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African Annals of Thoracic and Cardiovascular Surgery

Full Length Research Paper

Use of a composite survival curve to determine the age at which surgery offers the highest survival benefit for Tetralogy of Fallot

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Contemporary surgical practice relating to Tetralogy of Fallot is shifting towards earlier correction; however, a recent large study proposes later correction to increase event free survival. Surgery aims to improve the quantity and quality of life at minimal risk to the patient. Surgical outcome and risk assessment requires a comparison of externally valid studies of natural history and surgical outcome. The authors reviewed the literature to identify the most externally valid natural history and surgical outcome data and used it to develop a composite survival graph to help clinicians determine when surgery would offer the greatest survival advantage. The composite graph suggests that, for symptomatic patients, the greatest survival advantage occurs when corrective surgery is performed within the 1st week of life.

Key words: Pediatric, tetralogy of Fallot, operative, outcomes.

INTRODUCTION

Tetralogy of Fallot (ToF) is a congenital heart malformation characterised by obstruction of the right ventricular out flow tract, a ventricular septal defect, overriding aorta and ventricular hypertrophy; total surgical correction is the gold standard of treatment. A recent large series on correction of ToF concluded that it may be better to delay surgery to after 6 months of age to improve event-free survival (Van den Bosch et al., 2020). This is noteworthy as this conclusion runs contrary to contemporary philosophy regarding timing of repair. Of particular interest, with respect to this work, was the discussion on the timing of surgery as it relates to

outcome: specifically, the authors are concerned that the surgical outcome in relation to the age at surgery was discussed without providing a natural history context. It is impossible to reach a rational conclusion on the timing of surgery without doing so. Cardiac surgery aims to increase the duration of life and/or the quality life. Ideally these should be achieved with minimal risk of morbidity or mortality. A comparison of externally valid natural history and surgical outcome data is required to determine if surgery improves outcome. External validity depends on minimising random error (mostly sampling error), systematic error (bias) and confounding. An

Table 1. Proximal similarity model parameters.

Area of threat to external validity	NH studies: parameters used to assess validity	SO studies: parameters used to assess validity
Subjects	ToF; LSS	ToF; LSS; AAS
Geography	Anywhere	Multi-centre study
Time	Any time	Surgery performed after the year 2000

AAS= age at surgery; LSS=large sample size; NH=natural history; SO=surgical outcome; ToF=Tetralogy of Fallot.

Table 2. Search strategy.

Search number and terms
Tetralogy, Fallot, natural, history(GS,P)
Tetralogy, Fallot, survival(GS,P)
Tetralogy, Fallot, unoperated (GS,P)
Tetralogy, Fallot, long, term, outcome(GS,P)
Tetralogy, Fallot, long, term, results (GS)
Tetralogy, Fallot, long, term, survival (P)
Congenital, heart, disease, natural, history (GS,P)
Congenital, heart, disease, unoperated (GS,P)
Congenital, heart, disease, natural, survival (GS,P)
Natural, history, cardiac, malformations (GS,P)
Life expectancy Tetralogy Fallot(GS,P)

GS = Goggle scholar, P = Pubmed.

adequate study sample size is fundamental to minimising random error; there is evidence that most published studies do not have a sufficient sample size (Ioannidis, 2005). To minimise systematic error and confounding, one must ensure that a study examines the 'right' patients. The 'right' patients' means that the study population should pragmatically resemble the population of interest: demographically, physiologically and in exposure to interventions. ToF presents as a spectrum of deformity severity. The common pathway leading to death is hypoxia. The interplay between the various aspects of anatomical abnormality severity manifests as the demise of the patient at a specific age, the more severe the hypoxia, the earlier the demise.

Advanced age is known to detrimentally affect the surgical outcome of some forms of congenital heart disease (Gan et al., 2014). Accounting for natural and surgical survival in relation to age at surgery is a convenient and effective way to deal with systematic error and confounding and thereby improve external validity. The authors aimed to determine how age at surgery is related to survival benefit in ToF. A pilot study suggested that there would be insufficient data to conduct a credible meta-analysis or to generate receiver operator curves to facilitate this. For this reason we used the 'Proximal Similarity Model' (PSM) to determine which natural history and surgical outcomes studies had the greatest external validity (Polit and Beck, 2010:47).

