http:// ijp.mums.ac.ir
Original Article (Pages14225-14238)

The Clinical Outcome of Patients Undergoing Fontan Surgery; Over 10 Years of Experience in a Single Center

ghaffari, shamsi[1], Jamei Khosroshahi, Ahmad[1], Samadi, Mahmoud[1], Molaie, Akbar[1], Baghaei, Mohammadreza[2], *Basir, Tahereh[1]

[1]Pediatric Health Research Center, Tabriz Children Hospital, Tabriz University of Medical Sciences, Tabriz, Iran

[2]Shahid beheshti University of Medical Sciences, Tehran, Iran

Abstract

Background: The modified Fontan operation is one of the essential surgical techniques in children with congenital heart diseases. Thus, we sought to identify the characteristics as well as the early and late outcomes of patients who have undergone Fontan operation during more than 10 years.

Methods: The medical records of 52 patients who underwent modified Fontan operation from March 21th, 2006 to March 20th, 2018, at Tabriz Children's Hospital including the baseline, clinical and surgical data were extracted and reviewed. Patients were invited for follow up visits and clinical examination and echocardiographic evaluations were conducted.

Findings: The most prevalent heart anomaly was tricuspid valve disorders (28 cases, 51.9%). The majority of patients (42 cases, 80.2 %) underwent intracardiac lateral tunnel Fontan. The most prevalent complications were prolonged pleural effusion and neurologic events (each one in 10 cases, 19.2%). The in-hospital mortality rate was 15.3%. The patients were followed for a median of 7 years. The survival of those successfully followed was 75 percent. The most common valvular disorder was mitral valve regurgitation (MR), which was present in 84% of cases. The group of patients with single ventricle had a significantly higher mortality rate than the other groups (P = 0.018).

Conclusion: Survival rate of patients undergoing a Fontan completion is acceptable. However, patients remain at risk for morbid events. Moreover, patients with Fontan circulation should be strictly followed to investigate the development of MR and to timely repair in severe cases to prevent further deterioration. Of note, due to some limitations of our study, further multi-centric studies are required to confirm our findings.

Keywords: Complication, Extracardiac Fontan, Fontan operation, Intracardiac lateral tunnel Fontan, Outcome

*Please cite this article as: ghaffari Sh,, Jamei Khosroshahi A, Samadi M, Molaie A, Baghaei M, Basir T. The Clinical Outcome of Patients Undergoing Fontan Surgery; Over 10 Years of Experience in a Single Center Int J Pediatr 2021; 9(8): 14225-14238. DOI: **10.22038/ijp.2020.51756.4115**

* ***Corresponding Author:*** Tahereh Basir, MD; Pediatric Health Research Center, Tabriz Children Hospital, Tabriz University of Medical Sciences, Tabriz, Iran; Email: dr.rezab2007@gmail.com,

Received date: September 5, 2020; Accepted date: September 8, 2020

Introduction

After more than fifty years since the first clinical application of Fontan operation in 1968, the modified Fontan operation has become one of the essential surgical techniques in children with congenital heart diseases (1). This operation is conducted as a palliative surgical procedure in patients with cardiac malformations that are not amenable to biventricular repair, particularly tricuspid atresia and single ventricle (2-5). The concept of the operation is to divert the systemic blood circulation directly into the pulmonary arteries without passing through a ventricle and being pumped by it. Therefore, the Fontan circulation prevents systemic arterial hypoxemia and left ventricular overload (6).

The original procedure consisted of two steps in which the superior vena cava was connected to the right pulmonary artery (a classical Glenn shunt), and then the right atrium was connected to the left pulmonary artery with the interposition of a homograft (7, 8). However, several modified Fontan techniques were introduced afterward, including the modified atriopulmonary connection technique (9), right atrial-right ventricular connection, extracardiac total cavopulmonary connection (EC), and intracardiac lateral tunnel Fontan (LT) (1).

