patients were inpatient consults and 13 (33%) of inpatients were already on inotropic support at time of consult. Twenty-four (31%) patients had protein-losing enteropathy, of which 6 were receiving chronic albumin infusions. Twenty-six (34%) patients had at least moderate systolic dysfunction, whereas 28 (36%) had both normal systolic function and no or mild atrioventricular valve regurgitation. Forty-one (54%) were internal referrals. Median time between Fontan surgery and initial heart failure consultation was 9 (2, 12) years, but 16 (21%) patients had their initial heart failure consultation within 1 year of Fontan surgery.

Specific reasons for heart failure referral were provided for 73 patients and are shown in Figure 2. Of note, some patients had more than one reason listed, and clinical characteristics were not necessarily reflected in the primary reason provided for referral—for example, ventricular systolic dysfunction was listed as the reason for referral in 13 patients but 26 patients had moderate to severe systolic dysfunction. The most common reason provided for heart failure referral was lymphatic disease in 24% (protein-losing enteropathy = 16, plastic bronchitis = 3), followed by ventricular systolic dysfunction in 18%. Heart failure symptomatology was the stated reason for referral in 13% and concern related to liver disease in 7%. Other reasons for referral included information on transplantation (n = 3), not a surgical candidate (n = 1), and severe tricuspid regurgitation (n = 1).

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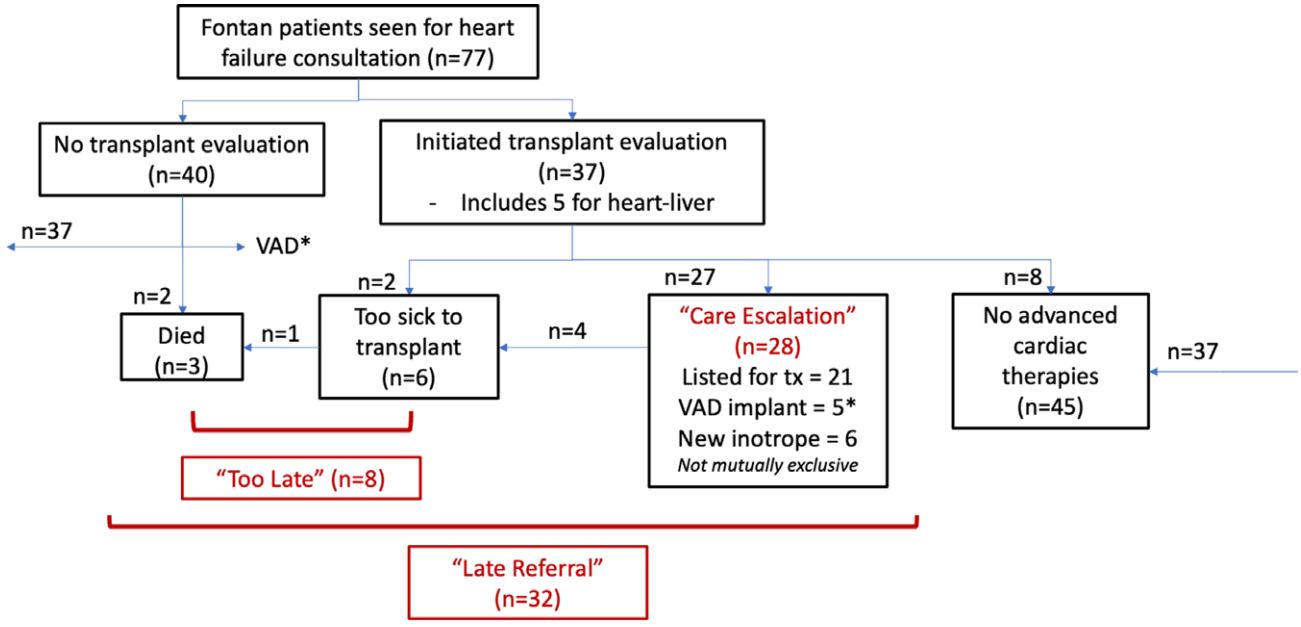

Figure 1. Outcomes after heart failure consultation.

