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Mid-term results and late events after the Fontan operation: A single-center experience

Fontan ameliyatı sonrası orta vadeli sonuçlar ve geç dönem olaylar: Tek merkez deneyimi

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ABSTRACT

Background: This study aimed to review our institutional experience with the Fontan operation, the adverse severe events we encountered during mid-term follow-up, and the associated risk factors.

Methods: In the study, the medical records of 40 patients (22 males, 18 females) who underwent Fontan operation between August 1993 and August 2020 were retrospectively reviewed. The patients were followed up for at least six months.

Results: The Fontan operation was performed at a median age of 6.5 years (range, 3 to 22 years), and the mean follow-up time was 4.1±3.8 years (range, 0.5 to 17 years). The most frequently occurring defect was tricuspid atresia (45.0%). Fifteen (37.5%) patients experienced 24 late adverse events. Late complications and severe side effects, in order of frequency, were arrhythmia in eight (53.3%) patients, hypoxia in five (33.3%) patients, and ventricular dysfunction in three (20%) patients. While protein-losing enteropathy and mortality were each observed in two (13.3%) patients, Fontan failure, thromboembolic event, pulmonary arteriovenous fistulae, and ascites were each observed in one (6.6%) patient. When possible risk factors for late complications were examined, a statistical significance was not found.

Conclusion: Life expectancy and quality of life of patients with Fontan circulation have increased with advances in surgical technique and increased management success. However, complications are not uncommon after the Fontan operation, and late events remain a significant problem. The results of our study indicate that in mid-term follow-up of patients who underwent Fontan surgery at our institution, although not statistically significant, those who underwent fenestration and those operated at a later age tended to experience more severe events and late complications.

Keywords: Fontan operation, late complication, outcomes, univentricular heart diseases.

ÖZ

Amaç: Bu çalışmada, Fontan ameliyatıyla ilgili kurumsal deneyimimiz, orta dönem takipte karşılaştığımız ciddi olumsuz olaylar ve ilişkili risk faktörleri gözden geçirildi.

Çalışma planı: Çalışmada, Ağustos 1993 ile Ağustos 2020 tarihleri arasında Fontan ameliyatı geçiren 40 hastanın (22 erkek, 18 kadın) tıbbi kayıtları retrospektif olarak incelendi. Hastalar en az altı ay takip edildi.

Bulgular: Fontan ameliyatı, median 6.5 (dağılım, 3-22 yıl) yaşında yapıldı ve ortalama takip süresi 4.1±3.8 yıl (dağılım, 0.5-17 yıl) idi. En sık görülen defekt triküspit atrezisi (%45.0) idi. On beş (%37.5) hastada 24 geç dönem olay yaşandı. Geç komplikasyonlar ve ciddi yan etkiler sıklık sırasına göre sekiz (%53.3) hastada aritmi, beş (%33.3) hastada hipoksi ve üç (%20) hastada ventriküler fonksiyon bozukluğu idi. Protein kaybettiren enteropati ve mortalite ikişer (%13.3) hastada görülürken, Fontan yetmezliği, tromboembolik olay, pulmoner arteriyovenöz fistül ve asit birer (%6.6) hastada gözlendi. Geç komplikasyonlarla ilişkili olası risk faktörlerini incelendiğinde istatistiksel anlamlılık bulunmadı.

Sonuç: Fontan dolaşımı olan hastalarda cerrahi teknikteki ilerlemeler ve artan yönetim başarısı ile yaşam beklentisi ve yaşam kalitesi artmıştır. Ancak Fontan ameliyatından sonra komplikasyonlar nadir değildir ve geç dönemde görülen olaylar önemli bir sorun olmayı sürdürmektedir. Çalışmamızın sonuçları, kurumumuzda Fontan ameliyatı geçiren hastaların orta dönem takiplerinde, istatistiksel olarak anlamlı olmasa da, fenestrasyon uygulananların ve geç yaşta ameliyat edilenlerin daha ciddi olaylarla ve geç komplikasyonlarla karşılaşma eğiliminde olduğunu göstermektedir.

Anahtar sözcükler: Fontan ameliyatı, geç komplikasyon, sonuçlar, tek ventrikül kalp hastalıkları.

