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Full Length Research Paper

Use of a composite survival graph to optimise the surgical strategy for Tricuspid atresia

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The introduction of the Fontan circulation has improved the long term survival of patients with Tricuspid Atresia (TA) in general. Neonates and infants with TA presenting reduced pulmonary blood flow (RPBF) are usually offered a systemic arterial-to-pulmonary artery shunt (SAPAS) in the hope that they will eventually achieve a Fontan circulation. There is evidence that palliative surgery may not improve survival in this subset of patients. Our aim was to determine whether palliative surgery improves survival in patients with TA and RPBF. An objective assessment of a treatment outcome necessitates a comparison of the treatment outcome with the natural history. We searched the literature for surgical outcome and natural history studies. The most external validity ones were used to create a composite survival graph to assess the efficacy of palliative surgery in patients with TA and RPBF. The data suggests that palliative cardiac surgery in patients with TA and RPBF is unlikely to improve the long-term survival compared to the natural history. There is also evidence that palliative cardiac surgery performed on patients with TA, who present for the first time after one year of age, is unlikely to improve long-term survival compared to the natural history. Palliative cardiac surgery should not be offered to patients with TA and RPBF. Palliative cardiac surgery probably should not be offered to any patient with TA who presents for the first time after 1 year of age.

Key words: Tricuspid atresia, surgery outcome.

INTRODUCTION

With respects to tricuspid atresia (TA), palliative cardiac surgery refers to the Fontan circulation or any cardiac surgery performed in anticipation of the Fontan circulation (Franklin et al., 1993), (Fontan and Baudet, 1971). When patients with TA are considered as a homogenous group, it is evident that the introduction of palliative cardiac surgery has improved the survival of these patients (Franklin et al., 1993; Samanek, 1992). Patients typically present with central cyanosis although some present in heart failure with increased pulmonary blood flow. The diagnosis is usually confirmed by echocardiography. Neonates and infants presenting with reduced pulmonary blood flow (RPBF) are often offered a SAPAS. There is evidence that palliative surgical outcomes in this subset of patients are worse than in patients with increased or balanced pulmonary blood flows (Franklin et al., 1993). An objective assessment of treatment outcomes necessitates a comparison of the treatment outcome with natural history. We systematically reviewed the literature with respects to TA surgical outcome and natural history studies. We then determined which of these studies had the greatest external validity and used these studies to

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Table 1. PSM parameters.

Areas affecting validity	Surgical outcome parameters	Natural history parameters
Subjects	TA; AAO; SS	TA; SS
Geography	Multiple centres	Any location
Era	Paper published after the 1981	Any era

AAO= age at operation; SS=sample size; TA=*Tricuspid atresia*.
Source: Author

Table 2. Search strategy.

Search number	Terms
1.	Tricuspid, atresia, natural, history(GS,PM)
2.	Tricuspid, atresia, survival(GS,PM)
3.	Tricuspid, atresia, unoperated(GS,PM)
4.	Tricuspid, atresia, survival(GS,PM)
5.	Natural, history, cardiac, malformations(GS,PM)
6.	Congenital, heart, disease, natural, survival(GS,PM)
7.	Tricuspid, atresia, long, term, survival(PM)
8.	Tricuspid, atresia, long, term, outcome(GS,PM)
9.	Tricuspid, atresia, long, term, results(GS,PM)
10.	Tricuspid, atresia, survival (GS,PM)
11.	Tricuspid, atresia, long, term, survival(PM)
12.	Fontan, long, term, outcome(GS)
13.	Bidirectional, cavopulmonary, tricuspid, atresia(PM)
14.	Cavopulmonary, Tricuspid, atresia(GS)
15.	Glenn, Tricuspid, atresia(GS)

GS = Goggle scholar, PM= Pubmed
Source: Author

create a composite survival graph to assess surgical efficacy (Polit and Beck, 2010). The results of a pilot study predicted that there would not be enough data to conduct a credible meta-analysis or credible receiver operator curve analysis. In view of this, we used the 'Proximal Similarity Model' (PSM) to assess the external validity (Polit and Beck, 2010). The natural history survival curve is an estimate of the probability of survival; it is appropriate to compare such survival curves with Kaplan-Meier surgical survival curves (Measures of Prognosis, 2021). This was our rational for the creation of the composite survival graph. The resultant composite survival graph, graphically demonstrates surgical efficacy as a function of pulmonary blood flow and patient age.

