JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2015 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.

VOL. 66, NO. 15, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.07.065

40-Year Follow-Up After the Fontan Operation

Long-Term Outcomes of 1,052 Patients

Kavitha N. Pundi, MD,* Jonathan N. Johnson, MD,*† Joseph A. Dearani, MD,‡ Krishna N. Pundi, BS,§ Zhuo Li, BS,‖ Cynthia A. Hinck, RN, BSN,* Sonja H. Dahl, RN, DNP,* Bryan C. Cannon, MD,*† Patrick W. O'Leary, MD,*† David J. Driscoll, MD,* Frank Cetta, MD*†

ABSTRACT

BACKGROUND There are limited long-term, single-cohort, follow-up studies available about patients after the Fontan operation.

OBJECTIVES This study sought to determine the long-term outcome of all patients who had a Fontan operation at the Mayo Clinic.

METHODS Records of all patients who had a modified Fontan operation between 1973 and 2012 were reviewed. A follow-up questionnaire was mailed to all patients alive at the time of the study.

RESULTS Overall, 10-, 20-, and 30-year survival for 1,052 patients was 74%, 61%, and 43%, respectively. Factors associated with decreased overall or late survival in multivariate analysis included pre-operative diuretic use, longer cardiopulmonary bypass time, operation prior to 1991, atrioventricular valve (AVV) replacement at the time of Fontan operation, elevated post-bypass Fontan (>20 mm Hg) or left atrial (>13 mm Hg) pressures, prolonged chest tube drainage (>21 days), post-operative ventricular arrhythmias, renal insufficiency, and development of protein-losing enteropathy (PLE). Pre-operative and intraoperative sinus rhythm were associated with improved survival. Long-term survival was similar for patients regardless of ventricular morphology. The most common reoperations were pacemaker insertion/revision in 212 patients (20%), Fontan revision/conversion in 117 patients (11%), and AVV repair/replacement in 66 patients (5%). Clinically significant late atrial or ventricular arrhythmias occurred in 468 patients (44%). Ninety-five patients (9%) developed PLE, and 5-, 10-, and 20-year survival after diagnosis of PLE was 50%, 35%, and 19%, respectively.

CONCLUSIONS As the surgical techniques for the Fontan operation have changed over the last 40 years, survival has improved. However, development of PLE and arrhythmias and the need for reoperation during long-term follow-up pose significant management challenges. (J Am Coll Cardiol 2015;66:1700–10) © 2015 by the American College of Cardiology Foundation.

In 1971, Fontan and Baudet described a surgical technique for successful palliation of patients with tricuspid atresia (1,2). Subsequently, this technique has been applied to treat most forms of functional single ventricles (3–7). Theoretically, the Fontan operation separates the systemic and pulmonary venous returns to ameliorate the disadvantages of long-term hypoxemia, reduce thromboembolic events, preserve ventricular function, and prolong survival for patients with single-ventricle physiology. Although some of these beliefs have been fulfilled, a number of adverse results of the

From the *Division of Pediatric Cardiology, Mayo Clinic, Rochester, Minnesota; †Division of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota; ‡Division of Cardiovascular Surgery, Mayo Clinic, Rochester, Minnesota; §Mayo Clinic College of Medicine, Mayo Clinic, Rochester, Minnesota; and the ‖Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota.
Dr. Cannon has served as a consultant to Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.
Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

Manuscript received April 22, 2015; revised manuscript received June 26, 2015, accepted July 24, 2015.

Fontan procedure have been recognized, including premature death, ventricular failure, thromboembolic disease, arrhythmia, liver disease, and protein-losing enteropathy (PLE) (8-14). In this study, we sought to determine long-term outcomes for all patients who had a Fontan operation at our institution.

SEE PAGE 1711

METHODS

In this institutional review board-approved, single-center, retrospective study, we reviewed the records of all patients (n = 1,052) who had their initial Fontan operation at the Mayo Clinic between October 1973 and June 2012 and who provided informed consent to participate in the study. Information regarding demographic, anatomic, pre-operative, operative, and post-operative variables, and Mayo follow-up was abstracted into a secure electronic database. Many of the patients had their follow-up care at other institutions. Any available correspondence regarding echocardiogram, cardiac catheterization, electrocardiogram, Holter/event monitor, laboratory tests, liver imaging, or surgical/procedural data was entered into the patient database.

A medical questionnaire was mailed to all patients not known to be dead at the initiation of the study. Nonresponders received second and third questionnaires, and if these were not returned or completed, an attempt was made to contact the patients by telephone. Quality-of-life surveys from patients rated their current health status on a scale of 1 to 4 (1 = excellent, 2 = good, 3 = fair, and 4 = poor). Data regarding death were updated using correspondence from physicians and patients/family members, chart review, and the Social Security Death Index. For the remaining patients, data curves were censured using the date of last available follow-up or date of transplant.

PLE was diagnosed based on documentation of enteric loss of alpha-1-antitrypsin or the presence of low serum total protein/albumin in addition to persistent or intermittent edema. Patients were excluded from subsequent PLE analysis if the timing of diagnosis was not known. Clinically significant arrhythmia was defined as the need for antiarrhythmic drug therapy (excluding digoxin), pacemaker placement, or electrical/pharmacological cardioversion. Patients with arrhythmias prior to the Fontan procedure were excluded from any analysis of post-operative arrhythmias. Cirrhosis was diagnosed based on liver biopsy/autopsy or characteristic findings on computed tomography, cardiac magnetic resonance imaging, magnetic resonance elastography, or ultrasound in conjunction with clinical diagnosis by a gastroenterologist. Patients with isolated liver function or ultrasound abnormalities were not considered to have proven cirrhosis.

Variables used in the Cox regression analysis were initially analyzed as continuous variables, and then discrete cutoffs were selected based on the hazard ratios. The cutoffs for discrete variables used in univariate/multivariate analyses were defined as follows: pre-operative pulmonary artery pressure (PAP) (>17 mm Hg), pre-operative systemic ventricular end-diastolic pressure (>12 mm Hg), pre-operative pulmonary arteriolar resistance (>3 U × m^2), post-bypass left atrial (LA) pressure (>13 mm Hg), post-bypass Fontan pressure (>20 mm Hg), and prolonged chest tube duration (≥21 days).

