MID-TERM OUTCOME OF A DECADE OF DELAYED TOTAL CAVO-PULMONARY CONNECTION COMPLETION STRATEGY AT RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL.

By

Dr Noel Dominic Swai
Student number: SWXNOE001

Submitted to the University of Cape Town In fulfilment of the requirements for the degree Master of Medicine In Cardiothoracic Surgery. Faculty of Health Sciences University of cape town

Date of submission: 20th December 2022

Supervisors:
Prof A. Brooks, Chris Barnard Division of Cardiothoracic Surgery, University of Cape Town
Prof L. Zühlke, Department of Paediatrics Cardiology, University of Cape Town

DECLARATION

I, Dr Noel Dominic Swai, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research, either the whole or any portion of the contents in any manner whatsoever.

Signature: ……Signed by candidate……

Date: ……**July 1, 2023**……

ACKNOWLEDGEMENTS

I would like to express my gratitude to all those who made it possible to complete this thesis. I thank the University of Cape Town (UCT) Research Ethics Committee for permission to undertake the research. I acknowledge the support of the Chris Barnard Division of Cardiothoracic Surgery and Red Cross Children's War Memorial Hospital at UCT for using departmental data to complete this research work.

I am indebted to my supervisors, Prof A Brooks and Prof Liesl Zühlke, from the University of Cape Town, for their guidance, stimulating suggestions, and encouragement during this research period.

Mainly, I would like to thank my wife, Rebecca and Mya, my daughter, for their patience and encouragement.

Table of Contents

List of appendices 5
List of Tables and Figures 5
Abbreviations 5
Abstract 6
CHAPTER 1: PUBLICATION-READY MANUSCRIPT 7
Abstract 7
INTRODUCTION 8
METHODS 9
RESULTS 11
DISCUSSION 13
    Survival in delayed TCPC strategy. 13
    ICU stay and infection. 13
    Other postoperative TCPC complications and hospital stay. 14
Study Limitations 15
Conclusion 15
Suggestions for future research 15
Acknowledgements 15
Conflict of interest 15

List of appendices

QUESTIONAIRE 28
ETHICAL APROVAL LETTER.....31
CARDIOLOGY IN THE YOUNG (Author instructions) 33

List of Tables and Figures

Table 1: Preoperative characteristics 22
Table 2: Intra-operative parameters for TCPC procedure 23
Table 3: Postoperative findings 24
Table 4: Risk of prolonged ICU stay and prolonged pleural drainage 25
Figure 1; Survival in months after the completion of Total Cavo-Pulmonary Connection.....26
Figure 2; Freedom from TCPC completion post-Bidirectional Glenn procedure with and without forward flow 27

Abbreviations

AVSD: Atrioventricular septal defect PS: Pulmonary atresia

BGS: Bidirectional Glenn Shunt

ccTGA: Congenital corrected Transposition of Great Arteries

DILV: Double Inlet Left Ventricle PA: Pulmonary Atresia, PDA: Patent Ductus Arteriosus

ICU: Intensive Care Unit

IQIC: International Quality Improvement Collaborative for Congenital Heart Disease

RCWMCH: Red Cross War Memorial Children's Hospital)

TCPC: Total cavo-pulmonary connection

TGA: Transposition of great arteries, DORV: Double Outlet Right Ventricle

Mid-term outcome of a decade of delayed total cavo-pulmonary connection completion strategy at Red Cross War Memorial Children's Hospital

Abstract

Background: Total cavo-pulmonary connection (TCPC) is currently the definitive palliative operation for single ventricle congenital anomalies. It is the last stage in the single ventricle pathway and can be completed following a bidirectional Glenn shunt (BGS), if a set of strict criteria are met. The TCPC is inherently an ineffective circulation, and long-term complications are inevitable. In an attempt to delay TCPC circulation-related complications, we have followed a delayed TCPC completion strategy and maintenance of forward flow at the time of bidirectional Glenn shunt circulation whenever possible. In this study, we will describe the results over the last decade.

Materials and Methods.

Single-centre, retrospective study from January 1, 2009, to December 31, 2018. A total of 42 patients underwent extracardiac TCPC procedures on cardiopulmonary bypass. The most common indication for TCPC was Tricuspid atresia (56%)**.** The median age at the time of operation was 9 [Interquartile range: 7 – 11] years. The median time interval between the bidirectional Glenn shunt and TCPC procedure was 6 [IQR: 4 - 9] years. The median follow-up was 24 [Interquartile range: 12 – 43] months.

Results: Most common postoperative morbidities were prolonged pleural effusion 22 (58%) and infection 16 (38%) which were independently risk factors for prolonged hospital or intensive care unit (ICU) stay respectively. There was no 30-day mortality, and the 1-year and 5-year survival rates were 98% and 88%, respectively. The preservation of forward flow at the time of BGS did not prolong the time interval between the two procedures.

Conclusion: Delayed TCPC strategy with or without retention of forward flow at the time of bidirectional Glenn circulation has shown acceptable outcomes. In this series, we did not show any benefit in the retention of forward flow. This strategy may be ideal in a resource-limited environment.

We recommend the implementation of infection and pleural drainage control management protocols to avoid prolonged ICU and hospital stays.

CHAPTER 1: PUBLICATION-READY MANUSCRIPT

Mid-term outcome of a decade of delayed total cavo-pulmonary connection completion strategy at Red Cross War Memorial Children's Hospital

Abstract

Background: Total cavo-pulmonary connection (TCPC) is currently the definitive palliative operation for single ventricle congenital anomalies. It is the last stage in the single ventricle pathway and can be completed following a bidirectional Glenn shunt (BGS), if a set of strict criteria are met. The TCPC is inherently an ineffective circulation, and long-term complications are inevitable. In an attempt to delay TCPC circulation-related complications, we have followed a delayed TCPC completion strategy and maintenance of forward flow at the time of bidirectional Glenn shunt circulation whenever possible. In this study, we will describe the results over the last decade.

Materials and Methods.

Single-centre, retrospective study from January 1, 2009, to December 31, 2018. A total of 42 patients underwent extracardiac TCPC procedures on cardiopulmonary bypass. The most common indication for TCPC was Tricuspid atresia (56%)**.** The median age at the time of operation was 9 [Interquartile range: 7 – 11] years. The median time interval between the bidirectional Glenn shunt and TCPC procedure was 6 [IQR: 4 - 9] years. The median follow-up was 24 [Interquartile range: 12 – 43] months.

Results: Most common postoperative morbidities were prolonged pleural effusion 22 (58%) and infection 16 (38%) which were independently risk factors for prolonged hospital or intensive care unit (ICU) stay respectively. There was no 30-day mortality, and the 1-year and 5-year survival rates were 98% and 88%, respectively. The preservation of forward flow at the time of BGS did not prolong the time interval between the two procedures.

Conclusion: Delayed TCPC strategy with or without retention of forward flow at the time of bidirectional Glenn circulation has shown acceptable outcomes. In this series, we did not show any benefit in the retention of forward flow. This strategy may be ideal in a resource-limited environment.

We recommend the implementation of infection and pleural drainage control management protocols to avoid prolonged ICU and hospital stays.

INTRODUCTION

The total cavopulmonary connection (TCPC) operation is currently the definitive palliative procedure for children with congenital cardiac anomalies who cannot undergo a biventricular repair, if specific strict criteria are met[1].