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Fontan operation is the final circulatory purpose of surgical palliation, where biventricular repair is impossible. This technique aims to direct systemic venous return to the pulmonary artery. Fontan and Baudet[1] first described this surgery in 1971 in tricuspid atresia. Since then, some surgical modifications have been developed to prevent early- and long-term complications.[2] Today, the procedure of choice is total cavopulmonary shunt using an extracardiac conduit or, less commonly, intracardiac lateral tunnel (LT) technique.[3-5] Staged palliation is generally applied. Early infancy starts with a pulmonary shunt or band, followed by Glenn anastomosis (superior vena cava with pulmonary artery), and finally, the connection of the inferior vena cava and pulmonary artery.[6-8] Elevated central venous pressure and impaired cardiac output as a result of this palliative circulation lead to adverse complications in Fontan patients. This situation negatively affects all organ systems over time.[9]

As the surgical technique improves and the experience in managing complications rises, these patients' success rate in long-term follow-up increases. Long-term survival rates are around 90% in studies conducted on large case series.[10] Although Fontan operation improves survival for patients with single ventricle physiology, mid- to long-term complications associated with this form of circulation are common and remain a significant concern. Late complications, such as ventricular dysfunction, dysrhythmias, cyanosis, cirrhosis, hepatic carcinoma, protein-losing enteropathy (PLE), plastic bronchitis, and venous thrombosis, were well-described.[11,12] This study aimed to review our institutional experience with the Fontan operation and the severe adverse events we encountered during mid-term follow-up and associated risk factors.

PATIENTS AND METHODS

In this retrospective study, 40 patients (22 males, 18 females) who underwent Fontan operation between August 1993 and August 2020 and were followed up for at least six months in the pediatric cardiology department of the Çukurova University Faculty of Medicine were examined. Preoperative, intraoperative, and postoperative medical records of the patients were reviewed. Patients' demographic data, diagnosis of cardiac disease, presence of noncardiac disease, catheterization reports, and previous palliative operations were examined. Before the Fontan operation, detailed physical examination findings, body weight, height, blood pressure, transcutaneous oxygen saturation at rest, and the New York Heart Association (NYHA) functional class of the patients were noted. Rhythm data were obtained by analysis of electrocardiograms and Holter examinations. Mean pulmonary artery pressure was noted in cardiac catheterization before the operation. Angiographic data were examined to calculate the diameter of pulmonary artery branches, pulmonary artery index, and Nakata index. Ventricular function and atrioventricular valve regurgitation were evaluated by transthoracic echocardiography. Atrioventricular valve regurgitation was recorded as none, mild, moderate, or severe.[13] Ventricular function was evaluated using M-mode ultrasonography or the Simpson method. A left ventricle ejection fraction of 55% or higher is considered normal.[14] Patients were classified according to their ventricular morphology, and dominant ventricular morphology was evaluated with a preoperative echocardiogram and catheterization report. Additional intraoperative procedures and types of Fontan procedures were noted.

Surgical technique

The majority of the patients had previously undergone various palliative surgical operations, such as aortopulmonary shunt, pulmonary artery banding, pulmonary artery reconstruction, and bidirectional Glenn surgery, depending on their cardiac morphology. In the extracardiac type Fontan (ECF) operation, the venous flow of the inferior vena cava was directed to the pulmonary arteries with a conduit of polytetrafluoroethylene tube grafts using Gore-Tex (W.L. Gore and Associates, Flagstaff, AZ, USA) with a median size 18 mm; range, 14 to 20 mm.

The isolated Fontan operation was performed using cardiopulmonary bypass with mild to moderate hypothermia. A circulatory arrest or deep hypothermia was used only when necessary. The decision for intraoperative fenestration was made in patients at high risk based on preoperative hemodynamics (e.g., pulmonary artery pressure above 15 mmHg or suboptimal Nakata index).