Within a month of initial heart failure consultation, 28 (36%) patients had care escalation. This included 21 who were listed for transplant, 5 who underwent ventricular assist device implant, and 6 with new inotrope initiated. These three interventions were not mutually exclusive, as shown in Supplemental Table S2, and only one patient had inotrope initiation as the sole reason for care escalation. Of the entire study cohort of 77 patients, eight (10%) were referred too late (four of these patients also had care escalation). Of the eight referred too late, six were determined to be too sick for transplant, of whom one died within the month, and two others died within a month of heart failure consultation, without being evaluated for transplant, for a total of three deaths (4%) in the study cohort. Overall, 32 (42%) patients were considered late referrals (Fig. 1, Supplemental Table S2).

Characteristics associated with being a late referral, requiring care escalation, or being referred too late are shown in Table 2. Heart failure referral within a year of Fontan surgery was strongly associated with being a late referral, with an odds ratio of 6.2 (95% CI 1.8–21.5, $p = 0.004$). This association was significant both with being referred too late (death or declined for transplant within a month) and with care escalation, with odds ratios of 4.8 (95% CI 1.0–21.7, $p = 0.044$) and 4.0 (95% CI 1.3–12.6, $p = 0.019$), respectively. Other characteristics associated with late referral, specifically due to increased risk for care escalation, included being inpatient at time of heart failure consult, having at least moderate atrioventricular valve regurgitation, being on inotropes, and having chronic or recurrent pleural effusions (Table 2).

Given the strong association between late referral and referral within a year of their initial Fontan surgery, the clinical characteristics of the 16 patients who were referred within a year of initial Fontan surgery were compared to those referred more than a year after Fontan surgery (Supplemental Table S3). Patients referred for heart failure consultation within a year of Fontan surgery were, as expected, younger, with a median age of 4.0 (3.8, 5.3) years. They were also more likely to be inpatient (75%) at the time of heart failure consultation. By study eligibility criteria, only patients who had been discharged from their initial Fontan surgery were included in the study, so these were presumed re-admissions within a year of Fontan surgery. There were significantly fewer internal referrals, and consequently more external referrals, among patients referred within a year of Fontan surgery than those referred greater than a year after Fontan surgery (75% external referrals versus 38%, $p = 0.009$). Of the 16 patients referred within a year of Fontan surgery, four (25%) were evaluated for transplant and found to be too sick for transplant listing, compared to four (7%) of 61 patients referred greater than a year from Fontan surgery ($p = 0.031$). Additionally, four had ventricular assist device implanted, four were listed for transplant, and an additional two had inotropes initiated, within 1 month of their heart failure consultation.

Not all heart failure consultations resulted in a formal transplant evaluation or listing within 30 days. Specifically, 40 (52%) patients did not undergo a formal transplant evaluation, and overall, there were 45 (58%) patients who were alive without advanced cardiac therapies within 30 days of consultation. Of these 45, eight patients (18%) were sent back to their primary cardiologist with no future visits scheduled with the heart failure team, nine (20%) had care assumed primarily by the heart failure team, and 19 (42%) were seen with a recommendation to continue joint management with both the primary cardiologist and heart failure team (nine patients did not have follow-up care plan specified).

Discussion

The outcomes of the Fontan operation have significantly improved over time, with estimated survival up to 90% at 30 years.[2,10,11] Despite improved survival, Fontan physiology is still inherently abnormal, with chronically elevated systemic venous pressures and passive pulmonary blood flow limiting the ability to augment

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Table 1. Patient characteristics at time of heart failure/transplant consultation (n = 77)

