Original Article

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Analysis of Risk Factors and Outcomes of Fontan Procedure in Single Ventricular Repair: A Retrospective Observational Study

Surgery Section

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ABSTRACT

Introduction: The Fontan operation is a surgical technique used to treat cyanotic heart diseases with single ventricle physiology. Although it has undergone several modifications since its inception in 1971, it is still associated with significant morbidity and mortality.

Aim: To examine the outcomes of the Fontan operation and identify various risk factors associated with it.

Materials and Methods: This retrospective observational study was conducted at the Postgraduate Institute of Medical Education and Research (PGIMER) in Chandigarh, India from January 2014 to December 2017. All patients who underwent the Fontan operation at PGIMER were included in the study. The study analysed outcomes such as survival, arrhythmias, neurological complications, heart failure, cirrhosis, and Protein Losing Enteropathy (PLE) following the Fontan operation. Various risk factors that could potentially influence the outcome of the Fontan operation were assessed, including preoperative, intraoperative, and postoperative factors. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software, version 25.0. The Chi-square test was utilised to determine predictors of survival and other long-term outcomes, with a p-value of <0.05 considered statistically significant.

Results: A total of 35 patients underwent the Fontan operation during the study period and completed five years of follow-up. Out of these, 28 were known to be alive at the last contact. There were six early deaths (less than one year). The overall one-year and five-year survival rates from the time of the operation were 29 (83%) and 28 (80%), respectively. Graft thrombosis/thromboembolism was observed in three cases (8.6%) and neurological complications in three cases (8.6%) during the early postoperative period. Arrhythmias in 6 cases (14%) were the most common late postoperative complication.

Conclusion: The Fontan procedure is currently the best available palliative treatment for cyanotic heart diseases with single ventricle physiology. Patient selection is crucial in this procedure, as the presence of risk factors may adversely affect the outcome.

Keywords: Fontan operation, Pulmonary artery pressure, Protein losing enteropathy

INTRODUCTION

In 1971, Francis Fontan and Eugene Baudet from Bordeaux, France, described a surgical technique that bypassed the hypoplastic right ventricle by creating a direct atrio-pulmonary connection. This technique completely separated the systemic and pulmonary circulation in patients with tricuspid atresia [1,2]. The procedure resulted in improved oxygenation, functional status, and enhanced quality of life and survival for the majority of patients with cyanotic congenital heart disease and single ventricle physiology. Over time, this technique has been successfully applied to treat various forms of functional single ventricle physiology [3].

Following the discovery of the Fontan circulation and its advantages, detailed studies on its physiology have revealed the critical importance of avoiding flow disturbances and energy losses in the constructed pathway. This understanding led to the development of the Total Cavo Pulmonary Connection (TCPC), which offers the least energy loss and flow disturbance pathway, overcoming the limitations of the classical atrio-pulmonary Fontan connection. Initially introduced as the lateral atrial tunnel, the TCPC concept later evolved into extracardiac or intracardiac conduits. Another significant surgical advancement was the introduction of fenestration and staging with a superior cavopulmonary connection [4].

However, the Fontan procedure is associated with several complications, including arrhythmias, premature death, ventricular failure, thromboembolic diseases, liver disease, and Protein-Losing Enteropathy (PLE). Although many risk factors determining the outcome of the Fontan procedure have been published in the literature [5-7], limited data is available from the Indian subcontinent. This study primarily focuses on the early and late outcomes of patients undergoing the Fontan operation and analyses various risk factors associated with these outcomes in the Indian population.

MATERIALS AND METHODS

This retrospective observational study was conducted at the Postgraduate Institute of Medical Education and Research (PGIMER) Chandigarh, India. Institutional Ethics Committee (IEC) approval was obtained (INT/IEC/2019/001599).

Inclusion criteria: The study included all patients with single ventricle physiology who underwent the Fontan operation at PGIMER between January 2014 and December 2017.

Exclusion criteria: Emergency surgeries were excluded from the study.