The initial Fontan procedure described by Drs Fontan and Kreutzer in the 1970s has evolved into what is currently known as the TCPC operation. The Fontan operation has undergone several modifications to improve flow hemodynamics and avoid complications of atrial dilatation such as arrhythmias and thromboembolic events[2]. In 1988, de Laval introduced the lateral tunnel TCPC, while in 1990, Marceletti[3] introduced the extracardiac TCPC. Of the two, extracardiac TCPC is currently the most frequently used TCPC surgical technique. The advancements in this surgical procedure, better patient selection and postoperative care have improved one and five-year survival rates from around 80% and 75%, respectively in the era of original Fontan, to 98% and 95%.[4–8]

The Fontan circulation completely changes the hemodynamic physiology to one of chronic low cardiac output and high venous pressure. These hemodynamic changes are accompanied by complications such as multiorgan dysfunction [9–17], continuous attrition of the TCPC circulation[9,18,19], and reduced physical quality of life[20,21] hence the institutions performing this procedure must be well prepared to deal with these TCPC-associated complications.

In an attempt to avoid and delay these known TCPC-associated complications and their cost implication in a resource-constrained environment, our institution, Red Cross War Memorial Children's Hospital (RCWMCH), opted to be conservative with TCPC completion by implementing a delayed TCPC completion strategy.[22,23]

In this delayed TCPC completion strategy, patients who have undergone the bidirectional Glenn shunt (BGS) procedure, are carefully followed up by a team of cardiologists. Those who develop symptoms and/or clinical signs of deterioration are further haemodynamically and anatomically evaluated and finally discussed in our 'Heart Team' (cardiology, anaesthetics, intensivists, and congenital cardiac surgeons) meeting for TCPC completion. This strategy differs from the early TCPC completion strategy, where the TCPC procedure is performed as early as possible whenever the anatomical and haemodynamic criteria are met.

As part of this delayed TCPC strategy, we perform a Bidirectional Glenn shunt with preservation of forward flow[24,25](presence of blood flow either through pulmonary artery band PDA or a systemic-to-pulmonary-artery-shunt.) when present. With the presence of forward flow, we hypothesise that the presence of forward flow may delay the need for TCPC completions.

We have opted not to offer TCPC surgery to patients with hypoplastic left heart syndrome after considering the known increased likelihood of adverse outcomes[7,26,27] and the challenges of dealing with complications in a resource-constrained environment.

This study aims to describe our experience with a delayed TCPC completion strategy and the preservation of forward flow when present. We describe preoperative characteristics, intraoperative characteristics, and postoperative outcomes.

METHODS

Study population

In this retrospective, single-centre study, we reviewed all the patients who had TCPC operations done at RCWMCH within ten years from January 1, 2009, to December 31, 2018. Approval for this study was obtained from the University of Cape Town Human Research Ethics Committee (HREC 364/2019).

Data collection

Patient demographics, preoperative and postoperative data were obtained from patients' folders, our paediatric cardiology and cardiothoracic surgical electronic databases (R046/2016), and the provincial hospital database.

Details of the cardiac surgical procedures performed before BGS procedures were also documented. For the TCPC procedure, the type of surgical approach (extracardiac or lateral conduit), conduit size used, fenestration construction, and cardiopulmonary bypass data were collected.

Postoperative data collected following the TCPC procedure included central venous pressures, duration of mechanical ventilation, length of intensive care (ICU) stay, pleural drainage duration (pleural drain in situ duration), length of hospital stay, and postoperative complications.

Early mortality was defined as when a patient died within 30 days postoperatively or as an inpatient after the TCPC procedure. Late mortality was defined as death 30 days postoperatively and after discharge from the hospital. The provincial hospital database was used to identify alive and demised patients.

Statistical Analysis

We used IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N.Y. USA) software for statistical analysis. Based on Shapiro-Wilk's test findings for normal values, continuous variables were summarised as mean (standard deviation) or median (range), and categorical variables as percentages and frequencies.

The Kaplan- Meier survival curve was constructed to estimate the patients' survival rate after the TCPC procedure. We also used the Kaplan-Meier survival curve to determine if there was a difference in freedom from TCPC completion between BGS patients with and without forward flow. The Log-rank value of less than 0.05 was considered significant.

Pleural drainage of more than 14 days was defined as prolonged pleural drainage (PLD), prolonged ICU stay when a patient remained in ICU for more than three days, and prolonged hospital stay when a patient remained in the hospital for more than 14 days. These cut-off points were selected based on the previous studies.[28–32]

Postoperative infection was defined as when the organism was isolated from sepsis screening or when the antibiotics were used empirically initiated based on clinical examination and/or septic markers.

The potential risk factors for prolonged ICU, hospital stay, and pleural drainage as dichotomous outcomes were evaluated using logistic regression analysis (Forward selection). In univariate

analysis, variables with p-values of less than 0.05 were further analysed in multivariable logistic regression to identify the independent risk factor for prolonged ICU, prolonged pleural drainage, and hospital stay.

Preoperative characteristic

Table 1 summarises the patients' demographics and clinical characteristics before the TCPC procedure. During this period, 42 patients, all with preserved ventricular function and adequate haemodynamic parameters for TCPC completion on their echocardiographic (ECHO) and catheterisation studies, underwent TCPC operation. In this group of patients, the BGS shunt with and without forward flow was performed in 23 and 17 patients, respectively.

One male patient at the age of 10 years had a TCPC procedure without initial staging palliative procedures. His ECHO findings showed; Situs Inversus, congenitally corrected TGA (ccTGA), severe pulmonary stenosis (PS) and non-committed ventricular defect (VSD).

Intra-operative (Anaesthetics and Surgical procedure)

Table 2 summarises the intraoperative details. TCPC procedures were performed under general anaesthesia and intraoperative transoesophageal echocardiography screening, with an intention to maintain hemodynamic stability and expedite the patient's extubation in theatre or ICU early after the procedure.

All operations were performed via the median sternotomy, and adhesions from previous operations were dissected to mobilise the heart and the great vessels. Standard central cardiopulmonary bypass (CPB) commenced, and forward flow if present was eliminated. Depending on the surgeon's preference, the cardioplegic arrest was with antegrade blood or crystalloid cardioplegia. The inferior vena cava (IVC) was divided off the right atrium and right atrium stamp oversewn. Depending on the size of the IVC, an adequate Gore-Tex conduit size was selected and interposed between the IVC and right pulmonary artery, frequently enlarging the previous BGS anastomosis

RESULTS

Post-operative complications/morbidities (Table 3)

Infection was the most common complication 16(38%). Ten patients presented with pneumonia of which five cases no organisms were isolated, while *H. influenza (3 cases)* and *Adenovirus (2 cases)* were isolated from trachea aspirates. The remaining six patients were treated with antibiotics empirically based on clinical features and infection markers. One patient with sternal wound infection was successfully managed with wound debridement and vacuum dressing.

All arrhythmias (6 nodal rhythms) and acute kidney injuries (Stage 1 and 2 based on RIFLE[33] criteria) recovered before the discharge, and none of these patients required pacemaker implantation or renal replacement therapy, respectively.

One postoperative bleeding patient required reoperation. However, no obvious area of bleeding was found. Chylothorax complications (4) were successfully managed conservatively with a low-fat diet.

There were two diaphragmatic paralysis complications, one patient required a diaphragmatic plication (a 3-year-old male with ccTGA/PA/VSD; he previously had a Left Modified Blalock Taussig shunt and a bidirectional Glenn shunt performed) while a second patient was successfully managed conservatively without surgical intervention (a 13-year-old male with tricuspid atresia, prior history of Right Modified Blalock Taussig shunt and bidirectional Glenn)

Survival.

Our cohort had no early mortality, and the one-year and five-year survival rate was estimated to be 98% and 88%, respectively *(figure 1.)*

We had two late deaths. A 12-year-old boy diagnosed with pulmonary atresia and intact interventricular septum died two months after the TCPC procedure during reoperation for a thrombosed superior vena cava extending into pulmonary arteries. The second patient was a 12-year-old male with unbalanced AVSD who demised from secondary heart failure 3.6 years after the TCPC procedure (moderate to severe AV valve regurgitation and estimated ejection fraction of 20%).