STATISTICAL ANALYSIS. Separate analyses were performed using either the date of the Fontan operation as time 0 ("overall survival") or 30 days after the operation as time 0 ("late survival"). All deaths, regardless of cause, after the Fontan operation were considered in the survival analysis. Descriptive statistics for categorical variables were reported as frequency and percentage, and continuous variables were reported as mean ± SD or median (range) as appropriate. Time to PLE was compared between Fontan type groups using analysis of variance. Kaplan-Meier curves were derived to calculate 10-, 20-, and 30-year survival statistics. Cox regression models were used to determine univariate and multivariate predictors of survival and other long-term outcomes. The multivariable model considered significant univariate variables ($p < 0.05$) with model selection using the stepwise method. All statistical tests were 2-sided with the alpha level set at 0.05 for statistical significance. SAS version 9.3 (SAS Institute, Inc., Cary, North Carolina) was used for the analysis. The set of variables evaluated for association of survival and long-term outcomes and results of univariate Cox regression analyses are listed in Online Tables 1 to 4.

ABBREVIATIONS AND ACRONYMS

AVV = atrioventricular valve

LA = left atrial

PAP = pulmonary artery pressure

PLE = protein-losing enteropathy

SVEDP = systemic ventricular end-diastolic pressure

RESULTS

Between 1973 and 2012, 1,052 patients had an initial Fontan operation at the Mayo Clinic (Table 1). At last follow-up, 426 patients (40%) were known to be dead. Of the 626 patients known to be alive, transplant-free survival was verified in 427 patients (68%) with follow-up information within 5 years of the study termination date. The mean age at initial Fontan procedure was 9.4 ± 7.5 years (median: 7 years; range: 7 months to 53 years). Mean follow-up after the Fontan operation was 15.3 ± 9.3 years

TABLE 1 Patient Demographics (N = 1,052)

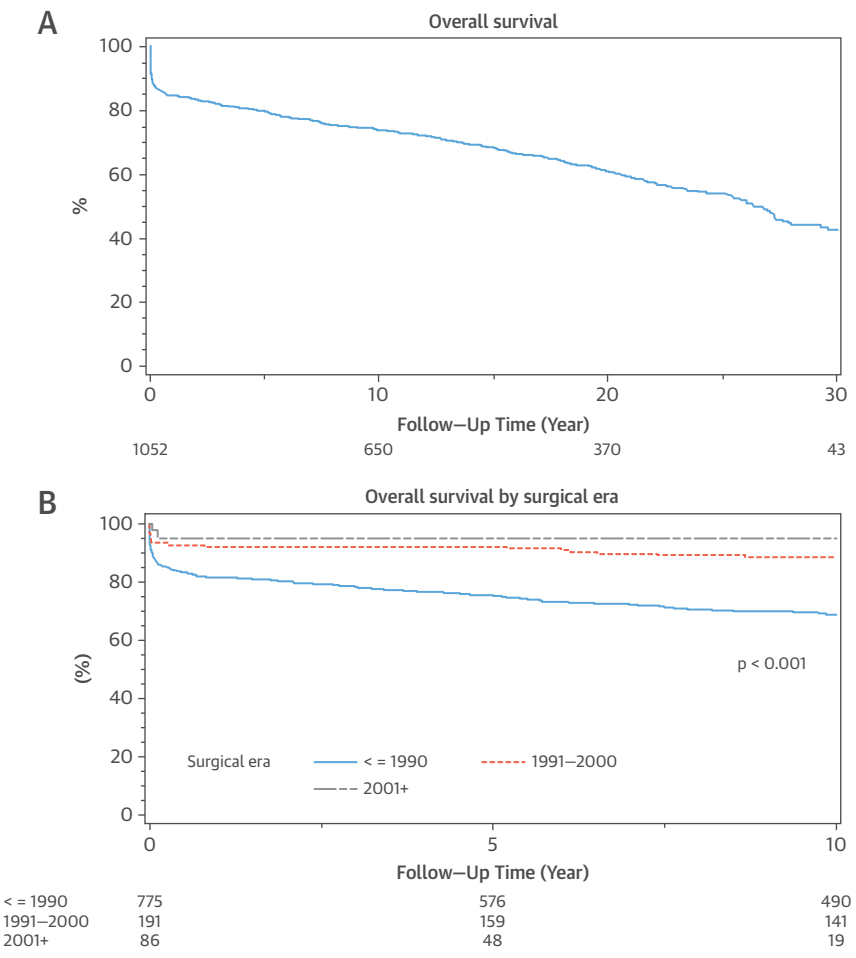
Male	637 (61)
Type of Fontan operation	
Atriopulmonary connection	616 (59)
Lateral tunnel	262 (25)
Extracardiac conduit	120 (11)
Other	54 (5)
Pre-operative anatomy	
Tricuspid atresia	273 (26)
Double inlet left ventricle	271 (26)
Heterotaxy	135 (13)
Pulmonary atresia/intact septum	35 (3)
Hypoplastic left heart syndrome	24 (2)
Other	314 (30)

Values are n (%).

(median: 15.1 years; range: 34 days to 37 years). The oldest survivor after the Fontan operation was 67 years of age (Fontan at age 39 years). Of the 723 follow-up questionnaires mailed out, 305 (42%) were returned.

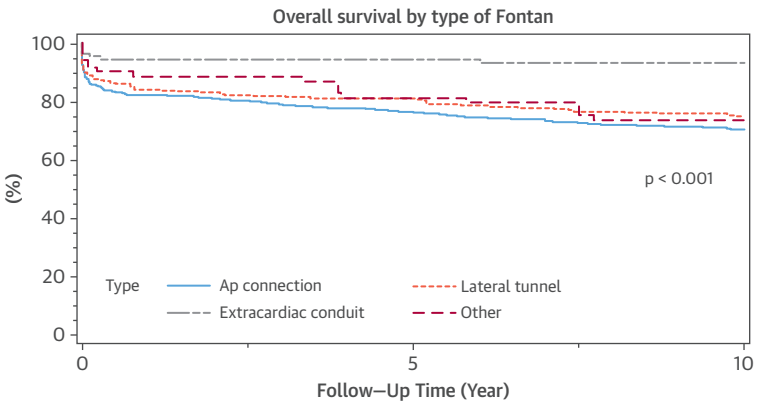
SURVIVAL. Overall, 10-, 20-, and 30-year survival after the Fontan operation was 74%, 61%, and 43%, respectively (Figure 1A). Overall survival by surgical era, type of Fontan procedure, and pre-operative anatomy are depicted in Figures 1B, 2, and 3, respectively. Kaplan-Meier estimates of overall survival are listed in Table 2, and factors associated with decreased overall survival in multivariate analysis are in Table 3. When only pre-operative variables were considered, factors associated with decreased overall survival in multivariate analysis included operation

FIGURE 1 Overall Survival



Over time, overall survival after the Fontan operation predictably decreased **(A)** but improved significantly in later surgical eras **(B)**.