Despite promising results, the consequences of the profoundly unphysiological modifications within Fontan operation are inevitable. The passive pulmonary blood circulation (without the pumping drive of the right ventricle) is mainly dependent on pulmonary vascular resistance and the competence of the systemic ventricle. Venous congestion with elevated venous pressures and decreased ventricular preload are the main consequences of Fontan operation that can lead to a chronic low output state. These consequences can result in diminished exercise tolerance, organ damage, and consequently, numerous complications, including ventricular failure, Fontan-associated liver disease, renal failure, arrhythmias, thromboembolic events, plastic bronchitis, and protein-losing enteropathy (10-13). The clinical outcomes and the mortality rate of the patients undergoing Fontan operation varies greatly among different studies worldwide (1, 14). In addition, the predictors of the final results of the operation remain to be elucidated (1, 14). To carry out further improvements, a better understanding of clinical characteristics, as well as early and late outcome of children undergoing Fontan operation, is required. Therefore, we sought to identify the characteristics as well as the early and late outcomes of patients who have undergone Fontan operation during more than 10 years in a pediatrics tertiary center in north-west Iran.

Methods

The medical records of 52 patients who underwent modified Fontan operation from March 21th, 2006 to March 20th, 2018, at Tabriz Children's Hospital were reviewed retrospectively and abstracted for findings before and after the operation. Fontan operation was defined as any form of total cavopulmonary connection, including EC conduit techniques and LT Fontan performed in accordance with standard guidelines (15). Patients undergoing Fontan revision or repeat Fontan after previous Fontan takedown, those with concurrent pulmonary or neurologic anomalies, and those with incomplete medical records were excluded.

The following information were extracted from the medical records: Baseline demographic, hemodynamic, angiographic, and echocardiographic recordings of patients before and after

Fontan operation, as well as the types of palliative operations prior to the Fontan operations, type of the Fontan techniques, the data of early after operation complications, and in-hospital mortality. Patients were invited for follow up visits during the three months from March 21th, 2019 to 21th June, 2019. Clinical examination and echocardiographic evaluations were conducted at follow up visits. Medical records of patients were reviewed for any re-admission and late onset-complications during follow up. The clinical examinations and echocardiography were conducted by an attending pediatric cardiologist. The two-dimensional transthoracic echocardiography was performed using a Philips affinity 70 ultrasound cardiovascular machine (KPI Healthcare Inc., United States) with harmonic imaging and continuous ECG monitoring. A parasternal window and apical four-chamber window were used in echocardiography with optimized gain, compression controls, and time-gain compensation.

Early complications were considered positive if at least one of the following complications were present; respiratory failure, prolonged pleural effusion, thrombosis/ thromboembolism, neurological or gastrointestinal complication, mediastinitis, infection, arrhythmia, and protein-losing enteropathy. Prolonged pleural effusions were considered as pleural effusions requiring drainage for greater than 3 days.

The study was performed according to the Helsinki Declaration. The study protocol was approved by the medical ethics committee of the Tabriz University of Medical Sciences. Informed consents were obtained from the parents or the guardians of the participants.

Statistical Analysis

The normal distribution of the variables was evaluated using the Kolmogorov Smirnov test. The continuous variables were reported as mean (±standard deviation) or median (min-max). The categorical variables were reported as frequency and percentage. The comparisons between two groups were conducted using the independent t-test or the Mann Whitney U test in normally and non-normally distributed distributions, respectively. The categorical variables were compared using the Chi-square or Fischer exact test (if necessary). The comparisons between three groups were conducted using ANOVA or Kruskal-Wallis test regarding their distributions. P-values less than 0.05 were considered significant. All analyses were conducted using SPSS version 22 (SPSS Inc., Chicago).

Findings

Overall 52 patients were included in this study. The mean age at the operation time was 7.1 ± 5.13 years. Twenty-six patients were male (50%), and 26 patients (50%) were female. The mean weight of patients was 18.0 ± 10.64 kg, and the mean height was 114.13 ± 22.39 cm. The mean body surface area (BSA) was calculated as 0.81 ± 0.29.

The most frequent heart anomaly indicated for Fontan surgery was tricuspid valve disorders (28 cases, 51.9%). Tricuspid Atresia type Ib was the most common type of tricuspid valve disorders, which was reported in 8 patients (Table 1). Preoperative oxygen saturation (SO2sat) was 78.18 ± 8.75, and the mean pulmonary artery pressure (PAP) was 14.74 ± 10.91. Bidirectional Glenn surgery was performed on 27 patients (51.9%) before complete Fontan surgery. Moreover, the pulmonary artery (PA) band and aortopulmonary shunt were performed before complete Fontan surgery in 11

(21.2%) and 14 (26.9%) patients, respectively.