Medical records of the patients were analysed to collect preoperative, intraoperative, and postoperative details. Data analysis was conducted in January 2023.

The following parameters were noted:

- Functional health status was assessed based on the current New York Heart Association (NYHA) status/six-min walk test.
- Data on deaths were updated through correspondence with physicians and the patients' family members. The survival analysis included all deaths after the Fontan operation, regardless of the cause.
- Postoperative complications were noted, and PLE was diagnosed based on documentation of enteric loss or the presence of a low total protein/albumin ratio in addition to persistent or intermittent oedema.

- Clinically significant arrhythmia was defined as the need for antiarrhythmic drug therapy (excluding digoxin), pacemaker placement, or electrical/pharmacological cardioversion, and the results of the Holter study were considered.
- Cirrhosis was diagnosed based on characteristic findings on ultrasound and Computed Tomography (CT) scans, in conjunction with clinical diagnosis by a gastroenterologist. Patients with isolated liver function or ultrasound abnormalities were not considered to have proven cirrhosis. Heart failure and valve dysfunction were assessed through echocardiographic examination.
- Various risk factors that could potentially affect the outcome of the Fontan operation were assessed, including preoperative, intraoperative, and postoperative factors.
- Preoperative risk factors included the participant's age at the time of the Fontan operation, SpO_2 levels, previous Bidirectional Glenn procedure, Pulmonary Artery Pressure (PAP), heart rhythm, type of systemic ventricle, and Major Aortopulmonary Collateral Arteries (MAPCA).
- Intraoperative risk factors included the type of Fontan procedure and atrioventricular valve intervention during the Fontan operation.
- Postoperative risk factors included chest tube duration, chylous effusions, low cardiac output, renal insufficiency, and reoperation before 30 days of surgery. Their association with outcomes was analysed.
- A five-year follow-up was conducted for all patients, and outcomes such as survival rate, pulmonary thromboembolism, neurological complications, arrhythmias, cirrhosis, and PLE were analysed at the end of the first year (early outcomes) and at the end of the fifth year (late outcomes).

STATISTICAL ANALYSIS

The statistical analysis was performed using SPSS software, version 25.0. Descriptive statistics for categorical variables were presented as frequencies and percentages. The Chi-square test was utilised to identify predictors of survival and other long-term outcomes. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 35 patients underwent the Fontan operation during the study period and completed five years of follow-up. Out of these, 28 were known to be alive at the last contact. The overall one-year and five-year survival rates from the time of the operation were 29 (83%) and 28 (80%) respectively [Table/Fig-1].

Outcome	Early (<1 year), (n%)	Late (1-5 years), (n%)
Mortality	6 (17)	1 (3)
Graft thrombosis and pulmonary thromboembolism	3 (8.5)	0
Neurological complications	3 (8.5)	1 (3)
Arrhythmias	2 (6)	5 (14)
PLE	2 (6)	1 (3)
Heart failure	5 (14)	2 (6)

[Table/Fig-1]: Shows early and late outcomes following Fontan operation.
*PLE: Protein losing enteropathy; Data given for 31 patients

Among the 25 male patients who underwent the operation, 20 were alive, and out of the 10 female patients, 8 were alive. The five-year survival rate was 80% in both groups. No difference in long-term outcomes was noted between the two groups (p-value >0.9). There were no intraoperative deaths. Six early deaths occurred within one year of surgery, of which three patients died within 30 days of surgery. Among these three immediate postoperative deaths, two patients had undergone the lateral tunnel Fontan procedure, and one had undergone the extracardiac Fontan procedure. All immediate postoperative deaths were associated with persistent low cardiac output and high post-bypass Fontan pressure (>20 mm of Hg). In the other three deaths that occurred within one year of surgery, two patients who underwent the extracardiac Fontan procedure died within two months of follow-up due to graft thrombosis and collateral formation leading to heart failure and multiorgan dysfunction. The third patient, who had undergone the lateral tunnel Fontan procedure, died 81 days postoperatively due to persistent low output state, bilateral chylothorax, PLE, multisystem organ failure, and sepsis. One late death occurred beyond one year of surgery. This patient had developed ongoing heart failure with an ejection fraction of 35% and associated PLE and serious pleural effusion, eventually resulting in death due to sepsis.