FIGURE 2 Overall Survival by Type of Fontan Procedure



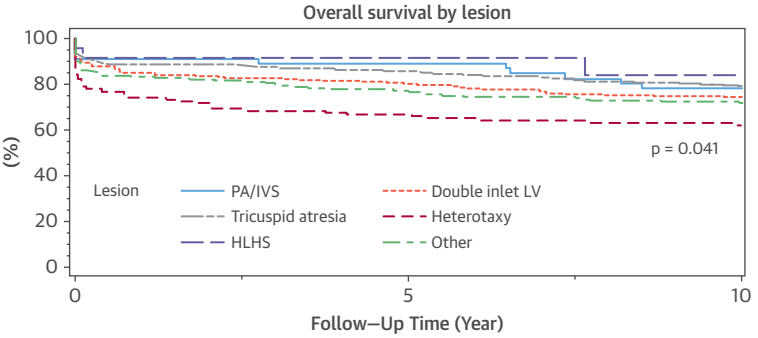
Ap connection	616	462	401
Lateral tunnel	262	200	167
Extracardiac conduit	120	77	45
Other	54	44	37

The type of procedure performed greatly impacted survival; patients who had their Fontan with an extracardiac conduit had significantly less mortality. Ap = atriopulmonary.

prior to 1991, use of pre-operative diuretics, asplenia, and lack of pre-operative sinus rhythm. Fenestration was associated with improved overall survival only on univariate analysis. However, only 86 patients (8%) underwent fenestration at the time of their initial Fontan procedure (most of which were performed after 1995). Ventricular morphology did not impact overall survival.

The 10-, 20-, and 30-year survival for the 932 patients who were alive 30 days after the Fontan operation was 83%, 68%, and 48% respectively. Kaplan-Meier estimates of late survival are listed in Table 4. Factors associated with decreased late survival in multivariate analysis are listed in Table 5. When only pre-operative variables were considered, factors associated with decreased late survival

FIGURE 3 Overall Survival by Pre-Operative Anatomy



PA/IVS	55	43	35
Double inlet LV	271	209	179
Tricuspid atresia	270	222	182
Heterotaxy	129	78	63
HLHS	24	16	10
Other	303	216	182

Patients with heterotaxy had the lowest overall survival after Fontan. LV = left ventricle; PA/IVS = pulmonary atresia with intact ventricular septum. HLHS = hypoplastic left heart syndrome.

TABLE 2 Overall Survival Estimate Post-Fontan Operation

	N	10-Yr Survival, %	20-Yr Survival, %	30-Yr Survival, %
Overall	1,052	74	61	43
Operative era				
1973–1990	775	69	57	39
1991–2000	191	89	74	
2001 onward	86	95		
Age at Fontan				
<2 yrs	24	79	62	
2–4 yrs	200	78	72	59
4–16 yrs	647	74	61	49
>16 yrs	181	71	54	28
Pulmonary vein anatomy				
Normal	931	76	63	44
Abnormal	121	61	46	28
Inferior vena cava				
Normal	976	75	62	44
Interrupted	76	61	53	
Bidirectional Glenn				
Absent	893	71	59	41
Present	159	94	68	
Pre-operative sinus rhythm				
Absent	64	55	33	15
Present	988	75	63	44
Pre-operative PAP				
Normal (≤17 mm Hg)	451	81	68	45
Abnormal (>17 mm Hg)	476	68	54	40
Pre-operative pulmonary arteriolar resistance				
Normal (≤3 mm Hg)	619	75	60	43
Abnormal (>3 mm Hg)	63	59	50	
Pre-operative SVEDP				
Normal (≤12 mm Hg)	608	79	66	48
Abnormal (>12 mm Hg)	355	67	54	36
Type of Fontan connection				
Atriopulmonary	616	70	58	41
Intra-atrial tunnel	262	75	63	35
Extracardiac conduit	120	94	60	60
Other	54	74	63	42
Fenestration				
Absent	966	73	60	42
Present	86	85	73	
AVV replacement at the time of Fontan				
No	1,029	75	62	43
Yes	23	25	8	
Post-bypass Fontan pressure				
≤20 mm Hg	887	79	66	48
>20 mm Hg	117	40	32	11

AVV = atrioventricular valve; PAP = pulmonary artery pressure; SVEDP = systemic ventricular end-diastolic pressure.

included operation prior to 1991, use of pre-operative diuretics or amiodarone, interrupted inferior vena cava (heterotaxy), and lack of pre-operative sinus rhythm.

TABLE 3 Overall Survival Post-Fontan Operation

	HR	95% CI	p Value
Surgical era 1991–2000*	0.52	0.36-0.75	<0.001
Surgical era 2001 onward*	0.28	0.09-0.87	0.03
Intraoperative sinus rhythm	0.70	0.52-0.95	0.02
Pre-operative use of diuretics	1.86	1.46-2.37	<0.001
Post-operative LA pressure >13 mm Hg	1.84	1.40-2.42	<0.001
Post-operative Fontan pressure >20 mm Hg	2.14	1.63-2.81	<0.001
Longer bypass time†	1.14	1.07-1.22	<0.001

*Compared with the surgical era from 1973 through 1990. †For every 30-min increase in overall bypass time.
CI = confidence interval; HR = hazard ratio; LA = left atrial.

EARLY REOPERATIONS AND COMPLICATIONS. A total of 177 of 1,052 patients (17%) had at least 1 early reoperation after their Fontan operation. The 3 most common indications for reoperation were bleeding (n = 74 [42%]), wound debridement (n = 38 [21%]), and placement of a permanent pacemaker (n = 35 [20%]). There were 21 patients who had early Fontan takedown (<30 days after Fontan operation). Of these, 12 patients (57%) died during long-term follow-up (9 [43%] died within 30 days of takedown). The incidence of atrial arrhythmias (n = 224) and ventricular arrhythmias (n = 86) prior to hospital discharge was 21% and 8%, respectively.

