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Original Research

The Long-term Outcomes and Risk Factors of Complications After Fontan Surgery: From the Korean Fontan Registry (KFR)

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AUTHOR'S SUMMARY

The retrospective, multi-center, observational study included patients who underwent Fontan surgery was performed in the Republic of Korea. Totally, 1,732 patients were enrolled, and 1,040 (58.8%) were men. The mean age at Fontan surgery was 4.3 years, and 395 (22.8%) patients presented with heterotaxy syndrome . The overall survival rates after Fontan surgery were 91.7%, 87.1%, 74.4% at 10, 20, and 30 years, respectively. The preoperative low mean pulmonary artery pressure and less atrioventricular valve regurgitation are associated with better early and long-term outcomes of Fontan surgery.

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Conflict of Interest
The authors have no financial conflicts of interest.

Data Sharing Statement
The data generated in this study is available from the corresponding author upon reasonable request.

Author Contributions
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ABSTRACT

Background and Objectives: This study aimed to analyze the outcomes of Fontan surgery in the Republic of Korea, as there were only a few studies from Asian countries.
Methods: The medical records of 1,732 patients who underwent Fontan surgery in 10 cardiac centers were reviewed.
Results: Among them, 1,040 (58.8%) were men. The mean age at Fontan surgery was 4.3±4.2 years, and 395 (22.8%) patients presented with heterotaxy syndrome. According to the types of Fontan surgery, 157 patients underwent atriopulmonary (AP) type; 303, lateral tunnel (LT) type; and 1,266, extracardiac conduit (ECC) type. The overall survival rates were 91.7%, 87.1%, and 74.4% at 10, 20, and 30 years, respectively. The risk factors of early mortality were male, heterotaxy syndrome, AP-type Fontan surgery, high mean pulmonary artery pressure (mPAP) in pre-Fontan cardiac catheterization, and early Fontan surgery year. The risk factors of late mortality were heterotaxy syndrome, genetic disorder, significant atrioventricular valve regurgitation (AVVR) before Fontan surgery, high mPAP in pre-Fontan cardiac catheterization, and no fenestration.
Conclusions: In Asian population with a high incidence of heterotaxy syndrome, the heterotaxy syndrome was identified as the poor prognostic factors for Fontan surgery. The preoperative low mPAP and less AVVR are associated with better early and long-term outcomes of Fontan surgery.

Keywords: Fontan procedure; Republic of Korea

INTRODUCTION

The circulatory system has a high efficiency according to the evolutionary stage of species. Humans are one of the most developed species and have the most efficient atrial and ventricular circulatory systems. Some patients with congenital heart disease (CHD) who do not have a 2-ventricle system die at an early age. Francis Fontan disregarded the 2-ventricular system and switched to the 1-atrial and ventricular circulation system, which is another opportunity for patients with functional single ventricle (SV) to take another step forward.[1)2)] However, changes in the circulatory system affect all organ functions, behavior patterns, and lifestyles, thereby causing changes in psychology. Fontan surgery has been applied for over 50 years, and this procedure is associated with numerous complications including premature death, ventricular failure, thromboembolic disease, arrhythmia, liver disease, and protein-losing enteropathy (PLE). Hence, Fontan surgery is not considered an ultimate treatment option.

Fontan surgery has been performed in the Republic of Korea (ROK) since the 1970s, and it has improving outcomes after medical staffs exert great efforts during several difficulties.[3)4)] The current study aimed to evaluate the long-term outcomes and risk factors of complications in patients who underwent Fontan surgery in the ROK.

METHODS

Ethical statement

This study was approved by the Institutional Review Board at the 10 pediatric cardiac centers as a retrospective study without obtaining consent (Seoul National University Hospital, IRB number: 2306-120-1440).

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The Korean Fontan Registry

We established the Korean Fontan Registry (KFR), which comprised 10 pediatric cardiovascular centers in the ROK. The working group of the KFR constructed web version case report systems. The electronic case reports comprised baseline characteristics, follow-up findings, long-term outcomes, and complications (**Supplementary Table 1**). Thereafter, the members of the working group recorded the clinical data of patients who underwent Fontan surgery in the ROK.

Inclusion criteria

All patients who underwent Fontan surgery in the ROK until December 31, 2019, were included in the study. Meanwhile, patients who underwent Fontan surgery in other countries and those who immigrated were excluded. The participants were identified from the centers' operation records, and their clinical data were collected until December 31, 2019. Patients with insufficient data, which can satisfy the minimum data set (age at Fontan surgery, type of Fontan surgery, and discharge status), were excluded from the analysis.

Data collection

We collected data such as demographic characteristics, cardiac anatomical variation, peri-Fontan operative data, current clinical status, social performance, and complications of Fontan circulation. Patients who were not follow-up within 2 years were classified as loss to follow-up, and their deaths were evaluated using data from the Korean Statistical Information Service.

Clinical outcomes and definitions

Overall survival was defined as the time from Fontan surgery to death. Early mortality was defined as death before 30 days or without discharge after Fontan surgery and late mortality was defined as death except early mortality. Early failure was defined as mortality, mechanical support, Fontan takedown, or major reoperation before 30 days or without discharge after Fontan surgery. Late failure was defined as late mortality, transplant, late takedown or New York Heart Association (NYHA) class 3 at the last follow-up, PLE/plastic bronchitis, and Fontan conversion.

Clinically significant arrhythmia was defined as the need for anti-arrhythmic medications, cardioversion/defibrillation, or pacing devices. Liver cirrhosis was diagnosed based on characteristic liver biopsy or computed tomography, cardiac magnetic resonance imaging, or ultrasonography findings obtained by radiologists. PLE was defined as enteric loss of alpha-1-antitrypsin in the stool and the presence of low serum total protein/albumin levels.

Statistical analysis

Categorical variables were presented as medians and ranges while continuous variables were expressed as either medians with ranges or means with standard deviations.

The Kaplan–Meier method was employed to estimate survival probabilities following Fontan surgery, stratified by the types of Fontan procedures and Fontan period. The log-rank test was applied to assess differences in survival among distinct strata by multiple comparisons. Time 0 was defined as time of Fontan surgery, after which patient-years were accrued until death or cardiac transplantation (TPL). We introduced covariates showing marginal significance for each endpoint of late mortalities into separate Cox proportional hazards (PHs) regression models. Multivariate analysis was applied to variables that were significant at the 20% level

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in univariate analysis, using stepwise selection to retain variables that were significant at the 5% level adjusted for sex, Fontan age, and Fontan operation period while accounting for multicollinearity. Entry and removal conditions during stepwise selection were set at $p<0.05$ and $p>0.10$, respectively. In cases where estimates and confidence intervals were unstable, a penalized maximum-likelihood method (Firth correction) was used to reduce the bias of the odds ratio or hazard ratio using the profile penalized likelihood approach. The PHs assumptions of the Cox PH models were verified using a Schoenfeld residual test. Logistic regression models were similarly employed to identify independent risk factors for early mortality and early failure, and late failure. All p values were 2-tailed and a p value <0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences software version 25.0 (IBM Corp., Armonk, NY, USA), R 4.4.0 (Institute for Statistics and Mathematics, Vienna, Austria), or SAS software for Windows, version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Overview