Out of the 28 patients on follow-up, 26 patients were in New York Heart Association functional Class-I, and two were in Class-II. During follow-up, all patients were able to complete the 6 Min Walk Test, with an average distance of 650 meters. All patients were on anticoagulants (Acitrom) for six months, followed by lifelong antiplatelet therapy. However, within two months of follow-up, two patients developed graft thrombosis associated with PLE and heart failure. They eventually died due to ongoing sepsis. One patient had isolated pulmonary thromboembolism involving the segmental branches during 10 months of follow-up. He received anticoagulation for two years and eventually showed improvement. Two patients developed cerebral oedema, likely due to raised intracranial pressure resulting from venous congestion involving the head and neck. One patient underwent decompressive craniotomy, and both patients recovered with some residual neurological deficits. One patient experienced a focal seizure but made a complete recovery. Three patients experienced arrhythmias in the postoperative period, and five patients had low cardiac output requiring high inotropic support.

Follow-up was available for all 28 surviving patients. All of them have had recent electrocardiograms, and 50% of the patients underwent 24-hour ambulatory Holter monitoring. Among the total of 23 patients, all were in normal sinus rhythm. One patient experienced brief supraventricular tachycardia of more than four consecutive beats, one patient had intermittent junctional rhythm, and three patients had occasional ventricular ectopics.

Out of the 35 patients, one developed PLE (Pleural Effusion) and serious pleural effusions that required tube thoracostomy four years after the operation. However, this patient unfortunately passed away due to persistent low cardiac output and ongoing sepsis. In present study, no patient exhibited clinical or radiological evidence of cirrhosis.

During the follow-up period beyond one year, reduced function of the systemic ventricle with an EF of less than 40% was observed in only two patients. Unfortunately, one of these patients died during follow-up, while the other is currently receiving antifailure treatment.

Four patients had mild Atrioventricular Valve Regurgitation (AVVR), and none of the patients experienced severe AVVR or required valve replacement during the follow-up period.

Among the seven preoperative risk factors analysed, only SpO_2 >70%, PAP >15 mmHg, and prior BDG were significantly associated with poor outcomes [Table/Fig-2].

Preoperative predictors	Number of cases	Early mortality, n (%)	Late mortality, n (%)	p-value
Age (in years)				
<2	0	0	0	0.4
2-5	6	1 (16.7)	0	
6-15	28	5 (17.8)	1 (3.5)	
>16	1	0	0	

Oxygen saturation				
<60%	9	1 (11.1)	0	0.03
60-69%	19	2 (10.5)	1 (5.2)	
70-79%	7	3 (43)	0	
>80%	0	0	0	
BD Glenn shunt				
Done	31	6 (19.3)	1 (3.2)	0.04
Not done	4	0	0	
Pulmonary Artery Pressure (PAP)				
≤15 mm of hg	30	3 (10)	0	<0.01
>15 mm of hg	5	3 (60)	1 (20)	
Type systemic ventricle				
Left	19	3 (15.8)	1 (5.3)	0.6
Right	10	2 (20)	0	
Mixed	6	1 (16.7)	0	

[Table/Fig-2]: Shows preoperative factors that predict survival after Fontan operation.
*BD Glenn shunt: Bi-directional Glenn shunt

Out of the three intraoperative risk factors analysed, only post-bypass Fontan pressure exceeding 20 mmHg was associated with a poor outcome [Table/Fig-3].

Intraoperative predictors	Number of cases	Early mortality	Late mortality	p-value
Type of fontan				
1. Lateral tunnel	18	3 (16.7)	1 (5.6)	0.8
2. Extracardiac	17	3 (17.7)		
Fontan pressure				
<20 mmHg	31	3 (9.7)	1 (3.2)	<0.01
>20 mmHg	4	3 (75)		

[Table/Fig-3]: Shows intraoperative factors that predict survival after Fontan operation.

