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More than the heart: Hepatic, renal, and cardiac dysfunction in adult Fontan patients

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Abstract

Setting: Fontan-associated liver disease universally affects adults with single ventricle heart disease. Chronic kidney disease is also highly prevalent in adult Fontan patients. In this study, we evaluate the relationship of Fontan hemodynamics invasively and noninvasively with extra-cardiac dysfunction as measured by MELD and MELD-XI.

Objective: We hypothesize that invasive and noninvasive measures of Fontan circuit congestion and ventricular dysfunction are associated with increased MELD and MELD-XI scores.

Design: Single-center data from adults with Fontan palliation who had ongoing care, including cardiac catheterization, were retrospectively collected. Hemodynamic data from cardiac catheterization and echocardiographic assessment of ventricular and atrioventricular valve function were tested for association with serum creatinine, MELD, and MELD-XI. Linear regression was used to perform multivariable analysis in the echocardiogram cohort.

Results: Fifty-seven patients had congruent lab and catheterization data for analysis. Sixty-three and sixty-nine patients had congruent lab and echocardiogram data for MELD and MELD-XI, respectively. Of the hemodynamic variables analyzed, only decreased systemic oxygen saturation had significant correlation with elevated MELD and MELD-XI ($P = .045$). Patients with moderately or severely reduced ejection fraction by echocardiogram had significantly higher MELD and MELD-XI scores compared to those with normal or mildly depressed systolic ventricular function ($P = .008$ and $P < .001$ for MELD and MELD-XI, respectively). Significant differences in creatinine were also found among the ventricular dysfunction groups ($P = .02$).

Conclusions: In adults following Fontan palliation, systolic ventricular dysfunction and decreased oxygen saturation were associated with hepatic and renal dysfunction as assessed by elevated serum creatinine, MELD, and MELD-XI scores.

KEYWORDS
extra-cardiac, Fontan, liver, MELD, renal

1 | INTRODUCTION

The Fontan operation is a surgical palliation for patients born with a single ventricle congenital heart disease.[1] The success of this procedure has improved life expectancy such that an adult Fontan population has emerged. In the population of adult Fontan patients, extra-cardiac organ dysfunction has been observed including Fontan-associated liver disease (FALD) and renal disease. FALD is characterized by progressive collagenous deposition leading to hepatic fibrosis and ultimately cirrhosis. This process results in at least some degrees of liver disease in all Fontan patients.[2] FALD has been recognized to be of clinical and prognostic importance.[3] Implications of FALD vary from a subacute course with limited clinical significance to complications such as synthetic liver dysfunction[4] and hepatocellular carcinoma.[4,5] Chronic kidney disease is also highly prevalent in adult Fontan patients with one study demonstrating at least mildly reduced glomerular filtration rates in the majority.[6]

The model for end-stage liver disease (MELD) score is a commonly used scoring system to assess clinically significant liver disease and includes bilirubin, INR, and creatinine.[7] The MELD-XI score, which eliminates INR from the scoring system, is useful in the Fontan population given the prevalence of warfarin use.[8] MELD-XI has been found to correlate with degree of hepatic fibrosis in Fontan.[9] Elevated MELD-XI scores are also associated with increased risk of sudden death, congestive heart failure death, and cardiac transplantation in patients with Fontan.[10]

Thus far, Fontan hemodynamic variables have inconsistently correlated with degree of liver fibrosis, synthetic dysfunction, and its sequelae;[8,11,12] however, noninvasive cardiac assessment by transthoracic echocardiogram (TTE) of systolic ventricular function as well as atrioventricular (AV) valve regurgitation as it relates to MELD and MELD-XI has not been studied previously. In this study, we evaluate the relationship of Fontan hemodynamics, both invasive and noninvasive, with MELD and MELD-XI. We hypothesize that markers of Fontan circuit congestion and dysfunction, particularly elevated Fontan pressure, time from Fontan, and impaired systolic ventricular function are associated with increased MELD and MELD-XI scores.

2 | METHODS

2.1 | Patient population and data collection

This study was approved by the Vanderbilt Institutional Review Board. Our study population includes patients with Fontan age of 15 years or older cared for at Vanderbilt University Medical Center who had undergone cardiac catheterization. Data were collected via retrospective chart review. In patients with multiple cardiac catheterizations, the most recent procedure was chosen. Laboratory and echocardiographic data were collected nearest to the catheterization date as possible. Patients with incomplete catheterization or lab data were excluded. Lab results more than 365 days from time of catheterization or TTE were also excluded. Accurate calculation of ejection fraction is not possible for morphologic right ventricle by TTE; therefore, ventricular dysfunction was categorized as none, mild, mild-moderate, moderate, moderate-severe, and severe. AV valve regurgitation was also classified as none, mild, mild-moderate, moderate, moderate-severe, and severe.

