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Mode of death and predictors of mortality in adult Fontan survivors: A Japanese multicenter observational study

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ABSTRACT

Background: Mortality rates may be high in adult Fontan patients; however, the clinical determinants remain unclear.
Purpose: We conducted a prospective multicenter study of adult Fontan survivors to determine the 5-year mortality rate and clarify the determinants.
Method and results: We followed 600 adult Fontan survivors from 40 Japanese institutions (307 men, 28 ± 7 years old, follow-up: 18 ± 6 years). The New York Heart Association (NYHA) functional class I and II was 51% and 42%, respectively. During the follow-up period of 4.1 ± 1.6 years, 33 patients died, and the 5-year survival rate was 93.5%. The mode of death was heart failure in 11 patients (34%), arrhythmia or sudden death in 8 (24%), cancer in 5 (15%), perioperative problems and hemostatic problems in 4 each (12% for each), and infection in 1 (3%). Left isomerism, prior hospitalization, protein losing enteropathy (PLE), pulmonary arteriovenous fistulae, NYHA functional class, impaired hemodynamics, hyponatremia, hepatorenal dysfunction, and use of diuretics were associated with a high mortality rate ($p < 0.05$–0.0001). Further, PLE (hazard ratio [HR]: 14.4), left isomerism (HR: 3.5), and NYHA (HR: 2.4) independently predicted a high 5-year high mortality ($p < 0.05$ for all). The incidence of cancer-related mortality increased markedly with age >40 years.
Conclusions: Majority of the Japanese adult Fontan survivors had good functional status, with an acceptable 5-year survival rate. However, the significant prevalence of non-cardiac mortality highlights Fontan pathophysiology as a multi-organ disease that requires a multidisciplinary management strategy to improve the long-term outcome.

1. Introduction

A cohort of patients with complex congenital heart disease were treated with Fontan procedure since early 70s and most of these patients are now adults [1]. Although several short-to-medium term studies have been published [2,3], limited data are available regarding long-term adult Fontan survivors [4]. In Fontan patients, the hemodynamics may change over time, and the effect on prognosis in adult patients may differ from that in pediatric patients [5,6]. In addition, adult Fontan patients commonly experience non-cardiac co-morbidities that may have a significant adverse impact on survival [7,8,9]. Moreover, patients who have undergone the Fontan procedure have an expected life span of 30–40 years less than that of the general population [10].

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However, it is unclear whether this applied to Japanese Fontan patients. Consequently, we conducted a 5-year prospective multi-center study to clarify the current clinical status of Japanese adult Fontan survivors and the clinical determinants of mortality.

2. Method

The clinical status of Japanese adult Fontan survivors was reported at the 13th annual meeting of Japanese Society for Adult Congenital Heart Disease in 2011 in collaboration with 94 institutions. In that meeting, the data on the total number of 1048 adult Fontan survivors (≥18 years old), the nation-wide distribution, and current management situations were reported. In 2013, we conducted a follow-up study, and 40 (43%) institutions were approved to join this retrospective and prospective study in 2013.

After obtaining approval from each local ethical committee, questionnaires were sent to each institution in 2013, and information was obtained by the physician in charge of adult Fontan survivors. The questionnaires requested the following information of the patients during their hospital visits in 2011: date of last hospital visit in 2011, birth date, department in charge, Fontan operation-related issues, New York Heart Association (NYHA) functional class, employment, marital status, physical findings, medications, major complications (protein losing enteropathy [PLE], pulmonary arteriovenous fistulae [PAVF]), history of unexpected hospitalization, biochemical data (liver function, renal function, electrolytes), cardiothoracic ratio (CTR) on chest radiography, electrocardiography (ECG) findings (presence/absence of sinus rhythm, heart rate, pacemaker implantation), cardiac function (ejection fraction [EF] of the systemic ventricle either with echocardiography or cine-ventriculography), arteriovenous (AV) valve regurgitation (non-mild, moderate, severe), and a history of pregnancy or childbirth. If these data from 2011 were missing, those from 2010 were reported.