Lateral tunnel Fontan was performed in 18 patients, while extracardiac Fontan was constructed in 17 patients. There was no significant difference in early and late mortality between the two groups. None of the patients underwent AV valve repair or replacement. Only four patients experienced post-bypass Fontan pressure exceeding 20 mmHg. Among these patients, three died in the immediate postoperative period due to persistent low cardiac output, renal failure, and shock. This factor was significantly associated with poor outcomes in early survival (p-value <0.001).

Among all the postoperative risk factors analysed, only Low Cardiac Output Syndrome (LCOS) and postoperative renal failure were associated with poor survival before one year [Table/Fig-4]. However, they did not impact the long-term outcome of the patients.

Postoperative predictors	Number of cases	Early mortality n (%)	Late mortality n (%)	p-value
Chest tube duration				
<2 weeks	29	4 (13.8)	1 (3.5)	0.3
>2 weeks	6	2 (33)	0	
Chylothorax				
Present	5	2 (40)	0	0.1
Absent	30	4 (13.3)	1 (3.3)	
Low cardiac output				
Present	4	3 (75)	0	0.01
Absent	31	3 (9.6)	1 (3.2)	
Renal insufficiency				
Present	4	3 (75)		0.01
Absent	31	3 (9.6)	1 (3.2)	
Re-operation in <30 days				
Yes	4	1 (25)	0	0.23
No	31	5 (16.1)	1 (3.2)	

[Table/Fig-4]: Shows postoperative factors that predict survival after Fontan operation.

DISCUSSION

Managing patients with single ventricle physiology poses great challenges. The identification of risk factors in these patients has significantly aided in better patient selection and management, leading to a reduction in mortality rates for those undergoing the Fontan procedure [5-7].

In our series, there were six early deaths. The overall one-year and five-year survival rates from the time of the operation were 83% and 80%, respectively. These figures are comparable to earlier reports from The Children's Hospital of Philadelphia and the Mayo Clinic [6], where the one-year survival rate was 77%, the five-year survival rate was 70%, and the ten-year survival rate was 60%. The improved early outcomes can be attributed to enhanced patient selection, the use of fenestration, and advancements in perfusion strategies, anaesthesia, and intensive care management over the past decade.

As an extension of Choussat et al.,'s ten commandments for the ideal Fontan circulation [8], authors were able to demonstrate poor outcomes in patients with SpO_2 >70%, PAP >15 mmHg, prior BDG, post-bypass Fontan pressure >20 mmHg, post-op LCOS, and RF. Interestingly, present study showed no significant difference in outcomes among patients operated on before the age of four, which deviates from the findings of Choussat et al.,'s ten commandments for the ideal Fontan circulation. The morphology of the systemic ventricle did not affect survival in present study, consistent with many other reports [9,10]. The association of high oxygen saturation and previous BD Glenn procedure with poor outcomes was not supported by the literature.

The impact of AVVR in patients who have survived the Fontan operation is significant. Even moderate AVVR can lead to the failure of Fontan circulation, necessitating early intervention or cardiac transplantation [11,12]. However, none of the patients in present study developed significant valvular regurgitation during follow-up.

In present study, arrhythmia (14%) was the most common complication in the late postoperative period, followed by heart failure (6%) and PLE (3%). These findings align with other studies [5-7,10], where arrhythmias were observed in around 20% of cases and PLE occurred in 6-7%. It is recommended annual follow-up with routine clinical examination and echocardiography for all patients, while ECG/Holter monitoring is reserved for selected patients with a history of arrhythmias. The risk of arrhythmia is high in the classical atrio-pulmonary type of Fontan connection, leading many centres to adopt the extracardiac conduit technique [13,14]. Several studies have suggested that sudden death in this patient group during follow-up is mainly attributed to arrhythmias [15,16]. PLE is estimated to occur in 3-8% of Fontan survivors [17,18]. Reversing PLE can be particularly challenging and is associated with poor survival [7,19,20]. Thrombosis and thromboembolism are well-known complications, accounting for upto 9% of deaths in long-term follow-up [7,21]. In many cases, thrombotic events after Fontan are likely multifactorial, involving factors such as intestinal protein loss, diminished hepatic synthesis of anticoagulant proteins, and/or sluggish flow in the systemic venous to pulmonary arterial circulation [22].