	All (n = 77)	Late referral (n = 32)	Not late referral (n = 45)	p-value
Age at consult (years)	13.5 (7, 15.5)	10 (5, 15)	14 (10, 17)	**0.019**
Time from Fontan (years)	9 (2, 12)	4 (1, 10)	11 (5, 14)	**<0.001**
≤ 1 year from Fontan	16 (21)	12 (38)	4 (9)	**0.002**
Weight (kg)	44 (20, 59)	24 (16, 60)	48 (32, 58)	0.079
Height (cm)	143 (110, 163)	116 (97, 158)	155 (126, 165)	**0.019**
Male	51 (66)	23 (72)	28 (62)	0.377
Inpatient	40 (52)	22 (69)	18 (40)	**0.013**
Internal referral	41 (54)	16 (50)	25 (56)	0.735
≥ Moderate systolic dysfunction*	26 (34)	15 (47)	11 (24)	**0.040**
≥ Moderate AVVR*	25 (33)	15 (47)	10 (23)	**0.032**
On inotropes	15 (20)	9 (28)	6 (13)	0.106
Exercise intolerance	50 (67)	21 (70)	29 (64)	0.617
NYHA Class 3-4	24 (31)	11 (34)	13 (29)	0.609
Pacemaker/ICD	17 (22)	5 (16)	12 (27)	0.250
Chronic/recurrent ascites	17 (22)	7 (22)	10 (22)	0.971
Chronic/recurrent pleural effusions	13 (17)	9 (28)	4 (9)	**0.026**
Protein-losing enteropathy	24 (31)	8 (25)	16 (36)	0.324
Plastic bronchitis	4 (5)	1 (3)	3 (7)	0.529
Liver fibrosis†	27 (36)	8 (26)	19 (43)	0.123
Liver dysfunction†	6 (8)	1 (3)	5 (11)	0.210
Lab data				
Total bilirubin (mg/dL)	0.9 (0.6, 1.3)	1.0 (0.7, 1.6)	0.8 (0.5, 1.3)	0.149
Creatinine (mg/dL)	0.56 (0.45, 0.80)	0.53 (0.41, 0.80)	0.58 (0.45, 0.85)	0.490
Cystatin C (mg/L)	0.94 (0.79, 1.27)	0.87 (0.74, 1.40)	1.04 (0.80, 1.20)	0.691
BUN (mg/dL)	14 (10, 18)	14 (11, 18)	13 (10, 18)	0.504
Cath data (last 2 years)				
Fontan pressure (mmHg)	16 (14, 19)	18 (14, 22)	15 (14, 17)	0.043
End-diastolic pressure (mmHg)	10 (8, 13)	12 (8, 15)	10 (9, 12)	0.924
Cardiac index (L/min/m^2)	2.9 (2.5, 3.5)	3.0 (2.7, 3.7)	2.8 (2.1, 3.1)	0.074
Systemic O2 saturation (%)	90 (85, 93)	86 (81, 91)	91 (87, 94)	**0.019**
In the past year . . .				
Diuretic added	29 (39)	14 (47)	15 (33)	0.245
Hospitalised‡	15 (20)	9 (29)	6 (13)	0.091
Arrhythmias§	19 (25)	11 (34)	8 (18)	0.107

AVVR = atrioventricular valve regurgitation; BUN = blood urea nitrogen; ICD = implantable cardioverter defibrillator; NYHA = New York Heart Association.
Data are presented as N (%) or median (25th, 75th percentiles).
*Systolic function and atrioventricular valve regurgitation from echo (n = 70), MRI (n = 2) or cath (n = 5).
† Liver fibrosis as described on any imaging study; synthetic liver dysfunction includes elevated international normalised ratio in the absence of anticoagulation with warfarin, abnormally low platelets, abnormally low pre-albumin, and other markers.
‡ Hospitalisation for ascites, pleural effusions, peripheral oedema, or fluid overload.
§ Any new arrhythmia; specific arrhythmia diagnosis not assessed in survey.

cardiac output.[12] Abnormal physiology affects all organ systems, resulting in a myriad of morbidities, and culminating in a constellation of symptoms and signs increasingly being recognised as Fontan circulatory failure.[13] One of the difficulties in managing Fontan circulatory failure is knowing when to refer for heart failure consultation. Given the growing Fontan population over time and subsequent increase in number of Fontan patients being referred for advanced heart failure therapies, improving the assessment and management of Fontan patients is imperative. This web-based survey study was conducted as part of a quality improvement

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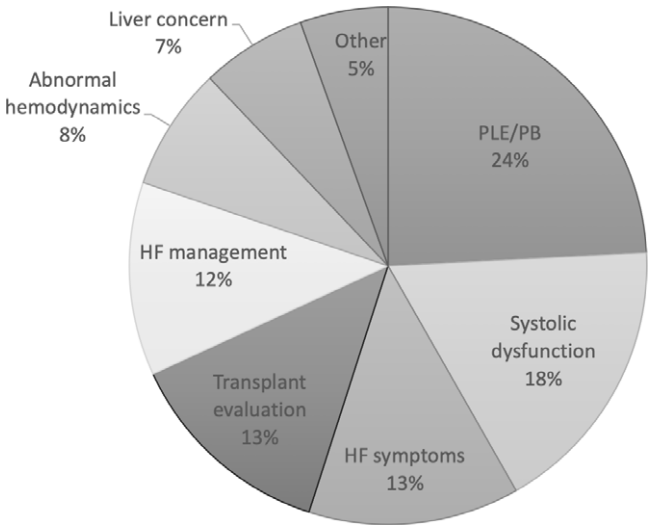

Figure 2. Reasons for heart failure referral (n = 83 reasons for 73 patients).

initiative undertaken by Advanced Cardiac Therapies Improving Outcomes Network, one of the largest collaborative learning networks for improving outcomes for paediatric patients with heart failure, to better understand outcomes following initial Fontan heart failure referral.