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 (Measures of prognosis available at http://ocw.jhsph.edu/courses/fundepi/pdfs/Lecture9.pdf. Accessed June 9, 2021). They used the most externally valid studies to generate a composite survival curve. This curve graphically demonstrates the surgical survival benefit as a function of age at the time of surgery.

PATIENTS AND METHODS

The proximal similarity model

According to this model, there are 3 major threats to external validity; these essentially relate to the study subjects, the study location and the study time. The proximal similarity model endeavours to establish which study most closely resembles the population of interest (that is which study has the greatest external validity). In this case the population of interest is patients being considered for surgical correction of Tetralogy of Fallot. Table 1 shows which parameters were used to choose the most externally valid natural history and surgical outcome studies.

Search strategy and selection criteria

Google Scholar and PUBMED were searched systematically until May 25th 2021. Table 2 shows the search terms and strategy. Google scholar searches used the "all in title" option; PUBMED
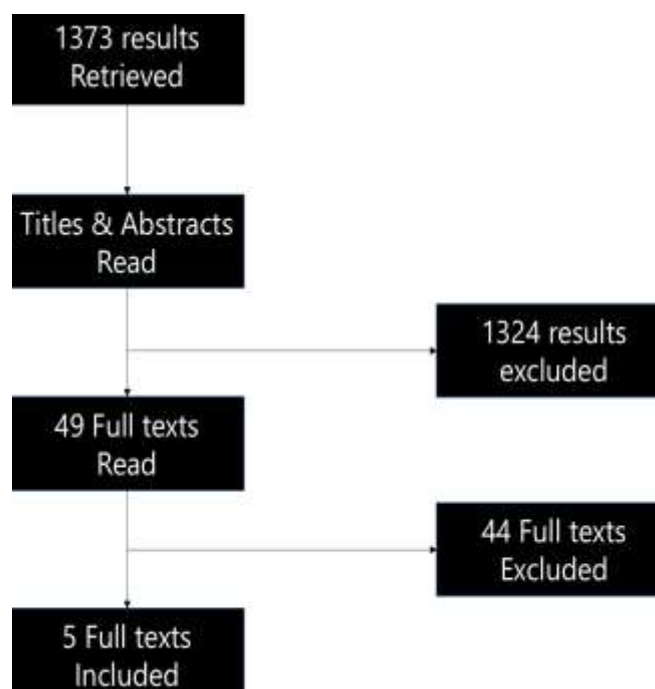
Figure 1. Shows the search flow.

searches used the "title/abstract" option. All search terms were combined with "AND". Titles and abstracts were interrogated and full-text articles were obtained when the abstract indicated that there was a possibility that data pertaining to natural history or surgical outcomes could be present. Studies that included Tetralogy with pulmonary atresia, absent pulmonary valve or compete atrioventricular canal defect were excluded. Non-English language studies and non-human studies were also excluded. After examining the natural history studies retrieved; it was concluded that the most externally valid study followed up patients for 15 years. To optimise the authors' comparison between the natural history and surgical outcome, they only included surgical outcome studies that followed a 'sufficient number' of patients for 15 years after surgery. A study with a 'sufficient number' of patients was defined as any study flowing-up enough patients to give a power of 80% when the surgical outcome was compare with the natural history. The sample size and certainty calculations were performed using the 'Clinicalc' free online interactive study sample size calculator (Sample size calculator. Available at https://www.calculator.net/sample-size-calculator.html. Accessed June 9 2021). The search flow is shown in Figure 1.

Creation of the composite graph

The natural history curve was created using data from the study deemed to have the greatest external validity. To quantify the certainty and the magnitude of the surgical survival benefit as a function of the age at the time of surgery, the most externally valid post-operative survival curves were systematically superimposed on the most externally valid natural history curve at various points along the natural history curve. The ages chosen along the natural history curve at which the superimposed post-operative survival curve started were as follows: 3 days, 3 months and 6 months. These ages were chosen in accordance with prevailing philosophies about the best age for surgery.