The majority of patients (42 cases, 80.2 %) underwent LT Fontan, while EC Fontan was performed in 10 patients (19.2 %).

The fenestration was conducted in all but one case (one of those who underwent EC Fontan surgery).

Table 1. Indications for Fontan surgery in the evaluated patients

Indication for Fontan surgery	Frequency	Percent
Tricuspid Valve Disorders	28	53.8
Tricuspid atresia IA	4	7.7
Tricuspid atresia IB	10	19.2
Tricuspid atresia IC	3	5.8
Tricuspid atresia IIA	4	7.7
Tricuspid atresia IIB	4	7.7
Tricuspid atresia IIC	2	3.8
Ebstein anomaly	1	1.9
Single ventricle (SV)	12	1.23
SV + PS	7	13.5
SV + PH	3	5.8
SV + PA	2	3.8
Imbalanced ventricle	12	23.1
DORV+ large sub pulmonic VSD + PS	6	11.6
Dextrocardia + TGV+ very large VSD + PS	5	9.6
TGV + VSD + PS + straddling MV	1	1.9

PS: Pulmonary stenosis, PH: Pulmonary hypertension, PA: Pulmonary valve atresia, VSD: Ventricular septal defect, DORV: Double outlet right ventricle, TGV: Transposition of the great arteries, MV: mitral valve

Early Outcomes

The postoperative data of patients are described in Table 2. The average postoperative left ventricular ejection fraction (LVEF) was 47.71 ± 7.36 %. A total of 28 patients (55.8%) had at least one major complication after surgery. The most prevalent complications were prolonged pleural effusion and neurologic events (each one in 10 cases, 19.2%). Eight patients died immediately after surgery or during hospitalization after surgery (in-hospital mortality rate was 15.3%).

Table 2. The postoperative data of patients during the hospital stay

Findings	Mean (SD)/ n(%)
Left ventricular ejection fraction (%) mean (SD)	47.71 (7.36)
Systemic arterial O2 saturation (%) mean (SD)	93.49 (10.08)
Central venous pressure (mmHg) mean (SD)	13.86 (5.74)
Systolic blood pressure (mmHg) mean (SD)	82.34 (14.47)
Diastolic blood pressure (mmHg) mean (SD)	47.69 (11.6)
In-hospital mortality n (%)	8 (15.3)
Total early after surgery complications * n (%)	28 (55.8)
Prolonged plural effusion	10 (19.2)
Neurologic events	10 (19.2)
Arrhythmia	6 (11.5)
Respiratory failure	6 (11.5)
Organ Infection	5 (9.6)
Thrombosis in Fontan circulation	3 (5.8)
Protein-losing enteropathy	3 (5.8)
Thromboembolism	1 (1.9)

*complications during the hospital stay after completion of the Fontan surgery

Late outcomes

Of 44 patients discharged, 11 patients were lost to follow up, and the other 34 patients were followed for a median of 7 years.

Kaplan-Meier curve plotted for the survival of the patients. Eight patients died during the follow-up, resulting in an overall 16 deaths (8 in hospital and during follow up). The survival of those successfully followed was 75 percent.