In total, 1,765 patients were evaluated, and **Table 1** shows the baseline characteristics of the participants. Thirty-three patients with insufficient data were excluded, and 1,732 patients were enrolled (**Figure 1**). Their mean age at Fontan surgery was 4.3±4.2 years old, and the mean follow-up duration was 12.6±8.4 years. In total, 185 (10.7%) patients died. Among them, 56 had early mortality, and most underwent Fontan surgery before 2010 (**Figure 2A**). Among initial 1,765 patients, even though 80 patients might be identified early mortality cases, 24 patients were excluded by insufficient data. Further, 129 (7.4%) patients had late mortality, and 19 underwent heart TPL after Fontan surgery. Eight patients underwent takedown to bidirectional cavopulmonary shunt (BCPS) (n=6) or shunt type (n=2) from Fontan circulation. Further, 4 underwent early Fontan takedown within 30 days after Fontan operation. Six of 8 patients who underwent takedown died. Among 19 patients who underwent heart TPL (median age: 17.4 years old, interquartile range [IQR]: 10.4–19.2), 3 died. The mortality rate of heart TPL after Fontan surgery was 15.8%. In total, 215 (12.4%) patients were lost to follow-up. However, information on their deaths were inquired through data from the Korean Statistical Information Service (**Figure 1**). Further, 1,314 patients who had Fontan circulation were followed-up until 2019.

In terms of the characteristics of populations, 22.8% patients had heterotaxy syndrome, and only 3.8% of patients presented with hypoplastic left heart syndrome (HLHS). This was a unique point of our subjects. Most common anatomical diagnosis was an unbalanced atrioventricular septal defect (20.5%), and the ratio of morphological left ventricle (LV), right ventricle (RV), and both ventricles were 36.1%, 35.3%, and 25.5%, respectively (**Table 1**).

In the ROK, Fontan surgery was a lot performed around 2000. The early mortality cases were observed mainly before 2010, and the early mortality rate decreased below 2% after 2010. **Figure 2A** shows the type of Fontan surgery. In total, 157 (9.0%), 303 (17.5%), and 1,266 (73.1%) patients underwent atriopulmonary (AP)-, lateral tunnel (LT)-, and extracardiac conduit (ECC)-type Fontan surgery, respectively. Six patients underwent the Fontan operation using extracardiac pericardial flap and were classified as other type. According to time period, the AP-type was mainly performed before 1990, the LT-type between 1990 and 2000, and the ECC-type after 2000 (**Figure 2A**). Ninety patients (60 with AP-type, 29 with LT-type, and 1 with

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Table 1. Baseline characteristics of the patients

Characteristics	Total (n=1,732)	Patients with AP-type (n=157)	Patients with LT-type (n=303)	Patients with ECC-type (n=1,266)	Others (n=6)
Male sex	1,023 (59.1%)	96 (61.1%)	177 (58.4%)	746 (58.9%)	4 (66.7%)
Diagnosis					
Unbalanced AVSD	355 (20.5%)	15 (9.6%)	71 (23.4%)	268 (21.2%)	1 (16.7%)
Tricuspid atresia	333 (19.2%)	56 (35.7%)	66 (21.8%)	210 (16.6%)	1 (16.7%)
DORV	255 (14.0%)	27 (17.2%)	43 (14.2%)	185 (14.6%)	0 (0.0%)
DILV	138 (8.0%)	4 (2.5%)	32 (10.6%)	101 (8.0%)	1 (16.7%)
DIRV	96 (5.5%)	18 (11.5%)	19 (6.3%)	59 (4.7%)	0 (0.0%)
PA with IVS	131 (7.6%)	7 (4.5%)	17 (5.6%)	107 (8.5%)	0 (0.0%)
CC-TGA	106 (6.1%)	5 (3.2%)	11 (3.6%)	89 (7.0%)	1 (16.7%)
HLHS	57 (3.3%)	0 (0.0%)	0 (0.0%)	57 (4.5%)	0 (0.0%)
Mitral atresia	67 (3.9%)	8 (5.1%)	12 (4.0%)	47 (3.7%)	0 (0.0%)
Criss-cross heart	39 (2.3%)	2 (1.3%)	5 (1.7%)	32 (2.5%)	0 (0.0%)
TGA VSD PS	31 (1.8%)	7 (4.5%)	8 (2.6%)	16 (1.3%)	0 (0.0%)
Ebstein anomaly	23 (1.3%)	0 (0.0%)	3 (1.0%)	20 (1.6%)	0 (0.0%)
Others	98 (5.7%)	8 (5.1%)	15 (5.0%)	73 (5.8%)	2 (33.3%)
Heterotaxy	395 (22.8%)	26 (16.6%)	85 (28.1%)	281 (22.2%)	3 (50.0%)
Right isomerism	308 (17.8%)	18 (11.5%)	62 (20.6%)	226 (17.9%)	2 (33.3%)
Left isomerism	87 (5.0%)	8 (5.1%)	23 (7.6%)	55 (4.3%)	1 (16.7%)
Dextrocardia or mesocardia	347 (20.0%)	37 (23.6%)	78 (25.7%)	229 (18.1%)	3 (50.0%)
Main ventricle					
Both	442 (25.5%)	15 (9.6%)	58 (19.3%)	366 (29.1%)	3 (50.0%)
LV	626 (36.1%)	70 (44.6%)	111 (36.9%)	442 (34.9%)	2 (33.3%)
RV	611 (35.3%)	58 (37.0%)	122 (41.1%)	431 (34.1%)	0 (0.0%)
Undetermined	31 (1.8%)	7 (4.5%)	5 (1.7%)	18 (1.4%)	1 (16.7%)
Unknown	22 (1.3%)	7 (4.5%)	6 (2.0%)	9 (0.7%)	0 (0.0%)
Pulmonary vein anomaly	150 (8.7%)	13 (8.3%)	28 (9.3%)	108 (8.5%)	1 (16.7%)
Obstructive TAPVR	29 (1.7%)	3 (1.9%)	4 (1.3%)	22 (1.7%)	0 (0.0%)
Non-obstructive TAPVR	105 (6.1%)	10 (6.4%)	18 (6.0%)	77 (6.1%)	0 (0.0%)
PAPVR	16 (0.9%)	0 (0.0%)	6 (2.0%)	9 (0.7%)	1 (16.7%)
Genetic disorders	25 (1.4%)	0 (0.0%)	3 (1.0%)	22 (1.7%)	0 (0.0%)
Previous BCPS surgery					
Shunt surgery	625 (36.1%)	55 (35.0%)	96 (31.9%)	471 (37.2%)	3 (50.0%)
PA banding	355 (20.5%)	11 (7.0%)	40 (13.2%)	304 (24.0%)	0 (0.0%)
Norwood procedure with RV to PA	44 (2.5%)	1 (0.6%)	1 (0.3%)	42 (3.3%)	0 (0.0%)
Norwood procedure with shunt	34 (2.0%)	1 (0.6%)	3 (1.0%)	30 (2.4%)	0 (0.0%)
Aortic arch procedure	56 (3.2%)	1 (0.6%)	4 (1.3%)	51 (4.0%)	0 (0.0%)
AV valve repair	22 (1.3%)	1 (0.6%)	3 (1.0%)	18 (1.4%)	0 (0.0%)
TAPVR repair	33 (1.9%)	2 (1.3%)	3 (1.0%)	28 (2.2%)	0 (0.0%)
PA reconstruction	24 (1.4%)	0 (0.0%)	2 (0.7%)	22 (1.7%)	0 (0.0%)
DKS procedure	23 (1.3)	1 (0.6%)	2 (0.7%)	20 (1.6%)	0 (0.0%)
BCPS	1,551 (89.5%)	66 (42%)	247 (81.5%)	1,232 (97.3%)	6 (100.0%)
Surgical intervention before Fontan surgery					
PA angioplasty	21			20	1
AV valve repair or replacement	16			16	
Diaphragm plication	19		2	17	
BCPS takedown to shunt	17			16	
PM insertion or battery change	11		2	9	
BCPS revision	8		1	7	
Thoracic duct ligation	5			5	
Others	27		1	26	
Pre-Fontan hemodynamics					
mPAP (mmHg) (n=1,344)	11.0 (9.0–14.0)	14.0 (10.0–16.0)	12.0 (10.0–15.0)	11.0 (9.0–13.0)	
VEDP (mmHg) (n=1,309)	8.0 (6.0–10.0)	8.0 (6.0–10.0)	8.0 (6.0–10.0)	8.0 (6.0–10.0)	
PVR index (WU·m^2) (n=1,109)	1.50 (1.09–2.17)	1.62 (1.18–2.57)	1.70 (1.20–2.35)	1.5 (1.04–2.10)	
Qs (L/min/m^2) (n = 858)	4.56 (3.60–5.66)	4.30 (3.46–6.22)	4.2 (3.40–5.35)	4.60 (3.62–5.70)	
Qp/Qs (L/min/m^2) (n = 872)	0.64 (0.51–0.80)	0.63 (0.42–1.09)	0.80 (0.59–1.27)	0.62 (0.50–0.79)	
Moderate to severe AVVR	136 (7.9%)	5 (3.2%)	24 (7.9%)	106 (8.4%)	1
Reduced ventricular function	39 (2.3%)	1 (6.4%)	0 (0.0%)	38 (3.0%)	