Postoperative variables

Complications occurring in the six months after Fontan operation were defined as early complications.[15] Pleural and pericardial effusion, ascites, chylothorax, and thromboembolic complications were evaluated as early complications. Adverse events occurring after the sixth month of follow-up were considered late complications. Ventricular dysfunction, rhythm problems, hypoxemia, PLE, arteriovenous fistula, thromboembolic complications, ascites, and Fontan takedown were recorded as late complications. Protein-losing enteropathy was diagnosed by the

Table 1. Demographic, hemodynamic, and morphological characteristics of patients before the Fontan operation

	n	%	Median	Min-Max
Demographics				
Age at Fontan procedure (year)			6.5	3.0-22.0
Sex				
Male	22	55.0		
Female	18	45.0		
Weight at Fontan (kg)			18.0	12.0-55.0
Morphological				
Tricuspid atresia	18	45.0		
Double outlet right ventricle	8	20.0		
Double inlet left ventricle	7	17.5		
Transposition of the great arteries	2	5.0		
Hypoplastic left ventricle	2	5.0		
CCTGA	1	2.5		
Unbalanced atrioventricular septal defect	1	2.5		
Single unknown ventricle	1	2.5		
Morphological ventricle				
Left	26	65		
Right	13	32.5		
Indeterminate/biventricular	1	2.5		
Other morphological				
Malposition of great arteries	11	27.5		
Bilateral SVCs	2	5.0		
MAPCAs	2	5.0		
Pulmonary atresia	2	5.0		
PAPVC	2	5.0		
Atrial isomerism	1	2.5		
Dextrocardia	1	2.5		
Non-cardiac anomalies				
MTHFR gene mutation	9	22.5		
Diaphragmatic eventration	2	5.0		
Hydrocephalus	1	2.5		
Scoliosis	1	2.5		
Additional cardiac treatment before the Fontan				
Pulmonary hypertension	2	5		
PA stent implantation	1	2.5		
MAPCAs transcatater occlusion	1	2.5		
Hemiazygos vein transcatheter occlusion	1	2.5		
AVV regurgitation before Fontan				
None-mild	30	75.0		
Moderate-severe	10	25.0		
Hemodynamics				
PA pressure (mean; mmHg)			12.0	7.0-19.0
PA index			241.0	171.0-400.0
McGoon ratio			2.0	1.4-2.7
Room air saturation before Fontan (%)			83.5	70.0-90.0

CCTGA: Congenitally corrected transposition of the great arteries; SVC: Superior vena cava; MAPCAs: Major aortopulmonary collateral arteries; PAPVC: Partial anomalous pulmonary venous connection; MTHFR: Methylenetetrahydrofolate reductase; AVV: Atrioventricular valve, PA: Pulmonary artery.

demonstration of persistent or intermittent edema, loss of enteric alpha-1-antitrypsin, or low serum total protein/albumin.[11] A thromboembolic event was defined as a thrombus in the Fontan circulation, transient ischemic attack/stroke, or thrombus in the venous circulation. The laboratory analyses and ultrasonographic imaging were performed periodically.[12,16]

Statistical analysis

Data were analyzed using IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA) statistical software package was used for all analyses. The Shapiro-Wilk test was used to confirm the normality of distribution for continuous variables. Continuous data with nonnormal distribution were summarized as median and minimum-maximum, while categorical variables were expressed as numbers and percentages. The chi-square test was performed to compare categorical variables between groups. A Kaplan-Meier curve was constructed to examine the relationship between Fontan operation time and late adverse events. Cox regression analysis was performed to determine significant predictors of late complication variables.

Table 2. Operative data of patients and outcomes after the Fontan procedure

	n	%	Median	Min-Max
Fontan type				
Extracardiac	35	87.5		
Intracardiac	3	7.5		
Lateral tunnel	2	5.0		
Single stage Fontan	3	7.5		
Additional intraoperative procedures				
Fenestration	10	25.0		
Atrioventricular valve repair	9	22.5		
PA reconstruction	5	12.5		
Radiofrequency ablation	1	2.5		
Mitral valve replacement	1	2.5		
Conduit size			18.0	14.0-20.0
Early complication				
Pleural and pericardial effusion	10	25.0		
Chylothorax	1	2.5		
Thrombus	1	2.5		
Ascites	1	2.5		
Late complication	15	37.5		
Transcatheter occlusion				
Fenestration	2	5.0		
Antegrade pulmonary blood flow	1	2.5		
Pacemaker implantation	4	10.0		
Pulmonary hypertension treatment	5	12.5		
PA stent implantation	1	2.5		
Anticoagulant therapy				
ASA	24	60.0		
ASA and warfarin	16	40.0		
Mortality	2	5.0		

PA: Pulmonary artery; ASA: Acetyl salicylic acid.