Systemic ventricular systolic function was graded as preserved (EF ≥ 50), reduced (30 ≤ EF < 50), or poor (EF < 30). Fontan operation-related issues included the era and age at the first Fontan operation, type of procedure, and history of conversion from atriopulmonary connection (APC) to total cavopulmonary connection (TCPC), referred to as TCPC conversion. In this study, we included patients with Bjork surgery as other type of Fontan procedure because the hemodynamics is somewhat similar to that in APC patients as previously analyzed [4]. The questionnaire also requested information regarding all-cause deaths that occurred over the 5-year study period. In addition, information of reinterventions during the follow-up was also requested. Causes of death were categorized into arrhythmia-related (including sudden death), heart failure (HF), surgery or catheter intervention, cancer, or other. Each institutional ethical committee waived the requirement for individual informed consent from the patients because the data of some deceased patients were also included in this study. However, according to the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects, an opt-out approach was used for each participating institution.

2.1. Definition of mode of death

Death was labeled secondary to HF if it complicated worsening HF as defined by evidence of at least one of the following: orthopnea, nocturnal dyspnea, pulmonary edema, increasing peripheral edema with or without inappropriate body weight gain, or radiological signs of congestive HF. Sudden death was defined as death due to cardiovascular causes within 1 h of onset, significant symptom worsening, or unwitnessed death during sleep [11]. Death was considered arrhythmia-associated if clinically relevant arrhythmia was detected at the time of death. We categorized sudden death and arrhythmia as a single event (arrhythmia or sudden death) because the clinical manifestations could sometimes not be differentiated. Death was considered perioperative if it occurred within 30 days of the surgery or before hospital discharge. Death was considered to have been caused by hemostatic problems, either thromboembolic if secondary to thrombus identified with image modalities, or hemorrhagic, if secondary to massive bleeding, such as gastrointestinal or cerebral bleeding. Death was considered to have occurred because of PAVF if it occurred with severe hypoxia without significant major Fontan-associated complications. The remaining causes of death were classified as "other."

2.2. Statistical analyses

Differences in demographics, functional capacity, cardiac function, and hemodynamic variables were analyzed using Student *t*-test and one-way analysis of variance with a Tukey post-hoc test for a comparison among two and three or more groups, respectively. Comparisons with respect to the prevalence of medications were evaluated using chi-square test. Cumulative hazards for mortality after patient registration were plotted on a linear scale using the product-limit technique. In addition, the associations between various causes of mortality and age were assessed using a nonparametric competing risk survival model that accounted for left truncation. The cumulative incidence of mortality in the

Table 1
Subject characteristics at registration.

	All		Fontan type at registration			
			APC	TCPC	Other	*p*
Cases	600	n/%	136	451	13	–
Male	307	52%	52%	53%	15%	0.0207
Age at registration (year)	28 ± 7	600	28 ± 7	27 ± 6	31 ± 10	0.1118
Body mass index (kg/m^2)	21 ± 3	551	21 ± 3	21 ± 3	20 ± 2	0.8447
Age at 1st Fontan operation (year)	10 ± 8	589	9 ± 6	10 ± 8	12 ± 12	0.2178
Era of 1st Fontan (1990s/2000s/2010s)	111/410/68	589	34/101/0	71/303/67	6/6/1	<0.0001
APC/TCPC/Other	236/343/21	600	136/0/0	100/343/8	0/0/13	<0.0001
History of TCPC conversion	127	–	0	127 (28%)	0	–
IAR/ECR	451	–	–	200/251	–	–
Follow-up at registration (year)	18 ± 6	578	19 ± 4	17 ± 6	20 ± 6	0.001
Lost to follow-up	26	4%	3%	5%	8%	0.5727
Diagnosis						
Heterotaxy syndrome	133	22%	21%	23%	0%	
Riso/Liso/No	79/53/468	600	13/16/107	66/37/348	0/0/13	0.0386
LV/Non-LV	261/275	536	57/76	191/199	13/0	<0.0001
UVH	171	29%	35%	27%	0%	–
TA	160	27%	22%	26%	92%	–
DORV	82	14%	13%	14%	0%	–
PA	50	8%	8%	8%	8%	–
MA	35	6%	4%	6%	0%	–
TGA	33	6%	10%	4%	0%	–
CAVC	25	4%	1%	5%	0%	–
AVD	22	4%	4%	4%	0%	–
Others	55	8%	13%	10%	0%	–
Medications (%)						
Diuretics	224	38%	35%	38%	77%	0.0126
Warfarin	324	55%	31%	67%	54%	<0.0001
Anti-platelet	389	66%	49%	73%	46%	<0.0001
ACEI/ARB	272	46%	17%	55%	46%	<0.0001
Beta blocker	195	33%	24%	33%	38%	0.0245
Anti-arrhythmia	125	21%	21%	21%	23%	0.985
Anti-hyperuricemia	56	10%	80%	10%	5%	0.6767
Dilator(s) of pulmonary artery	38	7%	40%	70%	15%	0.3129
Anti-convulsant	13	2%	0%	30%	0%	0.0221