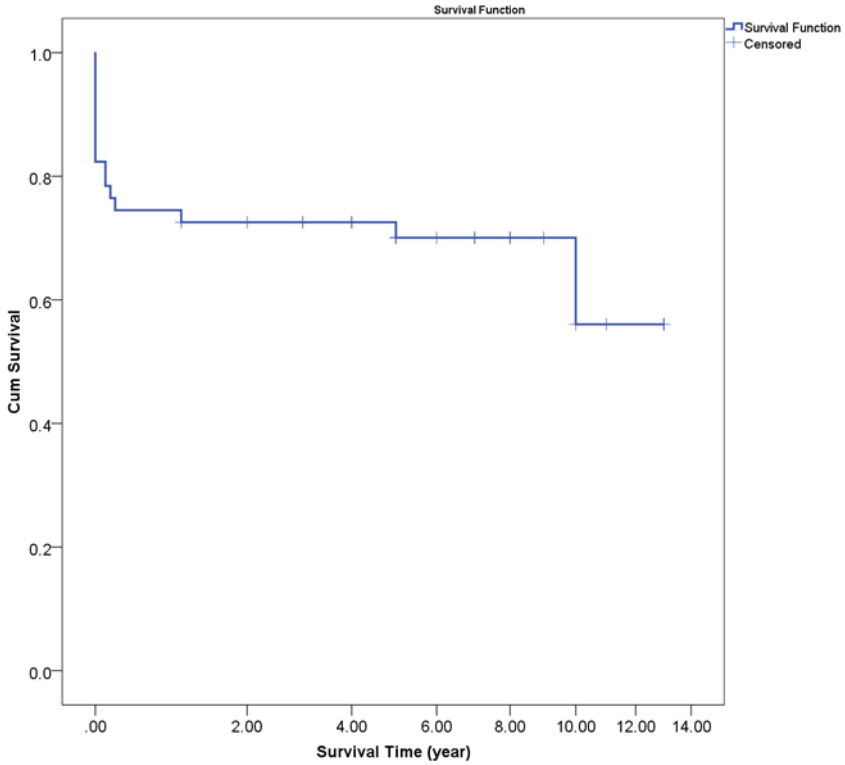

Figure 1. Kaplan-Meier curve for survival of patients undergoing Fontan surgery

The characteristics of the 25 patients, who were alive, are described in Table 3, based on the follow up visits. The mean age of patients was 13.77 ± 5.56 years. LV function (LV systolic function) was normal in 10 patients (40% of 25 live patients). While the LV function was mildly restricted in 10 patients (40%), moderately restricted in 4 patients (16%), and severely restricted in 1 patient (4%). RV function was normal in only 3 patients (12.5% of 25 live patients). While in 6 patients (25%), the restriction of RV function was mild, 5 patients (20.8%) were moderate, and 10 patients (41.7%) were severe.

Table 3. The characteristics of patients in follow up visits (n=25)

Findings		Mean (SD)/ n(%)
Demographic *mean (SD)*	Age (year)	13.77 (5.56)
	Weight (Kg)	44.48 (16.05)
	Height (cm)	144.48 (34.86)
	BSA (mm2)	1.33 (0.35)
Echocardiographic findings *mean (SD)*	EF (%)	51.48 (11.1)
	E / E'	7.89 (4.66)
	E / A	1.36 (0.49)
	Trans-pulmonary gradient (mmHg) median (IQR)	2 (0 - 6)
LV function n (%)	normal	10 (40)
	mild restriction (45≤EF <55)	10 (40)
	moderate restriction (35≤ EF<45)	4 (16)
	severe restriction (EF<35)	1 (4)
RV function n (%)	normal	4 (16)
	Mild restriction	6 (24)
	moderate restriction	5 (20)
	severe restriction	10 (40)
Diastolic function n (%)	normal	16 (64)
	Grade I restriction	5 (20)
	Grade II restriction	4 (16)
Valvular disorder n (%)	AS	1 (4)
	AI	5 (20)
	MR	21(84)
	TS	1 (4)
	TR	9 (36)
	PS	3 (12)
Other complications n (%)	Reversal SVC	2 (8)
	Obstruction in Fontan pathway	2 (8)
	RPA Stenosis	8 (32)
	LPA Stenosis	6 (24)
	Fontan Circuit thrombosis	2 (8)

BSA: body surface area, EF: ejection fraction, AS: aortic valve stenosis, AI: aortic valve insufficiency, MR: mitral regurgitation, TS: tricuspid valve stenosis, TR: tricuspid valve regurgitation, PS: pulmonary valve stenosis, SVC: superior vena cava, RPA: right pulmonary artery, LPA: left pulmonary artery

Diastolic function was normal in 16 patients (64% of 25 live patients). While in 5 patients (20%), diastolic dysfunction was grade I, and in 4 patients (16%), diastolic dysfunction was grade II.