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Table 1. (Continued) Baseline characteristics of the patients

Characteristics	Total (n=1,732)	Patients with AP-type (n=157)	Patients with LT-type (n=303)	Patients with ECC-type (n=1,266)	Others (n=6)
Fontan surgery	1,732	157	303	1,266	6
CPB time (minutes)	129.0 (89.0–156.0)	149.2 (109.0–182.0)	139.7 (111.0–161.0)	125.7 (83.0–154.0)	
Fenestration	659 (38.0%)	10 (6.4%)	190 (62.7%)	455 (35.9%)	4
Post-Fontan CVP (mmHg)	15.0 (13.0–18.0)	19.0 (15.0–22.0)	16.0 (13.0–19.0)	15.0 (13.0–17.0)	
Post-Fontan ICU day	4.0 (2.0–6.0)	6.0 (4.0–8.0)	4.0 (3.0–7.0)	3.0 (2.0–6.0)	
Post-Fontan hospital day	19.0 (13.0–30.0)	19.0 (13.5–26.5)	18.0 (13.0–27.0)	20.0 (14.0–31.0)	
Fontan surgery period					
~1989	84 (4.8%)	79 (50.3%)	3 (1.0%)	2 (0.2%)	0 (0.0%)
1990–1999	493 (28.5%)	77 (49.0%)	263 (86.8%)	148 (11.7%)	5 (83.3%)
2000–2009	678 (39.1%)	1 (0.6%)	36 (11.9%)	640 (50.6%)	1 (16.7%)
2010–2019	477 (27.5%)	0 (0.0%)	1 (0.3%)	476 (37.6%)	0 (0.0%)
Mean age at Fontan surgery (years)	4.3±4.2	4.8±3.9	3.9±4.0	4.3±4.3	3.3±1.0
<3 years	720 (41.6%)	62 (39.5%)	170 (56.1%)	495 (39.1%)	2 (33.3%)
3–7 years	814 (47.0%)	66 (42.0%)	104 (34.3%)	648 (51.2%)	4 (66.7%)
>7 years	183 (10.6%)	29 (18.5%)	29 (9.9%)	123 (9.7%)	0 (0.0%)
Concomitant procedure with Fontan					
Pulmonary angioplasty	175	6	45	121	3
Atrial septectomy	149	1	40	107	1
AV valve surgery	149	4	20	125	0
Arch surgery	6	0	0	6	0
Aortic valve surgery	8	0	1	7	0
PM insertion or battery change	41	1	7	32	1
Follow-up duration (years)	12.61 (4.84–18.83)	22.77 (2.57–29.30)	21.74 (17.10–23.40)	10.39 (4.37–15.62)	20.85 (17.18–21.24)

Data were expressed as number and percentage except when specified. Categorical/continuous variables expressed as either medians with ranges or means ± standard deviations.
AP = atriopulmonary; AV = atrioventricular; AVSD = atrioventricular septal defect; AVVR = atrioventricular valve regurgitation; BCPS = bidirectional cavopulmonary shunt; CC-TGA = congenitally corrected transposition of the great arteries; CVP = central venous pressure; DILV = double-inlet left ventricle; DIRV = double-inlet right ventricle; DKS = Damus-Kays-Stansel procedure; DORV = double-outlet right ventricle; ECC = extracardiac conduit; HLHS = hypoplastic left heart syndrome; ICU = intensive care unit; IQR = interquartile range; IVS = intact ventricular septum; LT = lateral tunnel; LV = left ventricle; mPAP = mean pulmonary artery pressure; PA = pulmonary atresia; PAPVR = partial anomalous pulmonary venous return; PM = pacemaker; PVR = pulmonary vascular resistance; Qp = pulmonary blood flow; Qs = systemic blood flow; RV = right ventricle; TAPVR = total anomalous pulmonary venous return; TGA VSD PS = transposition with ventricular septal defect and pulmonary stenosis; VEDP = ventricular end-diastolic pressure.
*The nine patients who underwent other types of Fontan surgery were included in this study.

other type) underwent Fontan conversion surgery, and most patients underwent surgery that was converted to ECC-type. As a result, most (77.8%) patients with Fontan circulation had ECC-type Fontan circulation (AP-type, 5.6%; LT-type, 16.2%) (**Figure 2B**).

Survival

The overall survival rates after Fontan surgery were 91.7%, 87.1%, 74.4% at 10, 20, and 30 years, respectively (**Figure 3A**). **Figure 3B and C** present the overall survival according to the type of Fontan surgery and surgical era. AP-type Fontan surgery (p<0.0001) and early operation period (before 2000) (p<0.0001) were associated with a significantly higher overall survival rate based on the log-rank test (**Figure 3**).