Potential factors that could be clinically significant variables (Fontan year, fenestration) were entered in the Cox regression analysis, and the model was adjusted for age. For all tests, the level of statistical significance was set at $p<0.05$.

RESULTS

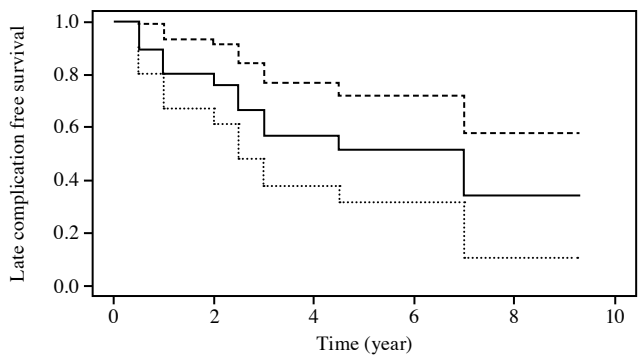
The median age at Fontan operation was 6.5 years (range, 3 to 22 years), and the mean follow-up time was 4.1±3.8 years (range, 0.5 to 17 years). Ventricular morphology was predominantly left in 26 (65%) patients, right in 13 (32.5%) patients, and indeterminate/biventricular in one (2.5%) patient. The predominant morphological diagnoses were tricuspid atresia in 18 (45%) patients, double outlet right ventricle in eight (20%) patients, and double-inlet left ventricle in seven (17.5%) patients. The preoperative mean transcutaneous oxygen saturation at rest in room air was 83.5±4.5 (range, 70.0 to 90.0), and the preoperative mean pulmonary arterial pressure (measured during catheterization) was 12.0±2.7 mmHg (range, 7.0 to 19.0 mmHg). Before the Fontan operation, two (5%) patients had pulmonary arterial hypertension and were therefore receiving medical treatment, and the mean pulmonary artery pressures of these two patients before the operation were 15 and 17 mmHg. Thirty (75%) patients had no or mild atrioventricular valve regurgitation. The patients' demographic, anatomical, and hemodynamic data are summarized in Table 1. Most patients (n=35, 87.5%), had an extracardiac Fontan, and the median conduit size was 18 mm (range, 14 to 20 mm). Atriopulmonary connection type Fontan was performed in three (7.5%) patients, and the LT technique for total cavopulmonary connections was created in two (5%) patients. The majority of the patients (n=37, 92.5%) had previously undergone various palliative surgical operations, such as aortopulmonary shunt, pulmonary artery banding, pulmonary artery reconstruction, and bidirectional Glenn surgery. A single-stage Fontan operation was performed in three (7.5%) patients. A fenestration was performed in 10 (25%) patients. Twenty-four (60%) patients received acetylsalicylic acid, and 16 (40%) received an acetylsalicylic acid and warfarin combination after the Fontan operation. Five (12.5%) patients were given medical treatment for pulmonary arterial hypertension with inhaled iloprost in the early postoperative period and later with oral sildenafil or bosentan. Thirty-eight patients (95%) functioned in NYHA class I or II. The operative data of patients and outcomes after the Fontan operation are presented in Table 2.

Fifteen patients experienced a total of 24 late adverse events. Late complications and severe adverse events are listed in Table 3. In order of frequency, arrhythmia was observed in eight (53.3%) patients, hypoxia was observed in five (33.3%) patients, and ventricular dysfunction was observed in three (20%) patients. While PLE and mortality were each observed in two (13.3%) patients, Fontan failure, thromboembolic events, pulmonary arteriovenous fistulae, and ascites were each observed in one (6.6%) patient. Event-free survival at one, two, and four years after the Fontan operation was 80.1%, 76.1%, and 57.1%, respectively (Figure 1). Moreover, as observed in Figure 1, late complications were less common since there was a flatter slope after the third time point compared to the other time points. Table 4 describes the variety of late complications and their

Table 3. Late complications and severe adverse events during follow-up

Patients	n	%
Arrhythmia	8	53.3
Hypoxia	5	33.3
Ventricular dysfunction	3	20.0
Protein-losing enteropathy	2	13.3
Mortality	2	13.3
Fontan takedown	1	6.6
Thromboembolic complications	1	6.6
Pulmonary AV-fistula	1	6.6
Ascites	1	6.6

AV: Arteriovenous.