Limitation(s)

Since it was a retrospective study, data on the incidence of early transient postoperative events, such as arrhythmias, thromboembolic events, and LCOS, could be underestimated. Additionally, the cause of sudden deaths during follow-up could not be established in all patients.

CONCLUSION(S)

Good outcomes have been achieved in patients undergoing the Fontan operation for single ventricular physiology. However, poor outcomes have been associated with high pulmonary artery pressure, previous bidirectional Glenn procedure, elevated oxygen saturation before the Fontan procedure, increased pressures in the Fontan circulation, low cardiac output, and renal failure after the Fontan procedure.

REFERENCES

[1] Fontan F, Mounicot FB, Baudet E, Simonneau J, Gordo J, Gouffrant JM. "Correction" de l'atrésie tricuspidienne. Rapport de deux cas "corrigés" par l'utilisation d'une technique chirurgicale nouvelle ["Correction" of tricuspid atresia. 2 cases "corrected" using a new surgical technic]. Ann Chir Thorac Cardiovasc. 1971;10(1):39-47. French. PMID: 5101717.

[2] Kreutzer G, Galíndez E, Bono H, De Palma C, Laura JP. An operation for the correction of tricuspid atresia. J Thorac Cardiovasc Surg. 1973;66(4):613-21. PMID: 4518787.

[3] Mott AR, Spray TL, Gaynor JW, Godinez RI, Nicolson SC, Steven JM, et al. Improved early results with cavopulmonary connections. Cardiology in the Young. Cambridge University Press. 2001;11(1):03-11.

[4] de Leval MR, Kilner P, Gewillig M, Bull C. Total cavopulmonary connection: A logical alternative to atriopulmonary connection for complex fontan operations: Experimental studies and early clinical experience. J Thorac Cardiovasc Surg. 1988;96(5):682-95.

[5] Dennis M, Zannino D, du Plessis K, Bullock A, Disney PJS, Radford DJ, et al. Clinical outcomes in adolescents and adults after the fontan procedure. J Am Coll Cardiol. 2018;71(9):1009-17. Doi: 10.1016/j.jacc.2017.12.054. PMID: 29495980.

[6] Driscoll DJ, Offord KP, Feldt RH, Schaff HV, Puga FJ, Danielson GK. Five- to fifteen-year follow-up after fontan operation. Circulation. 1992;85(2):469-96. Doi: 10.1161/01.cir.85.2.469. PMID: 1735145.

[7] Khairy P, Fernandes SM, Mayer JE Jr, 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):85-92. Doi: 10.1161/CIRCULATIONAHA.107.738559. Epub 2007 Dec 10. PMID: 18071068.

[8] Stern HJ. Fontan "Ten Commandments" Revisited and Revised. Pediatr Cardiol. 2010;31:1131-34. https://doi.org/10.1007/s00246-010-9811-9.

[9] Allen KY, Downing TE, Glatz AC, Rogers LS, Ravishankar C, Rychik J, et al. Effect of fontan-associated morbidities on survival with intact fontan circulation. Am J Cardiol. 2017;119(11):1866-71. Doi: 10.1016/j.amjcard.2017.03.004. Epub 2017 Mar 16. PMID: 28385177.

[10] Atz AM, Zak V, Mahony L, Uzark K, D'agincourt N, Goldberg DJ, et al. Pediatric heart network investigators. Longitudinal outcomes of patients with single ventricle after the fontan procedure. J Am Coll Cardiol. 2017;69(22):2735-44. Doi: 10.1016/j.jacc.2017.03.582. PMID: 28571639; PMCID: PMC5604334.