In the present study, we found that within a month of initial consultation, one out of ten Fontan patients died or were declined for transplant listing because they were already too sick. We considered this outcome as a referral that was *too late* because these patients did not have a chance to benefit from advanced cardiac therapies, as they were already deemed too ill for ventricular assist device support or transplant listing by the time of their evaluation. We are not able to determine from this study whether earlier referral would have changed the outcome for this 10% of patients—it is possible that for this subset of patients, even an earlier heart failure referral would not have changed the outcome. However, with the continued advancements in therapies such as with ventricular assist device support for Fontan patients, it would be quite a tragedy if these patients, unfortunately, missed their window for advanced cardiac therapies consideration before becoming too sick for ventricular assist device or heart transplant candidacy.

Beyond the 10% who were referred too late, one in three Fontan patients had significant care escalation—inotrope initiation, transplant listing, or ventricular assist device implant—within a month of their first heart failure consultation. Having to meet and get to know a new medical team, process the implications of living with a transplanted heart or ventricular assist device, and undergo major surgery, all within a short few weeks may contribute to the stress, anxiety, and medical trauma, often experienced by patients and families. From the heart transplant team's perspective, post-transplantation care involves a life-long partnership with patients and families. Having more than a few weeks before care escalation to get to know a patient and family helps in developing that partnership. Perhaps even more importantly, the rapidity of care escalation may lead to missed opportunities for medical optimisation and addressing modifiable risk factors prior to needing advanced therapies.

One likely contributor to late referral is the lack of classic heart failure signs and symptoms in Fontan circulatory failure. While severe systolic dysfunction, uncontrolled lymphatic disease, and significant heart failure symptoms may be obvious triggers for referral, other non-specific cardiac and non-cardiac signs may also indicate a failing Fontan circulation. Of the Fontan patients in our study, less than a third were classified as New York Heart Association Class 3–4, and over a third had normal systolic function with no significant atrioventricular valve regurgitation. Lab markers also did not indicate significant end-organ dysfunction and hemodynamic data were not generally out of anticipated range for Fontan patients.[14–16] The lack of significant end-organ dysfunction may be that Fontan patients present more often with chronic and progressive decline, rather than in acute cardiogenic shock. The lack of classic signs and symptoms of heart failure in Fontan patients, and the difficulty in identifying factors suggestive of impending poor outcome, are consistent with findings from other studies. Poh et al. described Fontan patients in the Australia and New Zealand Fontan Registry who died beyond 1 year after Fontan completion.[17] Of the 105 patients who died in the study, 32% were described as asymptomatic or clinically stable at their last clinical encounter within a year before death, 63% were classified as New York Heart Association Class 1 or 2, and only 43% had systolic dysfunction. Such findings highlight how the unique and subtle presentations of Fontan circulatory failure may delay timing of appropriate referral.

Even in patient populations where the signs and symptoms of heart failure are better defined and recognised, such as in adult general cardiology care, there is a lack of robust evidence to guide the *timing* of referral. The American Heart Association published a scientific statement in 2021 titled "Guidance for Timely and Appropriate Referral of Patients With Advanced Heart Failure."[18] The statement highlights factors known to be associated with worse prognosis to help identify adult patients with advanced heart failure yet acknowledges that "there is an art to the timing of referral for consideration of advanced therapies." The authors of the American Heart Association statement describe a "golden window" for referral when a patient approaches a level of illness that would warrant consideration of advanced therapies but has not yet developed progressive or irreversible end-organ damage. While there certainly will be a component of clinician expertise in identifying that golden window, having more robust data and evidence on outcomes after heart failure referrals, with more studies such as ours, can only help improve our ability to find that right window.