Time (year)	0.5	1.0	2.0	2.5	3.0	4.5	7.0
Number at risk	40	28	20	16	14	11	6

Figure 1. Kaplan-Meier survival curve for late adverse event-free survival with the confidence interval.

Table 4. Comparison of post-Fontan late complications with patient characteristics and operative data

	Late complication								
	Yes				No				
	n	%	Median	Min-Max	n	%	Median	Min-Max	*p*
Age (year)			7.0	3-17			6.5	4-22	0.643
Weight (kg)			20.0	12-53			18.0	14-55	0.801
Non-cardiac anomaly									>0.999
Yes	4	26.7			8	32.0			
None	11	73.3			17	68.0			
Glenn time (year)									0.474
≤1	6	40.0			7	28.0			
>1	7	46.6			16	64.0			
Fontan time (year)									0.049*
<4	2	13.3			1	4.0			
4-10	8	53.3			22	88.0			
≥10	5	33.3			2	8.0			
PA pressure (mean; mmHg)									>0.999
<15	12	80.0			20	80.0			
≥15	3	20.0			5	20.0			
Nakata index			250.0	171.0-400.0			240.0	190.0-400.0	0.976
Room air saturation									
Before Fontan			83.5	70.0-90.0			85.0	75.0-90.0	0.943
After Fontan			94.0	78.0-97.0			94.0	86.0-97.0	
McGoon ratio			2.1	1.4-2.7			2.0	1.7-2.5	0.627
Fontan type									
Extracardiac	12	80.0			23	92.0			0.173
Lateral tunnel	2	13.3			0	0.0			
Intracardiac	1	6.7			2	8.0			
Additional cardiac treatment before Fontan									0.081
Yes	5	33.3			2	8.0			
No	10	66.7			23	92.0			
Additional intraoperative procedures Fenestration									0.024*
Yes	7	46.7			3	12.0			
No	8	53.3			22	88.0			
AVV regurgitation before Fontan									
None-mild	11	73.3			19	76.0			>0.999
Moderate-severe	4	26.7			6	24.0			
Systemic ventricle									
Right	6	40.0			7	28.0			0.727
Left	9	60.0			17	68.0			
Time between Glenn and Fontan (year)									0.716
≤4	8	53.3			13	54.2			
>4	4	26.0			11	45.8			

PA: Pulmonary artery; AVV: Atrioventricular valve.

Table 5. Age-adjusted model of univariate and multiple Cox regression analyses of risk factors for late complications

	Univariate		Multiple	
Parameters	HR (95% CI)	*p*	HR (95% CI)	*p*
Fontan year				
<10	Ref.	0.115	Ref.	0.246
≥10	2.38 (0.81-6.96)		3.20 (0.45-22.91)	
Fenestration				
No	Ref.	0.040	Ref.	0.085
Yes	2.92 (1.05-8.12)		2.77 (0.87-8.81)	

HR: Hazard ratio; CI: Confidence interval.

relationship with patients' features. Twenty-two (73.3%) of the patients who underwent Fontan surgery between the ages of four and 10 did not develop late complications, while eight (26.6%) patients developed late complications (p=0.049). Furthermore, late complications were observed in seven of 10 patients who underwent fenestration, and no late complications were observed in three patients. In the chi-square test, we also found that fenestration and age at the time of the operation were associated with late complications, as shown in Table 4 (p=0.024). Fenestration evaluated by univariate analysis was found to be a risk factor for late complication (p=0.040). However, when evaluated in the multiple Cox regression model (adjusted for age) with Fontan year, it lost statistical significance (p=0.085). Therefore, no statistically significant risk factor was found in multiple Cox regression (Table 5). Moreover, no statistical difference was found when comparing other possible risk factors with late complications. Complications of stroke, liver failure, and plastic bronchitis were not observed in our cohort.