Patients and methods

Proximal Similarity Model (PSM)

This model asserts that significant threats to external validity occur in 3 areas: study subjects, study location and study era. The PSM determines which study best represents the population of interest (that is, it has the greatest external validity). Table 1 shows which parameters were considered when assessing external validity. We used this technique in an earlier study which examined the management of transposition of the great arteries (Awori et al., 2022). A surgical outcome paper was utilised to build the composite graph if it had the best combination of all four of the following characteristics: a large sample size; median age at SAPAS was less than 1 month old.; it considered the amount of pulmonary blood flow; the paper was published after 1981 (the Fontan circulation was introduced in 1971; 10 years should be an adequate duration to facilitate the widespread adoption of the Fontan circulation). A natural history paper was chosen to construct the composite graph if it had the best combination of all three of the following characteristics: it had a large sample size; it followed-up patients from birth until death; it had a robust way to diagnose tricuspid atresia (Echocardiography/ post-mortem). The 'best' surgical outcome graph was superimposed on the 'best' natural history survival graph to form the composite survival graph.

Search strategy and selection criteria

Systematic search was performed on PUBMED (PM) and Google Scholar (GS) between January 1st 1966 and October 30th 2021. The search terms and the search strategy are contained in Table 2: 11 GS searches were made and 11 PM searches were made. Titles, abstracts and where appropriate full-text articles were examined for natural history and surgical survival data. Studies published on languages other than English and animal studies were excluded. Hadjicosta et al. (Hadjicosta et al., 2021) reported a 10 year

Table 3. Surgical outcome full-texts included.

Author	YFSC	n	PBFC	SATY (%)
Hadjicosta et al. (2021)	2000	450	No	80
Pundi et al. (2015)	1973	270	No	75
Sittiwangkul et al. (2004)	1971	225	No	73
Franklin et al. (1993)	1972	237	Yes	45

n=number of patients; PBFC= pulmonary blood flow considered; SATY= survival at ten years; YFSC= year first surgery conducted.
Source: Author

Table 4. Surgical outcome full text(s) excluded that possibly.

Study	Study year	Number of patients
Karamlou et al.	2005	150

Source: Author

Table 5. Natural history full texts retrieved.

Author	Study year	Study type	Max age*of patient(s)	SpO2 (%)	Status
Koizumi et al.	2019	Case report	42	85	Alive
McKinney et al.	2017	Case report	30	-	Dead
Gerlis et al.	1998	Case report	60	85	Dead
Samanek et al.	1992	Descriptive cohort	15	-	Alive
Fesslova et al.	1989	Descriptive cohort	12.5	-	Alive
Beaver et al.	1988	Case report	65	85	Dead
Voci et al.	1987	Case report	22	85	Alive
Patel et al.	1987	Case report	57	-	Alive
Hart et al.	1984	Case report	34	82	Alive
Breisch et al.	1983	Case report	21	-	Dead
Campbell	1972	Descriptive cohort	24	-	Alive
Jordan and Sanders	1966	Case series	57	72	Alive

* years.
Source: Author

mortality rate of 25%; the survival curve had essentially become horizontal by 2 years of follow-up. To detect a 25% morality with a confidence level of 80%, a study should follow-up at least 123 patients to 10 years. As a result of these facts, we only considered surgical outcome studies that examined at least 123 patients for at least 2 years after surgery. We determined this sample size 'cut-off' using a free online sample size calculator (Available at https://www.calculator.net/sample-size-calculator.html. Accessed February 9 2022). The search flow is depicted in Figure 1.

RESULTS

The search yielded 929 results; after accounting for duplicate results, 49 relevant full-texts were examined. There were 21 natural history (NH) full texts and 28 surgical outcome (SO) full texts. A search of the references of these full texts was made to look for additional relevant publications. The pertinent details of each study considered for developing the SO branch of the composite survival graphs is shown in Table 3. A list of excluded full texts that may have followed-up a sufficient number of patients to 10 years, is shown in Table 4. All the natural history full texts retrieved are shown in Table 5. The natural history curve for TA is shown in Figure 2; composite graphs are shown in Figures 3 to 5. Franklin published more data in a thesis (Franklin, 1997). Of particular relevance was a natural history survival graph for a subset of TA patients with a particularly poor prognosis. We were unable to find any other data of this nature. We used this data to create our composite graph in figure 4. Key aspects of this study are as follows:

1. All patients presented at < 1 year of age, during the

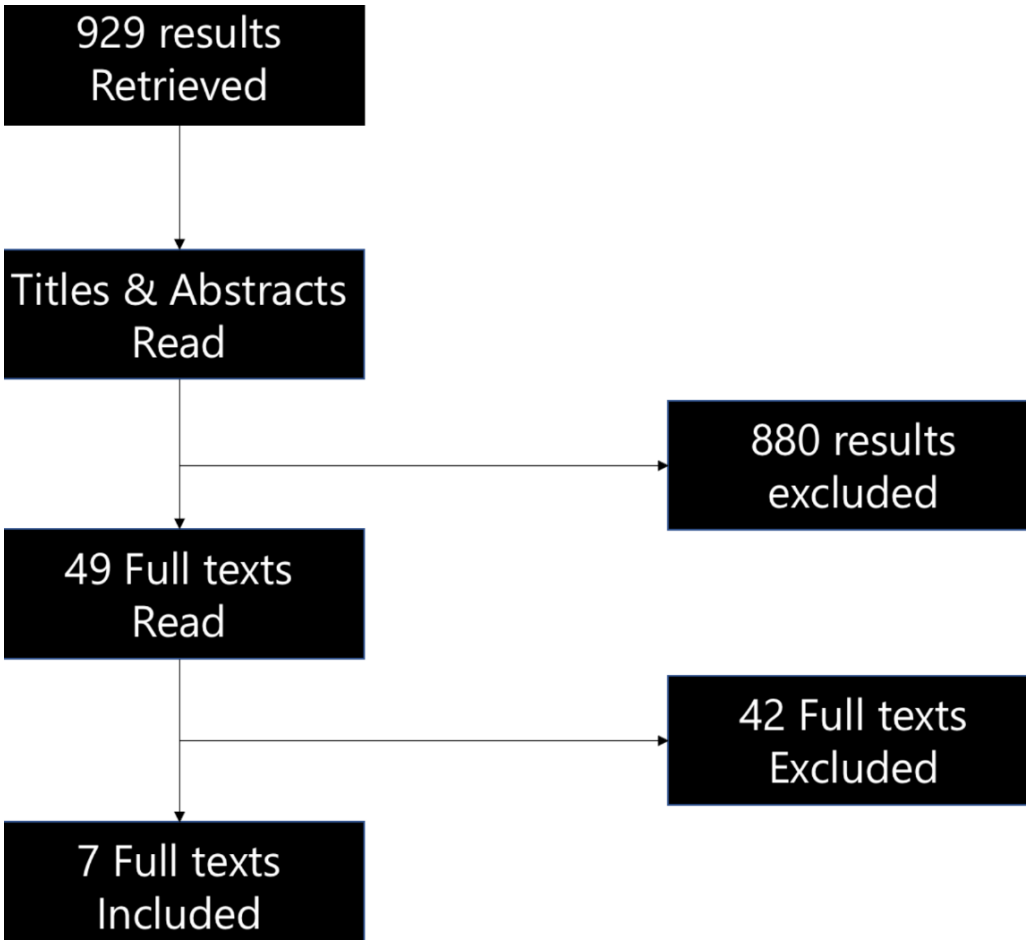

Figure 1. Search flow diagram.
Source: Author

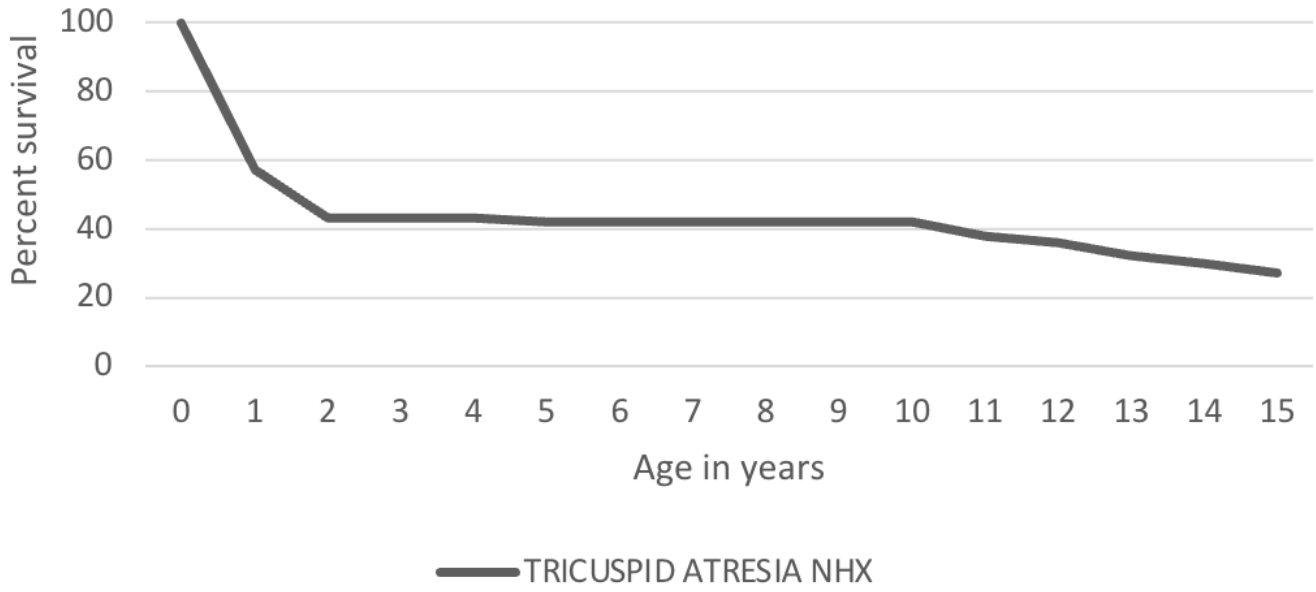

Figure 2. TA natural history.
Source: Author

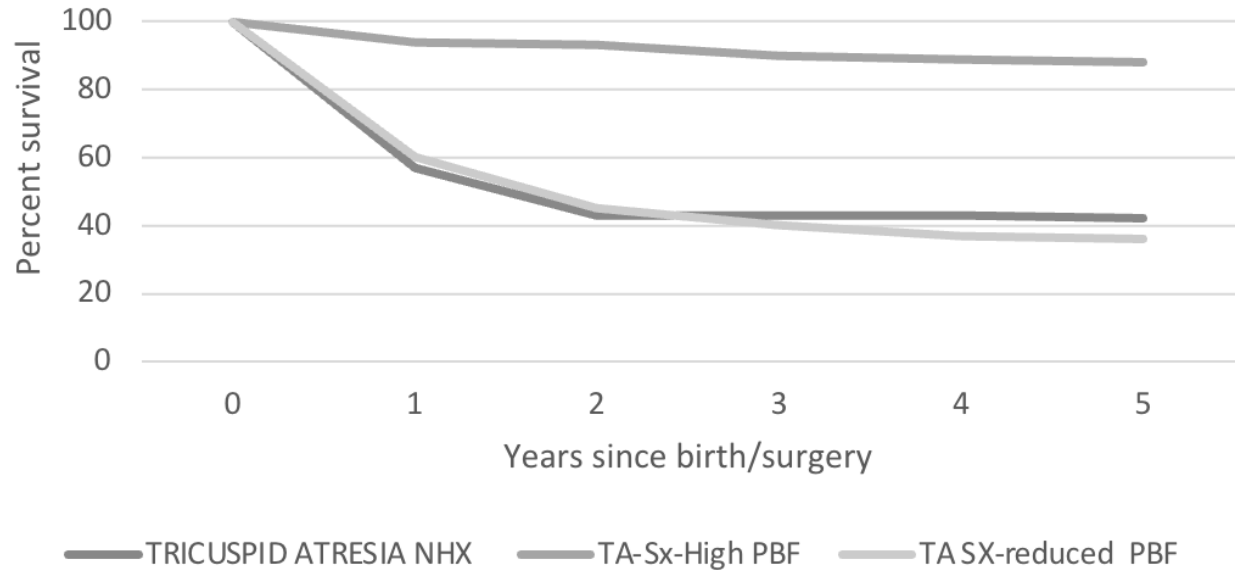

Figure 3. TA-NHx vs Sx outcome related to type of PBF
Source: Author

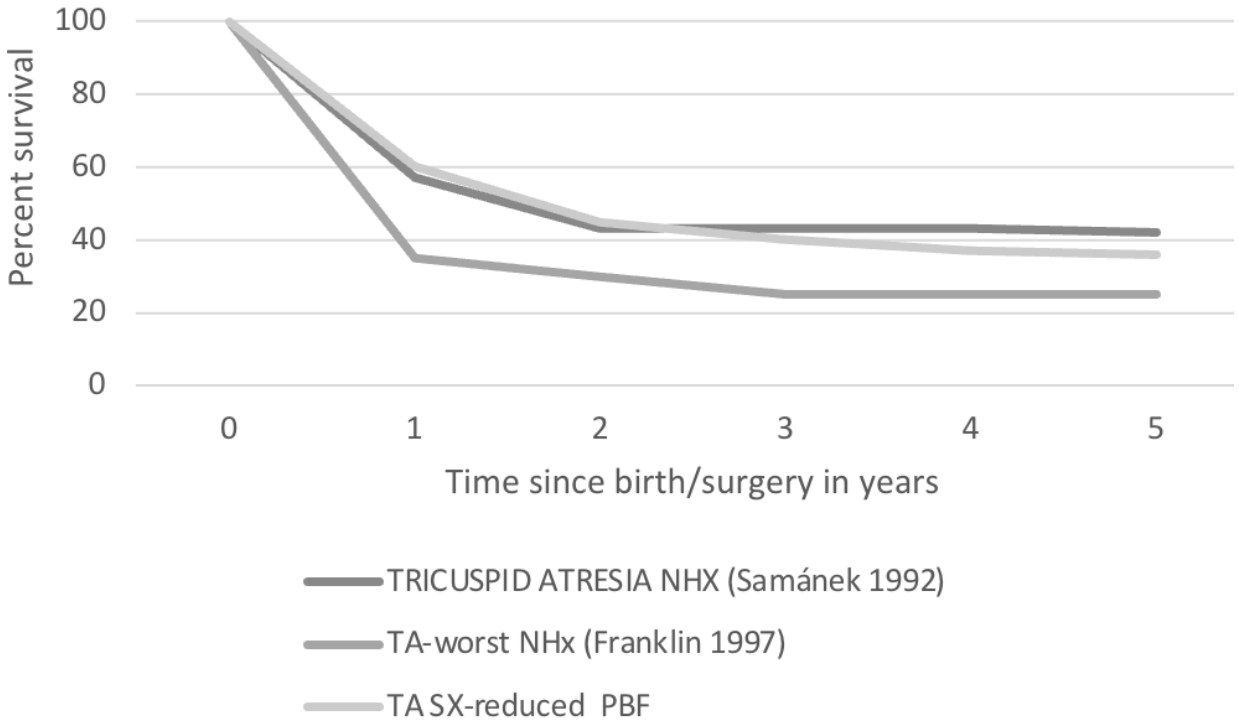

Figure 4. TA-Nhx vs worst NHx vs Sx with reduced PBF
Source: Author

Fontan Era
2. The Median age at the time presentation was 16 days (range; 1-362)
3. Ages at presentations:
4. < than 2 weeks of age; 99 patients (42%)
5. 2 weeks to 2 months of age; 60 patients (25%)

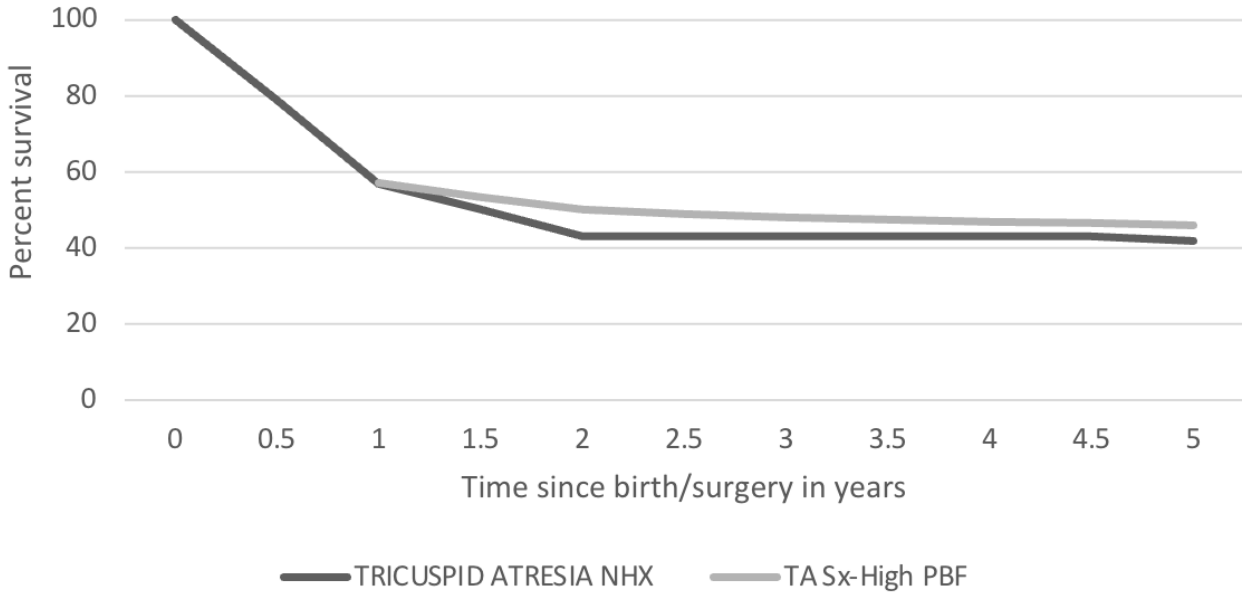

Figure 5. TA- composite graph-cut off for surgery
Source: Author