To help improve timeliness of referral, we examined factors associated with risks for late referral. Some of the risk factors for late referral are those known to be associated with adverse events, such as ventricular systolic dysfunction, atrioventricular valve regurgitation, and chronic pleural effusions.[19,20] Interestingly, the strongest association for late referral was being within a year of Fontan surgery. Patients referred within a year of Fontan surgery had a six-fold increased risk of dying, being declined for transplant, or requiring significant care escalation, within a month of initial heart failure consultation. There were insufficient data from our survey to better understand why this was a high-risk group, but many of these patients may have been high-risk surgical Fontan candidates to begin with, with factors such as elevated pulmonary vascular resistance, high aorto-pulmonary collateral burden, ventricular dysfunction, or atrioventricular valve regurgitation in their pre-Fontan stage. Earlier studies have demonstrated that waitlist mortality is significantly higher for patients listed for transplant within 6 months of Fontan surgery.[21,22] Our study demonstrates that prior to even making it onto the waitlist, heart failure referrals for patients within a year of Fontan surgery

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Table 2. Associations of clinical characteristic at time of initial heart failure consultation with outcomes.

	Too late OR (95% CI) p-value	Care escalation OR (95% CI) p-value	Late referral OR (95% CI) p-value
Age at consult (years)	0.97 (0.86–1.1) 0.551	**0.89 (0.82–0.97) 0.009**	**0.90 (0.83–0.98) 0.012**
Time from Fontan (years)	0.91 (0.80–1.05) 0.195	**0.86 (0.78–0.95) 0.002**	**0.85 (0.78–0.94) 0.001**
≤ 1 year from Fontan	**4.75 (1.04–21.70) 0.044**	**3.98 (1.26–12.60) 0.019**	**6.15 (1.76–21.50) 0.004**
Male	0.26 (0.06–1.20) 0.085	1.9 (0.68–5.32) 0.222	1.55 (0.58–4.13) 0.379
Inpatient	3.09 (0.58–16.37) 0.185	**2.81 (1.06–7.46) 0.037**	**3.30 (1.27–8.59) 0.014**
Internal referral	0.47 (0.10–2.14) 0.332	1.11 (0.43–2.84) 0.835	0.85 (0.34–2.14) 0.735
≥ Moderate systolic dysfunction*	1.20 (0.26–5.47) 0.814	**3.08 (1.15–8.27) 0.025**	**2.73 (1.03–7.21) 0.043**
≥ Moderate AVVR*	2.19 (0.50–9.61) 0.299	2.53 (0.94–6.81) 0.067	**2.91 (1.08–7.85) 0.035**
On inotropes	0.56 (0.06–4.94) 0.603	**3.39 (1.06–10.89) 0.040**	2.54 (0.80–8.07) 0.113
Exercise intolerance	3.27 (0.37–28.80) 0.285	1.00 (0.37–2.72) 1.00	1.29 (0.48–3.47) 0.617
NYHA Class 3–4	4.39 (0.95–20.17) 0.058	1.39 (0.52–3.74) 0.516	1.29 (0.49–3.41) 0.609
Pacemaker/ICD	0.47 (0.05–4.14) 0.499	0.46 (0.13–1.59) 0.219	0.51 (0.16–1.63) 0.254
Chronic/recurrent ascites	1.2 (0.22–6.56) 0.833	0.94 (0.31–2.90) 0.917	0.98 (0.33–2.93) 0.971
Chronic/recurrent pleural effusions	3.54 (0.73–17.20) 0.117	**3.52 (1.02–12.11) 0.046**	**4.01 (1.11–14.48) 0.034**
Protein-losing enteropathy	–	0.85 (0.30–2.27) 0.710	0.60 (0.22–1.65) 0.326
Plastic bronchitis	–	0.61 (0.06–6.21) 0.679	0.48 (0.05–4.87) 0.537
Liver fibrosis†	0.27 (0.30–2.36) 0.237	0.59 (0.22–1.61) 0.303	0.46 (0.17–1.25) 0.126
Liver dysfunction†	–	0.32 (0.035–2.88) 0.308	0.27 (0.3–2.40) 0.239
Lab data			
Total bilirubin (mg/dL)	1.02 (0.98–1.07) 0.265	0.98 (0.94–1.03) 0.560	1.01 (0.97–1.06) 0.465
Creatinine (mg/dL)	1.01 (0.98–1.04) 0.553	0.99 (0.96–1.02) 0.555	1.00 (0.98–1.03) 0.961
Cystatin C (mg/L)	1.52 (0.60–3.87) 0.378	0.32 (0.04–2.74) 0.301	0.74 (0.28–1.93) 0.537
BUN (mg/dL)	1.11 (0.99–1.24) 0.055	1.04 (0.97–1.12) 0.249	1.04 (0.97–1.11) 0.272
Cath data (last 2 years)			
Fontan pressure (per 1 mmHg)	1.14 (0.94–1.37) 0.179	**1.21 (1.02–1.42) 0.026**	**1.19 (1.01–1.40) 0.036**
End-diastolic pressure (per 1 mmHg)	0.65 (0.39–1.10) 0.111	1.05 (0.91–1.22) 0.489	1.00 (0.87–1.15) 0.999
Cardiac index (per 1 L/min/m^2)	1.06 (0.35–3.23) 0.922	1.54 (0.75–3.19) 0.241	1.93 (0.87–4.27) 0.107
Systemic O2 saturation (per 1%)	0.99 (0.93–1.07) 0.938	0.99 (0.95–1.03) 0.730	0.99 (0.95–1.03) 0.712
In the past year . . .			
Diuretic added	0.61 (0.11–3.36) 0.568	2.37 (0.90–6.25) 0.082	1.75 (0.68–4.52) 0.247
Hospitalised‡	1.41 (0.25–7.80) 0.694	2.53 (0.80–7.98) 0.114	2.66 (0.84–8.46) 0.098
Arrhythmias§	1.00 (0.18–5.42) 1.00	1.80 (0.64–5.17) 0.275	2.36 (0.82–6.78) 0.112