LONG-TERM FOLLOW-UP. Of the 426 patients known to be deceased, cause of death was known for 281 patients (66%). A total of 234 of 281 deaths (83%) were from a primary cardiac cause; however, the cause of death was multifactorial in many patients. Contributing factors in the reported cause of death for 281 patients included respiratory failure (n = 101 [36%]), renal insufficiency (n = 85 [30%]), sudden death or arrhythmia (n = 52 [19%]), bleeding complications or cardiac tamponade (n = 50 [18%]), disseminated intravascular coagulopathy/sepsis (n = 48 [17%]), PLE (n = 31 [11%]), and hepatic insufficiency (n = 29 [10%]). Four patients died from malignancies: 2 with hepatocellular carcinoma, 1 with metastatic cervical cancer, and 1 with multiple myeloma.

The 10-, 20-, and 30-year freedom from death or cardiac transplant was 73%, 59%, and 40%, respectively. Factors associated with decreased survival or transplant in multivariate analysis included elevated pre-operative PAP (>17 mm Hg), asplenia, use of pre-operative diuretics, operation prior to 1991, longer bypass time, absence of intraoperative sinus rhythm, and elevated post-bypass Fontan (>20 mm Hg) or LA (>13 mm Hg) pressures (Table 6). Thirty-eight patients in the cohort had heart transplants (mean age at transplant 24.0 ± 11.8 years), with 24 of 38 (63%) known

TABLE 4 Late Survival* Post-Fontan Operation

	N	10-Yr Survival, %	20-Yr Survival, %	30-Yr Survival, %
Overall	932	83	68	48
Operative era				
1973–1990	676	79	65	45
1991–2000	176	95	79	
2001 onward	80	98		
Age at Fontan				
<2 yrs	20	95	74	
2–4 yrs	175	88	80	67
5–16 yrs	569	83	68	50
>16 yrs	168	76	58	30
Bidirectional Glenn				
Absent	780	81	67	47
Present	152	96	70	
Pre-operative sinus rhythm				
Absent	56	62	37	16
Present	876	84	70	50
Pre-operative PAP				
Normal (≤15 mm Hg)	413	87	73	49
Abnormal (>15 mm Hg)	406	79	63	47
Pre-operative SVEDP				
Normal (≤12 mm Hg)	551	86	72	52
Abnormal (>12 mm Hg)	302	79	63	43
Type of Fontan				
Atriopulmonary	539	80	65	46
Intra-atrial tunnel	231	84	70	39
Extracardiac conduit	111	97	62	62
Other	51	78	67	45
AVV replacement at time of Fontan				
No	916	84	69	48
Yes	16	36	12	
Intraoperative sinus rhythm				
Absent	89	66	42	29
Present	843	85	71	49
Post-bypass Fontan pressure				
≤20 mm Hg	819	85	70	51
>20 mm Hg	76	62	50	17
Chest tube duration				
1–5 days	100	85	70	52
6–10 days	325	89	76	61
11–15 days	229	87	72	43
16–20 days	125	77	69	58
>21 days	145	68	46	23
Post-operative chylous effusions				
Absent	877	83	69	48
Present	55	73	55	44
Post-operative ventricular arrhythmias				
Absent	883	84	69	49
Present	49	61	46	28
Post-operative atrial arrhythmias				
Absent	735	84	70	52
Present	197	77	61	27
Post-operative low cardiac output (pressors >3 days)				
Absent	535	87	73	52
Present	397	77	62	34
Post-operative renal insufficiency				
Absent	858	85	71	50
Present	74	53	37	26
Reoperation <30 days after Fontan				
Absent	790	85	70	50
Present	142	72	56	36

*>30 days.
Abbreviations as in Table 2.

Continued in the next column

to be alive post-transplant (mean follow-up 10.4 ± 6.9 years).

Among the 932 patients who survived at least 30 days after the initial Fontan operation, the 10-, 20-, and 30-year freedom from death or reoperation was 69%, 50%, and 33%, respectively. Factors associated with decreased survival or reoperation in multivariate analysis included asplenia, use of pre-operative diuretics, elevated pre-operative PAP (>17 mm Hg), atriopulmonary type of Fontan connection, atrioventricular valve (AVV) replacement at the time of Fontan procedure, intraoperative rhythm other than sinus, longer bypass time, and elevated post-bypass Fontan pressure (>20 mm Hg) (Table 7). A prior bidirectional Glenn procedure was associated with improved survival and freedom from reoperation.

Most patients had their long-term follow-up at other medical institutions. The most common late reoperations were pacemaker insertion/revision (n = 212 [23%]), Fontan revision/conversion (n = 117 [13%]), and AVV repair/replacement (n = 66 [7%]). Implantable cardioverter-defibrillators were placed in 14 patients (2%) during long-term follow-up. At least 71 of 117 patients (61%) undergoing Fontan conversion/revision had a prior diagnosis of arrhythmia at a mean duration of 6.3 ± 5.6 years prior to their operation. Of these 117 patients, 10 (9%) died within 30 days of their Fontan conversion/revision. During long-term follow-up, 37 of 117 patients (32%) died at a mean duration of 5.2 ± 5.7 years (median 2.7 years) after reoperation. There were 17 patients who had late Fontan takedown; of these, 12 patients (71%) died during long-term follow-up (7 [41%] within 30 days of Fontan takedown).

Freedom from PLE at 10, 20, and 30 years after the Fontan procedure was 92%, 89%, and 83%, respectively. A total of 95 patients were diagnosed with PLE,

TABLE 5 Late Survival Post-Fontan Operation

	HR	95% CI	p Value
Pre-operative sinus rhythm	0.38	0.26-0.57	<0.001
AVV replacement at the time of Fontan	4.02	2.07-7.80	<0.001
Post-operative LA pressure >13 mm Hg	2.05	1.48-2.82	<0.001
Post-operative ventricular arrhythmias	1.79	1.18-2.72	0.006
Post-operative renal insufficiency	2.49	1.74-3.58	<0.001
Post-operative chest tube duration ≥21 days	1.15	1.05-1.26	0.003
PLE	1.97	1.48-2.63	<0.001

PLE = protein-losing enteropathy; other abbreviations as in Tables 2 and 3.

of whom 88 patients had an available date of diagnosis. For these 88 patients, mean age at Fontan was 11.2 ± 8 years and mean interval from Fontan to diagnosis of PLE was 8.1 ± 7.9 years (median: 5 years; range: 2 months to 32 years). Fifty-one of 88 patients with PLE (58%) had a date of diagnosis prior to 1995. Fenestration at the time of Fontan procedure was performed in 4 patients; 8 patients had late fenestration as an attempted therapy for PLE. There was no significant difference in mean duration to onset of PLE by type of Fontan operation. Factors associated with development of PLE in multivariate analysis are listed in Table 8.

