Research Article

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Use of a Composite Survival Curve to Optimise the Surgical Strategy for Double Inlet Left Ventricle

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ABSTRACT

Objectives: *Palliative surgery has improved the long-term survival of patients with Double inlet left ventricle (DILV). Neonates and infants with DILV presenting with reduced pulmonary blood flow (RPBF) are often offered a systemic arterial-to- pulmonary artery shunt (SAPAS). There is evidence that SAPAS in these patients, may not improve survival compared to the natural history. An objective assessment of the efficacy of a treatment requires a comparison of the treatment outcome with the natural history. Our aim was to review the literature to determine whether SAPASs in patients with DILV and RPBF improves survival compare to the natural history.*

Methods: *We reviewed the literature and used the most externally valid data to create a composite survival curve that facilitates the comparison of surgical outcome and natural history.*

Results: *The data suggests that SAPASs in patient with DILV and RBPF, may not improve long term survival compared to the natural history. There is also evidence that palliative surgery in general in patients older than 1 year of age with increased or balanced pulmonary blood flow may not improve survival compared to the natural history.*

Conclusions: *SAPASs probably should not be offered to patients with DILV and RPBF. In addition, cardiac surgery probably should not be offered to patients with DILV presenting for the first time after 1 year of age.*

Keywords
Double inlet ventricle surgery.

Introduction
With respect to double inlet left ventricle (DILV), palliative cardiac surgery refers to the following procedures: pulmonary artery banding, systemic arterial-to-pulmonary arterial shunts (SAPAS), and systemic venous- to-pulmonary artery shunts [1].

Systemic venous-to-pulmonary artery shunts include the 'Fontan circulation' [2]. The introduction of palliative cardiac surgery has improved the long-term survival of patients with DILV [1,3]. Neonates and infants presenting with reduced pulmonary blood flow (RPBF) are often offered SAPASs; there is evidence that surgical outcomes in this subset of patients are worse than in patients with balanced or increased pulmonary blood flows [1]. An objective assessment of the efficacy of a treatment requires a comparison of the treatment outcome with the natural history.

We reviewed the literature and used the most externally valid data to create a composite survival curve that facilitates the comparison of surgical outcome and natural history [4]. A pilot study suggested that there would be insufficient data to conduct a credible meta-analysis or receiver operator curve analysis; for this reason we used the 'Proximal Similarity Model' (PSM) to determine which natural history and surgical outcomes studies had the greatest external validity [4]. As the observed survival from a natural history curve is an estimate of the probability of survival, it can be directly compared with the postoperative Kaplan-Meier survival curves [5].

We used the most externally valid studies to generate a composite survival curve. This curve graphically demonstrates the surgical survival benefit as a function of pulmonary blood flow and patient age.

Patients and Methods

The Proximal Similarity Model

According to this model, there are essentially 3 major threats to external validity; these relate to the study subjects, the study location and the study time. The proximal similarity model is used to establish which study best represents the population of interest (i.e. which study has the greatest external validity). Table 1. Shows which parameters were utilised to decide which study had the greatest external validity with respects to natural history and surgical outcome studies.

Table 1: Proximal similarity model parameters.

Area of threat to External validity	NH studies: parameters used to assess the validity	SO studies: parameters used to assess the validity
1. **Subjects**	DILV; LSS	DILV; LSS; AAS
2. **Geography**	Anywhere	Multicenter
3. **Time**	Any time	Paper published after the year 1990

Abbreviations: AAS: Age At Surgery; DILV: Double Inlet Left Ventricle; LSS: Large Sample Size; NH: Natural History; SO: Surgical Outcome.

The following factors were considered when choosing which papers were to be used in the construction the surgical outcome curves:

- Study sample size.
- Median age at SAPAS
- Assessment of pulmonary blood flow
- Paper was published 10 years after the introduction of the Fontan circulation (This was to ensure that enough time had elapsed for broad adoption of the technique).

Search strategy and selection criteria

PUBMED and Google Scholar were systematically searched; the time frame for the search was January 1st 1966 to November 30th 2021. The search terms and search strategy are shown in Table 2. PUBMED searches utilised the "title/abstract" option and Google scholar searches utilised the "all in title" option; all search terms were combined with "AND". Titles and abstracts were reviewed and full-text articles were examined when the abstract suggested that there was a possibility that data pertaining to natural history or long-term surgical outcomes could be present. Non- English language studies and non-human studies were also excluded. A recent large study by Hadjicosta [6] reported a 10 year mortality rate of 12% and the survival curve had almost flattened by 2 years of follow-up. To detect this level of morality with a 85 % confidence level, a study would have to have followed-up at least 88 patients to 10 years. In view the fact that the survival curve had almost flattened out at 2 years post follow-up, we only considered surgical outcome studies that followed at least 88 patients to 2 years post-operatively. This sample size 'cut-off' was determined using a free online sample size calculator [7]. The search flow is shown in figure 1.