Risk factors for prolonged ICU stay, pleural drainage/effusion, and hospital stay.

The risk factors for prolonged ICU stay and prolonged pleural effusion are summarised in *Table 4*. Maximum time for prolonged pleural drainage was 38 days. In univariate analysis, ventilation (> 2 days) and infection were significantly associated with prolonged ICU stay (p-value of 0.036) and 0.009, respectively. Lastly, infection remained a statistically significant independent risk factor for prolonged ICU stay (P-value 0.039).

After analyzing the potential risk variables for PLD, none of them showed statistical significance. However, in univariable analysis, it was observed that PLD was the only independent risk factor for a prolonged hospital stay.

Freedom from TCPC procedure post bidirectional Glenn shunt, either with or without forward flow.

We noted that TCPC candidates could survive with a BGS for up to 12 years. The median interval between Glenn with pulsatile forward flow and TCPC procedure was 5 [1 - 12] years (27 patients), while without forward flow was 7 [3 - 11] years (14 patients) years (table 1). However, these findings had no statistical difference (P.value: 0.5) in these time intervals. Regarding freedom from TCPC completion after the Glenn procedure, we also did not find a significant statistical difference (Log Rank 0.469) between bidirectional Glenn with and without forward flow (figure 2).

DISCUSSION

Survival in delayed TCPC strategy.

After completing BGS, all our patients are closely followed-up by the cardiologist for any clinical deterioration; this implies that all BGS patients were in acceptable functional and clinical condition while the TCPC completion was being delayed. In our study, the BGS procedure has shown to provide acceptable clinical status for up to12 years prior to TCPC completion. This Bidirectional survival findings are similar to previous studies that showed BGS survival of more than 20 years with a good quality of life (NYHA I and II)[25,34].

Considering the BGS survival longevity shown by our study and Yeh's study that showed no survival difference between BGS alone and Fontan circulation patients[35] it is paramount to consider the BGS procedure not only as a bridge towards TCPC completion but as a palliative procedure that may provide sustainable functional and clinical conditions to delay TCPC completion and its complications. Taking into consideration the BGS survival longevity, the TCPC procedure will only be necessary if BGS becomes functionally inadequate.

Preserving forward flow during the BGS has potential theoretical advantages such as improved oxygen saturation, enhancement of pulmonary artery growth, preservation of endothelial function and prevention of thrombosis[36] hence we hypothesised forward flow to lengthen the time interval between BGS and the TCPC procedure. However, our study did not find forward flow to prolong the time interval between BGS and TCPC completion. Based on this finding, we cannot recommend the forward flow at the time of the BGS procedure for the purpose of leghtherning the time interval between BGS and TCPC procedure. Nevertheless, we can not give the account of the longterm benefit of forward flow in those patients who had forward at time of Glenn procedure hence this results should be interpreted with caution.

Regarding the TCPC survival, we had no early mortality; this reflects a good clinical judgement on patient selection, intra and perioperative care. The one-year and five-year survival were 98% and 88%, similar to previous studies[4,36–39] under different TCPC completion strategies. These survival results show that the delayed TCPC strategy does not negatively affect the mid-decade survival of TCPC patients; hence an acceptable strategy for avoiding early exposure to TCPC and its known complications. This may be one of the ideal strategy in places with limited resources to deal with TCPC-associated complications.

ICU stay and infection.

Spontaneous ventilation is advantageous in TCPC patients because the negative intrathoracic pressure during inspiration improves venous return, cardiac output, and hemodynamic stability. Despite expedited extubation, most of our patients had slightly longer ICU stays than in previous studies, which showed an average of 3 days[29,31,40] ICU stay. When we analysed the risk factors for prolonged ICU stay, we noted that postoperative infection was an independent predictor of prolonged ICU stay.

As shown by International Quality Improvement Collaborative for Congenital Heart Disease (IQIC)43 data, postoperative sepsis is one of the major postoperative complications in low- and mid-income countries. Some researchers reported postoperative cardiac surgery infection rates varying from 5 to 46%[41–44] where IQIC data for single ventricle palliation surgeries had an infection prevalence of 8%[45,46], the results that shows a high prevalence of surgical infection similar to our study.

Based on these previous postoperative infection prevalence in low- and mid-income countries, our hospital has recently joined the IQIC program to strengthen team-based practice, infection reduction, and safe perioperative practice. From 2010 to 2014, the IQIC program managed to reduce the infection rate from 22.5% to as low as 2.9% at other institutions[47]. We hope that our infection rate will decrease significantly by observing the IQIC infection control measures.

Apart from infection, another factor that could have contributed to longer ICU stay is the lack of an adequately staffed step-down facility. This necessitates a longer ICU stay for a patient to attain a clinical condition that can be accommodated by the high care unit in the ward.

Given the retrospective nature of this study, it was difficult to ascertain the source of infection. However, we recommend that the institution adheres to infection control measures.

Other postoperative TCPC complications and hospital stay.

Fenestration construction has previously been shown to reduce the incidence of prolonged pleural effusion[48–50]. However, despite routine construction of the fenestration in this study, prolonged pleural effusion was still the most common complication, similar to previous studies.[51] Other perioperative morbidity incidences (Table 3), such as sternal wound infection, arrhythmia, acute kidney injury, chylothorax, diaphragmatic paresis and paralysis, and thrombosis, were also comparable to other studies.[52,53,62,54–61].

We also noted that prolonged pleural effusion was significantly associated with a prolonged hospital stay in univariable analysis, similar to Ajay et al. and other researchers[26,63].

We did not find the independent risk factors for prolonged pleural effusion identified by the previous studies[30] to be statistically significant in our study. However, different studies have demonstrated inconsistency in factors contributing to prolonged pleural effusion.[64–66] Based on these different findings from various studies, prolonged pleural effusion is caused by a combination of multiple risk factors and can be grouped into hormonal, hemodynamic changes/hydrostatic, and inflammatory factors; hence its management should involve a combination of multiple approaches to address all the possible causes.

Some of the strategies that have shown positive outcomes in preventing prolonged pleural effusion are the WISCONSIN[67] and PORTLAND[68] protocols. In these protocols, multiple approaches such as reducing bypass time, postoperative use of angiotensin-converting enzymes inhibitors and diuretics, fluid intake restriction to 80% of the daily requirement, keeping nasal cannula oxygen (at least 0.5L) until the chest drain is removed, dietary modification (low-fat diet) and removal of the drain when drainage is < 2mL/kg/d. Adopting these well-established protocols to deal with this challenge may reduce the lengthy hospital stay and its consequences, such as patients' psychological trauma and cost implications to the hospital and the families.

Study Limitations

This study has considerable limitations. Postoperative infection was high, but more than one-third of infections were based on the use of antibiotics empirically, making it challenging to give accurate infection figures. Due to the study's small size, patients with forward and without forward flow at the time of BGS could not be matched; hence the results must be interpreted cautiously. Being a retrospective study, some data were missing, and there is a possibility of inaccurately recorded information.

However, this study has well demonstrated the outcome of a well-structured delayed TCPC strategy in a resource-constrained environment.

Conclusion

Delayed TCPC strategy with or without retention of forward flow has shown acceptable outcomes. In this series, we did not find the retention of forward flow to prolong the time interval between Bidirectional Glenn shunt and TCPC completion. This strategy may be ideal in a resource-limited environment.

We recommend the implementation of infection and pleural drainage control management protocols to avoid prolonged ICU and hospital stays.

Suggestions for future research

The functional status of these TCPC patients' needs to be evaluated in the future.