RESULTS

The search yielded 1,373 results; 49 relevant full-texts were obtained after examining titles and abstracts. Fourteen full-texts related to the natural history of ToF and 35 related to the surgical outcome of repair of ToF. The references of these full texts were examined for additional relevant references; none were found. Full text references for surgical outcome were excluded if they did not follow-up a sufficient number of patients for 15 years to yield a power of 80%; or if this could not be determined from the data in the full text. The important details of the 3 studies on surgical outcome included (representing 4,491 patients) for consideration when developing the composite survival curve is shown in Table 3. A list of excluded full texts that may have followed-up enough patients for 15 years, but survival data could not be determined from the texts, are shown in Table 4. A list of all the retrieved natural history full texts is included in Table 5. The natural history survival curve based on the most valid data (Samanek, 1992) is shown in Figure 2.

Comment

There are fundamentally 2 methods to determine the natural history of a disease:

1) Follow-up a group of live patients to determine when patients die.
2) 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.

The 1st method would have greater external validity as there remains a possibility that patient with the disease, who are still alive, would never be considered when the 2nd method is used. Despite an extensive search only 2 natural history studies were included. The most externally valid used the 1st method; the authors used it to generate their natural history curve. The study followed 946 patients with congenital heart disease (CHD) over 27 years (Samanek, 1992). It was conducted in Central Bohemia under circumstances that may not occur again. At that time, in Central Bohemia, all congenital heart disease was managed at one institution. Very little surgery was performed locally and patients did not travel abroad for surgery. Patient follow-up was rigorous and post-mortems in children were mandatory. These factors combined to provide 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 1st 15 years of life. The incidence of ToF in this study was 7.2% which implies that about 68 patients with ToF were followed up. From the data, the 15 year mortality was 96% (+/- 4.66%; 95% confidence interval). The natural history curve for ToF is shown in Figure 2. It shows that there is relentless attrition; only 4 % of unoperated patients survive to 15

Table 3. Surgical outcome full-texts included.

Study	Year of study	Era of surgery	N	Age at surgery(years)	Operative mortality (%)	15 year survival (%)	Number of patients followed up to 15 years
Van den Bosch	2020	1970-2012	453	0.7(md)	2	97	244
Smith et al.	2019	1980-2006	3283	0.9(md)	4.1	92	2387
Cuypers et al	2014	1968-1980	144	4.6(md)	-	82	116

Table 4. Surgical outcome full-texts excluded but may have followed up enough patients postoperatively to 15 years.

Study	Year of study	Numbers of patients
D'Udekem et al.	2014	675
Kim et al.	2013	326
Chiu et al.	2012	819
Lindberg et al.	2011	306
Park et al.	2010	734
D'Udekem et al.	2000	191
Nollert	1997	658
John et al.	1993	840

Table 5. Natural history full-texts retrieved.

| Study	Year of study	Numbers of patients	Age of patients (years)
Boyer et al.	2020	Case report	59
Franca et al.	2016	Case report	51
Prakash et al.	2014	Case report	67
Subhawong and Teytelboym	2009	Case report	87
Yokuşoğlu et al.	2008	Case report	68
Fairley et al.	2008	Case report	61
Tanaka et al.	2005	Case report	72
Yang et al.	2005	Case report	73
Makaryus et al.	2004	Case report	52
Fernicola et al.	1993	Case report	74
Samanek	1992	Descriptive cohort	0.02-15
Bertranou et al.	1978	Descriptive cohort	-
Campbell	1972	Descriptive cohort	0-59
Mitchell et al.	1971	Descriptive cohort	0-11

years of age.

The composite graph is shown in Figure 3. Although contemporary operative mortality rates as low as 1.1% has been reported (Jacobs et al., 2018), the authors did not use this figure to create the composite graph. Instead, they used figures from the study by Van den Bosch et al. (2020) for patients under 1 years of age at the time of surgery as we thought it had the greatest external validity for the patients under 1 years of age. In this study the operative mortality was the same in patients operated below 6 months of age and those operated above 6

months of age. We did not find any neonatal studies that followed up an adequate sample size to 15 years postoperatively. However a relatively recent meta-analysis of neonatal ToF repair by Loomba et al. (2017), found that the overall mortality (operative and follow-up) was 6%. We applied the same PSM protocol to the studies included in this meta-analysis and used the most externally valid study (Kolcz and Pizarro, 2005) to generate the composite graph for surgery at age 3 days.