6. > greater than 2 months of age; 78 patients (33%)
7. Blood flow categories:
8. Reduced pulmonary blood flow; 139 patients (59%).
9. High pulmonary blood flow; 75 patients (32%)
10. Balanced pulmonary blood flow; 23 patients (9%).
11. Types of palliative surgery:
12. SAPAS; 128 patients (median age, 0.7 months)
13. PA banding; 28 patients (median age, 3.8 months)
14. SCPAS; 8 patients (median age, 8.1 months)
15. Fontan completion; 72 patients (median age 53.1 months)

DISCUSSION

There are fundamentally two ways to determine the natural history of a disease: follow-up a cohort of patients to determine when and how they die; and perform autopsies on patients with a specific disease to determine when and how they died. Although we conducted and exhaustive search of the literature, we identified one study that was suitable for generating the natural history portion of our composite graph. The authors of this study followed 946 patients with congenital heart disease (CHD) over a period of 27 years (Samánek, 1992). The study took place in Central Bohemia under circumstances that may not be reproducible: diagnosis, treatment (only medical treatment was available) and follow-up occurred at a single institution; very few patients were sent abroad for surgery and autopsies were mandatory. We used the data from this study for the natural history portion of our composite graph. There were 14 patients with TA in this study (Samánek et al., 1988; Samánek, 1992). The 15 year natural history mortality was 73% (+/- 15%; 80% confidence interval).