Table 2 presents each end point such as early and late outcomes according to the type of Fontan surgery. In 41 (73.2%) of 56 patients with early mortality, the causes included Fontan failure with low cardiac output (n=23, 56.1%), sepsis and disseminated intravascular coagulation (DIC) (n=7, 17.1%), sudden death or arrhythmia (n=5, 12.2%), severe neurologic complications (n=4, 9.8%), and major bleeding (n=2, 4.9%). In 112 (86.8%) of 129 patients with late mortality, the cause included Fontan failure (n=55, 49.1%), major bleeding (n=19, 17.0%), sepsis and DIC (n=18, 16.1%), sudden death or arrhythmia (n=11, 9.8%), severe neurologic complications (n=5, 4.5%), and thromboembolism (n=4, 3.5%). According to a comparative analysis of mortality or failure according to Fontan type, the ECC-type had

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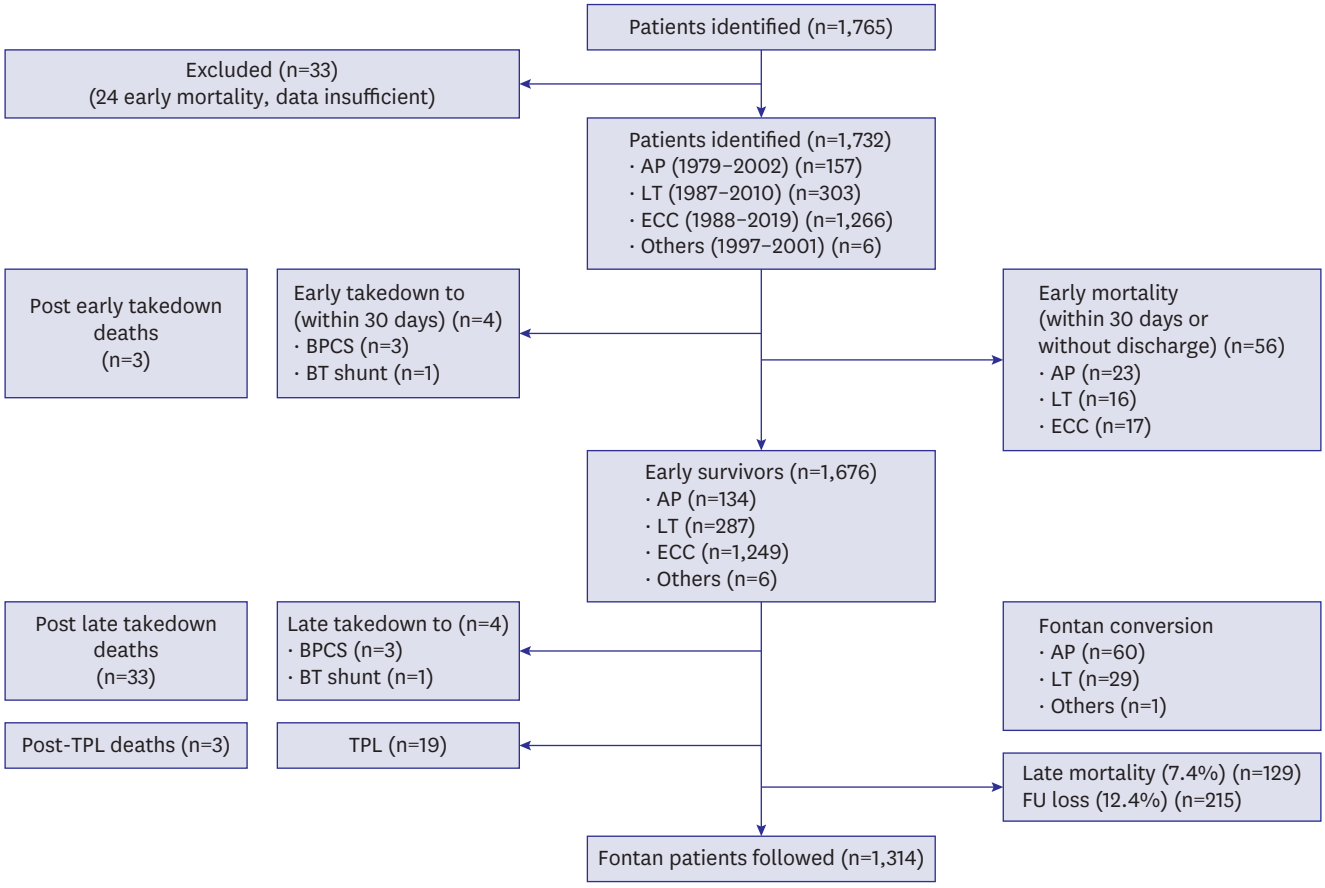

Figure 1. Summary of patients who underwent Fontan surgery in the Republic of Korea.
AP = atriopulmonary; BCPS = bidirectional cavopulmonary shunt; BT = Blalock-Taussig; ECC = extracardiac conduit; FU = follow-up; LT = lateral tunnel; TPL = transplantation.

better outcomes than the other types. However, the era of Fontan surgery type should be considered. Compared with the composite adverse early outcomes such as early failure, prolonged pleural effusion, and prolonged stay (>30 days), there was no significant difference in terms of Fontan surgery types (p=0.245). The risk factors of early and late mortality were analyzed using logistic regression or Cox PHs models (**Table 3**, **Supplementary Table 2**). In the multivariable analysis, male, heterotaxy syndrome, AP-type Fontan surgery, high mean pulmonary artery pressure (mPAP) in pre-Fontan cardiac catheterization, and early Fontan surgery year were considered as independent risk factors of early mortality. The risk factors of late mortality were heterotaxy syndrome, genetic disorder, significant atrioventricular valve regurgitation (AVVR) before Fontan surgery, high mPAP in pre-Fontan cardiac catheterization, and no fenestration. Further, the risk factors of early and late failure were analyzed using the logistic regression model (**Table 3**, **Supplementary Table 2**). In the multivariable analysis, the risk factor of early failure was heterotaxy syndrome, right ventricle morphology, AP-type Fontan surgery, and high ventricular end-diastolic pressure (VEDP) and mPAP in pre-Fontan cardiac catheterization (**Table 3**, **Supplementary Table 2**). Among the risk factors previously mentioned, AP-type Fontan surgery and early Fontan surgical period are no longer considered as risk factors to date, and heterotaxy syndrome and genetic disorder are not remediable risk factors.