Overall mortality in the PLE cohort was 72% (63 of 88) during 7.0 ± 7.4 years of follow-up. Cause of death was known for 36 of 88 patients: chronic heart failure in 13, sepsis/multiorgan failure in another 13, and other PLE-related complications in the remaining 10. Survival at 5, 10, and 20 years after PLE diagnosis was 50%, 35%, and 19%, respectively (Central Illustration).

There were 996 of 1,052 patients (95%) who did not have a known pre-operative arrhythmia; they were included in arrhythmia analyses. For these patients, the overall freedom from post-operative arrhythmias at 10, 20, and 30 years after the Fontan operation was 71%, 42%, and 24%, respectively. New arrhythmias were diagnosed more than 30 days after the Fontan operation in 412 of 996 patients (41%), with some patients having multiple arrhythmias. Late arrhythmias in these 412 patients included atrial flutter (n = 304 [74%]), atrial fibrillation (n = 161 [39%]), atrial tachycardia (n = 108 [26%]), re-entrant supraventricular tachycardia (n = 37 [9%]), and ventricular tachycardia (n = 40 [10%]).

A total of 195 patients had available liver imaging or biopsy/pathology data and of these, 40 patients (21%) were diagnosed with cirrhosis at a mean duration of 23.3 ± 6.3 years from the Fontan procedure; their average age at the time of Fontan operation was 9.6 ± 9.2 years. Five patients were diagnosed with hepatocellular carcinoma at a mean duration of 20 ± 2.9 years after the Fontan operation (2 patients died during long-term follow-up).

Patient rating of their current health and physical status on the surveys returned are shown in the Central Illustration and Figure 4.

DISCUSSION

We present the largest long-term follow-up study from a single institution for patients after the Fontan operation.

MORTALITY, TRANSPLANT, AND REOPERATION. As surgical techniques and management of patients after the Fontan operation have improved over the last 40 years, a number of investigators have reported improvement in early and intermediate-term survival (9,11,15). In our cohort, early mortality after Fontan operation was 13% in the surgical era prior to 1991 but decreased to 7.8% from 1991 to 2000 and 6.9% in the era following 2000. This increase in patient survival has been attributed to multiple factors, including better patient selection and improvement in operative techniques and post-operative patient management.

Indeed, studies from the Mayo Clinic–based on our early cohort–contributed to the development of more appropriate selection criteria (8,10). Compared with a similar cohort of patients having the Fontan operation at Boston Children's Hospital (median age 7.9 years), there was a comparable high incidence of early and late mortality after the initial Fontan operation (12). However, unlike the Boston study, in which there was significant attrition in late follow-up data, our 20-year data were based on 35% of the patients in our cohort. Many of the factors associated with long-term mortality or transplant in the Boston study (PLE, diuretic therapy, higher Fontan pressure) were consistent with our study's results.

Recent studies from the Children's Hospital of Philadelphia (15), the Australia/New Zealand registry (11,16), and the University of Alabama at Birmingham (9) noted that early and late survival after Fontan operation was excellent, with no increase in late mortality. However, these results are based on a more recent surgical era than patients in our series, and the Fontan connections were primarily lateral tunnel or extracardiac Fontan connections involving younger patients with a higher proportion of fenestrations. Additionally, the survival data at 20 years and beyond in these studies were based on a very small number of patients. The long-term survival of patients with lateral tunnel Fontan connections was poor in our study, likely due to several reasons: 1) many of the earlier "lateral tunnel" operations were performed in patients with heterotaxy syndromes, for which

TABLE 6 Risk of Death or Cardiac Transplant

	HR	95% CI	p Value
Surgical era 1991–2000*	0.63	0.44-0.90	0.01
Surgical era 2001 onward*	0.12	0.02-0.84	0.03
Intraoperative sinus rhythm	0.64	0.47-0.88	0.005
Pre-operative mean catheter PAP >17 mm Hg	1.42	1.15-1.77	0.001
Asplenia	1.55	1.07-2.25	0.02
Pre-operative use of diuretics	1.58	1.22-2.04	<0.001
Post-operative Fontan pressure >20 mm Hg	2.29	1.72-3.05	<0.001
Post-operative LA pressure >13 mm Hg	1.85	1.39-2.47	<0.001
Longer bypass time†	1.12	1.05-1.20	0.001

*Compared with the surgical era from 1973 through 1990. †For every 30-min increase in overall bypass time.
Abbreviations as in Tables 2 and 3.

TABLE 7 Risk of Death or Reoperation

	HR	95% CI	p Value
Bidirectional Glenn prior to Fontan	0.41	0.24-0.70	0.001
Intraoperative sinus rhythm	0.69	0.52-0.94	0.02
Pre-operative mean catheter PAP >17 mm Hg	1.43	1.17-1.76	<0.001
Asplenia	1.81	1.23-2.64	0.002
Pre-operative use of diuretics	1.77	1.39-2.26	<0.001
Atriopulmonary Fontan connection	1.48	1.16-1.88	0.002
AVV replacement at the time of Fontan	2.42	1.39-4.22	0.002
Post-operative Fontan pressure >20 mm Hg	3.16	2.45-4.07	<0.001
Longer bypass time*	1.08	1.009-1.16	0.03

*For every 30-min increase in overall bypass time.
Abbreviations as in Tables 2 and 3.

intra-atrial conduits were used; and 2) others incorporated a variable amount of native atrial tissue into the surgical repair, making them susceptible to some of the same long-term complications as operations in patients with atriopulmonary connections. Additionally, ventricular morphology did not influence overall survival in this study, presumably because a majority of the right ventricular morphology patients in this study did not have hypoplastic left heart syndrome (therefore, there was no need for a Norwood operation).