2.2 | Calculation of catheter-measured variables

The majority of catheterizations were performed under general anesthesia, with some performed with conscious sedation. At our institution, cardiac catheterizations are not performed routinely and instead are usually performed due to clinical deterioration or for pre-procedural planning. All catheterizations were performed in the supine position. Measures of cardiac output (CO), cardiac index (CI), systemic vascular resistance, and pulmonary vascular resistance were calculated using Fick principal. All other measures of hemodynamics were directly measured.

2.3 | Calculations

MELD was calculated using the equation: MELD = (3.78 × ln[total serum bilirubin (mg/dL)]) + (11.2 × ln[INR]) + (9.57 × ln[serum creatinine (mg/dL)]) + 6.43. The equation used for MELD-XI was (11.76 × ln[serum creatinine (mg/dL)]) + (5.11 × ln[total serum bilirubin (mg/dL)]) + 9.44.

2.4 | Statistical analysis

Continuous variables were expressed as medians (IQR) and categorical variables were expressed as proportions. To examine the associations between catheterization data and MELD, MELD-XI, and creatinine, Pearson correlation was calculated. MELD, MELD-XI, and creatinine were compared to ventricular dysfunction and degree of AV valve regurgitation using the Kruskal–Wallis test. Reduced ejection fraction was defined as ventricular dysfunction more than mild. AV valve regurgitation more than mild was regarded as clinically significant valvular dysfunction. Multiple linear regressions were utilized to examine the relationships between echocardiographic data and MELD, MELD-XI, and creatinine, controlling for age at Fontan, time from Fontan to TTE, sex, and ventricular morphology. Statistical significance was defined as a P value ≤.05.

3 | RESULTS

A total of 98 Fontan patients age of 15 years or older that had undergone catheterization were identified. Fifty-seven patients had complete and congruent lab and catheterization data for analysis (Figure 1). Within the TTE cohort, the number of patients with congruent and comprehensive laboratory data to calculate MELD and MELD-XI were 63 and 69, respectively. Median time from