Table 2: Search strategy.

Search number and terms
1. Double, inlet, left, ventricle, natural, history (GS,P)
2. Double, inlet, left, ventricle, survival (GS,P)
3. Double, inlet, left, ventricle, long, term, survival (GS,P)
4. Double, inlet, left, ventricle, unoperated (GS, P)
5. Natural, history, cardiac, malformations (GS,P)
6. Congenital, heart, disease, natural, survival (GS,P)
7. Double, inlet, left, ventricle, long, term, results (GS,P)
8. Double, inlet, ventricle (GS)
9. Fontan, long, term, outcome (GS)
10. Bidirectional, cavopulmonary, Double, inlet, left, ventricle (P)
11. Cavopulmonary, Double, inlet, left, ventricle (GS)
12. Glenn, Double, inlet, left, ventricle (GS)

Key: GS = Goggle scholar, P = Pubmed

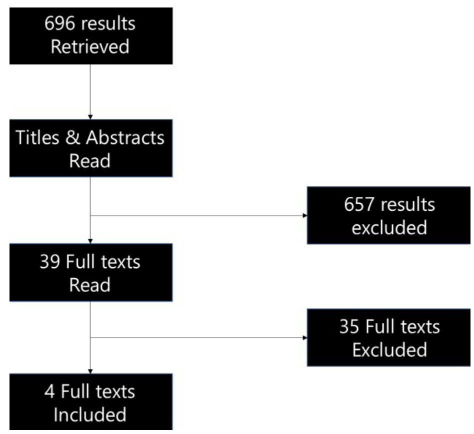

Figure 1: Search flow diagram.

Creation of the composite graph

The most externally valid natural history data (essentially the paper with the largest sample size of patients followed from birth till death) was used to create a natural history curve. We then examined the postoperative survival data of relevant retrieved full-texts. The most externally valid studies were used to generate the composite graphs. A paper on surgical outcome was considered to have the greatest external validity if it had all 3 of the following factors:

- The largest sample sizes
- The lowest median age at the time the SAPAS was performed.
- The paper was published after 1981 (10 years after the introduction of the Fontan circulation; this ensured adequate time for the procedure to be broadly adopted)

The chosen surgical outcome curves were then superimposed on the natural history curve.

Results

The search yielded 696 results; 39 relevant full-texts were obtained after examining titles and abstracts. Sixteen full-texts related to the natural history of DILV and 23 related to the surgical outcome. The references of these full texts were examined for additional relevant publications. The important details of the studies included for consideration when developing the postoperative survival branch of the composite survival curves are shown in table 3. A list of excluded full texts that may have followed-up enough patients for 10 years, but survival data could not be determined from the texts, is shown in table 4. A list of the retrieved natural history full texts is included in table 5. The natural history curve for DILV is shown in figure 2; composite graphs are shown in figures 3 and 4.

Table 3: Surgical outcome full-texts included.

Authors	YOES	TN	AOVPBF	10 YS(%)
Franken et al. [8]	-	152	No	93
Tham et al. [9]	1990	145	No	76
Franklin et al. [10]	1973	191	Yes	42

Key: AOVPBF: Assessed Outcome Versus Pulmonary Blood Flow; TN: Total Number of Patients; YOES: Year of Earliest Surgery; YS: Year Survival.

Table 4: Surgical outcome full texts excluded but may havefollowed up enough patients postoperatively to 10 years.

Study	Study Year	Number of patients
1. Hadjicosta et al. [6]	2021	327

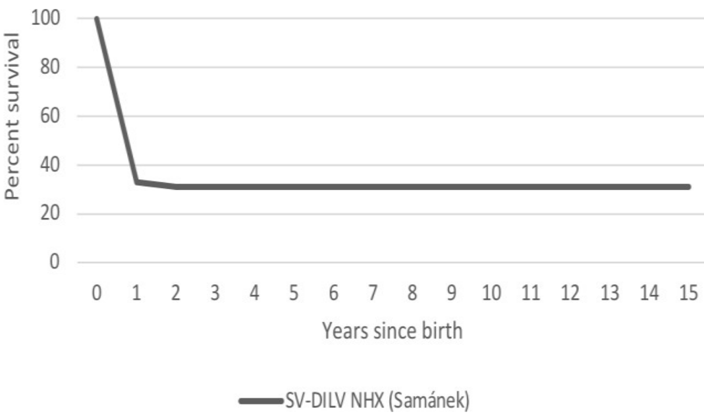

Figure 2: Natural history curve for Double inlet left Ventricle (DILV).
NHx= Natural History.