ACEI = angiotensin converting enzyme inhibitor, APC = atriopulmonary connection, ARB = angiotensin receptor blocker, AVD = atrioventricular discordance, CAVC = common atrioventricular canal, DORV = double outlet right ventricle; ECR = extracardiac rerouting, IAR = intraatrial rerouting, LV = left ventricle, MA = mitral valve atresia, PA = pulmonary valve atresia, TA = tricuspid valve atresia; TCPC = total cavopulmonary connection, TGA = transposition of the great arteries, UVH = univentricular heart. Values are mean ± SD.

presence of competing risks was estimated using the stcompet package for Stata (Version IC 14.2, College Station, TX). We used a Cox's proportional hazards model to predict the associations between the clinical variables and all-cause mortality. The variables that proved significant outcome predictors in the univariate analysis ($p < 0.05$) were included in the multivariate analysis to identify the independent predictors. During the Cox's model assessment of the impact of systemic ventricular EF and AV valve regurgitation on prognosis, HRs were computed using EF gradings (preserved = 3, reduced = 2, and poor = 1) and AV valve regurgitation levels (severe = 3, moderate = 2, and ≤ mild = 1). Systemic ventricular type was classified as follows: left ventricular type and non-left ventricular type. A free from all-cause death (time 0, the day of registration) status was estimated using the Kaplan-Meier method, and the differences in the event-free status in the two groups were assessed using log rank tests. In order to evaluate the influence of hepatorenal dysfunction on prognosis, we used the plasma levels of total bilirubin, creatinine, and a model for end-stage liver disease, excluding INR (MELD-XI) score. Estimated glomerular filtration rate was not included in the analysis because of the poor prognostic value [12]. Survival was compared with that predicted for an age-matched healthy cohort comprising Japanese residents using Life Table Data (2015 Life Table) published by the Japanese Government of Ministry of Health, Labour, and Welfare (http://www.mhlw.go.jp/toukei/saikin/hw/life/22th/index.html). Equivalent age was defined as the age of Japanese residents with the most similar categorical 5-year mortality as in our patients. Estimate standardized mortality ratios were determined by comparison with an age- and sex-matched sample of the general population, as reported previously [13]. A p value <0.05 was considered statistically significant. Data are expressed as the mean ± standard deviation (SD) values. Analyses were performed using the software packages JMP 12 Pro (SAS Institute, Cary, NC, USA) and STAT (Version IC 14.2, College Station, TX).

3. Results

3.1. Clinical characteristics at registration

Four patients were excluded from the initial total cohort ($n = 604$; 1 patient was excluded because the patient was <18 years of age, 1 was excluded because of a total cavopulmonary shunt, and 2 were excluded because no clinical data were available. The remaining 600 patients were included in the analyses, which was 57.3% of the initial total number of 1048 patients reported at the 13th Japanese meeting in 2001. The patients' clinical characteristics at registration are shown in Table 1. TCPC conversion had been performed in 127 (28.2%) patients before study registration. There was no difference in the age at the time of registration with respect to the type of the final Fontan procedure. Extracardiac rerouting procedure was predominant among TCPC patients. The post-Fontan follow-up duration was shorter and anticoagulant usage rate was higher in the TCPC patients as compared to that in the APC patients.

The Fontan pathophysiology, including the cardiovascular and non-cardiovascular issues, is summarized in Table 2. There was no difference in the major complications among the three Fontan subgroups. TCPC patients showed a smaller CTR, higher resting heart rate, and higher incidence of pacemaker implantation. With respect to the extra-cardiac pathophysiology, hepatorenal function was more impaired in the APC patients than in TCPC patients.