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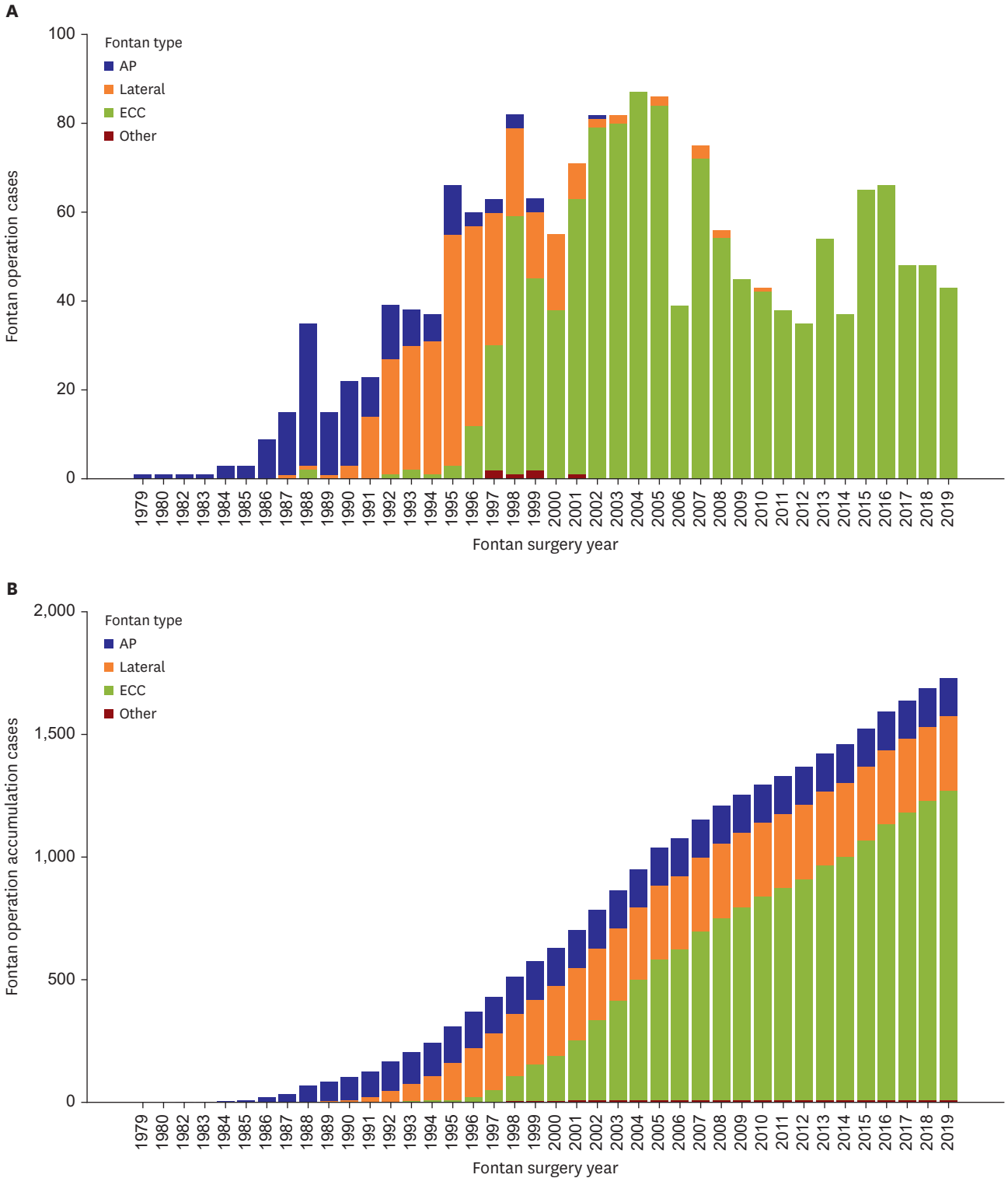

Figure 2. The number of Fontan surgery. (A) The number of Fontan surgeries according to type and (B) cumulative number of Fontan surgeries according to year. The blue color indicates AP; red, LT; and green, ECC type.
AP = atriopulmonary; ECC = extracardiac conduit; LT = lateral tunnel.

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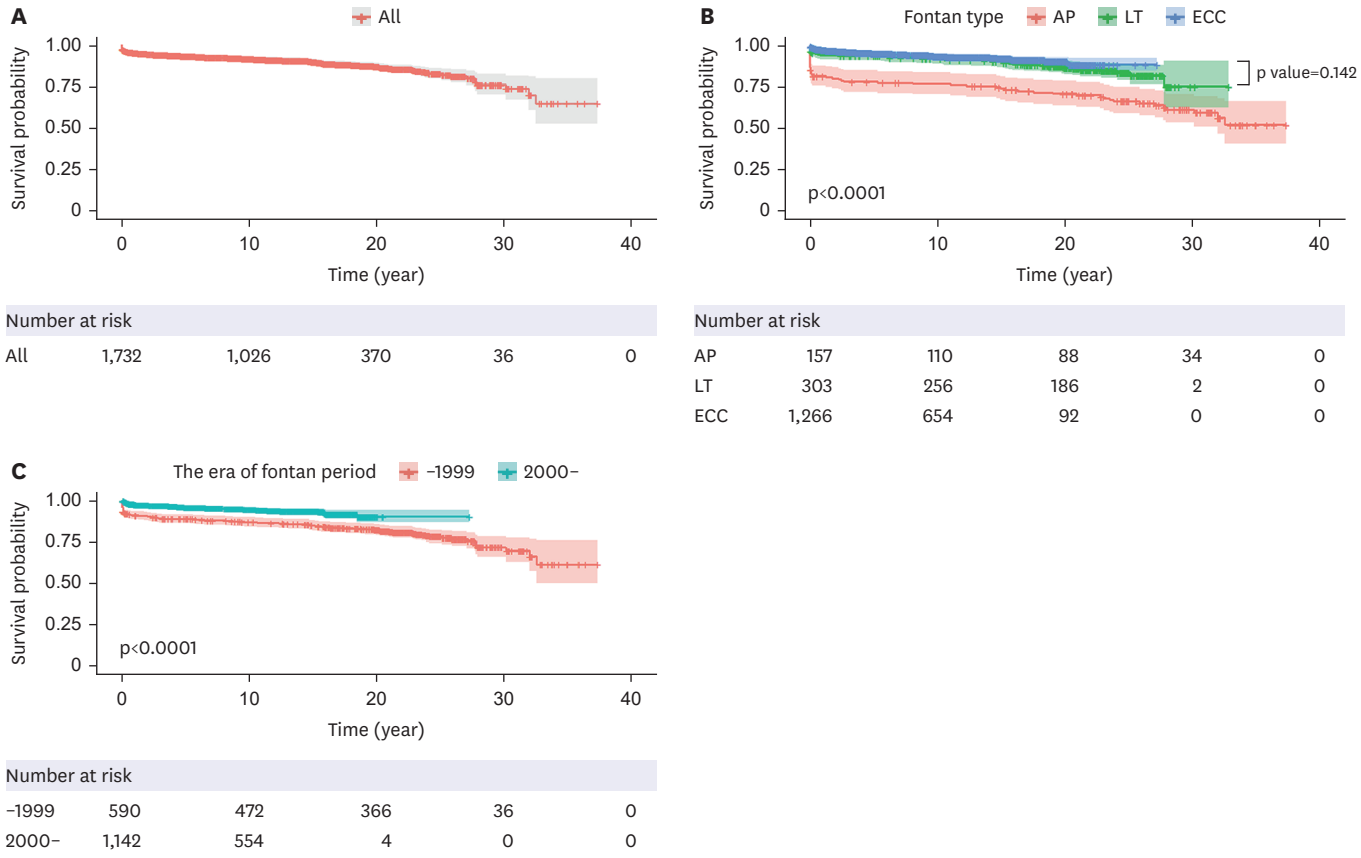

Figure 3. Kaplan–Meier curve of (A) the overall survival curve, (B) survival curve according to Fontan type, and (C) Fontan survival curve according to Fontan operation period. Overall, the 10-, 20-, and 30-year survival rates were 91.7%, 87.1%, and 74.4%, respectively. AP-type (p<0.0001) and period before the 2000 of Fontan surgery (p<0.0001) were associated with a significantly lower overall survival rate.
AP = atriopulmonary; ECC = extracardiac conduit; LT = lateral tunnel.