The timing of Fontan conversion, or listing for cardiac transplant, in a patient with a long-standing atriopulmonary Fontan connection is not always straightforward. In this study, we noted that the <30-day mortality with Fontan conversion/revision was 9%. Studies from multiple institutions (17–19) have identified risk factors for poor outcome with Fontan conversion, such as PLE, systemic right ventricular/intermediate ventricular morphology, significant AVV regurgitation, older age (>27 years), elevated systemic ventricular end-diastolic pressure, renal dysfunction, and cirrhosis. However, either concomitant arrhythmia operation or concomitant surgery for Fontan obstruction is associated with better overall outcome. The Boston Children's group evaluated the outcomes of failing Fontan patients listed for transplant and noted decreased survival in patients with preserved ventricular function compared with those with impaired ventricular function (20). This was attributed to the challenges of determining the ideal timing of cardiac transplant in patients with preserved ventricular function because it has been shown that long-term survival is reasonable in patients with PLE despite increased early post-operative mortality after transplant (21,22). However, in the older atriopulmonary Fontan patients who do not clearly meet criteria for a low-risk Fontan conversion or listing for transplant, management decisions need to be made on an individual basis after careful consideration of associated risks and benefits.

In other large single-center studies, approximately 2% of patients required late cardiac transplant, and there has been limited long-term follow-up (11,12). In our cohort, 38 patients (3.6%) had heart transplants (mean age at transplant 24.0 ± 11.8 years), and 63% of these patients were known to be alive at last follow-up.

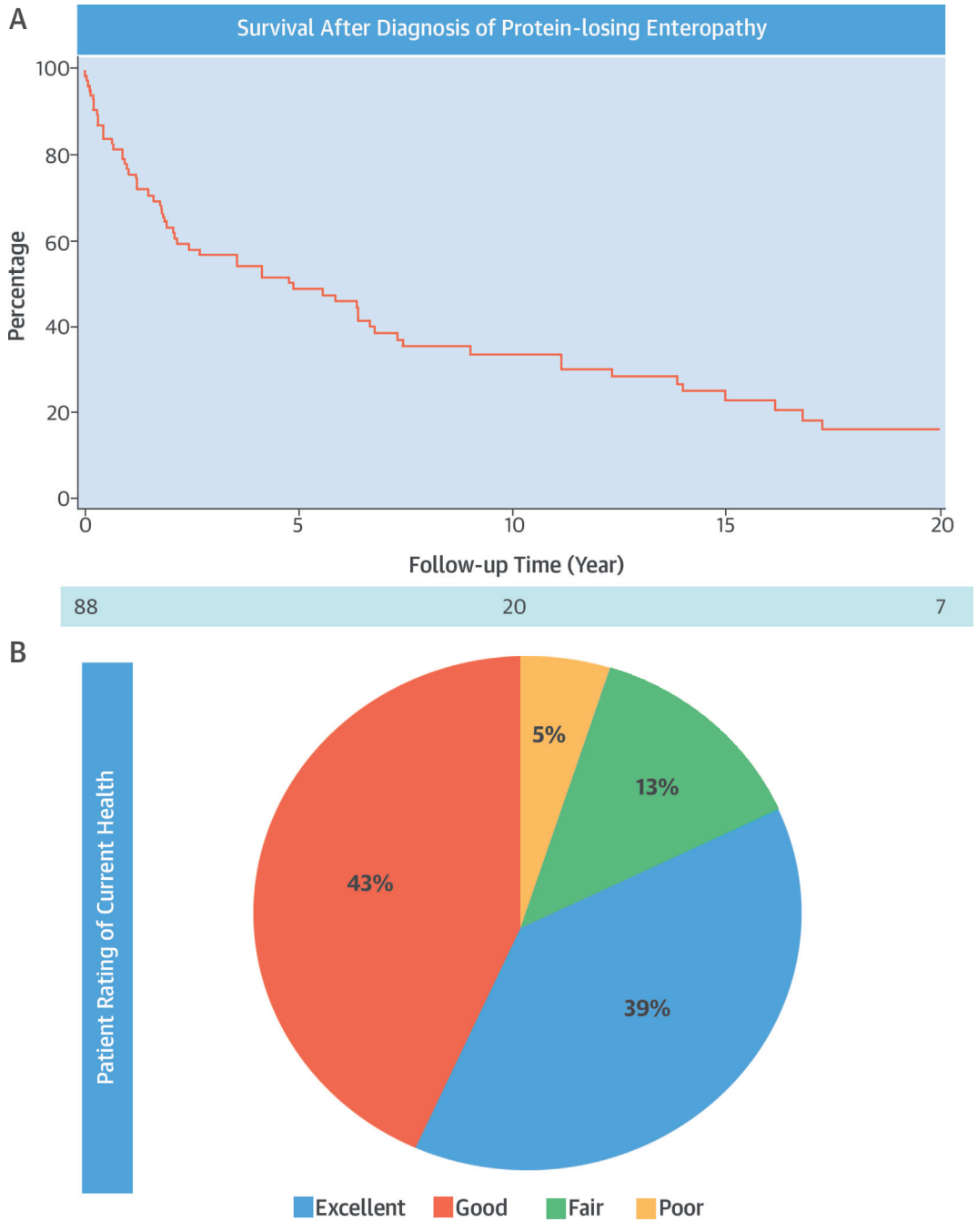
ABNORMALITIES RELATED TO FONTAN PHYSIOLOGY. The overall incidence of PLE in this study was 9%, which is similar to the 5% to 15% incidence quoted in other large studies (23–25). Freedom from developing PLE at 10, 20, and 30 years post-Fontan procedure was 92%, 89%, and 83%, respectively. Survival at 5, 10, and 20 years after diagnosis of PLE was 50%, 35%, and 19%, respectively. As noted in previous studies, elevated pre-operative mean PAP and post-bypass LA pressure were associated with an increased risk of developing PLE (23). A contemporary cohort of patients with PLE followed at our institution had much better survival (25); however, this study included patients who did not have their Fontan operations at our institution. Hence, it is not a cohort study, and one cannot directly compare those survival statistics with those of a cohort study such as ours. Nonetheless, the substantial mortality in our cohort would suggest that aggressive management of PLE and

TABLE 8 Risk of Developing PLE Post-Fontan Operation

Variable	HR	95% CI	p Value
Pre-operative catheter mean PAP pressure >17 mm Hg	1.82	1.14-2.91	0.01
Post-operative LA pressure >13 mm Hg	3.10	1.70-5.66	<0.001
Late arrhythmia (as time-dependent covariate)	1.81	1.07-3.06	0.03

Abbreviations as in Tables 2, and 3.