Only three studies followed-up more than 123 patients for at least 2 years after surgery; Franklin et al.(1993) were the only group to consider how pulmonary blood flow (PBF) affected surgical outcome. In this study, cardiac catheterisation and chest radiography were used to classify PBF at presentation. They examined the second largest cohort of patients and did so during an era when the modern concepts for medical and surgical management of TA had been established. We considered this study to be the most externally valid and used it to create the surgical outcome portion our composite graphs. A meta-analysis of randomised clinical trials (RCT's) or observational studies is considered to be the best way to review scientific literature. Our search did not yield any RCT's and the observational studies we did retrieve did not yield appropriate data for a meta-analysis or receiver-operator curve analysis. Figure 3 demonstrates that the SO was significantly worse for patients with TA and reduced pulmonary blood flow. Although not shown in Figure 3, the SO for patients with balanced circulation was slightly better than that for patients with increased pulmonary blood flow (Franklin et al., 1993). Pulmonary blood flow (PBF) was determined at presentation by cardiac catheterisation (Franklin et al., 1993) and described as the ratio of pulmonary to systemic blood flow (Qp:Qs): >1.5:1(high flow); <1:1(low flow); and 1:1 to 1.5:1(balanced flow).

Clinical evaluation in combination with chest radiography was also used to determine the type of PBF

in Franklin's report (Franklin et al., 1993). One pragmatic method used to classify PBF has been described by Magoon et al. (2020): an arterial oxygen saturation of less than 75% is designated as RPBF; arterial oxygen saturation between 75 to 85% is designated as balanced PBF; arterial oxygen saturation and greater than 85% PBF; designated as increased PBF. Figure 3, demonstrates that the surgical survival for patients with TA with reduced BPF is essentially the same as the natural history survival. However, to truly appreciate any difference in survival the following must be considered:

1. The natural history curve describes the survival of a heterogenous group of patients; about half of which do not have RPBF (Franklin, 1997).
2. Patients who do not have RPBF, will improve the natural history survival curve for TA as a whole.

To see the actual difference in outcomes, one should compare the SO in patients with RPBF with the natural history survival of patients with RPBF. Our search did not yield any studies that directly made such a comparison. However, we were able to pragmatically compare outcomes in these patients by using the following argument:

1. Systemic ventricular outflow tract obstruction and/or aortic arch obstruction are factors that have been shown to adversely affect SO (Franklin et al. 1993; Franklin, 1997).
2. The combination of reduced pulmonary blood flow and obstruction to systemic circulation has been shown to lead to the worst SO (Franklin, 1997). There is evidence that the SO in this subset of patients is no better than the natural history of this subset of patients (Franklin, 1997).
3. Figure 4 shows two natural history survival curves: the actual natural history curve for TA and the worst possible natural history survival curve (patients with both reduced pulmonary blood flow and obstruction to the systemic circulation).

Figure 4 also shows the surgical survival curve for patients with reduced pulmonary blood flow (Franklin et al. 1993). At 5 years post-surgery, this curve essentially lies between the actual natural history curve and the worst possible natural history curve. It would be reasonable to assume that the natural history survival curve for patients with only reduced pulmonary blood flow would lie between the actual natural history curve and the worst possible natural history curve. This implies that the 5-year surgical survival for patients with reduced pulmonary blood flow may essentially be the same as the natural history survival for patients with reduced pulmonary blood flow. This implies that palliative cardiac surgery for patients with TA and RBPF may not significantly improve survival compared to the natural history. This is a significant implication and it is also counterintuitive as this subset of patients should, in principle, benefit most from palliative cardiac surgery; particularly a SAPAS. The natural history curve for TA is essentially horizontal from 2 years of age; it remains horizontal up to 15 years of age. This suggests that once an infant has survived the first 2 years of life, they will survive the next 13 years. Although robust natural history survival data beyond 15 years of age does not exist, there are several reports of un-operated patients surviving beyond the 4th the decade (Table 5). Taken together, these two facts suggest that once a patient has survived beyond the first two years of life, it would be reasonable to expect them to survive to the 4th decade of life. If this is so, offering palliative cardiac surgery to patients who present for the first time after 2 years of age may not offer a survival advantage. In actual fact, figure 5 demonstrates that the surgical survival is essentially the same as the natural history survival when palliative cardiac surgery is performed on patients who present for the first time after one year of age. This knowledge critically affects surgical decision making in developing countries where the diagnosis of congenital heart disease is often confirmed after 1 year of age (Awori et al., 2007).