All 25 patients had at least one type of valvular disorder in echocardiographic examination. The most common valvular disorder was mitral valve regurgitation (MR) (84%), which was mild in 16 patients, moderate in 4 patients, and severe in 1 patient.(table4)

Table 4. The early and late clinical outcomes of patients based on the indications for Fontan surgery

Findings		Type of indication for Fontan surgery			
		Tricuspid atresia	**Single ventricle**	**imbalanced ventricle**	**P value**
Early after surgery findings mean (SD)	EF (%)	47.32 (7.87)	45.45 (6.50)	51.67 (5.59)	0.179
	SpO2 after operation (%)	94.61 (8.5)	88.27 (14.72)	96.1 (6.3)	0.167
	CVP	11.68 (3.65)	18.67 (6.97)	14.2 (4.24)	0.002
	Diastolic BP (mmHg)	79.43 (14.35)	82.17 (12.36)	90.7 (15.22)	0.091
	Systolic BP (mmHg)	45.82 (12.14)	51.18 (9.54)	49.1 (12.13)	0.245
Early complications n (%)	Yes	15 (53.6)	9 (75)	5 (41.7)	0.244
	No	13 (46.4)	3 (25)	7 (58.3)	
In-hospital mortality n (%)	Yes	6 (21.4)	3 (25)	0 (0)	0.188
	No	22 (78.6)	9 (75)	12 (100)	
LV function n (%)	normal	4 (33.3)	2 (0.5)	4 (44.4)	0.513
	mild restriction (45≤EF <55)	6 (50)	2 (50)	2 (22.2)	
	moderate restriction (35≤ EF<45)	1 (8.3)	0 (0)	3 (33.3)	
	severe restriction (EF<35)	1 (8.3)	0 (0)	0 (0)	
RV function n (%)	normal	1 (8.3)	1 (33.3)	1 (11.1)	0.459
	Mild restriction	3 (25)	0 (0)	3 (33.3)	
	moderate restriction	1 (8.3)	1 (33.3)	3 (33.3)	
	severe restriction	7 (58.3)	1 (33.3)	2 (22.2)	
Mortality n (%)	Yes	11 (39.3)	6 (50)	0 (0)	0.018
	No	17 (60.7)	6 (50)	12 (100)	

EF: ejection fraction, CVP: central venous pressure, BP: blood pressure, RV: right ventricle, LV: left ventricle

Effects of indications for operation and its type on the results of Fontan surgery

Studying the relationships between indications for operation and the results of Fontan surgery early after surgery and in the long term revealed that the overall mortality rate was significantly different between groups (P = 0.018). The group of patients with single ventricle had a significantly higher mortality rate than the other groups. There was no mortality in patients with imbalanced ventricles early after surgery or during the follow-up.

Central venous pressure (CVP) after operation was significantly different among groups, and it was higher in patients with single ventricle compared to the other two groups (11.68 ± 3.65 in tricuspid atresia, 18.67 ± 6.97 in single ventricle, and 14.2 ± 4.24 mmHg in imbalanced ventricle, p=0.002).

Early and late outcomes were not different among the group of patients who received Glenn, PA band, or aortopulmonary shunt (p >0.05 for all cases, Table 5).

Table 5. The early and late clinical outcomes of patients based on the types of the operation before complete Fontan surgery

		Type of operation before complete Fontan surgery			
Findings		**Glenn**	**PA Band**	**Aortopulmonary Shunt**	**P value**
Early after surgery findings mean (SD)	EF (%)	46.25 (8.24)	48.18 (6.43)	50 (6.12)	0.341
	SpO2 after operation (%)	94.28 (11.22)	94.45 (5.76)	91.15 (10.89)	0.116
	CVP (mmHg)	14.92 (5.95)	13.18 (6.09)	12.3 (3.47)	0.284
	Systolic BP (mmHg)	79.92 (13.56)	82.36 (18.17)	87.15 (12.6)	0.219
	Diastolic BP (mmHg)	44.76 (10.7)	49.72 (13.11)	51.61 (11.3)	0.228
Early complications n (%)	Yes	18 (66)	5 (45)	6 (42)	0.257
	No	9 (33)	6 (54)	8 (57)	
In-hospital mortality n (%)	Yes	3 (25)	3 (60)	4 (50)	0.211
	No	7 (58)	1 (20)	2 (25)	
LV function n (%)	normal	1 (8)	1 (20)	2 (25)	0.504
	Mild restriction (45≤EF <55)	1 (8)	0 (0)	0 (0)	
	moderate restriction (35≤ EF<45)	0 (0)	2 (40)	1 (12)	
	Severe restriction (EF<35)	5 (45)	0 (0)	1 (12)	