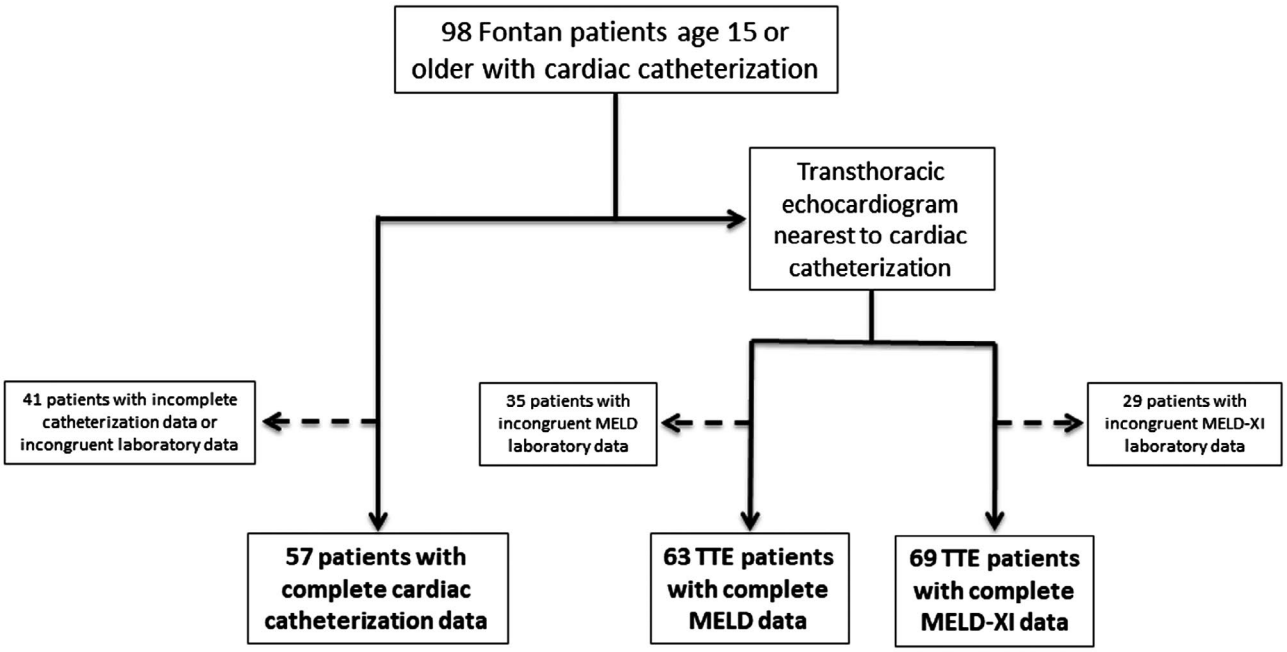

FIGURE 1 Patient selection for catheterization and TTE analysis. Incongruent laboratory data were defined as > 365 days from time of catheterization or TTE

catheterization to laboratory data was 26.5 days while median time from TTE to laboratory data was 23.0 days.

The majority of our patients were female (57%) (Table 1). Original congenital cardiac malformations varied in our cohort with the most common being tricuspid atresia (31%) followed by double inlet left ventricle (25%). Almost two-thirds of our patients had a morphologic left ventricle as their systemic ventricle (66%). The majority of our patients had total cavopulmonary anastomosis Fontan palliation with either lateral tunnel (47%) or extra-cardiac conduit (23%). Some patients had patent Fontan fenestration at the time of catheterization (21%). Venovenous collaterals were found in 45% and aortopulmonary collaterals in 12%. The median age of Fontan palliation was 5 years and median time from Fontan palliation to date of subsequent cardiac catheterization was 17.2 years. The median age at catheterization was 23.3 years. About 14% of our patients have died since the time of their last catheterization.

Of the hemodynamic variables analyzed, only systemic oxygen saturation had significant correlation to MELD (Table 2). Lower systemic oxygen saturation correlated with increased MELD (r: −0.28; P = .045) and trended towards significance with an elevated MELD-XI score (r: −0.27; P = .051). When analyzed independently, creatinine was also significantly associated with lower levels of systemic oxygen saturation (r: −0.33; P = .01). The remaining hemodynamic variables analyzed did not correlate with elevated MELD and MELD-XI. Notably, Fontan pressure and time from Fontan to catheterization were not found to be significantly associated with MELD, MELD-XI, or creatinine.

Significant differences were found for MELD and MELD XI among ventricular dysfunction groups (P = .008 and P < .001 for MELD and MELD-XI, respectively) (Table 3 and Figure 2). Median MELD and MELD-XI in patients with no ventricular dysfunction were 6.57 and 6.06, respectively, while median MELD and MELD-XI in patients with mild ventricular dysfunction were 8.21 and 9.50, respectively. In the group with reduced ejection fraction, median MELD was 11.93 and median MELD-XI was 10.99. Significant differences in creatinine were also found among the ventricular dysfunction groups (P = .02). Median creatinine in Fontan patients with reduced ejection fraction was 0.98 compared to 0.80 for the group with no ventricular dysfunction. The degree of AV valve regurgitation by TTE was not significantly associated with elevated MELD or MELD-XI scores (Table 4).

In multiple linear regression analysis, compared to patients with no ventricular dysfunction, Fontan with reduced ejection fraction by TTE was significantly associated with elevated MELD (b = 6.6; P < .001), MELD-XI (b = 6.7; P < .001), and creatinine (24.4% higher; P = .03). Male gender was also significantly related to MELD-XI score (b = 3.2; P = .015). AV valve regurgitation again did not significantly correlate with elevated MELD or MELD-XI scores. Age at Fontan, time from Fontan to TTE, and type of morphologic systemic ventricle were not related with elevated MELD or MELD-XI scores in multiple linear regression analyses.

