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Full Length Research Paper

Use of a composite survival curve to optimise timing of surgical repair of *Truncus arteriosus*

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Surgical repair of *Truncus arteriosus* aims to improve long term survival. A clear understanding of the natural history and achievable surgical outcomes informs surgical decision making with respect to the timing of surgery. We sought to determine if it is ever too late to repair *T. arteriosus*. Pubmed and Google scholar were searched between January 1st 1966 and July 31st 2021. The proximal similarly model was used to determine the most externally valid natural history and surgical outcome data. The most externally valid data were used to develop a composite survival graph to help clinicians optimize surgical decision making. Four hundred and twenty eight results were retrieved. Five studies representing 938 patients who had repair of *T. arteriosus* were included for external validity assessment. The resultant composite graph suggests that repair after 5 month of age, may not improve 15 year survival when compared to non-operative care. *T. arteriosus* repair after 5 months of age may not improve survival.

Key words: Pediatric, truncus artriosus, operative, outcomes.

INTRODUCTION

Truncus arteriosus is an abnormal ventriculo-arterial connection where the branch pulmonary arteries originate either from a main pulmonary artery that branches off a large common arterial trunk (Type 1) or originate as two separate branches directly from a common arterial trunk(Type 2 and 3). A large ventricular septal defect (VSD) is usually part of this lesion. The goal of surgery is to improve the quality and quantity of life and involves:

(i) Closure of the VSD by routing the left ventricle to the systemic circulation.
(ii) Re-establishing continuity between the right ventricle and the pulmonary arterial tree.

Surgical decision making may be facilitated by considering post-operative survival data in the form of Kaplan-Meier curves. In this regard, survival curves can be used in 2 ways: to compare surgical outcome with the natural history or to compare the outcomes of different surgical strategies. Externally valid surgical outcome data, applied in the context of a sound understanding of the natural history of a disease, optimises surgical decision making. Surgical outcomes considered in isolation, could results in patients being offered unnecessary surgery. We reviewed the literature to establish the most externally valid natural history data for *T. arteriosus* and the most externally valid surgical

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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	TA; LSS	TA; LSS; AAS
Geography	Anywhere	Multi-centre study
Time	Any time	Paper published after the year 2000

AAS= age at surgery; LSS=large sample size; NH=natural history; SO=surgical outcome; TA=*Truncus arteriosus.*

outcome data for the repair of *T. arteriosus*. 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). 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 (Available at http://ocw.jhsph.edu/courses/fundepi/pdfs/Lecture9.pdf Accessed June 9 2021). 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 age at the time of surgery.

MATERIALS AND METHODS

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 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 repair of *T. arteriosus*. Table 1 shows which parameters were used to choose the most externally valid natural history and surgical outcome studies (Figure 1).

Search strategy and selection criteria

PUBMED and Google Scholar were searched systematically from January 1st 1966 to July 31st 2021. Table 2 shows the search terms and strategy. Google scholar searches used "all in title" option; PUBMED searches used "title/abstract" option. All search terms were combined with "AND". Titles and abstracts were reviewed and full-text articles were obtained when the abstract indicated that there was a possibility that data pertaining to natural history or long-term surgical outcomes might be present. Natural history studies that included Type IV truncus (Tetralogy with pulmonary atresia) were excluded. Non-English language studies and non-human studies were also excluded. A recent large study by Naimo et al. (2021) showed that the late mortality rate was 10.4%. In view of this, we only included surgical outcome studies that examined a sufficient number of patients to detect this degree of late mortality with a 90% confidence interval. This essentially meant that studies with a sample size of less than 102 patients were excluded. This sample size 'cut-off' was determined using a free online sample size calculator (Available at https://www.calculator.net/sample-size-calculator.html. 2021).

Creation of the composite graph

The natural history curve was created using data from the study deemed to have the greatest external validity. To determine 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 curve were superimposed on the most externally valid natural history curve.

RESULTS

The search yielded 428 results; 35 relevant full-texts were obtained after examining titles and abstracts. Twelve full-texts related to the natural history of *T. arteriosus* and 23 related to the surgical outcome of repair. The references of these full texts were examined for additional relevant references; none were found. Five studies, representing 938 patients, were included for consideration when developing the postoperative survival branch of the composite survival curve. The important details of these studies are shown in Table 3. A list of the retrieved natural history full texts is included in Table 4. The natural history curve for *T. arteriosus* is shown in Figure 2; the composite graph is shown in Figure 3.

DISCUSSION

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

(i) Follow-up a group of live patients to determine when patients die.
(ii) 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.