DISCUSSION

This retrospective study described a population who underwent the Fontan operation at our institution followed for at least six months after surgery while also highlighting the severe adverse outcomes that may occur in the mid-term. Additionally, this study was designed to reveal the risk factors associated with these adverse conditions. In our cohort of 40 patients, late complications were more common among patients over 10 years of age and in those who underwent fenestration, although this finding was not statistically significant. Furthermore, reviewing our institutional experiences through this study provides valuable information.

Since the Fontan operation was first described in 1971, there have been ongoing developments in preoperative patient selection, surgical modifications, and postoperative management. The median age at surgery in our center was 6.5 years (range, 3 to 22 years). Excluding the two late deaths, all other patients were evaluated as NYHA class I or II. Although the type of Fontan operation varied, the majority of our patients (87.5%) underwent an extracardiac type Fontan. Most of the patients in our study had a left ventricular structure, which is expected to result in better ventricular performance, and the majority did not exhibit significant atrioventricular valve regurgitation. Complications occurring during follow-up and their management continue to be important factors affecting the quality of life. De Vadder et al.[17] published complications and severe side effects (thromboembolic complications, arrhythmia, pacemaker, PLE, and severe cardiac events) in 73 Fontan patients. They reported that NYHA class, ventricular function, transcutaneous oxygen saturation, supraventricular arrhythmia, and atrioventricular valve regurgitation were associated with severe adverse outcomes.

Many studies have investigated the effect of fenestration on Fontan results. Bouhout et al.[18] reviewed the literature and evaluated the effect of fenestration on Fontan procedure results. They stated that fenestration effectively reduced pulmonary pressure and long-term pleural drainage requirement, but the risk of Fontan failure was not changed. Although there was no statistical difference between fenestration and late complications in our cohort, late complications were observed in seven of 10 patients who underwent fenestration. Furthermore, in our cohort, patients with fenestration had significantly higher rates of atrioventricular valve failure, higher

pulmonary artery pressures, and higher pulmonary vascular resistance. Therefore, differences in these baseline characteristics may have affected the results.

In our study, the incidence of arrhythmia was slightly lower compared to other series in the literature.[17,19] Eight patients (20%) developed postoperative arrhythmias in our study. One of the patients was being followed up for atrial tachyarrhythmia before the Fontan operation. Patients with Fontan circulation are more likely to develop arrhythmia; both tachyarrhythmias and bradyarrhythmias can be observed.[10] This situation complicates the management of the disease. Reasons such as the expansion of the atrial structure, damage to the sinus node by atrial incisions and suture lines, left atrial isomerism, inappropriate atrioventricular connection, and atrioventricular valvar regurgitation contribute to arrhythmias in Fontan patients.[12] Furthermore, intermediate-stage procedures performed before the Fontan operation may increase the risk of developing arrhythmias, as they may cause damage to the sinus node area.[20] Only one of our patients had atrial tachyarrhythmia before the Fontan operation. While arrhythmia is a common problem after the original Fontan operation, postoperative arrhythmia frequency decreased with modified techniques, particularly with the extracardiac Fontan type.[12,21,22] Dahlqvist et al.[23] found the rate of permanent pacemaker implantation to be 13% after a mean follow-up of 12.2±7.3 years with 599 patients who had a Fontan operation. They stated that sinus node dysfunction was the most common pacemaker indication (64%). In our cohort, eight patients developed arrhythmia after an average of 2.5 years (range, 0.5 to 7 years), four patients had tachyarrhythmia, two patients had bradyarrhythmia, and two patients had both tachyarrhythmia and bradyarrhythmia. Four patients required a permanent pacemaker after the operation (range, 1 to 6.5 years). A permanent pacemaker was implanted in all patients due to sinus node dysfunction.