AVVR = atrioventricular valve regurgitation; BUN = blood urea nitrogen; ICD = implantable cardioverter defibrillator; NYHA = New York Heart Association.
Data are presented as N (%) or median (25th, 75th percentiles).
*Systolic function and atrioventricular valve regurgitation from echo (n = 70), MRI (n = 2) or cath (n = 5).
† Liver fibrosis as described on any imaging study; synthetic liver dysfunction includes elevated international normalised ratio in the absence of anticoagulation with warfarin, abnormally low platelets, abnormally low pre-albumin, and other markers.
‡ Hospitalisation for ascites, pleural effusions, peripheral oedema, or fluid overload.
§ Any new arrhythmia; specific arrhythmia diagnosis not assessed in survey.

portends worse outcome. Whether they were high risk prior to surgery or uniquely intolerant of Fontan physiology after surgery, Fontan circulatory failure in close proximity to Fontan surgery should prompt immediate involvement of a heart failure team given poor post-referral outcomes.

It is also notable that those who were referred for heart failure consultation within a year of Fontan surgery were more likely to be external referrals—75% of patients referred *within* a year were referred by a provider who was not at the same centre as the heart failure team, while only 38% of patients referred *after* a year were external referrals. There may be many reasons for this finding, but one potential explanation is that at centres with an internal heart failure/transplant team, a patient who is at high-risk pre-Fontan may be offered transplant, rather than Fontan surgery, whereas a centre without an internal heart failure/transplant team may proceed with a high-risk Fontan surgery. More detailed analyses of high-risk pre-Fontan patients are needed to understand this better. Regardless, this finding serves as a reminder that to avoid being referred too late, a heart failure consultation before Fontan surgery should be strongly considered for any pre-Fontan patient who is considered a borderline or high-risk Fontan candidate.

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While there is much to improve on in terms of decreasing the number of late referrals to heart failure care, it is important to point out that over half of Fontan patients were alive, without advanced cardiac therapies (that is, not listed, not maintained on inotropes, and without a ventricular assist device), at 30 days after their initial heart failure consultation. For these patients, the most common (42%) follow-up recommendation was for continued collaborative care between the primary cardiologist and heart failure cardiologist, while 18% were sent back to their primary cardiologist with no further heart failure follow-up. Follow-up plans are often factored by variables such as location, travel distance, and pre-existing, or developing, relationships between the primary and heart failure cardiologists (and their respective institutions). As such, it is possible that there were more patients referred "too early," or without need for heart failure follow-up. Implications for referrals to heart failure care that are too early include the cost of travel or additional clinic visits or testing, as well as the unnecessary anxiety for patients and families, with potentially little added benefit. However, the penalties for late referrals may be more catastrophic, as we have highlighted in our study. In general, a collaborative approach among all who provide care for this unique population will move us closer to the overall goal of prolonging a high-quality life, with or without transplant, for patients with single ventricle CHD after Fontan palliation.

Limitations

While we found that a significant proportion of Fontan patients were referred late to heart failure care, an important limitation of this study is that we were unable to address the important question of whether earlier referral leads to better post-transplant outcomes. To understand this, we would need to understand the full spectrum and clinical course of patients who have undergone Fontan palliation, including after transplantation. As a survey-based study with voluntary participation of heart failure clinicians, this study was also subject to selection bias. It is not possible to ascertain whether participating centres entered all, or only select, Fontan patients seen for initial heart failure consultation during the study period. It is also possible that there were inherent differences in outcomes at centres that chose to participate in this study versus centres that did not participate.