One might argue that the natural history should be compared with the Fontan surgical outcome. However, based on the best available natural history data (Samánek, 1992), about 25% of patients with TA will have died before 3 months of age. The surgical outcome of BT shunting in these patients has traditionally be considered as one homogenous group; irrespective of the volume of pulmonary blood flow. Considered as one homogenous group, BT shunting has improved the survival of these patients. However, we noticed that BT shunting in patients with TA and RPBF resulted in high operative mortalities. We wanted to be sure that we were offering these patients a survival advantage over the natural history. We isolated this subset from the literature and compared their surgical survival with the natural history. We found that BT shunting offered no survival advantage in this subset of patients (TA with RPBF). Comparing the surgical outcome of BT shunting in this subset of patients with the natural history is the only way to actually determine if surgery offers a survival advantage. To our knowledge this has never been reported in the literature before. Our findings have important implications: firstly we probably should not offer BT shunts to this subset of patients. Secondly, even if a patient from this subset survives without surgery to 4 months of age; they are very unlikely to be good Fontan candidates as they are likely to always have hypoplastic pulmonary arterial trees. Although a significant proportion of the cardiac surgical community think that shunting causes 'catch-up' growth of the pulmonary arterial tree, the evidence for this in the literature is equivocal (Godart et al., 1998). For these reasons we think that patients with TA and RPBF would not benefit from surgical intervention and probably should not be offered any

cardiac surgery.

It is not unusual for a surgeon to be asked to perform an urgent BT shunt on a patient who presents for the first time after one week of life and with a diagnosis of a 'closing' ductus. These patients are often very cyanosed and have significant metabolic acidosis; the operative mortality is high. Nonetheless, the surgical team is often encouraged to proceed with surgery because surgery may be the 'only chance' at survival that the patient has. As there is evidence that Prostaglandin (PGE_1) increases pulmonary blood flow in cyanotic patients with ductus dependent pulmonary blood flow (Freed et al., 1981); these patients are often started on prostaglandin infusions at presentation. An examination of available evidence reveals the following:

1. There is evidence that PGE_1 is unlikely to be effective at opening a closed ductus if administered after after 4 days of life (Freed et al., 1981).
2. A large natural history study on PDA's found that 96% of PDAs close by 7 days of life and the percentage-patency curve is essentially horizontal by this age. This implies that the remaining PDAs are very unlikely to close beyond 7 days of life (Nagasawa et al., 2016).

Taken together, these two facts suggest that the actual interval where an 'urgent' SAPAS would be indicated for a 'closing PDA' would only be day 5 to day 7 of life. Where prostaglandin has been commenced prior to 5 days of age, and the patient currently has a SPO_2 of >75%, a SAPAS is indicated. This is because there is no safe way of knowing whether the patients reasonable saturations are because the ductus is being kept open by the prostaglandin; the PDA may close when PGE_1 is stopped (Lewis, 1978). A limitation of our study is the lack of data to facilitate a direct comparison of the natural history survival and the SO of patients with TA and reduced PBF; however we do not think this has significantly affected our results. We did not examine whether palliative cardiac surgery in patients with TA and RPBF improves patient symptoms. This should be the subject of future work.

Conclusion

The results of the study suggest the following: SAPAS probably should not be offered to patients with TA and RPBF; and palliative cardiac surgery probably should not be offered to any patient with TA who present for the first time after the age of 1 year. These results should provide a rational basis for surgical decision making in patients with TA.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

REFERENCES

Awori MN, Ogendo SW, Gitome SW, Ong'uti SK, Obonyo NG (2007). Management pathway for congenital heart disease at Kenyatta National Hospital, Nairobi. East African Medical Journal 84(7):312-317.

Awori MN, Awori JA, Makkoukdji N, Takow S (2022). Use of a composite survival curve to optimise the surgical strategy for repair of transposition of the great arteries. African Annals of Thoracic and Cardiovascular Surgery 14(2):14-22.

Beaver TR, Shroyer KR, Muro-Cacho CA, Miller GJ, Blount SG (1988). Survival to age 65 years with tricuspid and pulmonic valve atresia. American Journal of Cardiology 62(1):165-166.

Breisch EA, Wilson DB, Laurenson RD, Mazur JH, Bloor CM (1983). Tricuspid atresia (type Ia): survival to 21 years of age. American Heart Journal 106(1): 149-151.

Campbell M (1972). Natural history of cyanotic malformations and comparison of all common cardiac malformations. British Heart Journal 34(1):3-8.

Fesslova V, Hunter S, Stark J, Taylor JF (1989). Long-term clinical outcome of patients with tricuspid atresia. I. "Natural history". Journal of Cardiovascular Surgery 30(2):262-272.

Fontan F, Baudet E (1971). Surgical repair of tricuspid atresia. Thorax 26(3):240-248.