In patients with total cava pulmonary anastomosis, systemic arterial oxygen saturation at rest in room air rarely reaches >95% and is usually in the 90 to 95% range. There are several reasons for this mild arterial oxygen desaturation. First, deoxygenated coronary sinus vein blood drains into the left atrium and causes moderate desaturation. Second, nonpulsatile pulmonary arterial blood flow tends to be directed to the lung's lower segments, while pulmonary ventilation supports the upper segments, causing a ventilation-perfusion mismatch. When the arterial oxygen saturation drops below 90% at rest, the conditions that cause this should be investigated. Residual/progressive right-to-left shunt (atrial septal defect, fenestration, intrapulmonary arteriovenous fistula, or abnormal systemic venous drainage into the pulmonary venous atrium) are the factors that can cause this situation.[22,24] If these connections cause symptomatic cyanosis, they can be closed with a transcatheter intervention using various devices. Webb et al.[25] reported that 59 (50%) of 118 patients with a fenestrated Fontan were closed with a device, device embolization developed in one patient, and cardiopulmonary death was not observed in any patient. Moreover, they have reported that spontaneous closure was observed in 23 (19%) of 118 patients. Şahin et al.[26] reported that pulmonary antegrade flow was successfully closed in two patients after the Fontan operation using Amplatzer Septal Occluder (ASO; St. Jude Medical, St. Paul, MN, USA). After the Fontan operation, we closed the fenestration of two patients with decreased oxygen saturation during follow-up with ASO and the pulmonary antegrade flow of one patient with Amplatzer Duct Occluder II (ADO II; St. Jude Medical Corporation, Plymouth, MN, USA). Additionally, pulmonary arteriovenous fistula incidence increases with age in patients undergoing Fontan operation.[27] An angiographic examination of one of our patients, who developed low saturation during follow-up, revealed a pulmonary arteriovenous fistula. We did not administer specific treatment for pulmonary arteriovenous fistula in this patient with diffuse pulmonary arteriovenous fistula. For these reasons, diagnostic angiographic examination is necessary in patients with unexplained low saturation.

Leakage into the intestine leads to PLE, the most common lymphatic problem in long-term follow-up. There is excessive protein loss from the serum to the intestinal lumen in PLE. Symptoms include edema, immunodeficiency caused by hypogammaglobulinemia, fat absorption disorder, electrolytic disturbances, hypocalcemia, and hypomagnesemia. Patients should undergo a comprehensive evaluation, including catheterization, to assess for venous obstruction, atrioventricular valve regurgitation, myocardial dysfunction, and atrial arrhythmias, which may contribute to hemodynamic disturbances. Following the hemodynamic assessment, the severity of the disease and the duration of symptoms are determined, and personalized treatment is initiated.[11,21] For PLE therapy, patients' diets should be rich in high-calorie,

high-protein content and medium-chain triglyceride fatty acids, and low salt intake is recommended. Treatment with diuretics and albumin infusion can be initiated in symptomatic patients after a detailed evaluation. Oral corticosteroids, specifically budesonide, are effective in treating PLE by reducing intestinal inflammation in these patients. Pulmonary vasodilator therapy may increase cardiac output in Fontan patients by reducing pulmonary vascular resistance. Additionally, treatment with high molecular weight heparin acts as a mechanical barrier by decreasing the permeability of the basal membrane. Moreover, octreotide, a somatostatin analog, reduces lymphatic flow and can be used in PLE treatment.[11,12,28]

After the failure of medical drug treatments, surgical or transcatheter fenestration should be considered. Fenestration may provide hemodynamic benefits such as reduced venous congestion and increased cardiac output, which may lower the risk of PLE, despite the potential for causing low arterial oxygen levels and stroke. Various hemodynamic problems can be solved with catheter techniques such as balloon dilatation and stent implantation to stenosis.[12,21] Alkofair et al.[29] stated that 28 (19%) of 147 Fontan patients developed PLE, and the 10-year nontransplant survival rate for these patients was 65.7%. Allen et al.[30] stated that freedom from PLE in 20 years was 88% in their cohort. In our study, PLE developed in two patients in the 12th and 15th months of their follow-up. Surgical fenestration was performed in one of our patients because the clinical findings did not improve with medical treatment. One year after the fenestration, the patient developed a severe decrease in oxygen saturation. Therefore, transcatheter fenestration occlusion was performed with the ASO. The device was also modified to allow little fenestration.[31] For this purpose, a 14-mm sheath dilator was used to create a 4.5 to 5 mm opening. Additionally, a stent was placed to relieve the stenosis in the pulmonary artery. During this patient's follow-up, a stent was placed in the narrowed fenestration due to the redevelopment of clinical and laboratory findings associated with PLE. The other patient who developed PLE clinical and laboratory findings improved with medical treatment.