[11] King G, Ayer J, Celermajer D, Zentner D, Justo R, Disney P, et al. Atrioventricular valve failure in fontan palliation. J Am Coll Cardiol. 2019;73(7):810-22. Doi: 10.1016/j.jacc.2018.12.025. PMID: 30784675.

[12] Stephens EH, Dearani JA. Management of the bad atrioventricular valve in fontan time for a change. J Thorac Cardiovasc Surg. 2019;158(6):1643-48. Doi: 10.1016/j.jtcvs.2019.08.129. Epub 2019 Oct 18. PMID: 31635860.

[13] Pundi KN, Pundi KN, Johnson JN, Dearani JA, Li Z, Driscoll DJ, et al. Sudden cardiac death and late arrhythmias after the fontan operation. Congenit Heart Dis. 2017;12(1):17-23. Doi: 10.1111/chd.12401. Epub 2016 Aug 22. PMID: 27545004.

[14] Li D, Fan Q, Hirata Y, Ono M, An Q. Arrhythmias after fontan operation with intra-atrial lateral tunnel versus extra-cardiac conduit: A systematic review and meta-analysis. Pediatr Cardiol. 2017;38(4):873-80. Doi: 10.1007/s00246-017-1595-8. Epub 2017 Mar 7. PMID: 28271152.

[15] Rijnberg FM, Blom NA, Sojak V, Kuipers IM, Rammeloo LAJ, Jongbloed MRM, et al. A 45-year experience with the Fontan procedure: Tachyarrhythmia, an important sign for adverse outcome. Interact Cardiovasc Thorac Surg. 2019;29(3):461-68. Doi: 10.1093/icvts/ivz111.

[16] Sakamoto T, Nagashima M, Hiramatsu T, Matsumura G, Park IS, Yamazaki K. Fontan circulation over 30 years. What should we learn from those patients? Asian Cardiovasc Thorac Ann. 2016;24(8):765-71. Doi: 10.1177/0218492316667771. Epub 2016 Aug 24. PMID: 27563102.

[17] Schumacher KR, Stringer KA, Donohue JE, Yu S, Shaver A, Caruthers RL, et al. Fontan-associated protein-losing enteropathy and plastic bronchitis. J Pediatr. 2015;166(4):970-77. Doi: 10.1016/j.jpeds.2014.12.068. Epub 2015 Feb 4. PMID: 25661406; PMCID: PMC4564862.

[18] Mertens L, Hagler DJ, Sauer U, Somerville J, Gewillig M. Protein-losing enteropathy after the fontan operation: An International multicenter study. PLE study group. J Thorac Cardiovasc Surg. 1998;115(5):1063-73. Doi: 10.1016/s0022-5223(98)70406-4. PMID: 9605076.

[19] 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. J Am Coll Cardiol. 2015;66(15):1700-10. Doi: 10.1016/j.jacc.2015.07.065. PMID: 26449141.

[20] Alsaied T, Bokma JP, Engel ME, Kuijpers JM, Hanke SP, Zuhlke L, et al. Predicting long-term mortality after fontan procedures: A risk score based on 6707 patients from 28 studies. Congenit Heart Dis. 2017;12(4):393-98. Doi: 10.1111/chd.12468. Epub 2017 May 8. PMID: 28480627.

[21] Egbe AC, Connolly HM, Niaz T, Yogeswaran V, Taggart NW, Qureshi MY, et al. Prevalence and outcome of thrombotic and embolic complications in adults after fontan operation. Am Heart J. 2017;183:10-17. Doi: 10.1016/j.ahj.2016.09.014. Epub 2016 Oct 4. PMID: 27979032.

[22] Attard C, Huang J, Monagle P, Ignjatovic V. Pathophysiology of thrombosis and anticoagulation post fontan surgery. Thromb Res. 2018;172:204-13. Doi: 10.1016/j.thromres.2018.04.011. Epub 2018 Apr 14. PMID: 29685556.

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