4 | DISCUSSION

Noninvasive measures of ventricular dysfunction by TTE are associated with increased creatinine, MELD, and MELD-XI in adults with Fontan physiology. While it may seem intuitive, to our knowledge, this is the first study to find correlation with reduced ejection fraction on echocardiogram with markers of liver and renal disease in

TABLE 1 Adult patients following Fontan procedure with cardiac catheterization >15y/o

N = 98	No. (%)
Male	42 (43%)
Original anatomy	
Tricuspid atresia	30 (31%)
Double inlet left ventricle	24 (25%)
Double outlet right ventricle	13 (13%)
Unspecified single ventricle	10 (10%)
Unbalanced AVSD	9 (9%)
Hypoplastic left heart syndrome	7 (7%)
Pulmonary atresia with intact ventricular septum	5 (5%)
Morphologic systemic ventricle	
Left ventricle	65 (66%)
Right ventricle	28 (29%)
Indeterminate ventricle	5 (5%)
Type of Fontan palliation	
Classic (atriopulmonary)	23 (23.5%)
Fontan with Bjork modification	6 (6%)
Lateral tunnel	46 (47%)
Extracardiac	23 (23.5%)
Fenestration or collaterals	
Patent fenestration	21 (21%)
Venovenous collaterals	44 (45%)
Aortopulmonary collaterals	12 (12%)
Morbidity and mortality	
Fontan revision	29 (30%)
Death	14 (14%)
Age at Fontan procedure	3.0 5.0 13.0[a] 9.1 ± 9.0[b]
Age at catheterization	18.4 23.3 30.6[a] 25.5 ± 8.9[b]

[a]For continuous variables, numbers represent the lower quartile, the median, and the upper quartile.
[b]Mean ± 1SD.

Fontan. Our findings carry particular clinical relevance as TTE is routinely performed in conjunction with outpatient visits. In the absence of clear guidelines regarding extra-cardiac assessment in Fontan, reduced ventricular function, once identified, may alert clinicians to higher likelihood of multi-organ involvement and prompt hepatic and renal evaluation.[13] Detection of liver or kidney dysfunction may impact management decisions including need for single vs multi-organ transplantation.[14]

Single ventricle physiology is complex and ultimately becomes a multi-system disease requiring expert care. Like FALD, renal disease in Fontan is not fully understood. Decreased glomerular filtration rate has been associated with increased Fontan pressure, and progressive renal dysfunction in Fontan is known to portend mortality.[15,16] We felt it important to analyze renal dysfunction independently given the previous recognition that poor outcome related to MELD in Fontan is primarily driven by the serum creatinine component of the score.[10] Our data found that increased creatinine alone is significantly associated with reduced ejection fraction. We acknowledge that a limitation of this study is the inability to determine whether increased MELD scores are driven primarily by comorbid liver disease, by kidney disease, or both. Therefore, it is possible that the MELD score in Fontan may provide application as an assessment of multi-organ dysfunction rather than an assessment of FALD alone.

Decreased systemic oxygen saturation was significantly associated with elevated MELD and serum creatinine and trended toward significance with elevated MELD-XI. This was our only catheterization-derived variable that correlated with MELD. Though this was measured invasively in our study, decreased systemic oxygen saturation can be detected noninvasively in the outpatient setting via ambulatory oxygen saturations. The discovery of decreased oxygen saturation may also be a prompt to evaluate for extra-cardiac dysfunction and may be a sign of increased right-to-left shunting through venovenous collaterals or Fontan fenestration.

It is notable that many hemodynamic variables in our study did not significantly correlate with elevated MELD and MELD-XI scores. As has been demonstrated previously,[2,10] elevated Fontan pressure was not associated with clinically significant liver dysfunction. The majority of cardiac catheterizations were performed under general anesthesia, which may have resulted in underestimating Fontan pressure. Also, the presence of patent Fontan fenestration and venovenous collaterals would potentially lower Fontan pressure; the presence of aortopulmonary collaterals would potentially raise Fontan pressure. CO and CI also did not correlate with elevated MELD and MELD-XI, which is consistent with previous findings.[8,10] One explanation for our CO and CI findings may be a discrepancy between assumed and actual VO2 during the catheterization procedure, leading to an overestimation of these measures. Another consideration is the possibility of ventricular volume loading in the context of progressive FALD,[17] thought to be due to increased arterialization of the liver in areas of hepatic fibrosis, leading to increased inferior vena cava flow and CO. The absence of hemodynamic variables such as Fontan pressure, CO, and CI correlating with elevated MELD and MELD-XI scores is an important reminder that clinicians should not be discouraged from screening for extra-cardiac disease in the presence of reassuring hemodynamics.