In our study, three (7.5%) patients suffered from ventricular dysfunction (2.5 to 6 years after the Fontan operation), which was similar to the findings reported in the literature.[32] Two patients who developed ventricular dysfunction had moderate to severe atrioventricular valve regurgitation. Additionally, one of these patients had a pacemaker. Hemodynamic changes such as decreased preload, remodeling, decreased compliance, and poor ventricular filling observed after the Fontan operation may lead to a decrease in cardiac output. Systemic ventricles with right or left ventricular morphology and abnormal atrioventricular valve structure may cause volume overload and chronic systemic afterload problems. When examining studies on the treatment of ventricular dysfunction, it is evident that the effectiveness of drugs is limited.[12]

As known, early completion of Fontan is advantageous since it limits the harmful effects of ventricular volume overload and cyanosis. However, the disadvantage is that it increases the possibility of suboptimal Fontan hemodynamics due to inadequate development of the pulmonary vasculature. There have been various studies on the outcomes of patients who underwent surgery in the late period.[12,33,34,35] The majority of our patients were between the ages of four and 10, and only three patients were operated on at an early age (three years). In our study, 22 (88%) of the patients who did not develop late complications had undergone Fontan surgery between the ages of four and 10. The oldest patient who underwent surgery was 22 years old. Although this patient was initially scheduled for Fontan surgery at the age of seven, their family did not want to have it performed. However, due to an increase in cyanosis symptoms, the patient later sought medical attention. Fontan surgery was once again recommended, and the patient underwent the procedure successfully.

Pundi et al.[19] stated that the 10-year survival for 1,052 patients was 74%, which fell to 43% in 30 years. They stated that asplenia, preoperative use of diuretics, preoperative pulmonary artery pressure >17 mmHg, atriopulmonary connection type Fontan, atrioventricular valve replacement during the Fontan operation, arrhythmia, and long bypass duration after Fontan are risk factors associated with decreased survival and reoperation. In our investigation, mortality occurred in two patients. One of the patients with mortality functioned in NYHA class IV and had severe AV valve regurgitation and pacemaker implantation. The death occurred in the 14th year of follow-up. The other patient also developed severe ascites approximately two years after the operation. In this patient, anti-pulmonary hypertension treatment was started after the Fontan operation, and the pulmonary artery pressure was high in the angiography performed due to clinical deterioration. The patient, who underwent a Fontan takedown because complaints did not regress with medical treatment, died after the operation.

During long-term follow-up, hypoxia, PLE development, ventricular failure, arrhythmias, cirrhosis, and the need for interventional procedures continue to pose significant management challenges. After Fontan circulation, these patients should be subject to strict and multidisciplinary follow-up aimed at preventing multiple organ failure, even if they appear clinically well.

There are some limitations to this study. The study was conducted at a single center with a limited number of cases, which may explain why we could not demonstrate the risk factors associated with late complications in the literature. Our analysis is limited to the data recorded in graphs. The numbers in the parameters may be insufficient to predict the results. Since our study aimed to investigate late complications, patients with a short follow-up period and early death were not considered. Pulmonary vascular resistance and ventricular end-diastolic pressure were evaluated before the Fontan operation. However, due to incomplete data, these parameters could not be included in this study. Additionally, cardiac magnetic resonance imaging could not be performed on our patients. A national multicenter study would provide more evidence of the outcomes after the Fontan operation.

In conclusion, the results of this study identified risk factors associated with adverse outcomes during mid-term follow-up of the Fontan population at our institute. Since the inception of the Fontan operation, patient life expectancy and quality of life have increased due to improvements in surgical techniques and increased management success. However, a significant number of side effects still cause significant morbidity and mortality during follow-up. We aimed to contribute to the literature by presenting our 27-year experience in the mid-term follow-up of patients who underwent Fontan operation.

Ethics Committee Approval: The study protocol was approved by the Çukurova University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (date: 02.10.2022, no: 104). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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