RV function n (%)	Normal	3 (27)	0 (0)	2 (25)	0.109
	Mild restriction	3 (27)	3 (60)	4 (50)	
	moderate restriction	7 (25)	1 (9)	1 (7)	
	Severe restriction	20 (74)	10 (90)	13 (92)	
Mortality n (%)	Yes	11 (40)	3 (27)	2 (14)	0.211
	No	16 (60)	8 (73)	12 (86)	

EF: ejection fraction, CVP: central venous pressure, BP: blood pressure, RV: right ventricle, LV: left ventricle

Discussion

Fontan surgery is one of the most important palliative surgeries in congenital heart diseases (1). This study was, thus, performed to evaluate the characteristics and outcomes of patients undergoing Fontan surgery. The results of our study showed that the most prevalent heart anomaly, which was indicated for Fontan surgery, was tricuspid valve disorders, in particular tricuspid atresia type Ib. Also, traditionally, tricuspid atresia was the first anomaly, which was indicated for Fontan surgery by Francis Fontan et al. (7). Furthermore, in the study by Khairy et al., the most frequently reported cardiac anomaly among those who underwent Fontan surgery was tricuspid atresia that was present in 82 patients (31.4%) (16). Therefore, after fifty years, the main indication for Fontan surgery has remained the same. Among the cases reviewed in the current study, Glenn was more frequently performed before complete Fontan operation as compared to the PA band or aortopulmonary shunt. The study by Tanoue et al. showed that the bidirectional Glenn procedure increases the mechanical efficiency of a total cavopulmonary connection in high-risk Fontan candidates (17). The volume reduction by bidirectional Glenn procedure preceding complete Fontan allows for any afterload mismatch to be corrected, thereby improves ventricular energetics after complete Fontan (17). However, there was no difference between the early and long term outcomes among the patients in terms of the type of operation before complete Fontan surgery in our study.

In the current study, the higher frequency of Fontan surgery was performed as LT as compared to EC Fontan. However, other recent studies reported a higher frequency of EC type of Fontan circulation (5, 18, 19). One of the reasons for this inconsistency could be that the EC method was not recognized as the routine method during those years that we investigated in our study, especially in the initial years. As reported by Downing et al., in a single center in Philadelphia between 1992 and 1996, only 4 percent of the Fontan operations were conducted as EC; however, from 1997 to 2002, it was increased up to 40 percent, and during 2003-2009, the majority of the Fontan operations (78%) were EC (an overall 773 patients underwent Fontan operation in that study)(20). Accordingly, two other studies which were reported the data of Fontan operations during 1973-2008 and 1992-2007 reported EC Fontan operation to be only 1 and 8 percent, respectively (16, 21).

Fenestration was made in nearly all patients in the institute under investigation in the present study. Similarly, the reports of other institutes worldwide demonstrate that this technique is performed on the majority of the Fontan patients (20, 21).

Lemler et al. showed that baffle fenestration enhances short-term outcomes in standard-risk patients undergoing Fontan surgery by reducing pleural drainage, length of hospital stay, and the need for additional postoperative procedures (22).

Few studies have reported the complications after Fontan surgery separately. We found that the most prevalent complications among the patients undergoing Fontan surgery were prolonged pleural effusion, neurologic events, and arrhythmia. Hirsch et al., also reported that arrhythmias, prolonged chest tube drainage, and neurologic events were the major early complications after the Fontan surgery (21). During the about 10 years investigated in the current study, the in-hospital mortality rate was 15.3 percent, and long-term survival was 75 percent. Likewise, Khairy et al. reported an event-free survival at 1, 5, and 10 years of 80.1, 77.5, and 74.8 percent, respectively (16). Also, Pundi et al. reported a 10-year survival of 74 percent for 1,052 patients with Fontan circulation (23). However, some studies reported higher survival rates. Downing et al. reported 85 percent survival at 15 years (95% CI, 82%-88%), and 74 percent at 20 years (95% CI, 67%-80%)(20). However, these rates were calculated for those with intact Fontan circulation, not the total number of mortality (20).