All the registered patients should have had a total of 5 years of follow-up period: a 2-year retrospective follow-up period (because the questionnaires were administered in 2013, 2 years after the 13th annual meeting in 2011) and a 3-year prospective follow-up period. However, the 2-year retrospective information was not reported in 297 patients for whom only prospective information was available. Conversely, in 253 of the remaining 303 patients, 3 year retrospective information (since 2010) was available, resulting in a total follow-up period of up to 6 years.

Table 2
Cardiovascular and non-cardiovascular status at registration.

	All	APC	TCPC	Others	p
Variables					
Prior hospitalization					
Arrhythmias	232 (40%)	51 (38%)	172 (39%)	9 (69%)	0.0872
History of heart failure admission	51 (9%)	9 (7%)	38 (9%)	4 (31%)	0.0527
History of thromboembolic events	48 (8%)	8 (6%)	39 (9%)	1 (8%)	0.5371
Complications					
PAVF	22 (4%)	5 (4%)	16 (4%)	1 (8%)	0.8011
PLE	22 (4%)	3 (2%)	18 (4%)	1 (8%)	0.4551
Cardiovascular status					
NYHA class (I/II/III/IV/Unknown)	307/249/26/5/6	62/65/4/1/0	241/178/19/4/6	4/6/3/0	
NYHA class	1.5 ± 0.6	1.6 ± 0.6	1.5 ± 0.6	1.9 ± 0.8	0.0496
Cardiothoracic ratio (%)	49 ± 7	52 ± 7*	48 ± 6	59 ± 9*!	<0.0001
ECG findings					
Heart rate (bpm)	73 ± 14	70 ± 13	74 ± 14!	72 ± 11	0.0331
Sinus rhythm	488 (86%)	114 (87%)	364 (85%)	10 (77%)	0.6308
Pacemaker implantation	56 (10%)	7 (5%)	49 (11%)	0 (0%)	0.0242
Ventricular systolic function	2.8 ± 0.5	2.7 ± 0.6	2.8 ± 0.4	2.6 ± 0.5	0.0336
(Preserved = 3/reduced = 2/poor = 1)	435/99/10	91/23/6	337/71/4	7/5/0	–
Atrioventricular valve function	1.2 ± 0.4	1.2 ± 0.4	1.2 ± 0.4	1.3 ± 0.5	0.5552
(≤slight = 1/moderate = 2/severe = 3)	442/90/4	102/16/1	331/71/3	9/3/0	–
Blood pressure (mm Hg)					
Systolic	107 ± 14	109 ± 14	106 ± 14	105 ± 10	0.1462
Diastolic	64 ± 10	65 ± 9	63 ± 10	67 ± 9	0.1676
Mean	78 ± 10	80 ± 9	78 ± 11	80 ± 8	0.1081
Hemoglobin (g/dL)	15 ± 2	16 ± 2	15 ± 2!	14 ± 2	0.0027
Arterial oxygen saturation (%)	93 ± 4	92 ± 5	93 ± 4	93 ± 4	0.6675
BNP (pg/mL) ($n = 199$)	62 ± 103	88 ± 58	58 ± 104	205	0.0895
Non-cardiovascular status					
Electrolytes					
Na	140 ± 3	139 ± 4	140 ± 2	139 ± 2	0.3756
Hepatorenal function					
Albumin	4.4 ± 0.5	4.5 ± 0.5	4.4 ± 0.5	4.5 ± 0.4	0.573
Total-bilirubin	1.3 ± 1.0	1.5 ± 0.7	1.3 ± 1.1	1.2 ± 0.6	0.1747
ALT	25 ± 15	27 ± 15	25 ± 15	20 ± 6	0.1467
BUN	14 ± 7	15 ± 9	14 ± 7	14 ± 4	0.6813
Creatinine	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.1411
eGFR (mL/min/1.73)	99 ± 25	94 ± 23*	100 ± 25	89 ± 26	0.0164
MELD-XI score	10.4 ± 1.8	11.0 ± 2.1*	10.2 ± 1.8	10.0 ± 1.5	0.0009

ALT = alanin aminotransferase, BNP = brain natriuretic peptide, BUN = blood urea nitrogen, eGFR = estimated glomerular filtration rate. MELD-XI = model for end-stage liver disease eXcluding INR score, NYHA = New York Heart Association, PAVF = pulmonary arteriovenous fistulae, PLE = protein losing enteropathy. ! and * indicate statistically significant ($p < 0.05$) vs. group of APC and TCPC, respectively.