Figure 3 shows the natural history curve for the 1st 12 months of life. It also shows the surgical survival curves
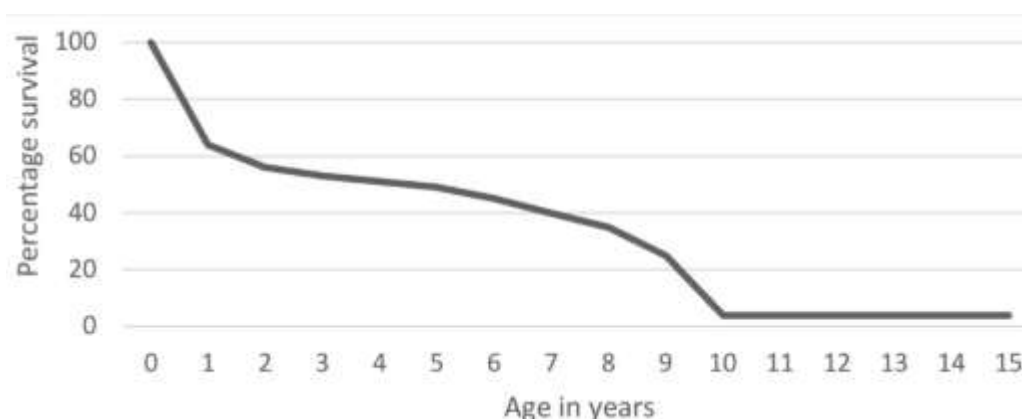
Figure 2. The natural history curve for D-TGA
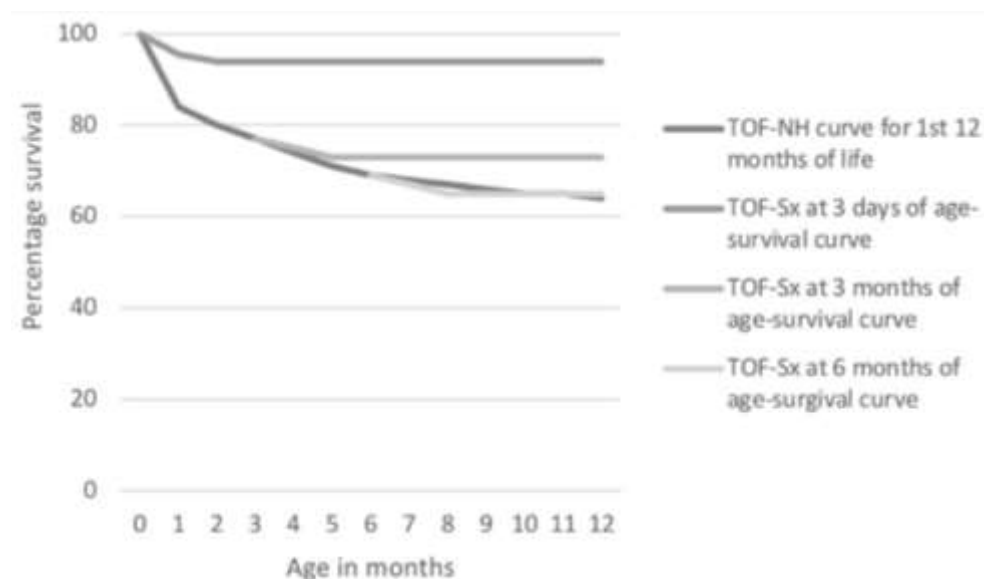
Figure 3. The composite graph

superimposed on the natural history curve when surgery is performed at 3 days of age, 3 months of age and 6 months of age. It is evident that the earlier surgery is performed, the greater the chance of survival.