Another limitation is that we do not have the denominator of *all* Fontan patients, and thus were not able to compare the patients referred for heart failure consultation to those who have not been referred. In order to better understand the indications for timely heart failure referral, we need robust longitudinal cohort studies and registries that capture the entire life course, from pre-Fontan surgery to post-transplant, of individuals with single ventricle CHD, not just data that describes transplant-free, waitlist or post-transplant survival. We need to understand the patients who could have, but did not, made it to transplant. The Fontan Outcomes Network is a multi-centre learning network that is attempting to establish such a lifespan registry,[23] and on-going collaboration between general cardiology and heart failure networks will be critical in further elucidation of the appropriate timing and indications for heart failure referral.

Lastly, our sample size, accrued over a 2-year period, did not allow for multi-variable analysis. Barriers to heart failure consultation were not assessed, though we were able to obtain dates of referral and of consultation to be reassured that there were no significant delays between time of referral to consultation. Further, as this survey aimed to define the cohort for future quality improvement studies from Advanced Cardiac Therapies Improving Outcomes Network, granular data about the extent of Fontan-associated complications were not collected and can't be applied to analyses.

Conclusion

This study provides important characterisation of Fontan patients seen for an initial heart failure consultation. Over 40% of Fontan patients seen for an initial consultation by an advanced heart failure team are late referrals, with 10% dying or being declined for transplant within a month of initial consultation. Given the progressive nature of Fontan circulatory failure and lack of traditional heart failure signs and symptoms in this population, earlier heart failure referral for Fontan patients, particularly for those who struggle early after Fontan surgery, should be strongly considered.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S1047951123003852.

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Competing interests. Dr Angela Lorts is a consultant for Abbott, Berlin Heart, Abiomed, and Bayer. The other authors report no conflicts.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation (Belmont Report) and with the Helsinki Declaration of 1975, as revised in 2008. Each Advanced Cardiac Therapies Improving Outcomes Network centre obtains approval to participate in the registry from their respective Institutional Review Boards, with many sites utilising the central Institutional Review Board at Cincinnati Children's Hospital Medical Center (Cincinnati, OH). Informed consent and assent were waived by the central Institutional Review Board for the retrospective arm of the Advanced Cardiac Therapies Improving Outcomes Network registry.

References

1. Riggs KW, Broderick JT, Price N, Chin C, Zafar F, Morales DLS. Transplantation for congenital heart disease: focus on the impact of functionally univentricular versus biventricular circulation. World J Pediatr Congenit Heart Surg 2021; 12: 352–359. DOI: 10.1177/2150135121990650.
2. Simpson KE, Pruitt E, Kirklin JK, et al. Fontan patient survival after pediatric heart transplantation has improved in the current era. Ann Thorac Surg 2017; 103: 1315–1320. DOI: 10.1016/j.athoracsur.2016.08.110.
3. Amdani S, Simpson KE, Thrush P, et al. Hepatorenal dysfunction assessment with the model for end-stage liver disease excluding INR score predicts worse survival after heart transplant in pediatric fontan patients. J Thorac Cardiovasc Surg 2022; 163: 1462–1473.e12. DOI: 10.1016/j.jtcvs.2021.02.014.
4. Das BB, Blackshear CT, Lirette ST, et al. Impact of 2016 UNOS pediatric heart allocation policy changes on VAD utilization, waitlist, and post-transplant survival outcomes in children with CHD versus Non-CHD. Clin Transplant 2023; 37: e14843. DOI: 10.1111/ctr.14843.
5. Bedzra EKS, Adachi I, Peng DM, et al. Systemic ventricular assist device support of the fontan circulation yields promising outcomes: an analysis of the society of thoracic surgeons pedimacs and intermacs databases. J