Acknowledgements

The authors would like to acknowledge sister Charnette Elliott for her assistance in data collection.

Conflict of interest

None declared.

REFERENCES

1. Stern HJ. Fontan "ten commandments" revisited and revised. *Pediatr Cardiol*. 2010;31(8):1131-1134. doi:10.1007/s00246-010-9811-9

2. 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):682-695. http://www.ncbi.nlm.nih.gov/pubmed/3184963. Accessed December 23, 2018.

3. Marcelletti C, Corno A, Giannico S, Marino B. Inferior vena cava-pulmonary artery extracardiac conduit. A new form of right heart bypass. *J Thorac Cardiovasc Surg*. 1990;100(2):228-232. doi:10.1016/S0022-5223(19)35562-X

4. Pundi KN, Johnson JN, Dearani JA, et al. 40-Year Follow-Up After the Fontan Operation: Long-Term Outcomes of 1,052 Patients. *J Am Coll Cardiol*. 2015;66(15):1700-1710. doi:10.1016/J.JACC.2015.07.065

5. Kim S-J, Kim W-H, Lim H-G, Lee J-Y. Outcome of 200 patients after an extracardiac Fontan procedure. *J Thorac Cardiovasc Surg*. 2008;136(1):108-116. doi:10.1016/J.JTCVS.2007.12.032

6. Khairy P, Fernandes SM, Mayer 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

7. d'Udekem Y, Iyengar AJ, Galati JC, 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-S38. doi:10.1161/CIRCULATIONAHA.113.007764

8. Ohuchi H, Kagisaki K, Miyazaki A, et al. Impact of the evolution of the fontan operation on early and late mortality: A Single-center experience of 405 patients over 3 decades. *Ann Thorac Surg*. 2011;92(4):1457-1466. doi:10.1016/j.athoracsur.2011.05.055

9. Helbing WA, Bosch E Van Den, Bogers AJCC. State of the art of the Fontan strategy for treatment of univentricular heart disease [version 1 ; peer review : 2 approved]. 2019;7:1-14.

10. Rychik J, Atz AM, Celermajer DS, et al. *Evaluation and Management of the Child and Adult with Fontan Circulation: A Scientific Statement from the American Heart Association*. Vol 140.; 2019. doi:10.1161/CIR.0000000000000696

11. Giannakoulas G, Dimopoulos K, Yuksel S, et al. Atrial tachyarrhythmias late after Fontan operation are related to increase in mortality and hospitalisation. *Int J Cardiol*. 2012;157(2):221-226. doi:10.1016/j.ijcard.2010.12.049

12. Peters NS, Somerville J. Arrhythmias after the Fontan procedure. *Heart*. 1992;68(8):199-204. doi:10.1136/hrt.68.8.199

13. Hilscher MB, Johnson JN, Cetta F, et al. Surveillance for liver complications after the Fontan procedure. *Congenit Heart Dis*. 2017;12(2):124-132. doi:10.1111/chd.12446

14. Yoon JS, Lee DH, Cho EJ, et al. Risk of Liver Cirrhosis and Hepatocellular Carcinoma

after Fontan Operation: A Need for Surveillance. *Cancers (Basel)*. 2020;12(7):1805. doi:10.3390/cancers12071805

15. Gordon-Walker TT, Bove K, Veldtman G. Fontan-associated liver disease: A review. *J Cardiol*. 2019;74(3):223-232. doi:10.1016/j.jjcc.2019.02.016

16. Yoo BW, Choi JY, Eun LY, Park HK, Park YH, Kim SU. Congestive hepatopathy after Fontan operation and related factors assessed by transient elastography. *J Thorac Cardiovasc Surg*. 2014;148(4):1498-1505. doi:10.1016/j.jtcvs.2014.04.010

17. Allen KY, Downing TE, Glatz AC, et al. Effect of Fontan-Associated Morbidities on Survival With Intact Fontan Circulation. *Am J Cardiol*. 2017;119(11):1866-1871. doi:10.1016/j.amjcard.2017.03.004

18. Akintoye E, Veldtman GR, Miranda WR, Connolly HM, Egbe AC. Optimum age for performing Fontan operation in patients with univentricular heart. *Congenit Heart Dis*. 2019;14(21. Akintoye E, Veldtman GR, Miranda WR, Connolly HM, Egbe AC. Optimum age for performing Fontan operation in patients with univentricular heart. Congenit Heart Dis. 2019;14(2):138-139. doi:10.1111/chd.12690):138-139. doi:10.1111/chd.12690

19. Than P, Brubaker A, Ebel N, Profita E, Esquivel C. The Emerging Need for Combined Heart and Liver Transplantation in Congenital Heart Disease. *Curr Transplant Reports*. 2020;7(3):180-186. doi:10.1007/s40472-020-00286-y

20. Idorn L, Jensen AS, Juul K, et al. Quality of life and cognitive function in Fontan patients, a population-based study. *Int J Cardiol*. 2013;168(4):3230-3235. doi:10.1016/J.IJCARD.2013.04.008

21. Uzark K, Zak V, Shrader P, et al. Assessment of Quality of Life in Young Patients with Single Ventricle after the Fontan Operation. *J Pediatr*. 2016;170:166-172.e1. doi:10.1016/j.jpeds.2015.11.016

22. Pace Napoleone C, Oppido G, Angeli E, Giardini A, Resciniti E, Gargiulo G. Results of the modified Fontan procedure are not related to age at operation. *Eur J Cardio-Thoracic Surg*. 2010;37(3):645-650. doi:10.1016/j.ejcts.2009.09.003

23. Pace Napoleone C, Giardini A, Gargiulo G. Reply to d'Udekem et al. *Eur J Cardio-thoracic Surg*. 2011;39(1):144-145. doi:10.1016/j.ejcts.2010.04.008

24. Calvaruso DF, Rubino A, Ocello S, et al. Bidirectional Glenn and Antegrade Pulmonary Blood Flow: Temporary or Definitive Palliation? *Ann Thorac Surg*. 2008;85(4):1389-1396. doi:10.1016/j.athoracsur.2008.01.013

25. Kowatari R, Suzuki Y, Daitoku K, Fukuda I. Long-term results of additional pulmonary blood flow with bidirectional cavopulmonary shunt. *J Cardiothorac Surg*. 2020;15(1):279. doi:10.1186/s13019-020-01335-4

26. Iyengar AJ, Winlaw DS, Galati JC, et al. Trends in Fontan surgery and risk factors for early adverse outcomes after Fontan surgery: The Australia and New Zealand Fontan Registry experience. *J Thorac Cardiovasc Surg*. 2014;148(2):566-575. doi:10.1016/J.JTCVS.2013.09.074

27. D'Udekem Y, Xu MY, Galati JC, et al. Predictors of survival after single-ventricle palliation: The impact of right ventricular dominance. *J Am Coll Cardiol*. 2012;59(13):1178-1185. doi:10.1016/j.jacc.2011.11.049

28. Rogers LS, Glatz AC, Ravishankar C, et al. 18 Years of the Fontan Operation at a Single Institution: Results From 771 Consecutive Patients. *J Am Coll Cardiol*. 2012;60(11):1018-1025. doi:10.1016/J.JACC.2012.05.010

29. Forsdick V, Iyengar AJ, Carins T, et al. Unsatisfactory Early and Late Outcomes After Fontan Surgery Delayed to Adolescence and Adulthood. *Semin Thorac Cardiovasc Surg*. 2015;27(2):168-174. doi:10.1053/J.SEMTCVS.2015.05.001

30. Talwar S, Das A, Khadgawat R, Sahu MK, Choudhary SK, Airan B. A prospective study of risk factors associated with persistent pleural effusion after total cavopulmonary connection with special reference to serum cortisol level. *Indian J Thorac Cardiovasc Surg*. 2018;34(3):345-354. doi:10.1007/s12055-017-0617-8

31. Mutsuga M, Quiñonez LG, MacKie AS, et al. Fast-track extubation after modified Fontan procedure. *J Thorac Cardiovasc Surg*. 2012;144(3):547-552. doi:10.1016/j.jtcvs.2012.05.047

32. Morales DLS, Carberry KE, Heinle JS, McKenzie ED, Fraser CD, Diaz LK. Extubation in the Operating Room After Fontan's Procedure: Effect on Practice and Outcomes. *Ann Thorac Surg*. 2008;86(2):576-582. doi:10.1016/j.athoracsur.2008.02.010

33. Criteria for acute kidney injury - UpToDate. https://www.uptodate.com/contents/image?imageKey=NEPH%2F83168. Accessed February 13, 2022.