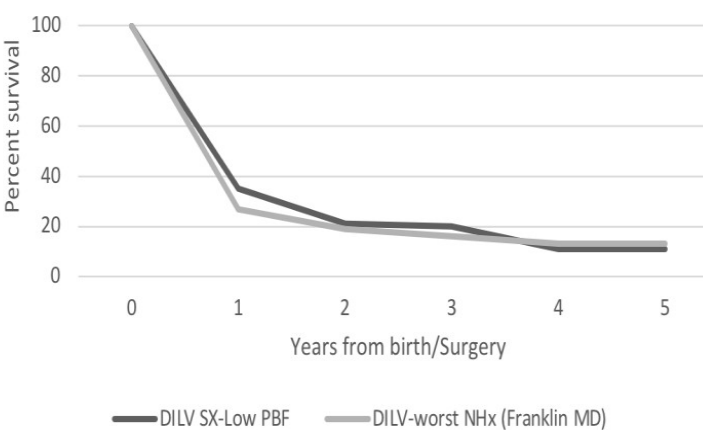

Figure 3: Comparative NHx composite graph DILV.
NH=Natural History, PBF=pulmonary blood flow; Sx= Surgery.

Discussion

Two methods are used to determine the natural history of a disease:

- Follow-up a group of live patients to determine when patients die.
- Perform an autopsy study on a group of patients thought to have died from the disease to determine the age pattern at the time of death.

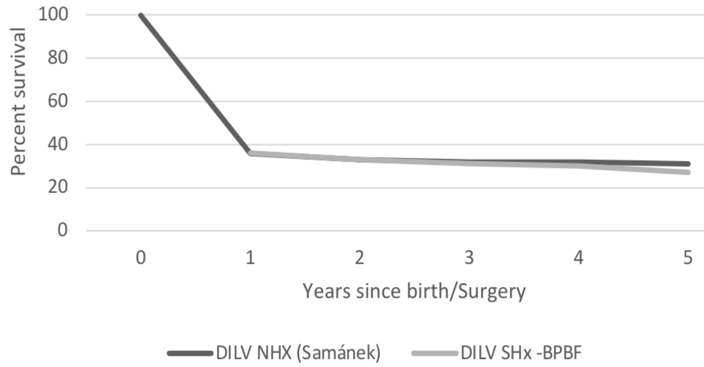

Figure 4: The composite graph: age 'cut-off' for surgery.
NH=Natural History, BPBF= balanced pulmonary blood flow; Sx= Surgery.

Despite an extensive search, only one study was found that could potentially be used to generate our natural history curve. This study followed 946 patients with congenital heart disease (CHD) over 27 years [3]. This study was conducted in Central Bohemia under circumstances that may not occur again: at the time of the study, all patients with congenital heart disease were managed at one institution. Minimal surgery was performed locally and patients did not travel out of the country for surgery. Patient follow-up was rigorous and post-mortems in all children were mandatory. Together, these factors provided an ideal opportunity to study the natural history of CHD. We used the data from this study to develop our natural history curve for the first 15 years of life. There were 32 patients with DILV in this study [3,24]. The 15-year natural history mortality was 69% (+/- 11.77%; 85% confidence interval).

Only 3 surgical outcome studies included more than 88 patients at 2 years of follow- up; Franklin et al were the only group to consider how pulmonary blood flow affects surgical outcome [10]. They examined the third largest cohort of patients in the papers we retrieved and did so during an era when the treatment of DILV by shunts or pulmonary artery (PA) banding was already established. They also gave the actual number of patients at various durations of flow-up. For these reasons we considered this study to be the most externally valid and we used it to create our composite graphs. Franklin published additional data in his MD thesis [1]; specifically, he published a natural history survival curve for a subset of DILV patients with a particularly poor prognosis. This was the only data of this kind that we retrieved from our search. We used it to create our composite curve in figure 3.

Table 5: Natural history full texts retrieved.

Author	Study Year	Study type	Max age*of patient(s)	SpO2 (%)	Status
1. Salame-Waxman et al. [11]	2019	Case report	28	80	Alive
2. Alpat et al. [12]	2018	Case report	45	85	Alive
3. Herbert et al. [13]	2017	Case report	54	77	Alive
4. Agrawal et al. [14]	2017	Case report	41	-	Alive
5. Brida et al. [15]	2016	Case report	21	-	Alive
6. Poterucha et al. [16]	2016	Descriptive cohort	77	82(median)	Alive
7. Park et al. [17]	2007	Case report	41	86.9	Alive
8. Kaya et al. [18]	2007	Case report	34	-	Alive
9. Book et al. [19]	2007	Case report	71	75	Alive
10. Restaino et al. [20]	2004	Case report	57	-	Alive
11. Hager et al. [21]	2002	Case report	62	88	Alive
12. Ammash et al. [22]	1996	Descriptive cohort	66	-	Alive
13. Vitarelli et al. [23]	1996	Case report	59	78	Alive
14. Samanek et al. [3]	1992	Descriptive cohort	15	-	Alive

Key: * years.