Liver disease has gained attention in transplant evaluation for patients with Fontan; however, accurately predicting the risk of FALD that adds to cardiac transplantation is difficult.[14] For Fontan patients with both advanced heart failure and progressive FALD, combined heart–liver transplantation has been successfully pursued,[18,19] though the potential for perioperative morbidity and mortality is significant and long-term outcomes remain unknown. These challenges place emphasis on early detection of clinically

TABLE 2 Correlations between cardiac catheterization hemodynamic data and MELD, MELD-XI, and creatinine

		MELD		MELD-XI		Creatinine	
Hemodynamic variables (N = 57)	Median (IQR)	Correlation coefficient	*P*	Correlation coefficient	*P*	Correlation coefficient	*P*
Time from Fontan to catheterization (years)	17.2 (13.6-21.6)	0.09	.549	0.01	.937	0.09	.481
Fontan pressure (mm Hg)	15.0 (11.8-17.3)	0.06	.671	0.05	.734	.23	.075
Ventricular End Diastolic Pressure (mmHg)	9.0 (7.0-12.0)	0.08	.585	0.03	.817	0.08	.555
Pulmonary capillary wedge pressure (mmHg)	9.0 (7.0-13.0)	0.12	.4	0.03	.842	0.21	.109
Systemic vascular resistance (Wood units)	13.2 (9.0-15.9)	0.17	.255	0.15	.291	0.06	.651
Pulmonary vascular resistance (Wood units)	1.2 (1.0-1.9)	0.02	.886	0.01	.964	0.09	.536
Systemic saturation (%)	91 (87-94)	−0.28	***.045***	−0.27	***.051***	−0.33	***.01***
Cardiac output (L/min)	4.4 (3.7-5.8)	0.08	.605	0.02	.885	0.11	.395
Cardiac index (L/min/m^2)	2.7 (2.1-3.1)	−0.02	.869	−0.8	.593	0.07	.628

Bold, italic values are *P* values that are represent a statistically significant difference.

TABLE 3 Ventricular dysfunction compared to MELD, MELD-XI, and creatinine

		None	Mild	REF	Combined	
	N	(N = 42)	(N = 21)	(N = 12)	(N = 75)	*P*
MELD	63	$_{3.71}$ 6.57 $_{8.13}$ 6.43 ± 4.36	$_{3.76}$ 8.21 $_{11.03}$ 7.75 ± 4.81	$_{9.37}$ 11.93 $_{15.36}$ 12.03 ± 5.17	$_{3.98}$ 7.41 $_{10.62}$ 7.81 ± 5.00	***.008***
MELD-XI	69	$_{3.42}$ 6.06 $_{8.20}$ 5.99 ± 5.08	$_{2.64}$ 9.50 $_{10.96}$ 8.25 ± 4.99	$_{9.61}$ 10.99 $_{16.37}$ 12.48 ± 4.84	$_{3.92}$ 7.62 $_{10.68}$ 7.71 ± 5.46	***<.001***
Creatinine	75	$_{0.70}$ 0.80 $_{0.90}$ 0.83 ± 0.31	$_{0.70}$ 0.87 $_{1.03}$ 0.90 ± 0.32	$_{0.81}$ 0.98 $_{1.20}$ 1.01 ± 0.23	$_{0.70}$ 0.80 $_{0.96}$ 0.88 ± 0.30	***.02***

Bold, italic values are *P* values that are represent a statistically significant difference. For continuous variables, numbers represent the lower quartile, the median, and the upper quartile.
x ± s represents mean ± 1SD.
Test used: Kruskal–Wallis test.
REF = reduced ejection fraction.