We lost 26 patients (4.3%) to follow-up after registration, and the remaining 574 patients were analyzed for mortality. At registration, there were no differences in the age at registration, age at the time of the first Fontan operation, sex, post-Fontan follow-up duration, NYHA functional class, CTR, incidence of rhythm abnormality, including pacemaker implantation, blood pressure, medications, arterial blood oxygen saturation, EF, AV valve regurgitation, plasma levels of albumin, sodium, total bilirubin, blood urea nitrogen, creatinine, and major complications between patients analyzed and those lost to follow-up.

3.2. Reinterventions

There were 22 reinterventions during the follow-up period, including 15 cardiac surgical procedures (seven TCPC conversions, three re-Fontan operations, three AV valve replacements, one aortic valve replacement, and one plasty of the AV valve), four catheter interventions (three coil embolizations for veno-venous collaterals and one stent implantation for pulmonary stenosis), and three pacemaker implantations (two for complete AV block and one for sick sinus syndrome). The 5-year reintervention-free rate was 95.3%.

3.3. All-cause mortality

During a follow-up of 4.1 ± 1.5 years, 33 patients died, and the 5-year survival rate was 93.5% (Fig. 1-a). The mode of death was HF in 11 patients (34%), arrhythmia or sudden death in 8 (24%), cancer in 5 (15%) (hepatocellular carcinoma: 4, malignant lymphoma: 1), perioperative problems and hemostatic problems in 4 patients each (12% for each), and infection in 1 patient (3%). Type of Fontan procedure at the time of registration had no significant impact on the survival (Fig. 1-b). Significant associations of the clinical variables with all-cause mortality are summarized in Table 3, and the cumulative hazard and incidence rate for mortality are shown in Fig. 1-c and -d. HF and arrhythmia or sudden death-related deaths steadily increased after registration. With regard to the associations between mortality and age at registration, cancer-related mortality rapidly increased after the age of 40 years (Fig. 1-d).

3.4. Patient characteristics and Fontan procedures

Heterotaxy syndrome, especially left isomerism, was associated with a high mortality. A history of TCPC conversion was not associated with a high mortality (HR: 0.90, 95% confidence interval [CI]: 0.32–2.24, $p = 0.82$). Major complications of PAVF and PLE were also associated with high mortality. Prior hospitalization for any cause, including HF, arrhythmia, PAVF and PLE, were also associated with high mortality.

3.5. Cardiovascular status and medications

Lower NYHA functional class, greater CTR, lower EF, AV valve regurgitation ≥ moderate, lower systemic blood pressure, and lower arterial blood oxygen saturation were found to be associated with high mortality. The use of diuretics was strongly associated with high mortality; however, other medications were not associated with mortality.

3.6. Electrolytes and hepatorenal function

Lower plasma levels of sodium and albumin as well as high blood urea nitrogen were associated with high mortality. Even after excluding patients with PLE, a lower plasma albumin level was associated with a high mortality (HR: 0.47, 95%CI: 0.30–0.74, $p = 0.0012$). A higher MELD-XI score was also associated with high mortality.