Thorac Cardiovasc Surg 2022; 164: 353–364. DOI: 10.1016/j.jtcvs.2021.11.054.
6. Cedars A, Kutty S, Danford D, et al. Systemic ventricular assist device support in Fontan patients: a report by ACTION. J Heart Lung Transplant 2021; 40: 368–376. DOI: 10.1016/j.healun.2021.01.011.
7. Lubert AM, Cedars A, Almond CS, et al. Considerations for advanced heart failure consultation in individuals with Fontan circulation: recommendations from ACTION. Circ Heart Fail 2023; 16: e010123. DOI: 10.1161/circheartfailure.122.010123.
8. Sadat-Hossieny S, Karamlou T, Marino BS, et al. Contemporary provider management practices and attitudes toward referral for advanced heart failure therapies in Fontan patients across North America. J Card Fail 2022; 28: 576–587. DOI: 10.1016/j.cardfail.2021.10.016.
9. O'Connor MJ, Lorts A, Kwiatkowski D, et al. Learning networks in pediatric heart failure and transplantation. Pediatr Transplant 2021; 25: e14073. DOI: 10.1111/petr.14073.
10. Dennis M, Zannino D, du Plessis K, et al. Clinical outcomes in adolescents and adults after the Fontan procedure. J Am Coll Cardiol2018; 71: 1009–1017. DOI: 10.1016/j.jacc.2017.12.054.
11. Rychik J, Atz AM, Celermajer DS, et al. Evaluation and management of the child and adult with fontan circulation: a scientific statement from the American heart association. Circulation 2019; 140(6): e234–e284. DOI: 10.1161/cir.0000000000000696.
12. Van De Bruaene A, Claessen G, Salaets T, Gewillig M. Late Fontan circulatory failure. What drives systemic venous congestion and low cardiac output in adult fontan patients? Front Cardiovasc Med 2022; 9: 825472. DOI: 10.3389/fcvm.2022.825472.
13. Alsaied T, Rathod RH, Aboulhosn JA, et al. Reaching consensus for unified medical language in Fontan care. ESC Heart Fail 2021; 8: 3894–3905. DOI: 10.1002/ehf2.13294.
14. Egbe AC, Connolly HM, Miranda WR, et al. Hemodynamics of Fontan failure: the role of pulmonary vascular disease. Circ Heart Fail 2017; 10(12): e004515. DOI: 10.1161/circheartfailure.117.004515.
15. Miranda WR, Hagler DJ, Taggart NW, Borlaug BA, Connolly HM, Egbe AC. Elevated ventricular filling pressures and long-term survival in adults post-Fontan. Catheter Cardiovasc Interv 2020; 95: 803–809. DOI: 10.1002/ccd.28340.
16. Peck D, Averin K, Khoury P, et al. Occult diastolic dysfunction and adverse clinical outcomes in adolescents and young adults with Fontan circulation. J Am Heart Assoc 2023; 12: e026508. DOI: 10.1161/jaha.122.026508.
17. Poh C, Hornung T, Celermajer DS, et al. Modes of late mortality in patients with a Fontan circulation. Heart 2020; 106: 1427–1431. DOI: 10.1136/heartjnl-2019-315862.
18. Morris AA, Khazanie P, Drazner MH, et al. Guidance for timely and appropriate referral of patients with advanced heart failure: a scientific statement from the American heart association. Circulation 2021; 144: e238–e250. DOI: 10.1161/cir.0000000000001016.
19. Moon J, Shen L, Likosky DS, et al. Relationship of ventricular morphology and atrioventricular valve function to long-term outcomes following Fontan procedures. J Am Coll Cardiol 2020; 76: 419–431. DOI: 10.1016/j.jacc.2020.05.059.
20. Poh CL, Cordina RL, Iyengar AJ, et al. Pre- and post-operative determinants of transplantation-free survival after Fontan. The Australia and New Zealand experience. Int J Cardiol Heart Vasc 2021; 35: 100825. DOI: 10.1016/j.ijcha.2021.100825.
21. Bernstein D, Naftel D, Chin C, et al. Outcome of listing for cardiac transplantation for failed Fontan: a multi-institutional study. Circulation 2006; 114: 273–280. DOI: 10.1161/circulationaha.105.548016.
22. Kovach JR, Naftel DC, Pearce FB, et al. Comparison of risk factors and outcomes for pediatric patients listed for heart transplantation after bidirectional Glenn and after Fontan: an analysis from the pediatric heart transplant study. J Heart Lung Transplant 2012; 31: 133–139. DOI: 10.1016/j.healun.2011.11.004.
23. Alsaied T, Allen KY, Anderson JB, et al. The fontan outcomes network: first steps towards building a lifespan registry for individuals with Fontan circulation in the United States. Cardiol Young 2020; 30: 1070–1075. DOI: 10.1017/s1047951120001869.

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