34. Sethasathien S, Silvilairat S, Lhodamrongrat C, et al. Risk factors for morbidity and mortality after a bidirectional Glenn shunt in Northern Thailand. *Gen Thorac Cardiovasc Surg*. 2021;69(3):451-457. doi:10.1007/s11748-020-01461-9

35. Yeh T, Williams WG, McCrindle BW, et al. Equivalent survival following cavopulmonary shunt: With or without the Fontan procedure. *Eur J Cardio-thoracic Surg*. 1999;16(2):111-116. doi:10.1016/S1010-7940(99)00153-0

36. Dabal RJ, Kirklin JK, Kukreja M, et al. The modern Fontan operation shows no increase in mortality out to 20 years: A new paradigm. *J Thorac Cardiovasc Surg*. 2014;148(6):2517-2524.e1. doi:10.1016/j.jtcvs.2014.07.075

37. Uhm JY, Jhang WK, Park JJ, Seo DM, Yun SC, Yun TJ. Postoperative use of oral sildenafil in pediatric patients with congenital heart disease. *Pediatr Cardiol*. 2010;31(4):515-520. doi:10.1007/s00246-009-9632-x

38. Malec E, Schmidt C, Lehner A, Januszewska K. Results of the Fontan operation with no early mortality in 248 consecutive patients. *Kardiol Pol*. 2017;75(3):255-260. doi:10.5603/KP.a2016.0170

39. Poh CL, d'Udekem Y. Life After Surviving Fontan Surgery: A Meta-Analysis of the Incidence and Predictors of Late Death. *Hear Lung Circ*. 2018;27(5):552-559. doi:10.1016/J.HLC.2017.11.007

40. Kintrup S, Malec E, Kiski D, et al. Extubation in the Operating Room After Fontan Procedure: Does It Make a Difference? *Pediatr Cardiol*. 2019;40(3):468-476. doi:10.1007/s00246-018-1986-5

41. Patwary ME liya., Khan MS hahba., Marwah A, Singh V, Shekhawat S, Sharma R. Arterial Switch for Transposition of the Great Arteries With Large Ventricular Septal

Defect and for Taussig Bing Anomaly: Experience From a Tertiary Care Center in the Developing World. *World J Pediatr Congenit Heart Surg*. 2015;6(3):413-421. doi:10.1177/2150135115593128

42. Mrowczynski W, Wojtalik M, Zawadzka D, et al. Infection risk factors in pediatric cardiac surgery. *Asian Cardiovasc Thorac Ann*. 2002;10(4):329-333. doi:10.1177/021849230201000411

43. Kollef MH, Sharpless L, Vlasnik J, Pasque C, Murphy D, Fraser VJ. The impact of nosocomial infections on patient outcomes following cardiac surgery. *Chest*. 1997;112(3):666-675. doi:10.1378/chest.112.3.666

44. Zhang J, Yuan Y, Li P, et al. Postoperative nosocomial infections among children with congenital heart disease. *Pakistan J Med Sci*. 2014;30(3):554. doi:10.12669/pjms.303.4648

45. Schidlow DN, Gauvreau K, Cherian KM, et al. Single-Ventricle Palliation in Low- and Middle-Income Countries. *J Am Coll Cardiol*. 2019;74(7):928-931. doi:10.1016/j.jacc.2019.07.004

46. IQIC - Children's HeartLink. https://childrensheartlink.org/iqic/. Accessed September 3, 2020.

47. IQIC - Children's HeartLink. https://childrensheartlink.org/iqic/. Accessed September 21, 2021.

48. Bridges ND, Mayer JE, Lock JE, et al. Effect of baffle fenestration on outcome of the modified fontan operation. *Circulation*. 1992;86(6):1762-1769. doi:10.1161/01.cir.86.6.1762

49. Lemler MS, Scott WA, Leonard SR, Stromberg D, Ramaciotti C. Fenestration improves clinical outcome of the Fontan procedure: A prospective, randomised study. *Circulation*. 2002;105(2):207-212. doi:10.1161/hc0202.102237

50. Bridges ND. Fenestration of the Fontan Baffle: Benefits and Complications. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu*. 1998;1(1):9-13. doi:10.1016/s1092-9126(98)70004-3

51. Mascio CE, Iii EHA. Pleural effusions following the Fontan procedure. 2010. doi:10.1097/MCP.0b013e3283396efc

52. Mpisane F, Brooks A, Basera W, Zuhlke LJ. Post cardiac surgery sternal wound sepsis burden, risk factors and outcomes at Red Cross War Memorial Children's Hospital, Cape Town, South Africa: A five-year experience. *SA Hear*. 2020;17(1). doi:10.24170/17-1-4021

53. Lemaignen A, Birgand G, Ghodhbane W, et al. Sternal wound infection after cardiac surgery: Incidence and risk factors according to clinical presentation. *Clin Microbiol Infect*. 2015;21(7):674.e11-674.e18. doi:10.1016/j.cmi.2015.03.025

54. Rosanova MT, Allaria A, Santillan A, et al. Risk factors for infection after cardiovascular surgery in children in Argentina. *Brazilian J Infect Dis*. 2009;13(6):414-416. doi:10.1590/S1413-86702009000600005

55. Tokunaga S, Kado H, Imoto Y, et al. *Total Cavopulmonary Connection With an Extracardiac Conduit: Experience With 100 Patients*.; 2002.

56. Ono M, Beran E, Burri M, et al. Long-term outcome of preadolescents, adolescents, and adult patients undergoing total cavopulmonary connection. 2018. doi:10.1016/j.jtcvs.2018.03.155

57. Esch JJ, Salvin JM, Thiagarajan RR, Del Nido PJ, Rajagopal SK. Acute kidney injury after Fontan completion: Risk factors and outcomes CONGENITAL HEART DISEASE: FONTAN. 2015. doi:10.1016/j.jtcvs.2015.04.011

58. Lo Rito M, Al-Radi OO, Saedi A, et al. Chylothorax and pleural effusion in contemporary extracardiac fenestrated fontan completion. *J Thorac Cardiovasc Surg*. 2018;155(5):2069-2077. doi:10.1016/j.jtcvs.2017.11.046

59. Deraz S, Ismail MF, Jamjoom A. Outcome of early and late onset Fontan operation in patients with univentricular heart repair. *Egypt Hear J*. 2014;66(2):171-176. doi:10.1016/j.ehj.2013.06.001

60. Ono M, Beran E, Burri M, et al. Long-term outcome of preadolescents, adolescents, and adult patients undergoing total cavopulmonary connection. *J Thorac Cardiovasc Surg*. 2018;156(3):1166-1176.e4. doi:10.1016/j.jtcvs.2018.03.155