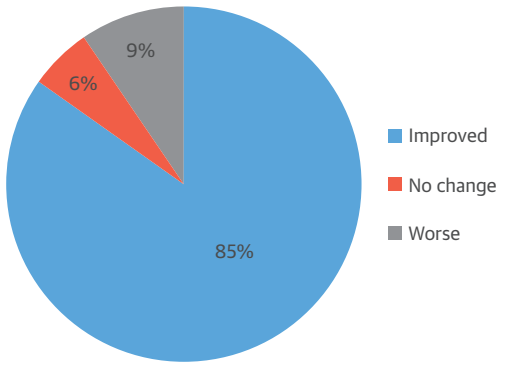
CENTRAL ILLUSTRATION **40-Year Follow-Up After the Fontan Operation**



Pundi, K.N. et al. J Am Coll Cardiol. 2015; 66(15):1700–10.

Although the Fontan procedure has improved overall survival in patients with single ventricles, various events impact long-term survival, including diagnosis of protein-losing enteropathy **(A)**. Other factors that adversely affect survival are pre-operative diuretic use, longer cardiopulmonary bypass time, timing of surgery, simultaneous atrioventricular valve replacement, and post-operative ventricular arrhythmias. Post-operatively, 82% of patients responding (n = 305 surveys) rated their current health status as good or excellent **(B)**.

FIGURE 4 Pre- and Post-Operative Physical Status



The Fontan operation improved physical status in 85% of patients (n = 284 surveys).

earlier consideration of heart transplant might be important in these patients, especially if the PLE is refractory to medical management.

Overall, 44% of patients had a diagnosis of a new clinical arrhythmia during long-term follow-up. Freedom from arrhythmia at 10, 20, and 30 years after the Fontan operation was 71%, 42%, and 24%, respectively. A majority of these patients had atrial flutter or fibrillation, and a smaller proportion had re-entrant supraventricular tachycardia, atrial tachycardia, or ventricular tachycardia.

Increased attention is being paid to the development of cirrhosis and hepatocellular carcinoma in patients who have had the Fontan operation (26–32). Presumably, this results at least in part due to elevated hepatic venous pressure, but understanding of the pathophysiology of liver dysfunction after Fontan procedure is evolving. There is likely a strong referral bias accounting for the high incidence of cirrhosis in our patient cohort. However, it still highlights the need for more aggressive evaluation and management of liver disease in these patients. The role of cardiac transplant (with or without concomitant liver transplant) continues to be debated in these patients (21,33–40).

QUALITY OF LIFE. Eighty percent of the patients after the Fontan operation rated their current health as excellent, and a similar percentage of patients thought that their physical status was improved. There is likely a selection bias in these data because the patients who chose to complete these surveys may be healthier than their counterparts and had their Fontan surgery during a later era. However, this is consistent with previously reported data suggesting that patients tend to perceive themselves as having a higher functional status compared with control populations (41).

STUDY LIMITATIONS. One limitation of our study is that it was a single-center cohort from a large tertiary referral center over an almost 4-decade time frame. Therefore, in all the late follow-up outcomes, the data curves were censured using the date of last available follow-up on each patient. Some of these results may not be directly translatable to a younger cohort of patients in a recent surgical era. Liver disease may be underreported in this cohort because imaging studies were not routinely performed in patients operated on in the early surgical era. However, as more patients with congenital heart disease live into adulthood, these data are relevant in the medical management of patients with atriopulmonary or lateral tunnel Fontan operations, especially those who have survived 20 to 30 years after their initial operation.

CONCLUSIONS

With better patient selection and evolution of surgical techniques and medical management of patients after the Fontan operation, there has been improvement in survival over the last 40 years. The overall 10-, 20-, and 30-year survival in our study from the time of operation was 74%, 61%, and 43%, respectively. However, the development of PLE, ventricular failure, cirrhosis, arrhythmias, and the need for reoperation during long-term follow-up pose significant management challenges.

ACKNOWLEDGMENTS The authors thank Drs. Dwight McGoon, Gordon Danielson, Francisco Puga, and Harold Burkhart, who performed many of the operations in this study, and Matt Cetta for assistance with data abstraction.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Frank Cetta, Division of Pediatric Cardiology, Mayo Clinic, Gonda 6335, 200 First Street SW, Rochester, Minnesota 55905. E-mail: cetta.frank@mayo.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Over the last 40 years, surgical techniques used in the Fontan operation have evolved and survival rates have improved, but post-operative protein-losing enteropathy and arrhythmias and the need for reoperation during long-term follow-up remain considerable challenges.

TRANSLATIONAL OUTLOOK: Further long-term studies are needed to examine the occurrence of late complications in patients who have undergone atriopulmonary Fontan procedures.

REFERENCES

1. Fontan F, Mounicot FB, Baudet E, et al. "Correction" of tricuspid atresia. 2 cases "corrected" using a new surgical technic. Ann Chir Thorac Cardiovasc 1971;10:39–47.

2. Kreutzer G, Galindez E, Bono H, et al. An operation for the correction of tricuspid atresia. J Thorac Cardiovasc Surg 1973;66:613–21.

3. Russo P, Danielson GK, Puga FJ, et al. Modified Fontan procedure for biventricular hearts with complex forms of double-outlet right ventricle. Circulation 1988;78:III20–5.

4. Puga FJ. Modified Fontan procedure for hypoplastic left heart syndrome after palliation with the Norwood operation. J Am Coll Cardiol 1991;17:1150–1.

5. Humes RA, Feldt RH, Porter CJ, et al. The modified Fontan operation for asplenia and polysplenia syndromes. J Thorac Cardiovasc Surg 1988;96:212–8.

6. Mayer JE Jr., Helgason H, Jonas RA, et al. Extending the limits for modified Fontan procedures. J Thorac Cardiovasc Surg 1986;92:1021–8.

7. Norwood WI Jr., Jacobs ML, Murphy JD. Fontan procedure for hypoplastic left heart syndrome. Ann Thorac Surg 1992;54:1025–30.

8. Cetta F, Feldt RH, O'Leary PW, et al. Improved early morbidity and mortality after Fontan operation: the Mayo Clinic experience, 1987 to 1992. J Am Coll Cardiol 1996;28:480–6.

9. Dabal RJ, Kirklin JK, Kukreja M, et al. The modern Fontan operation shows no increase in mortality out to 20 years: a new paradigm. J Thorac Cardiovasc Surg 2014;148:2517–24.

10. Driscoll DJ, Offord KP, Feldt RH, et al. Five- to fifteen-year follow-up after Fontan operation. Circulation 1992;85:469–96.