Table 2. Various outcomes according to the type of Fontan surgery

Outcomes	Total patients (n=1,732)	Patients with AP-type (n=157)	Patients with LT-type (n=303)	Patients with ECC-type (n=1,266)	Others (n=6)
Early mortality	56 (3.2%)	23 (14.6%)	15 (5.0%)	16 (1.3%)	0 (0.0%)
Early failure*	83 (4.8%)	24 (15.3%)	18 (6.0%)	41 (3.2%)	0 (0.0%)
Prolonged hospital stays (>30 days)†	406/1,537 (26.4%)	21/92 (21.7%)	48/222 (21.6%)	331/1,175 (28.1%)	2/5 (40.0%)
Composite adverse early outcomes‡	680/1,559 (43.6%)	56/119 (47.1%)	93/240 (38.4%)	529/1,193 (44.3%)	2/5 (40.0%)
Late mortality	129 (7.4%)	33 (21.0%)	28 (9.2%)	67 (5.3%)	1 (16.7%)
Late failure§	263 (15.2%)	92 (58.6%)	64 (21.1%)	104 (8.2%)	3 (50.0%)
Thromboembolic events	60 (3.5%)	15 (9.6%)	19 (6.3%)	26 (2.1%)	0 (0.0%)
PLE/plastic bronchitis	71 (4.1%)	9 (5.7%)	8 (2.7%)	54 (4.3%)	0 (0.0%)
Late adverse event¶	518 (29.9%)	103 (65.6%)	141 (46.5%)	270 (21.3%)	4 (66.7%)

Data were expressed as number and percentage except when specified.
AP = atriopulmonary; ECC = extracardiac conduit; LT = lateral tunnel; NYHA = New York Heart Association; PLE = protein-losing enteropathy.
*Early failure: death, mechanical support, takedown, or major reoperation.
†Prolonged hospital stays (>30 days): except patients with early mortality or insufficient data.
‡Composite adverse early outcomes: early failure, prolonged pleural effusion, or prolonged hospital stay (>30 days).
§Late failure: late deaths, transplants, late takedown, NYHA class 3 disease at the last follow-up, PLE/plastic bronchitis, and conversion.
¶Late adverse events: late failure, reoperation, catheter reintervention (excluding fenestration closure and embolization of aortopulmonary. collaterals), PLE, plastic bronchitis, thromboembolic event, arrhythmia or pacemaker, and overt pulmonary arteriovenous fistula.

Adverse events and current status

Arrhythmia was defined as the need for anti-arrhythmic drugs or cardioversion for tachy-arrhythmia and pacemaker (PM) for brady-arrhythmia (**Table 4**) and the overall freedom rates

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Table 3. Each end point assessed via logistic or Cox proportional hazards regression analysis

	Adjusted OR*	Adjusted HR*	95% CI	p value
Early mortality				
Sex (male)	2.5		1.1–5.9	0.039
Heterotaxy syndrome	3.3		1.5–7.3	0.004
AP-type Fontan surgery	3.9		1.2–12.9	0.025
mPAP in pre-Fontan cardiac catheterization (mmHg)	1.2		1.1–1.3	<0.001
Fontan surgery year	0.9		0.9–1.0	0.008
Early failure				
Heterotaxy syndrome	2.8		1.5–5.3	0.001
RV morphology	1.9		1.0–3.4	0.047
AP-type Fontan surgery	15.5		4.9–48.9	<0.001
VEDP in pre-Fontan cardiac catheterization (mmHg)	1.1		1.0–1.2	0.036
mPAP in pre-Fontan cardiac catheterization (mmHg)	1.1		1.0–1.2	0.024
Late mortality				
Heterotaxy syndrome		1.8	1.1–3.0	0.028
Genetic disorder		4.0	1.2–13.6	0.028
Significant AVVR before Fontan surgery (≥ moderate)		2.2	1.2–4.1	0.016
mPAP in pre-Fontan cardiac catheterization (mmHg)		1.1	1.1–1.2	<0.001
Fenestration		0.5	0.3–0.9	0.023
Late failure				
Heterotaxy syndrome	2.0		1.3–3.2	0.004
AP-type Fontan surgery	19.6		7.2–53.0	<0.001
Old Fontan age	1.1		1.0–1.1	0.011
Significant AVVR before Fontan surgery (≥ moderate)	2.2		1.2–3.9	0.008
mPAP in pre-Fontan cardiac catheterization (mmHg)	1.1		1.1–1.2	<0.001
Fontan surgery year	0.9		0.9–1.0	<0.001

All analysis results for each end point are provided in the **Supplementary Table 2**.
AP = atriopulmonary; AVVR = atrioventricular valve regurgitation; CI = confidence interval; CPB = cardiopulmonary bypass time; ECC = extracardiac conduit; HR = hazard ratio; LT = lateral tunnel; mPAP = mean pulmonary artery pressure; OR = odds ratio; RV = right ventricle.
*Adjusted for Fontan age, sex, Fontan surgery year.

of arrhythmia were 96.1%, 88.5%, and 79.8% at 10, 20, and 30 years, respectively. In total, 153 patients experienced tachyarrhythmia. Among them, 21 underwent a radiofrequency tachycardia, and 11 had implantable cardioverter defibrillators. Moreover, 77 patients with symptomatic bradycardia and conduction disorders had an implantable PM. Next, PLE (4.1%), thromboembolism (3.5%), pulmonary arteriovenous fistula (2.4%), major bleeding (2.0%), ventricular failure (2.0%), renal failure (0.9%), and endocarditis (0.4%) were the most frequent complications (**Table 4**). In total, 71 (4.1%) patients presented with PLE after Fontan surgery. After a mean period of 6.5±5.8 years after Fontan surgery, PLE was diagnosed at a mean age of 11.2±7.9 years. The mean follow-up period was 7.5±6.0 years. PLE resolved in 20 of 71 patients after treatment using diuretics, heparin, selective pulmonary vasodilator, transcatheter treatment, or surgery. In total, 24 (33.8%) of 71 patients died, and the survival rates were 76.6% at 5 years and 66.9% at 10 years. Further, 60 (3.5%) patients experienced a thromboembolic event at a median age of 17.8±10.9 years. Sixteen patients experienced stroke or transient ischemic attack, and 17 had pulmonary thromboembolism. Twenty-four patients underwent surgical thrombectomy, and treatment with vitamin K antagonists, which are long-term anti-thrombotic agents, was maintained. In the thromboembolism rate according to Fontan type, AP-type Fontan surgery showed higher prevalence (**Table 2**).