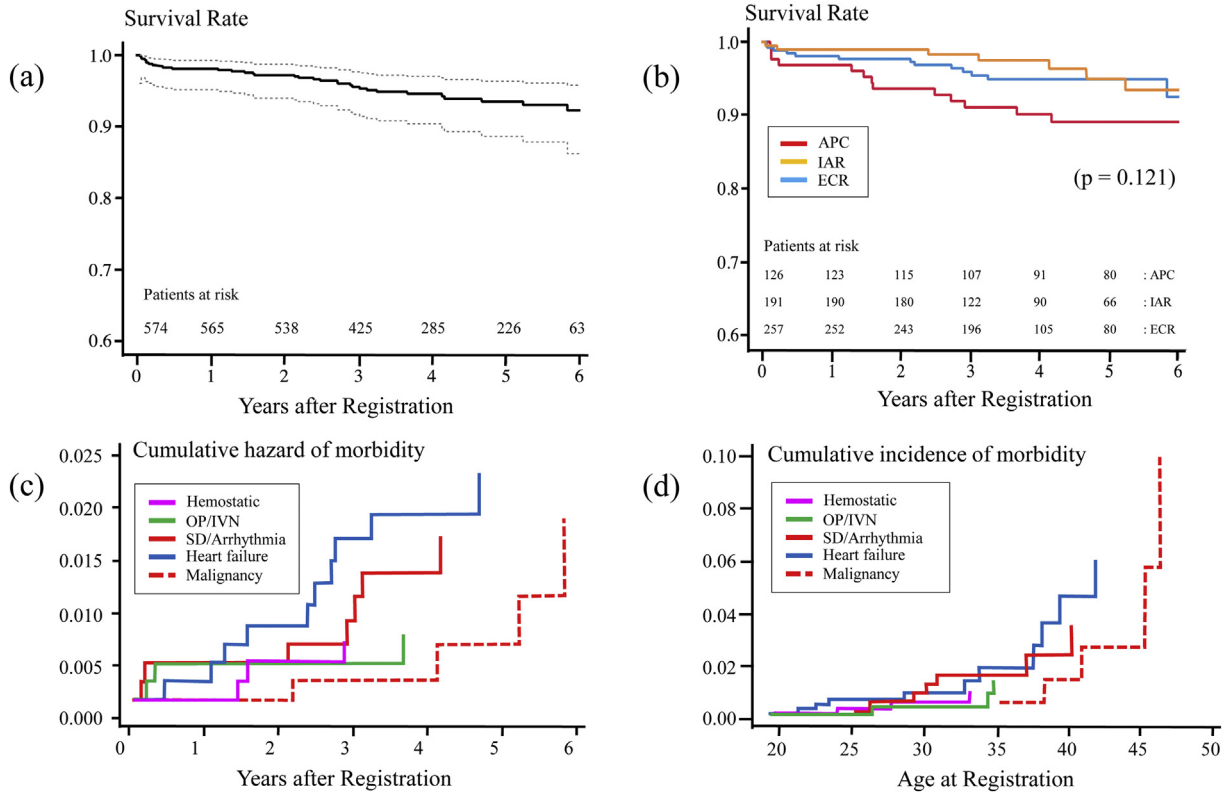

Fig. 1. The Kaplan-Meier all-cause mortality curve with 95% confidence interval in all registered adult Fontan patients (a). The Kaplan-Meier all-cause mortality curves by the type of Fontan procedure at the time of registration (b). Cumulative hazard ratio as per the mode of mortality after registration (c), and cumulative incidence as per the mode of mortality based on the age at registration in adult Fontan patients (d). APC = atriopulmonary connection, ECR = extracardiac rerouting, IAR, intracardiac rerouting, OP/IVN = cardiac operation and/or catheter intervention, SD = sudden death, PLE = protein losing enteropathy.

Table 3
Predictors of all-cause mortality.