61. Komori M, Hoashi T, Shimada M, et al. Impact of Phrenic Nerve Palsy on Late Fontan Circulation. In: *Annals of Thoracic Surgery*. Vol 109. Elsevier USA; 2020:1897-1902. doi:10.1016/j.athoracsur.2019.09.064

62. Agarwal A, Firdouse M, Brar N, et al. Incidence and Management of Thrombotic and Thromboembolic Complications Following the Superior Cavopulmonary Anastomosis Procedure: A Literature Review. *Clin Appl Thromb*. 2018;24(3):405-415. doi:10.1177/1076029617739702

63. Rogers LS, Glatz AC, Ravishankar C, et al. 18 Years of the Fontan Operation at a Single Institution. *JAC*. 2012;60:1018-1025. doi:10.1016/j.jacc.2012.05.010

64. Gupta A, Daggett C, Behera S, Ferraro M, Wells W, Starnes V. Risk factors for persistent pleural effusions after the extracardiac Fontan procedure. *J Thorac Cardiovasc Surg*. 2004;127(6):1664-1669. doi:10.1016/j.jtcvs.2003.09.011

65. Downing TE, Allen KY, Glatz AC, et al. Long-term survival after the Fontan operation: Twenty years of experience at a single center. *J Thorac Cardiovasc Surg*. 2017;154(1):243-253.e2. doi:10.1016/j.jtcvs.2017.01.056

66. Zou M, Wang Y, Cui H, et al. Outcomes of total cavopulmonary connection for single ventricle palliation. *J Thorac Dis*. 2016;8(1):43-51. doi:10.3978/j.issn.2072-1439.2016.01.41

67. Pike NA, Okuhara CA, Toyama J, Gross BP, Wells WJ, Starnes VA. Reduced pleural drainage, length of stay, and readmissions using a modified Fontan management protocol. *J Thorac Cardiovasc Surg*. 2015;150(3):481-487. doi:10.1016/j.jtcvs.2015.06.042

68. Sunstrom RE, Muralidaran A, Gerrah R, et al. A defined management strategy improves early outcomes after the fontan procedure: The portland protocol. In: *Annals of Thoracic Surgery*. Vol 99. Elsevier USA; 2015:148-155. doi:10.1016/j.athoracsur.2014.06.121

TABLES AND FIGURES

Table 1: Preoperative characteristics

Variables	Values
Gender (M/F)	18/24
Age at the time of TCPC procedure (year)	9 [IQR: 7 – 11]
Weight (Kg)	26 [IQR: 18 – 30]
Pre-operative saturation (%)	87 [IQR: 82 – 88]
Pre-op normal sinus rhythm (n)	42 (100%)
Pre-op mean Pulmonary pressure (mmHg)	10.8 ± 2
Diagnosis	
Tricuspid atresia	22 (52%)
TGA/DORV	4 (9.5%)
Unbalanced AVSD	4 (9.5%)
TGA/PS	4 (9.5%)
ccTGA/PA	2 (4.8%)
DILV/DOLV/PS	2 (4.8%)
Pulmonary atresia	2 (4.8%)
DORV/AVSD	2 (4.8%)
Dominant Ventricle	
Left Ventricle	23 (55%)
Co-ventricles	19 (45%)
Pre-Glenn Procedures	
Modified Blalock-Taussig shunts	22
PA banding	4
Central shunts	2
PDA stents	2
PDA ligation	1
Bidirectional Glen Procedure	
Median age at the time of Glenn procedures (months)	26 [IQR: 18 – 50]
The median time interval between the Glenn and Fontan Procedure (years)	6 [IQR: 4 - 9]
Glenn procedure with the pulsatile forward flow (%)	23 (56%)

Table 2: Intra-operative parameters for TCPC procedure

Variables	Values (%)
Extra-cardiac TCPC (n)	42 (100)
Graft/conduit size	
18mm	19 (45)
20mm	15 (36)
16mm	7 (17)
22mm	1 (2)
CPB duration (minutes)	120 [IQR: 99 – 144]
Fenestration	40 (95)
Fontan pressure (CVP) mmHg	15 [IQR: 12 – 17]

Table 3: Postoperative findings

Mechanical ventilation termination	
Extubated within 12 hours after the operation	29(78%)
Extubated between 12 and 24 hours of the operation	3 (8%)
Ventilated for more than 24 hours	5 (14%)
Pleural drainage duration (days) - median	8 [IQR:6 – 14]
Complications:	
Infections	16 (38%)
Arrhythmias (nodal rhythm)	6 (14%)
Chylothorax	4 (9%)
Diaphragmatic paralysis	2 (4%)
Thrombosis	2 (4%)
Acute kidney injury	2 (4%)
Reoperation for bleeding	1 (2%)
Superficial sternal wound infection	1 (2%)
ICU stay (days) - mean	4.5 ± 2.6
Hospital stay (days) - median	14 (9-23)
Survival	
30-day mortality	0
Late mortality (n)	2 (4.8%)
Median follow – up (months)	24 [IQR:12 – 43]

Table 4: Risk of prolonged ICU stay and prolonged pleural drainage

Variables	Univariate		Multivariate	
	OR (95% CI)	P - value	OR (95% CI)	P-value
Risk factors for prolonged ICU stay (>3 days)				
Age	1.0 (0.82 – 1.3)	0.9	-	-
Mean pulmonary pressure	0.9 (0.74 – 1.3)	0.97	-	-
Pre-operative saturation	1.0 (0.85 – 1.2)	0.75	-	-
Post-operative CVP > 15mmHg	1.0 (0.19 – 5.1)	1	-	-
Post-operative infection	7.6 (1.64 – 35)	0.009	5.48 (1.09 - 27)	0.039
Post-operative arrythmia	1.0 (0.23 - 1.9)	0.99	-	-
Prolonged ventilation (2 days ≤)	10 (1.17 – 97)	0.036	7.82 (0.78 - 78)	0.080
Risk factors for pleural drainage (>14 days)				
Age	0.9 (0.69 – 1.2)	0.57	-	-
Mean pulmonary pressure	1.0 (0.74 - 1.4)	0.85	-	-
Pre-operative saturation	1.0 (0.79 - 1.3)	0.99	-	-
Bypass time	1.0 (0.98 – 1.0)	0.73	-	-
Post-operative infection	1.7 (0.37 – 8.3)	0.49	-	-
Post-operative arrythmia	0.7 (0.71 - 7.1)	0.77	-	-
Prolonged ventilation (2 days ≤)	1.2 (0.81 – 7.6)	0.84	-	-
Post-operative CVP > 15mmHg	1.5 (0.61 - 30)	0.14	-	-
Risk factors for a prolonged hospital stay (>14 days)				
Prolonged pleural drainage	0.1 (0.10 – 0.9)	0.038	Only significant variable	
Mean pulmonary pressure	0.8 (0.66 – 1.2)	0.48	-	-
Bypass time	1.0 (0.99 – 1.0)	0.21	-	-
Pre-operative saturation	1.0 (0.89 – 1.3)	0.39	-	-
Post-operative CVP > 15mmHg	0.4 (0.08 – 2.2)	0.33	-	-
Post-operative infection	0.3 (0.08 – 1.2)	0.10	-	-
Post-operative arrythmia	1.0 (0.17 – 5.7)	1.00	-	-

Figure 1; Survival in months after the completion of Total Cavo-Pulmonary Connection