The medications currently taken by patients were as follows: anti-thrombotic agents such as aspirin (56.7%), warfarin (31.8%), and direct oral anti-coagulants (0.5%). The other medications include anti-heart failure agents (59.5%) such as angiotensin-converting enzyme inhibitor/angiotensin receptor blocker or carvedilol, diuretics (12.5%), selective pulmonary vasodilators (7.2%), anti-arrhythmic drugs (5.7%), and others (5.4%) (**Table 4**).

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Table 4. Adverse events and current medications

	Mean time from Fontan surgery (years)	Incidence (%)
Adverse events		
Arrhythmia		216 (12.5)
Tachyarrhythmia		153 (8.8)
Bradyarrhythmia		77 (4.4)
Protein-losing enteropathy		71 (4.1)
Thromboembolism		60 (3.5)
Pulmonary arteriovenous fistula		42 (2.4)
Major bleeding		35 (2.0)
Ventricular failure		35 (2.0)
Renal failure		16 (0.9)
Endocarditis		7 (0.4)
Others		101 (5.8)
Current medications		
Anti-thrombotic agents		
Aspirin		754 (57.4)
Warfarin		418 (31.8)
Direct oral anti-coagulants		7 (0.5)
Anti-heart failure medication such as ACEi or ARB or carvedilol		782 (59.5)
Diuretics		164 (12.5)
Selective pulmonary vasodilator		94 (7.2)
Anti-arrhythmic drug		75 (5.7)
Others		71 (5.4)
Additional surgery after Fontan surgery		
Fontan conversion	15.6±7.6	90 (5.2)
Atrioventricular valve surgery	9.3±5.2	52 (3.0)
Fontan conduit revision	10.3±5.9	28 (1.6)
Pulmonary artery angioplasty	7.78±5.9	16 (0.9)
Aortic valve surgery	10.3±5.2	14 (0.8)
Others		
PM-related surgery		76 (4.4)
Included subaortic or BVF widening, diaphragm plication, wound problem, and anti-arrhythmic surgery		201 (11.6)

Data were expressed as number and percentage except when specified.
ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BVF = bulbo-ventricular foramen; PM = pacemaker.

In total, 817 patients underwent ultrasonography or computed tomography scan for hepatic disease. Their mean age was 21.2 years old, and the mean duration from Fontan surgery was 16.9 years. Further, 305 (37.4%) patients presented with cirrhotic change, and 12 (1.5%) were diagnosed with hepatocellular carcinoma. Patients who had a longer follow-up duration after Fontan operation frequently presented with cirrhotic changes in the liver.

In total, 518 patients performed the cardiopulmonary exercise test. Their mean age was 21.2±7.2 years old, and the mean duration from Fontan surgery was 17.1±6.4 years. The mean respiratory exchange ratio was 1.11, and the peak oxygen consumption was 26.1 mL/kg/min (percentage of prediction for age and sex, 58.3%).

Moreover, 313 patients had late additional operation after Fontan surgery, and the total number of cases was 488. Fontan conversion was the most common additional surgery, which was performed on 90 (5.2%) patients mainly for AP-type and occasionally for LT-type Fontan circulation. They underwent Fontan conversion at an average age of 15.6±7.6 years after the initial Fontan surgery. Next, atrioventricular valve surgery (3.0%), Fontan conduit revision (1.6%), pulmonary artery angioplasty (0.9%), and aortic valve surgery (0.8%) were

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the most frequent procedures performed. The PM-related generator or lead was changed in 76 cases, similar to other surgeries (**Table 4**).

DISCUSSION

This article is the first national report by the KFR in Asian countries. This paper contains more than 90% of patients who underwent Fontan surgery in the ROK, so it can be considered a national study. To date, even though there are several reports for outcomes of Fontan operations from Western countries,[5-7] national reports in Asian countries were limited. The Asian population might have different genetic characteristics and other types of functional SV. The heterotaxy syndrome and HLHS are the representative difference in disease entity. Compared with Western countries reports,[8][9] the proportion of patients with heterotaxy syndrome (22.6%) was relatively high in our subjects (Australia and New Zealand group 7% and PHN-Fontan 7.7%). The proportion of patients with HLHS is relatively low (3.8%, Australia and New Zealand group 8% and PHN-Fontan 20.6%).[8][9] The proportion of patients with heterotaxy syndrome or HLHS is similar to that in reports from other Asian countries, such as Japan.[10]

In our report, the overall survival rates after Fontan surgery were 91.7%, 87.1%, and 74.4% at 10, 20, and 30 years, respectively. Our subjects included elderly patients who underwent Fontan surgery from 1980s, and 21.4% were followed-up for over 20 years after Fontan surgery. In addition, the ratio of AP-type Fontan surgery was 9.1%, and 38.0% of patients who underwent Fontan surgery presented with fenestration. The outcomes of KFR are comparable to those of other Western institutions or countries,[11][12] and this finding is attributed to several causes. First, the centralization of patients occurred unintentionally, and 6 institutions commonly performed Fontan surgery in the ROK (96.8%). The rapid accumulation of experiences on Fontan surgery could gather more information on patient selection and facilitate the stabilization of surgical techniques and postoperative management. Second, there is a rapid transition to ECC-type Fontan surgery. Therefore, AP and ECC types account for 9.1% and 73.1% of all cases, respectively. In the multivariable analysis (**Table 3**), the AP-type Fontan surgery was a significant risk factor of mortality and Fontan failure. The overall survival rates of the ECC-type group were 93.4% and 90.5% at 10 and 20 years, respectively (**Figure 2B**). The transition to LT-type started from the late 1980s, and transition to the ECC-type started from the early 1990s. Therefore, the proportion of AP-type Fontan surgery was small, and early transition to ECC-type Fontan surgery was associated with good outcomes. Third, early and preemptive atrioventricular (AV) valve repair was performed on candidates for Fontan operation.[13] Even if this article did not show the time of AV valve repair, most surgeons in the ROK considered AV valve regurgitation in single ventricular physiology as a silent killer, and they performed AV valve repair if required if the patient undergoes staged palliative surgery as a functional SV. Fourth, early diagnosis of complex heart disease can be obtained using a fetal echocardiography.[14] Recently, most obstetric physicians performed a detailed evaluation of congenital heart anomalies using ultrasonography in the fetal period, and most neonates with complex CHDs were diagnosed in the fetal period. Therefore, prepared delivery was performed in most neonates with complex CHDs, and sudden collapse caused by the constriction of patent ductus arteriosus could be prevented. Therefore, stable hemodynamic conditions before the initial stage of surgery and controlled optimal pulmonary blood flow before Fontan surgery were associated with better outcomes. According to several previous investigations and our results, low

pulmonary artery pressure, good development of pulmonary vasculature, and preserved ventricular function are essential for good Fontan physiology.[15][16]