	Univariate			Multivariate		
Variables	HR	95% CI	*p*	HR	95% CI	*p*
Patient characteristics						
Age (year)	1.03	0.98–1.07	0.1977			
Male	1.62	0.81–3.40	0.1745			
Body mass index (kg/m2)	1.03	0.92–1.12	0.5896			
Fontan operation						
Age at 1st Fontan operation (year)	1.02	0.97–1.06	0.4733			
Year at 1st Fontan operation (year)	0.96	0.91–1.02	0.2202			
Original type (APC/Bjork)	1.3	0.65–2.62	0.4611			
Current type at registration (APC/Bjork)	1.63	0.78–3.26	0.185			
Follow-up at registry (year)	1.02	0.96–1.09	0.4551			
Heterotaxy syndrome						
Heterotaxy	3.48	1.74–6.92	0.0006			
Right isomerism	1.5	0.43–4.04	0.487			
Left isomerism	5.83	2.78–11.7	<0.0001	3.49	1.02–10.3	0.0464
Prior hospitalization and complications						
History of hospitalization for any cause	4.57	2.30–9.43	<0.0001			
History of arrhythmia admission	1.99	1.00–4.05	0.0487	–	–	–
History of heart failure admission	5.03	2.29–10.3	0.0002	–	–	–
History of thromboembolic events	1.94	0.66–4.61	0.2065	–	–	–
PAVF	8.59	3.43–18.8	<0.0001			
PLE	4.82	1.64–11.5	0.007	14.4	1.30–311	0.0268
Cardiovascular status						
NYHA class	5.25	3.36–8.09	<0.0001	2.41	1.04–5.68	0.0397
Non-LV	1.76	0.86–3.80	0.124			
Cardiothoracic ratio (%)	1.11	1.06–1.45	<0.0001			
Heart rate (bpm)	1.01	0.99–1.03	0.3768			
Non-sinus	1.66	0.66–3.65	0.2629			
Pacemaker implantation	1.66	0.56–3.98	0.325			
SVEF (poor = 1, reduced = 2, preserved = 3)	0.49	0.27–0.95	0.0349			
AVVR (no-mild = 1, moderate = 2, severe = 3)	3.69	1.89–6.83	0.0003			
Systolic arterial blood pressure (mm Hg)	0.98	0.95–1.01	0.1368			
Hemoglobin (g/dL)	0.93	0.80–1.07	0.3045			
Arterial oxygen saturation (%)	0.88	0.84–0.94	0.0001			
Medications (%)						
Diuretics	5.25	2.38–13.2	<0.0001			
Warfarin	0.91	0.45–1.84	0.7947			
ACEI/ARB	0.57	0.26–1.17	0.1276			
Beta blocker	0.75	0.33–1.56	0.4511			
Anti-arrhythmia	1.64	0.74–3.38	0.2091			
Non-cardiovascular status						
Na (meq/L)	0.86	0.83–0.91	<0.0001			
Albumin (g/dl)	0.29	0.20–0.45	<0.0001			
Total-bilirubin (mg/dL)	1.19	0.97–1.33	0.0788			
ALT (U/L)	0.99	0.96–1.02	0.587			
BUN (mg/dL)	1.05	1.03–1.06	<0.0001			
Creatinine (per 0.1 mg/dL)	1.18	0.97–1.42	0.1025			
MELD-XI score (per 1)	1.33	1.13–1.54	0.0008			

3.7. Independent predictors of mortality

Of the significant mortality-associated variables, left isomerism, PLE, and greater NYHA functional class were independently associated with a high mortality.

3.8. Comparison of the 5-year Fontan mortality rate and mortality expected in age-matched healthy Japanese residents

We calculated the 5-year mortality rates for 5 age-based categorical subgroups (18–24 years, 25–29 years, 30–34 years, 35–39 years, and 40–49 years) and compared the rates with the expected mortality rates in age-matched healthy Japanese residents. The 5-year mortality rate (%) for the 20–24-year-old, 25–29-year-old, 30–34-year-old, 35–39-year-old, and 40–49-year-old age-matched healthy Japanese cohorts was 0.00035, 0.00041, 0.00049, 0.00065, and 0.00256, respectively. In our Fontan patients, the 5-year mortality rate for the 5 categorized subgroups was 0.0400, 0.0409, 0.0075, 0.1094, and 0.0645, respectively. The corresponding equivalent ages of these 5 subgroups were between 65 and 75 years in age-matched healthy Japanese residents, with the mortality rate being 0.0092–0.0244, indicating that our Fontan patients were 20–40 years older than their actual ages in terms of mortality. The standardized mortality rate was high (115.6).

4. Discussion

Several studies have addressed late status after the Fontan operation [2–4,14,15]. This is one of the largest studies on adult Fontan survivors aged ≥18 years that addresses mortality-related issues. The first result of our study was that the major causes of death were HF (34%), arrhythmia or sudden death (24%), cancer (15%), hemostatic events (12%), and perioperative death (12%). It is noteworthy that the cancer-related mortality rate increased markedly beyond the age of 40 years. Second, left isomerism heart, in addition to PLE and greater NYHA functional class, was a strong predictor of mortality.

A recent systematic review reported that the main causes of death were HF (22%), arrhythmia (16%), respiratory impairment (15%), renal disease (12%), and thromboembolism (10%) [16], and these incidences were similar to those found in our study.

We have reconfirmed that prior HF hospitalization is a strong predictor of high mortality in Fontan patients [17]. There has been limited evidence of the efficacy of HF management in Fontan patients with

ventricular dysfunction, particularly in those with HF with preserved EF [6]. Much more effort should be needed to establish ant-HF management strategy in these patients.