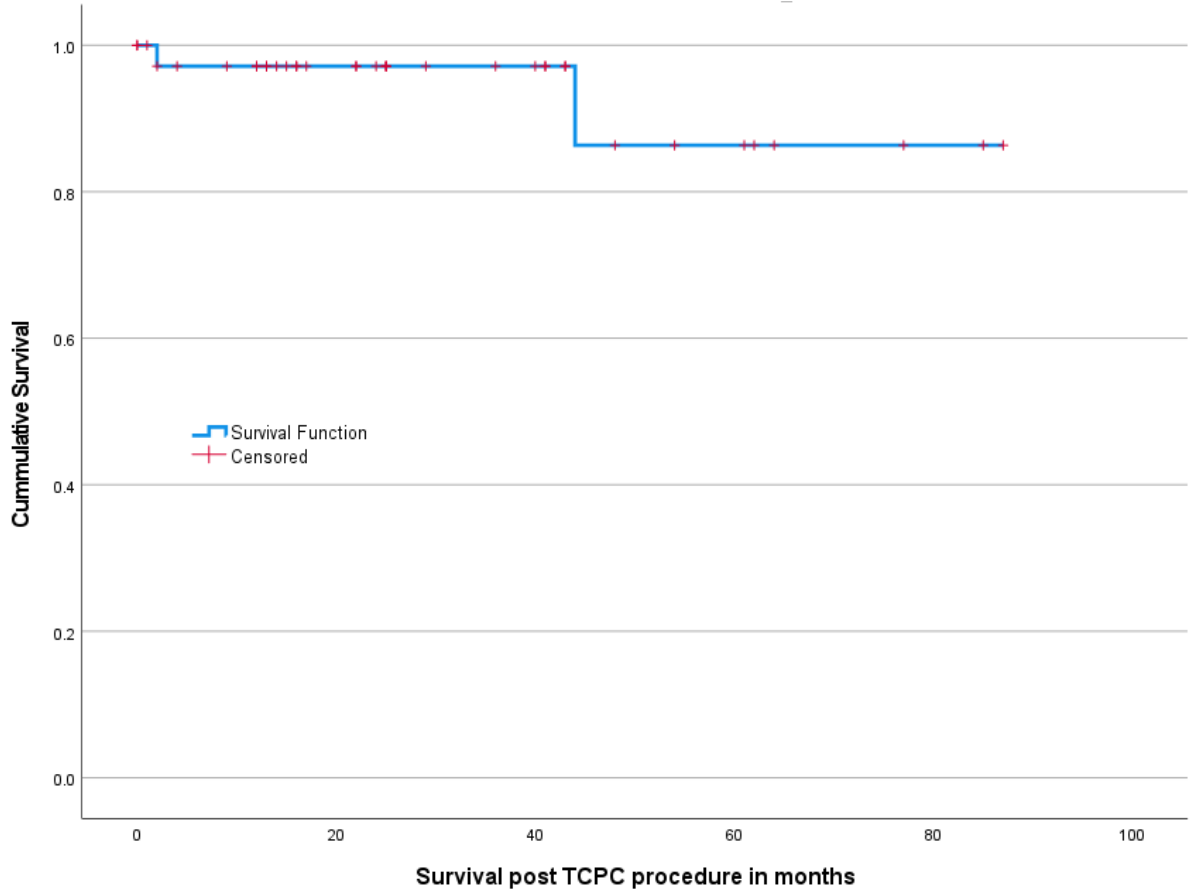
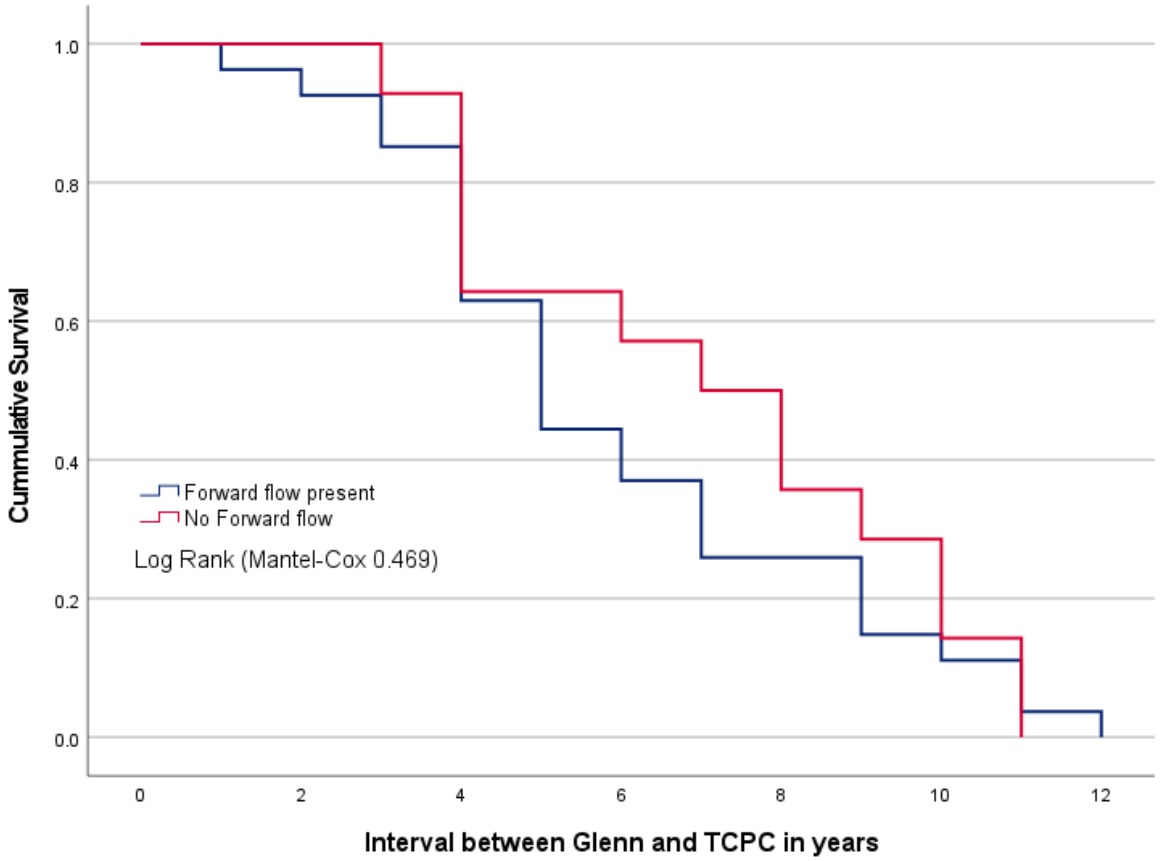


Figure 2; Freedom from TCPC completion post-Bidirectional Glenn procedure with and without forward flow



QUESTIONAIRE

FONTAN PROCEDURE: MID-TERM OUTCOME OF A DECADE OF DELAYED TOTAL CAVO-PULMONARY CONNECTION COMPLETION STRATEGY AT RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL.

Patient demographics

1. Date of birth ☐

2. Gender

   Male ☐ Female ☐

Preoperative assessment

3. The initial anatomical diagnosis

   - ☐ Tricuspid atresia
   - ☐ Hypoplastic Left Ventricle
   - ☐ Double outlet right ventricle
   - ☐ Pulmonary atresia
   - ☐ Others, mention _____

4. Fontan criteria

   - ☐ Date of operation ☐
   - ☐ McGoon ratio ☐
   - ☐ Nakata index ☐
   - ☐ Mean pulmonary arterial pressure ☐
   - ☐ Left ventricular ejection fraction ☐
   - ☐ Pre-operative oxygen saturation ☐
   - ☐ Cardiac rhythm.
   - ☐ Sinus rhythm Yes ☐ No ☐

     Type of arrythmia_____(*If the above response was '**No'***)

5. Previous interventions, 'STAGE I palliation.'

   i. Pulmonary flow augmentation Yes ☐ No ☐ *(If '**No**' skip the options below)*

   A. Central shunt ☐ B. Left MBT shunt ☐ C. Right MBT shunt ☐

   D. Date of Operation ☐

ii. Pulmonary banding Yes ☐ No ☐

A. Date of operation ☐

6. Previous intervention 'STAGE II palliation' (Glenn procedure) Yes ☐ No ☐

i. Date of operation ☐

ii. Done on cardiopulmonary bypass machine? Yes ☐ No ☐

Intra and Post-operative data

7. Bypass duration(minutes) ☐
8. Type of Fontan procedure
   - ☐ Extra-cardiac conduit
   - ☐ Lateral tunnel baffle
9. Presence of fenestration Yes ☐ No ☐
10. ICU stay duration(days) ☐

Early outcome (within 30days)

11. Number of days on ventilator ☐
12. Arrhythmia? Yes ☐ No ☐
    - *i. The type of arrhythmia* ☐
    - *ii. H ow many days post Fontan?* ☐
    - *iii. Resolved at the time of discharge* YES ☐ NO ☐

Note: duplicate Question 12 options if there was a different type of arrhythmia.