In the analysis of risk factors, male, heterotaxy syndrome, AP-type Fontan surgery, high mPAP in pre-Fontan cardiac catheterization, and early Fontan surgery year were the risk factors of early mortality based on our results obtained via multivariable using the logistic regression analysis. The results of each outcome were similar to those of a previous Mayo Clinic's report.[12] Intraoperative sinus rhythm, postoperative mPAP, and mean left atrial pressure were the risk factors associated with decreased survival or transplant based on the Mayo Clinic's report. However, the intraoperative sinus rhythm, mean left atrial pressure, and postoperative mean pulmonary artery pressure were not included in the analysis of risk factors due to lack of data. The heterotaxy syndrome, genetic disorder, significant AVVR before Fontan operation, high mPAP in pre-Fontan cardiac catheterization, and no fenestration are the risk factors of late mortality. The previous BCPS and morphological RV was identified as the risk factors of early and late mortality only in univariate analysis (**Supplementary Table 2**). The absence of Fenestration was a risk factor of late mortality. However, as there is continuous controversy on these factors in previous Fontan studies,[12][17][18] it is necessary to validate this finding through a more detailed statistical analysis such as propensity score matching analysis. Heterotaxy syndrome, right ventricular morphology, AP-type Fontan surgery, high VEDP and mPAP in pre-Fontan cardiac catheterization were risk factors for early failure and heterotaxy syndrome, AP-type Fontan surgery, older age at Fontan surgery, significant AVVR before Fontan surgery, mPAP in pre-Fontan cardiac catheterization, and early Fontan surgery year were considered as the risk factors of late failure (**Table 3**, **Supplementary Table 2**). Overall, AP-type Fontan surgery was the strongest risk factor of overall mortality and failure, and high mPAP in pre-Fontan cardiac catheterization, heterotaxy syndrome, and early Fontan surgery year were the significant risk factors of overall mortality and failure. To date, AP-type Fontan surgery and early Fontan surgery year are no longer considered as risk factors, and heterotaxy syndrome and genetic disorder are not correctable factors. Therefore, among the risk factors of each outcome based on our study, VEDP and mPAP in pre-Fontan cardiac catheterization might be controllable risk factors. The high VEDP and mPAP in pre-Fontan cardiac catheterization could be prevented by optimal timed-stage palliative surgery (e.g., shunt, pulmonary artery banding, bidirectional cavo-pulmonary shunt), which promote good pulmonary artery growth, preserve ventricular function, and prevent valve deformation. In addition, although the AVVR might be caused by innate valve anomalies, it can be induced by ischemic insults or ventricular dysfunctions from inappropriate pulmonary blood flow control. Hence, the optimal staged palliative preparations for Fontan operation might be the most important factor of good prognosis after Fontan surgery, except for the part caused by congenital cardiac anomalies.

Arrhythmia was a common complication related to Fontan surgery or functional SV. The overall freedom rates from arrhythmia were 96.1%, 88.5%, and 79.8% at 10, 20, and 30 years, respectively. Compared with other reports,[12] the freedom rate from arrhythmia was better because the ratio of AP-type was relatively low, and the proportion of ECC-type Fontan surgery was relatively high in our participants. Most patients had atrial flutter or fibrillation, and a smaller proportion had reentrant supraventricular tachycardia, atrial tachycardia, or ventricular tachycardia.

The incidence rate of PLE was 4.1%, which is similar to that in other studies in the range of 3 to 5% (3.1% in the Australia and New Zealand Fontan registry, 3.7% in 35 multicenter study

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and 4.6% in ROK multicenter reports incidence 4.6%).[19-21] Based on the multicenter study in the ROK, NYHA functional classification III or IV, low aortic oxygen saturation (<90%), and ventricular dysfunction at the time of PLE diagnosis were considered as predictors of mortality.[21] In the ROK, most patients with PLE were controlled by medications such as diuretics, heparin, steroid, and pulmonary vasodilators. Recently, a few patients with PLE underwent lymphatic interventions. The anticoagulant use rate is 31.8%, but the thromboembolism event rate is 3.5%, and the bleeding rate is still similar to that of other studies (2%). It is thought that less thromboembolisms and usual bleeding rate were affected by racial characteristics.

The current study had several limitations. That is, it was a 40-year multi-center cohort registry study. Therefore, the treatment strategy and criteria might differ, and treatment decisions were made by various medical staff and different surgical periods. Even if the general outcomes of Fontan surgery were identified, it was not an outcome from the uniform management of patients with functional SV. Further, it was retrospective in nature. Previous medical records had several missing values. Therefore, only available data were analyzed in the multivariable analysis of the risk factors of each outcome. To date, because most institutions in the ROK used an electrical medical record system, a later study with more data might be performed. In addition, in all the late follow-up outcomes, the data curves were censored using the date of the last available follow-up of each patient.

In conclusion, the KFR comprised 10 pediatric cardiovascular centers and reviewed the clinical data of patients who underwent Fontan surgery in the ROK. The overall survival rates after Fontan surgery were 91.7%, 87.1%, and 74.4% at 10, 20, and 30 years, respectively. With the evolution of patient selection, surgical techniques, and postoperative management, the outcomes of Fontan surgery have improved. The preoperative preparation for Fontan operation such as low mPAP and good atrio-ventricular valve function by the optimal timed-stage palliative operation will improve the Fontan surgery outcomes. The outcomes of Fontan surgery in the ROK were generally good and comparable with those in other countries.

ACKNOWLEDGMENTS

We thank the pediatric cardiologists and pediatric cardio-thoracic surgeons involved in Fontan surgery in the Republic of Korea (**Appendix 1**). The statistical analysis was supported by Seoul National University Hospital Medical Research Collaborating Center.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Variables collected in electronic case report form

Supplementary Table 2
Univariate and multivariate analyses for each end point using logistic regression or Cox-proportional hazard ratio analysis

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Appendix 1. Key members of the Korean Fontan Registry Committee

Key Members	Affiliations
Jeong Jin Yu, Tae-Jin Yun	Asan Medical Center, Seoul, Korea
Hyoung Doo Lee, Hyungtae Kim	Pusan National University Children's Hospital
Chang Hyu Choi	Gacheon University Gil Medical Center
Myung Chul Hyun, Joon Yong Cho	Kyungpook National University Hospital
Tae-Gook Jun, Ji-Hyuk Yang	Samsung Medical Center
Yong-Jin Kim, Jeong-Il Noh, Seong-Ho Kim	Sejong General Hospital
Woong-Han Kim, Eun-Jung Bae, Gi-Beom Kim	Seoul National University Children's Hospital
Young Hwan Park, Han Ki Park, Jae Young Choi	Severance Cardiovascular Hospital
Cheul Lee	The Catholic University of Korea Seoul St. Mary's Hospital

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