Arrhythmia is associated with high mortality in Fontan patients [18]. Although all ECG abnormalities were not associated with a high mortality, prior hospitalization because of arrhythmias was associated with a high mortality. Ventricular fibrillation was documented as a cause of death in two cases in our cohort, and the prevalence of ventricular arrhythmia as a cause of sudden death may be significant in adult Fontan patients [19]; therefore, an implantable cardioverter defibrillator may help improve long-term survival [19,20].

Hepatorenal dysfunction is closely associated with poor outcomes in patients with HF [21]. The same story may hold true for adult Fontan patients because a high MELD-XI score predicted high mortality in our patients as previously demonstrated [9]. High blood urea nitrogen level was also strongly associated with high mortality in univariate analysis, indicating the presence of "vasomotor nephropathy," as described in HF patients with the activation of neurohormones and/or low kidney perfusion [22]. In addition, liver cirrhosis has a strong adverse impact on survival [7], and more attention should be paid to this hepatorenal pathophysiology in adult patients.

The present study also revealed that cancer, especially hepatocellular carcinoma, was a significant cause of mortality (15%), and the mortality rate was about 20-fold higher than that (0.7%) in a previous study [16]. This difference may be due to the age difference in the study populations; our study only included adult Fontan survivors, while most other studies analyzed pediatric and adult patients. The incidence of cancer was also much higher than that in groups of adults with congenital heart disease [10].

High prevalence of liver cirrhosis due to chronic increased venous pressure is the most likely underline background of hepatocellular carcinoma in adult Fontan patients. Marked chronic liver congestion itself also might be a causal factor for cancer development because hepatocellular carcinoma was demonstrated in patients with Budd-Chiari syndrome [23]. In addition, a high prevalence of impaired glucose tolerance may be another carcinogenic pathophysiology [24,25]. Another study demonstrated that cancer, especially hepatocellular carcinoma, was a major cause of mortality in patients with diabetes mellitus [26]. Furthermore, non-alcoholic fatty liver disease is highlighted as a cause of carcinogenesis [23]. In this regard, there was a high prevalence of obesity in Fontan patients, and these patients may be at risk of this type of cancer and HF [27], providing the potential for possible interventions.

We also found that left isomerism heart was independently associated with high mortality. Isomerism heart has been considered one of the risk factors of high mortality [28]. The exact reason remains unclear; however, in left isomerism heart, the high prevalence of bradyarrhythmia and PAVF might be responsible for the high mortality rate [29]. In fact, the rate of pacemaker implantation tended to be higher (17.3% vs. 9.1%, $p = 0.07$) and the rate of PAVF was also higher (18.8% vs. 2.8%, $p < 0.0001$) in these patients compared to that in those without left isomerism with lower arterial blood oxygen saturation (89.6%% vs. 93.0%, $p < 0.0001$). PAVF and hypoxia were actually significant predictors for all-cause mortality in these patients.

Finally, we reconfirmed that the equivalent age of Japanese adult Fontan patients was 20–40 years higher than their actual age in terms of all-cause mortality. It is noteworthy that these statistics were similar to those reported in the UK [10], and the standardized mortality rate was 116 times higher than that of the age-matched healthy Japanese residents.

5. Limitations

First, our data may not represent real-world adult Fontan status in Japan because only 43% of the institutions that participated in the first survey were included in the second survey. We lost 4.3% of the patients who initially registered. In addition, the follow-up period was shorter in some patients than originally designed. Second, the major cause of death was sometimes difficult to determine as sicker Fontan patients often had more than one complication, such as arrhythmia and PLE. In this study, we were required to trust the decisions and information provided by the in-charge physician at each institution. Third, we could not evaluate the prognostic values of the established variables, such as peak oxygen uptake [30] because of the lack of data in this study. Finally, age has been reported to be an important predictor of mortality in adult HF patients [31]; however, age was not associated with all-cause mortality in the present study. Possible reasons for this are that the follow-up period was short (5 years) and that most adult Fontan survivors were still young (in their 20s or 30s). Future studies with a longer follow-up period may therefore find additional risk factors for mortality, including age, to stratify aging adults with Fontan circulation.

6. Conclusions

Majority of the study population (adult Japanese Fontan survivors) exhibited good functional status with an acceptable 5-year survival rate (93.5%). However, a significant proportion of non-cardiac mortalities, especially cancer-related deaths, highlights Fontan pathophysiology as a multi-organ disease requiring multidisciplinary management strategy to improve the long-term outcomes.

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