Although there was no statistically significant difference in terms of in-hospital mortality among the three groups of patients based on their heart anomaly, the in-hospital mortality was relatively higher in the group of patients with single ventricle in our study. Accordingly, CVP was significantly higher in those with single ventricle. Moreover, the mortality rate during the follow up was significantly higher in those who were indicated for Fontan surgery with single ventricle. Similarly, Parikh et al. reported that out of 24 patients with single ventricular who underwent modified Fontan surgery, 7 patients (29%) died after surgery (17). Day et al. suggested that additional palliation with a Fontan procedure may increase the risk of complications in patients with single ventricle, and it is better that the bidirectional Glenn procedure not be followed with complete Fontan surgery (24). Therefore, further investigations are required to ascertain the best strategies to reduce mortality in these patients.

The majority of patients in our study suffered from RV and LV dysfunction in long-term follow-up. Moreover, nearly all patients had a grade of MR, ranging from mild to severe. MR has been proposed to increase late mortality and reoperation rates in Fontan patients (25). In a case report, it was reported that longstanding MR resulted in a poor left ventricular function that was masked by the severe MR, but it became evident after the MR was repaired (26). Accordingly, the study of Hager et al. demonstrated the patients with more than trivial atrioventricular regurgitation showed a less-pronounced end-diastolic flow acceleration (27). The excessive volume induced by MR can lead to an early filing of the ventricle in diastole and impaired hemodynamically important suctioning mechanism (27). Thus, the occurrence of MR should be strictly followed and, in severe cases, timely get repaired.

This study had some limitations. It was performed in the largest pediatrics tertiary center in north-west Iran; however, as with any single-center study, a limited number of patients with congenital heart diseases are admitted each year, and those who are indicated for Fontan surgery are not available in large numbers. Furthermore, some of those cases admitted in the institute are coming from other countries such as Azerbaijan. Therefore, following these patients was not feasible, especially for longer durations. Thus, the loss to follow up in our study was relatively high. Therefore, due to the small sample size,

controlling the effect of confounding factors was not feasible, and the generalizability of the findings has become relatively low. However, the findings of our study can underpin future multi-centric projects.

Conclusion

Survival rate of patients undergoing a Fontan completion is acceptable; however, patients remain at risk for morbid events, especially the neurologic events and prolonged pleural effusion during the hospitalization as well as ventricular dysfunction and MR in the long-term. The heart morphology is associated with mortality in the long term; in particular single ventricle has a higher mortality rate. Moreover, patients with Fontan circulation should be strictly followed for investigating the development of MR and for timely repairs in severe cases to prevent further deterioration. Of note, due to some limitations of our study, further multi-centric studies are required to confirm our findings.

Acknowledgment:

This study was funded by the Tabriz University of Medical Sciences. We would like to thank the members of the pediatrics research center of the Tabriz University of Medical Sciences for their help that greatly improved the manuscript. The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest:

None

References

1. Kverneland LS, Kramer P, Ovroutski S. Five decades of the Fontan operation: A systematic review of international reports on outcomes after univentricular palliation. Congenital Heart Disease. 2018;13(2):181-93.

2. Hosein RBM, Clarke AJB, McGuirk SP, Griselli M, Stumper O, De Giovanni JV, et al. Factors influencing early and late outcome following the Fontan procedure in the current era. The 'Two Commandments'? European journal of cardio-thoracic surgery. 2007;31(3):344-53.

3. Driscoll DJ. Long-term results of the Fontan operation. Pediatric cardiology. 2007;28(6):438-42.

4. Bartz PJ, Driscoll DJ, Dearani JA, Puga FJ, Danielson GK, O'Leary PW, et al. Early and late results of the modified Fontan operation for heterotaxy syndrome: 30 years of experience in 142 patients. Journal of the American College of Cardiology. 2006;48(11):2301-5.

5. d'Udekem Y, Iyengar AJ, Galati JC, Forsdick V, Weintraub RG, Wheaton GR, et al. Redefining expectations of long-term survival after the Fontan procedure: twenty-five years of follow-up from the entire population of Australia and New Zealand. Circulation. 2014;130(11_suppl_1):S32-S8.