A meta-analysis of randomized clinical trials (RCT's) or observational studies is the preferred method of reviewing scientific literature. Our search did not yield any RCT's and the observational studies found had insufficient data for a meta-analysis or receiver-operator curve analysis. We chose the PSM technique to assess bias and confounding. The most externally valid studies where then used to create the composite curves. Although Franklin [10] categorized the degree of pulmonary blood flow using cardiac catheterization and chest radiographs, the degree of pulmonary blood flow (PBF) may be pragmatically defined as follows [25]:

- Reduced PBF: arterial oxygen saturation of less than 75%
- Balanced PBF: arterial oxygen saturation between 75% to 85%
- Increased PBF: arterial oxygen saturation and greater than 85% PBF.

According to figure 3, the surgical survival for patients with DILV and RPBF is essentially the same as the worst possible natural history survival. This 'worst possible natural history' curve was derived from survival data from a subset of patients with DILV and multiple risk factors for poor surgical outcomes: there is evidence that RPBF, systemic outflow obstruction and aortic obstruction are risk factors for poor outcome. Franklin examined the natural history of a subset of patiens with a combination of these factors [1]. As expected, they had particularly poor outcomes; these results were used to produce the worst possible natural history curve in figure 3. Figure 3 demonstrates that surgery in patients with DILV and RPBF may not significantly improve survival compared to the natural history. This is a significant and counterintuitive point as this is the subset of patients one would assume could benefit most from a SAPAS.

The actual natural history curve for DILV is flat from 1 year of age and remains flat up to 15 years of age [3]. This implies that once an infant has survived to 1 year of age, they should survive to 15 years of age. Although we do not have adequate natural history survival data beyond 15 years of age, we retrieved several reports of unoperated patients living beyond the 4th the decade of life (table 5). Considered together, the flat natural history survival curve beyond 1 year of age and the reports of unoperated patients surviving beyond the 4th decade of life, imply that there is a possibility that once a patient survives to 1 year of age they should survive beyond the 4th decade of life. If this is the case, surgery beyond 1 year of age may not improve survival compared to the natural history. To develop this argument, consider that the composite graph in figure 4 demonstrates that the surgical survival curve is essentially the same as the natural history curve when surgery is performed on patients after 1 year of age. This evidence suggests that offering cardiac surgery to any patient with DILV who presents for the first time after one year of age may not improve 15 year survival compare to the natural history. This has important implications with respects to surgical decision making in developing countries where the diagnosis of congenital heart disease is often confirmed after one year of age [26].

Prostaglandin (PGE1) has been shown to increase pulmonary blood flow in cyanotic patients with ductus dependent pulmonary blood flow [27]. PGE1 is unlikely to be effective if given after after 4 days of age [27]. The use of PGE1 was well established during the era that the data used to construct the composite graph was obtained; the median age at presentation of these patients was 1 day [1]. It is reasonable to assume that patients who had an increase in SPO2 from < 75% to 75% or greater, were not considered to be in the category of "reduced pulmonary blood flow". In this regard, palliative surgery would be indicated in these patients. There are reports of patients who present with features of reduced pulmonary blood flow and are diagnosed as having a 'closing' persistent ducts; an emergency SAPAS is usually offered to these patients. A large natural history study found that 96% of persistent ducti have closed by 7 days of age; the percentage-patency curve has essentially flattened by this age, implying that the remaining ducti are unlikely to close beyond this age [28]. When this fact is considered in conjunction with the fact the prostaglandin is only effective during the first 4 days of life, the actual interval where an 'emergency' SAPAS would be indicated would be days 5, 6 and 7 of life. Clearly, where a neonate has been started on PGE1 before the 5th day of life, and currently has a SPO2 of >75%, an urgent

SAPAS should be performed. This should be offered whether the infant showed improvement after starting PGE1 or had a SPO2 of > 75% at the time PGE1 was started. The rational for this is that there is no way of knowing, in the latter case, whether this was an infant whose duct would remain open if PGE1 was stopped.

In conclusion our results suggest the following:
- SAPASs probably should not be offered to patients who have DILV with RPBF.
- Cardiac surgery probably should not be offered to patients with DILV who present for the first time after 1 year of age.
- An 'Emergency SAPAS' for a 'closing PDA' is probably only indicated during the first week of life.

We hope that our results will be used to optimise surgical decision making in patients with DILV.

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