The recent study by Van den Bosch et al. (2020) suggests that where possible, corrective surgery should be delayed to after 6 months of age; the rationale for this is that it improves event-free survival. In this regard, the key event was re-do surgery to address right ventricular outflow tract obstruction (RVOTO) or pulmonary valve replacement. The natural history curve predicts that 31% of patients with ToF will have died by 6 months of age.

Delaying surgery could result in the death of up to a third of patients. Although it is reasonable to assume that the most cyanosed patients die earlier, there is no data available to predict time of death as a function of the degree of cyanosis. However, the natural history curve may provide some insight into the relationship between cyanosis and death. The curve appears to have 3 sections. The first section shows a rapid demise of about 30% of all patients within months of birth. When this section is expanded to examine the first 12 months alone (Figure 3), it is evident that most of the deaths occur in the first 6 months of life and almost half of these occur in the first month. These early deaths most likely represent patients with duct dependent variants of ToF and are very cyanosed at birth or shortly after birth when the duct begins to close. They could be considered as a relatively homogeneous group for purposes of comparing survival benefits based on age at surgery. The second section occurs from about 1 year to 10 years of age where there is a slower but steady attrition of a further 60% of

Table 6. Comparison of survival advantage of surgery at various ages.

Age at surgery	NPA out of 100	NPA 1 year later	RR(OR)	NOLS
3 days	92	86	0.54(0.46)	12
3 months	77	74	0.77(0.68)	8
6 months	69	66	N/A	N/A

N/A = not applicable; NPA = number of patients alive; NH = natural history; NOLS = number of lives saved from surgery at this age and not next age on composite graph; OR= Odds Ratio; RR = Risk Ratio; Sx = surgery.

patients. This probably represents a group of patient who develop worsening cyanosis as they age. The third section comprises a flat segment from 10 to 15 years of age. This represents 4% of patients and likely comprises ToF variants that have sufficient blood flow to the lungs. They remain alive for years and presumably have the potential to live well into adult life. Table 6 summarises the survival advantage of performing surgery at various ages on the relatively homogenous group in the first section of the natural history curve. It assumes that you start with 100 patients and then quantifies what is shown by the composite graph. Neonatal surgery has a RR and an OR of less than 1 when compared to surgery at 3 months of age. Similarly, surgery at 3 months of age has a RR and an OR of less than 1 when compared to surgery at 6 months of age. This means that surgery at 3 days of age will potentially save more lives than surgery at 3 months of age. Similarly, surgery at 3 months of age will save more lives than surgery at 6 months of age. For each 100 patients with ToF: corrective surgery performed at 3 days of age, instead of 3 months of age, could potentially save 12 lives. Corrective surgery performed at 3 months of age, instead of 6 months of age, could potentially save 8 lives. One could argue that the risk of death for acyanotic patients or patients with mild cyanosis is small. Following this rational it would be reasonable to delay corrective surgery in these patients until 6 months of age to take advantage of the better event-free survival described by Van den Bosch et al. (2020). A counter argument would be that early surgery (before 3 months of age) tends to be performed in patients who are more symptomatic. The worse event free survival described by Van den Bosch et al. (2020) may not be because of early surgery but rather may be as a result of a more severe substrate of the disease. If this is the case, early surgery on mildly cyanosed patients may not result in reduced event-free survival.

The authors think that the available evidence, as summarised by the composite graph (95% confidence interval) suggests that the optimal operative strategy for symptomatic ToF is early operative surgery; as early as 3 days of life; particularly for duct dependent neonates. Their work shows, that despite the impression to the contrary, there is a dearth of literature on the natural history of ToF and on long-term surgical outcomes of correction. To the best of our knowledge, this work represents the only attempt to compare the most externally valid surgical outcome data with the most externally valid natural history data for ToF, in order to determine the optimal age for surgical correction. The paucity of data precluded the use of traditional methods to answer this question.

Conclusion

The results suggest that the optimal surgical strategy for neonates is an early corrective surgery; as early as 3 days old. Cyanosed neonates are likely to benefit most from this strategy.

CONFLICT OF INTERESTS

The authors have not declared any conflicts of interests.

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