6. Gewillig M. The fontan circulation. Heart. 2005;91(6):839-46.

7. Fontan F, Baudet E. Surgical repair of tricuspid atresia. Thorax. 1971;26(3):240-8.

8. Glenn WWL. Circulatory bypass of the right side of the heart: shunt between superior vena cava and distal right pulmonary artery—report of clinical application. New England Journal of Medicine. 1958;259(3):117-20.

9. Kreutzer C, Kreutzer J, Kreutzer GO. Reflections on five decades of the Fontan Kreutzer procedure. Frontiers in pediatrics. 2013;1:45.

10. Rychik J, editor Forty years of the Fontan operation: a failed strategy2010: Elsevier.

11. Gewillig M, Goldberg DJ. Failure of the fontan circulation. Heart failure clinics. 2014;10(1):105-16.

12. Johnson JN, Driscoll DJ, O'Leary PW. Protein-losing enteropathy and the Fontan operation. Nutrition in Clinical Practice. 2012;27(3):375-84.

13. De Leval MR. The Fontan circulation: a challenge to William Harvey? Nature clinical practice Cardiovascular medicine. 2005;2(4):202-8.

14. Gewillig M, Brown SC. The Fontan circulation after 45 years: update in physiology. Heart. 2016;102(14):1081-6.

15. Fredenburg TB, Johnson TR, Cohen MD. The Fontan procedure: anatomy, complications, and manifestations of failure. Radiographics. 2011;31(2):453-63.

16. Khairy P, Fernandes SM, Mayer JE, Triedman JK, Walsh EP, Lock JE, et al. Long-term survival, modes of death, and predictors of mortality in patients with Fontan surgery. Circulation. 2008;117(1):85.

17. Tanoue Y, Sese A, Ueno Y, Joh K, Hijii T. Bidirectional Glenn procedure improves the mechanical efficiency of a total cavopulmonary connection in high-risk Fontan candidates. Circulation. 2001;103(17):2176-80.

18. Border WL, Syed AU, Michelfelder EC, Khoury P, Uzark KC, Manning PB, et al. Impaired systemic ventricular relaxation affects postoperative short-term outcome in Fontan patients. The Journal of Thoracic and Cardiovascular Surgery. 2003;126(6):1760-4.

19. Nakano T, Kado H, Tatewaki H, Hinokiyama K, Oda S, Ushinohama H, et al. Results of extracardiac conduit total cavopulmonary connection in 500 patients. European Journal of Cardio-Thoracic Surgery. 2015;48(6):825-32.

20. Downing TE, Allen KY, Glatz AC, Rogers LS, Ravishankar C, Rychik J, et al. Long-term survival after the Fontan operation: twenty years of experience at a single center. The Journal of thoracic and cardiovascular surgery. 2017;154(1):243-53.

21. Hirsch JC, Goldberg C, Bove EL, Salehian S, Lee T, Ohye RG, et al. Fontan operation in the current era: a 15-year single institution experience. Annals of surgery. 2008;248(3):402-10.

22. Lemler MS, Scott WA, Leonard SR, Stromberg D, Ramaciotti C. Fenestration Improves Clinical Outcome of the Fontan Procedure. Circulation. 2002;105(2):207-12.

23. Pundi KN, Johnson JN, Dearani JA, Pundi KN, Li Z, Hinck CA, et al. 40-Year Follow-Up After the Fontan Operation. Long-Term Outcomes of 1,052 Patients. 2015;66(15):1700-10.

24. Day RW, Etheridge SP, Veasy LG, Jenson CB, Hillman ND, Di Russo GB, et al. Single ventricle palliation: Greater risk of complications with the Fontan procedure than with the bidirectional Glenn procedure alone. International Journal of Cardiology. 2006;106(2):201-10.

25. Rao PS. Fontan Operation: Indications, Short and Long Term Outcomes. The Indian Journal of Pediatrics. 2015;82(12):1147-56.

26. Petzuch K, Eicken A, Marek J, Vogel M, Schreiber C, Hess J. Tissue Doppler echocardiography before and after the surgical reconstruction of an insufficient mitral valve in a patient with Fontan

circulation. Pediatric cardiology. 2006;27(4):508-10.

27. Hager A, Fratz S, Schwaiger M, Lange R, Hess J, Stern H. Pulmonary Blood Flow Patterns in Patients With Fontan Circulation. The Annals of Thoracic Surgery. 2008;85(1):186-91.