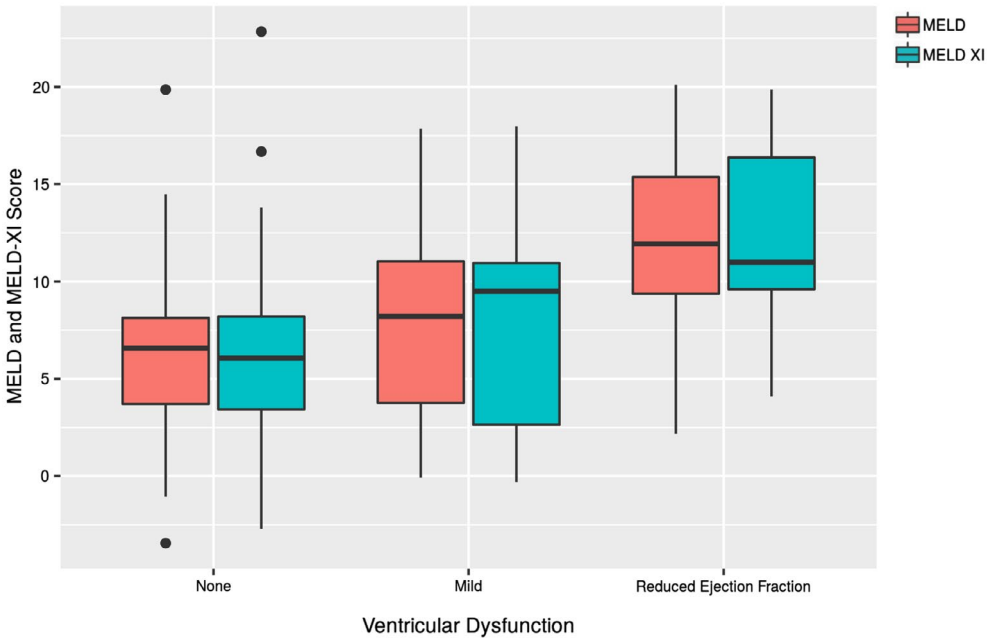

FIGURE 2 Ventricular dysfunction compared to MELD and MELD-XI. MELD and MELD-XI

TABLE 4 Atrioventricular valve regurgitation compared to MELD, MELD-XI, and creatinine

	N	None (N = 37)	Mild (N = 28)	CSVD (N = 10)	Combined (N = 75)	P
MELD	63	$_{3.38}$ 7.94 $_{10.58}$ 7.22 ± 5.08	$_{4.02}$ 7.19 $_{10.14}$ 7.60 ± 4.78	$_{6.63}$ 8.50 $_{11.93}$ 10.46 ± 4.92	$_{3.98}$ 7.41 $_{10.62}$ 7.81 ± 5.00	.308
MELD-XI	69	$_{3.12}$ 7.14 $_{10.48}$ 7.43 ± 5.88	$_{3.23}$ 6.63 $_{9.51}$ 7.05 ± 5.33	$_{7.46}$ 9.66 $_{13.15}$ 10.30 ± 3.61	$_{3.92}$ 7.62 $_{10.68}$ 7.71 ± 5.46	.155
Creatinine	75	$_{0.70}$ 0.83 $_{0.96}$ 0.88 ± 0.28	$_{0.70}$ 0.77 $_{0.90}$ 0.87 ± 0.36	$_{0.80}$ 0.82 $_{0.99}$ 0.91 ± 0.19	$_{0.70}$ 0.80 $_{0.96}$ 0.88 ± 0.30	.367

For continuous variables, numbers represent the lower quartile, the median, and the upper quartile.
x ± s represents mean ± 1SD.
Test used: Kruskal–Wallis test.
CSVD = clinically significant valvular dysfunction.

significant liver dysfunction to aid in timing of transplant consideration. Based on our data, the identification of ventricular dysfunction and decreased systemic oxygen saturation, given their association with increased MELD and MELD-XI scores, may be useful in this regard. However, these associations need further analysis in a prospective manner to establish an associative timeline between the onset of ventricular dysfunction and decreased systemic oxygen saturation and the development of elevation in creatinine, MELD, and MELD-XI scores.

5 | LIMITATIONS

There are inherent limitations in single-center, retrospective studies. This is a cross-sectional study, and as such, causation cannot be determined. The rationale to undergo catheterization was not protocolized in our study, though this did help increase the heterogeneity within our population, which includes individuals of varied symptomatology. In addition, variability in data procurement exists within our study given all catheterizations were not performed by a single operator. Likewise, a single reader did not analyze all echocardiograms. It is also important to note that Fontan hemodynamics as well as the laboratory values used to calculate MELD and MELD-XI scores are dynamic in nature. As such, future studies trending these data in a longitudinal fashion may enhance our understanding of their associative relationships. Finally, our study is limited by population size, though we are hopeful that future studies with larger cohorts will provide additional information via subgroup analysis.

6 | CONCLUSION

In adults following Fontan palliation, reduced ejection fraction by TTE and decreased oxygen saturation were associated with hepatic and renal dysfunction as assessed by elevated serum creatinine, MELD, and MELD-XI scores.

CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest with the contents of this article.

AUTHOR CONTRIBUTIONS

Data collection: Byrne
Concept/design: Byrne, Weingarten, Clark, Markham, Frischhertz
Drafting article: Byrne
Critical revision of article: Byrne, Weingarten, Clark, Huang, Perri, Scanga, Menachem, Markham, Frischhertz
Approval of article: Weingarten, Perri, Scanga, Menachem, Markham, Frischhertz
Data analysis/interpretation: Huang

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