13. Reoperation Yes ☐ No ☐
    - i. Reason for reoperation _____
    - ii. How many days post Fontan? ☐

Note: Duplicate Question 13 in case of multiple operations

14. Pleural drain duration ☐
15. Chylothorax Yes ☐ No ☐
16. Other complications *(Mention them)* ……..
17. Total days spent in the hospital after the operation ☐ *(If patient was discharged)*

18. Death Yes ☐ No ☐

19. Date of death ☐ *(If the above answer was 'Yes')*

Late Outcome(After 30 days)

20. Arrhythmia Yes ☐ No ☐

i. *The type of arrhythmia* ☐

ii. *How many days post Fontan?* ☐

iii. *Intervention:* *surgical* ☐ *medical* ☐ *None* ☐

iv. *Resolved* Yes ☐ No ☐

21. Pleural effusion Yes ☐ No ☐

22. Other complications *(Mention them)* ……..

23. Death? YES ☐ NO ☐

24. If yes, when? Date of death ☐

ETHICAL APROVAL LETTER

UNIVERSITY OF CAPE TOWN
Faculty of Health Sclences
Human Research Ethics Committee
Room E53-4S Old Main Building
Groote Schuur Hospltal
O
bservatory 7925 Telephone [021] 406 6492
Email; sumauah.afletdien@uct.ac.za
Webslte:
www.health.uct.ac.za/fhs/research/humanethics/forms

14 June 2019

HREC REF: 364/2019

Dr A Brooks
Chris Barnard Division of Cardiothoraclc Surgery

D24.12

NGSH

Dear Dr Brooks

PROJECT TITLE: FONTAN PROCEDURE: TEN-YEAR EXPERIENCE AT RED CROSS CHILDREN'S HOSPITAL (MMED CANDIDATE - DR N SWAI)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It Is a pleasure to inform you that the HREC has formally approved the above-mentloned study.

Approval Is granted for one year until the 30 June 2020.

Please submit a progress form, uslng the standardised Annual Report Form If the study continues beyond the approval perlod. Please submlt a Standard Closure form if the study is completed wlthin the approval perlod.

(Forms can be found on our website: www.health.uct.ac.zalfhs/research/humanethics/forms)

We acknowledge that the student: Dr Noel Swal will also be involved in thls study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remalns the responsibillty of the principal investigator.

Please note that for all studles approved by the HREC, the princlpal Investigator obtain appropriate Instltutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.

Instltutional Revlew Board (IRB) number: IRB00001938

NHREC-reglstratlon number: REC-21nnnn007

Thls serves to confirm that the University of Cape Town Human Research Ethics Commlttee complies to the Ethics Standards for Clinical Research with a new drug In patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for

Harmonisatlon of Technical Requlrements for Pharmaceuticals for Human Use: Good Cllnlcal Practice (ICH GCP), South African Good Cllnical Practice Guidelines (DOH 2006), based on the Associatlon of the British Pharmaceutlcal Industry Guldelines (ABPI), and Declaration of Helsinki (2013) guidelines.

The Human Research Ethlcs Commlttee grantlng this approval is In compllance with the ICH

Harmonised Trlpartlte Guldelines E6: Note for Guidance on Good Cllnical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation

CARDIOLOGY IN THE YOUNG

Author instructions

Editorial Policies

https://www.cambridge.org/core/journals/cardiology-in-the-young/information/author-instructions

Cardiology in the Young is devoted to cardiovascular issues affecting the young and the older patient with the sequels of cardiac disease acquired in childhood. Submission of both basic research and clinical papers is encouraged. Articles on fundamental principles will also be considered for publication. Reviews on recent developments are welcome. The Journal serves the interest of all professionals concerned with these topics. By design, the Journal is international and multidisciplinary in its approach, and the members of the Editorial Board take an active role in the Journal's mission. Prospective authors are encouraged to consult with the editors and members of the Editorial Board with any enquiries. The editors encourage the submission of articles from developing countries.

Articles should be concerned with original research not published previously and not being considered for publication elsewhere. Submission of a manuscript to the Journal gives the publisher the right to publish that paper if it is accepted. Authors sign a license to publish with the journal and retain copyright of their manuscript. Manuscripts may be edited to improve clarity and expression.

Authors must ensure that their studies comply with appropriate institutional and national guidelines for ethical matters. Specifically, by submission of a manuscript, the authors are responsible for compliance with guidelines and regulations of the authors' institution and all appropriate governmental agencies.

Articles including human subjects must include a statement that informed consent was obtained and that the study was reviewed and approved by the institution's committee on human experimentation. Articles including animal experimentation must conform to the principles of the American Physiological Society, and a statement acknowledging conformation to these standards must be included in the *Materials and methods* section of the manuscript. Authors are also requested to identify possible conflicts of interest, especially if they relate to commercial sponsorship or equity holdings.

Social Media

Social Media Synopsis: Each author preparing a manuscript for submission should include a suggested tweet, which will be used for dissemination and promotion on social media if the manuscript is accepted. Please limit the suggested tweet to 160 characters including spaces, which summarises the main findings or overall take-home from the manuscript. When appropriate, please also include relevant author Twitter handles (ex. @CardiologyYoung) or relevant topical hashtags (ex. #PedsCards) - the author handles and hashtags do not count towards the 160 character limit. Relevant media, such as an image of the first or senior authors or a graphical representation of the data should be submitted as a .jpeg file under the Social Media section of the submission process.

Clinical Trials

As a condition of consideration for publication, registration of clinical trials in a public trials registry is required. A clinical trial is defined by the International Committee of Medical

Journal Editors (in accordance with the definition of the World Health Organisation) as any research project that prospectively assigns human participants or groups of humans to one or more health- related interventions to evaluate the effects on health outcomes. Trials must be registered before the start of patient enrolment. The registry must be accessible to the public at no charge. It must be open to all prospective registrants and managed by a not-for-profit organisation. There must be a mechanism to ensure the validity of the registration data, and the registry should be electronically searchable. An acceptable registry must include at minimum a unique trial number, trial registration date, secondary identification information if assigned by sponsors or others, funding source(s), primary and secondary sponsor(s), responsible contact person, research contact person, official scientific title of the study, research ethics review, the medical condition being studied, intervention(s), key inclusion and exclusion criteria, study type, anticipated trial start date, target sample size, recruitment status, primary outcome, and key secondary outcomes. Registration information must be provided at the time of submission.

Trial registry name, registration identification number, and the URL for the registry should be included at the end of the abstract.

Manuscripts reporting the results of randomised controlled trials should include a "CONSORT" flow diagram to illustrate the progress of all patients in the study (See: Schulz KF, Altman D, for the CONSORT Group. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. JAMA. 2001;285(15):1987–1991.) The flow diagram should be uploaded as a separate file to the manuscript.