11. d'Udekem Y, Iyengar AJ, Galati JC, et al. Redefining expectations of long-term survival after the Fontan procedure: twenty-five years of follow-up from the entire population of Australia and New Zealand. Circulation 2014;130 11 Suppl 1:S32–8.

12. Khairy P, Fernandes SM, Mayer JE Jr., et al. Long-term survival, modes of death, and predictors of mortality in patients with Fontan surgery. Circulation 2008;117:85–92.

13. Bartz PJ, Driscoll DJ, Dearani JA, et al. Early and late results of the modified Fontan operation for heterotaxy syndrome: 30 years of experience in 142 patients. J Am Coll Cardiol 2006;48:2301–5.

14. Deal BJ, Jacobs ML. Management of the failing Fontan circulation. Heart 2012;98:1098–104.

15. Rogers LS, Glatz AC, Ravishankar C, et al. 18 years of the Fontan operation at a single institution: results from 771 consecutive patients. J Am Coll Cardiol 2012;60:1018–25.

16. Iyengar AJ, Winlaw DS, Galati JC, et al. The extracardiac conduit Fontan procedure in Australia and New Zealand: hypoplastic left heart syndrome predicts worse early and late outcomes. Eur J Cardiothorac Surg 2014;46:465–73.

17. Mavroudis C, Deal BJ, Backer CL, et al. J. Maxwell Chamberlain Memorial Paper for congenital heart surgery. 111 Fontan conversions with arrhythmia surgery: surgical lessons and outcomes. Ann Thorac Surg 2007;84:1457–66.

18. Said SM, Burkhart HM, Schaff HV, et al. Fontan conversion: identifying the high-risk patient. Ann Thorac Surg 2014;97:2115–22.

19. van Son JA, Mohr FW, Hambsch J, et al. Conversion of atriopulmonary or lateral atrial tunnel cavopulmonary anastomosis to extracardiac conduit Fontan modification. Eur J Cardiothorac Surg 1999;15:150–8.

20. Griffiths ER, Kaza AK, Wyler von Ballmoos MC, et al. Evaluating failing Fontans for heart transplantation: predictors of death. Ann Thorac Surg 2009;88:558–64.

21. Kanter KR, Mahle WT, Vincent RN, et al. Heart transplantation in children with a Fontan procedure. Ann Thorac Surg 2011;91:823–30.

22. Gambetta K, Backer C, Deal B, et al. Insights into heart transplantation for protein losing enteropathy: a 24 year experience. J Heart Lung Transplant 2013;32 Suppl:S193.

23. Feldt RH, Driscoll DJ, Offord KP, et al. Protein-losing enteropathy after the Fontan operation. J Thorac Cardiovasc Surg 1996;112:672–80.

24. Mertens L, Hagler DJ, Sauer U, et al., for the PLE Study Group. Protein-losing enteropathy after the Fontan operation: an international multicenter study. J Thorac Cardiovasc Surg 1998;115:1063–73.

25. John AS, Johnson JA, Khan M, et al. Clinical outcomes and improved survival in patients with protein-losing enteropathy after the Fontan operation. J Am Coll Cardiol 2014;64:54–62.

26. Friedrich-Rust M, Koch C, Rentzsch A, et al. Noninvasive assessment of liver fibrosis in patients with Fontan circulation using transient elastography and biochemical fibrosis markers. J Thorac Cardiovasc Surg 2008;135:560–7.

27. Ginde S, Hohenwalter MD, Foley WD, et al. Noninvasive assessment of liver fibrosis in adult patients following the Fontan procedure. Congenit Heart Dis 2012;7:235–42.

28. Yoo BW, Choi JY, Eun LY, et al. Congestive hepatopathy after Fontan operation and related factors assessed by transient elastography. J Thorac Cardiovasc Surg 2014;148:1498–505.

29. Schwartz MC, Sullivan L, Cohen MS, et al. Hepatic pathology may develop before the Fontan operation in children with functional single ventricle: an autopsy study. J Thorac Cardiovasc Surg 2012;143:904–9.

30. Samsky MD, Patel CB, DeWald TA, et al. Cardiohepatic interactions in heart failure: an overview and clinical implications. J Am Coll Cardiol 2013;61:2397–405.

31. Rychik J, Veldtman G, Rand E, et al. The precarious state of the liver after a Fontan operation: summary of a multidisciplinary symposium. Pediatr Cardiol 2012;33:1001–12.

32. Johnson JA, Cetta F, Graham RP, et al. Identifying predictors of hepatic disease in patients after the Fontan operation: a postmortem analysis. J Thorac Cardiovasc Surg 2013;146:140–5.

33. Simpson KE, Esmaeeli A, Khanna G, et al. Liver cirrhosis in Fontan patients does not affect 1-year post-heart transplant mortality or markers of liver function. J Heart Lung Transplant 2014;33:170–7.

34. Rossano JW, Shaddy RE. Heart transplant after the Fontan operation. Cardiol Young 2013;23:841–6.

35. Michielon G, van Melle JP, Wolff D, et al. Favourable mid-term outcome after heart transplantation for late Fontan failure. Eur J Cardiothorac Surg 2015;47:665–71.

36. Davies RR, Sorabella RA, Yang J, et al. Outcomes after transplantation for "failed" Fontan: a single-institution experience. J Thorac Cardiovasc Surg 2012;143:1183–92.

37. Coskun TS, Coskun OK, El Arousy M, et al. Heart transplantation after Fontan procedure in adults. ASAIO J 2007;53:e3–4.

38. Bernstein D, Naftel D, Chin C, et al. Outcome of listing for cardiac transplantation for failed Fontan: a multi-institutional study. Circulation 2006;114:273–80.

39. Hollander SA, Reinhartz O, Maeda K, et al. Intermediate-term outcomes after combined heart-liver transplantation in children with a univentricular heart. J Heart Lung Transplant 2013;32:368–70.

40. Daly RC, Topilsky Y, Joyce L, et al. Combined heart and liver transplantation: protection of the cardiac graft from antibody rejection by initial liver implantation. Transplantation 2013;95:e2–4.

41. McCrindle BW, Zak V, Pemberton VL, et al. Functional health status in children and adolescents after Fontan: comparison of generic and disease-specific assessments. Cardiol Young 2014;24:469–77.

KEY WORDS Fontan procedure, protein-losing enteropathy, survival

APPENDIX For supplemental tables, please see the online version of this article.