Franklin RC, Spiegelhalter DJ, Sullivan ID, Anderson RH, Thoele DG, Shinebourne EA, Deanfield JE (1993). Tricuspid atresia presenting in infancy. Survival and suitability for the Fontan operation. Circulation 87(2):427-439.

Franklin RCG (1997). The fate, survival and suitability for definitive surgery of infants with double inlet ventricle and tricuspid atresia. Doctoral thesis (Ph.D.), University College London (United Kingdom).

Freed MD, Heymann MA, Lewis AB, Roehl SL, Kensey RC (1981). Prostaglandin E1 infants with ductus arteriosus-dependent congenital heart disease. Circulation 64(5):899-905.

Gerlis LM, Mayet J, Somerville J (1998). A complex variant of tricuspid atresia: survival to 60 years without surgery. Cardiology in the Young 8(2):275-280.

Godart F, Qureshi SA, Simha A, Deverall PB, Anderson DR, Baker EJ (1998). Effects of modified and classic Blalock-Taussig shunts on the pulmonary arterial tree. The Annals of Thoracic Surgery 66(2):512-517.

Hadjicosta E, Franklin R, Seale A, Stumper O, Tsang V, Anderson DR, Pagel C, Crowe S, Espuny Pujol F, Ridout D, Brown KL (2021). Cohort study of intervened functionally univentricular heart in England and Wales (2000-2018). Heart 108(13):1046-1054.

Hart AS, Vacek JL (1984). Prolonged survival in tricuspid atresia with Eisenmenger's physiology. Clinical Cardiology 7(10):555-556.

Jordan JC, Sanders CA (1966). Tricuspid atresia with prolonged survival. A report of two cases with a review of the world literature. The American Journal of Cardiology 18(1):112-119.

Karamlou T, Ashburn DA, Caldarone CA, Blackstone EH, Jonas RA, Jacobs ML, Williams WG, Ungerleider RM, McCrindle BW (2005). Matching procedure to morphology improves outcomes in neonates with tricuspid atresia. Journal of Thoracic and Cardiovascular Surgery 130(6):1503-1510.

Koizumi S, Matsuo K, Kabasawa M (2019). Aortic root replacement in a patient with un-operated tricuspid atresia. Cardiology in the Young 29(9):1211-1213.

Lewis AB, Lurie PR (1978). Prolonged prostaglandin E_1 infusion in an infant with cyanotic congenital heart disease. Pediatrics 61:534-536.

Magoon R, Makhija N, Jangid SK (2020). Balancing a single-ventricle circulation: 'physiology to therapy'. Indian Journal of Thoracic and Cardiovascular Surgery 36(2):159-162.

McKinney ZJ, Alley EM, Weinhaus AJ (2017). Remarkable case of uncorrected type IC tricuspid atresia with adaptive pulmonary trunk dilatation to allow prolonged survival: Case report and CT fly-through. Translational Research in Anatomy 7:5-11.

Measures of Prognosis (2021). Available at http://ocw.jhsph.edu/courses/fundepi/pdfs/Lecture9.pdf. Accessed June 9 2021.

Nagasawa H, Hamada C, Wakabayashi M, Nakagawa Y, Nomura S,

Kohno Y (2016). Time to spontaneous ductus arteriosus closure in full-term neonates. Open Heart 3(1):e000413.
Patel MM, Overy DC, Kozonis MC, Hadley-Fowlkes LL (1987). Long-term survival in tricuspid atresia. Journal of the American College of Cardiology 9(2):338-340.
Polit DF, Beck CT (2010). Generalization in quantitative and qualitative research: Myths and strategies. International Journal of Nursing Studies 47(11):1451-1458.
Pundi KN, Johnson JN, Dearani JA (2015). 40-Year Follow-Up After the Fontan Operation: Long-Term Outcomes of 1,052 Patients. Journal of the American College of Cardiology 66(15):1700-1710.
Samánek M, Benesová D, Goetzová J, Hrycejová I (1988). Distribution of age at death in children with congenital heart disease who died before the age of 15. British Heart Journal 59(5):581-585.
Samánek M (1992). Children with congenital heart disease: probability of natural survival. Pediatric Cardiology 13(3):152-158.
Sample size calculator. Available at https://www.calculator.net/sample-size-calculator.html. Accessed February 9 2022.
Sittiwangkul R, Azakie A, Van Arsdell GS, Williams WG, McCrindle BW (2004). Outcomes of tricuspid atresia in the Fontan era. Annals of Thoracic Surgery 77(3):889-894.
Voci G, Diego JN, Shafia H, Alavi M, Ghusson M, Banka VS (1987). Type Ia tricuspid atresia with extensive coronary artery abnormalities in a living 22 year old woman. Journal of the American College of Cardiology 10(5):1100-1104.