Despite an extensive search, only one suitable study was found and used to generate our natural history curve; it used the first method. The study followed 946 patients with congenital heart disease (CHD) over 27

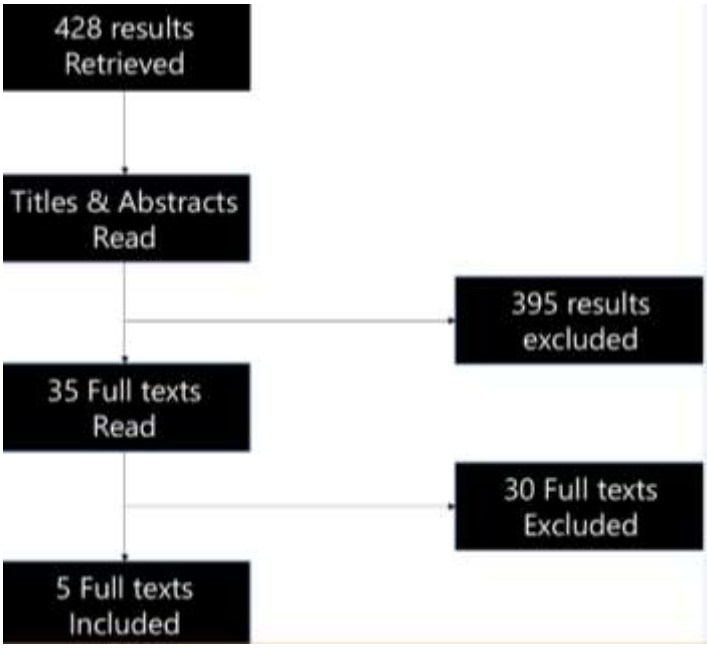

Figure 1. Search flow diagram.

Table 2. Search strategy.

Search number and terms
Truncus arteriosus, natural, history (GS,P)
Truncus arteriosus, unoperated (GS,P)
Truncus arteriosus, long, term, survival(P)
Truncus arteriosus, survival (GS)
Natural, history, cardiac, malformations (GS,P)
Congenital, heart, disease, natural, survival (GS,P)
Truncus arteriosus, long, term, outcome (GS,P)
Truncus arteriosus, long, term, results (GS,P)
Truncus arteriosus, neonate (GS,P)
Truncus arteriosus, neonatal (GS, P)

GS = Goggle scholar, P = Pubmed

Table 3. Surgical outcome full texts included.

Study	Year of study	Era of surgery	N	Median age at surgery (Days)	Operative mortality (%)	15 year survival (%)	Number of patients followed up to 15 years
Guariento et al.	2021	1984-2018	204	13	5	84	75
Naimo et al.	2021	1979-2018	255	44	13.3	78	104
Gellis et al.	2020	1985-2016	170	10.5	13	75	53
Lund et al.	2011	1989-2008	156	14	8	-	-
Henaine et al.	2008	1986-2003	153	35	17	80	4

years (Samánek, 1992). This study 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

Table 4. Natural history full texts retrieved.

Study	Year of study	Type of study	Age of patients (years)
Dangrungroj et al.	2020	Descriptive cohort	0.04 - 32.8
Abid et al.	2015	Case report	41
Ginelliová et al.	2015	Case report	46
Kharwar et al.	2014	Case report	11
Carvalho et al.	2002	Case report	48
Samánek	1992	Descriptive cohort	0.02-15
Marcelletti et al.	1976	Descriptive cohort	0.005 - 26
Carter et al.	1973	Case report	52
Campbell	1972	Descriptive cohort	30-Mar
Hicken and Evans	1966	Case report	38

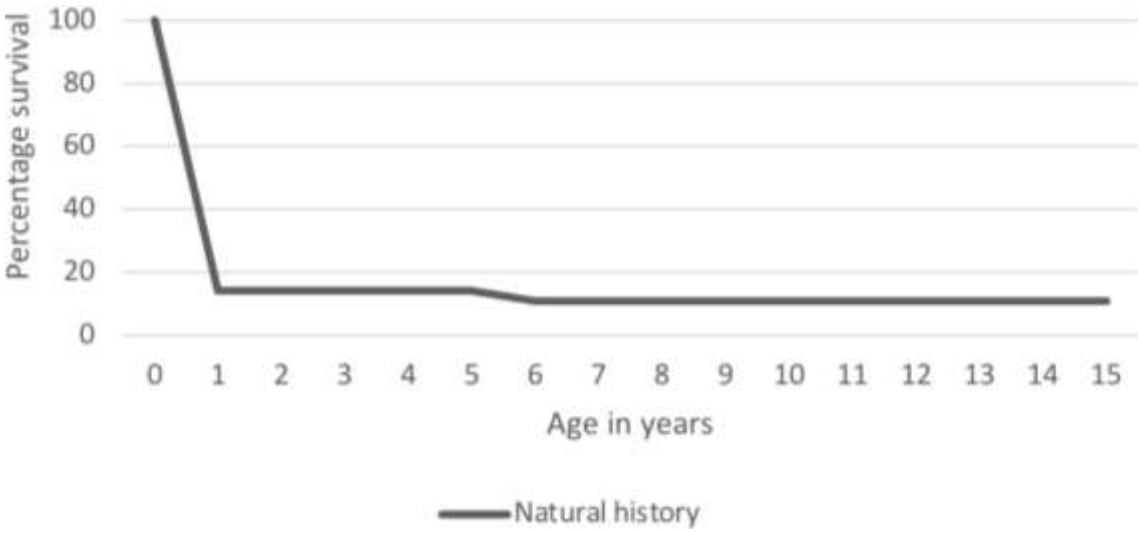

Figure 2. Natural history curve for *T. arteriosus.*

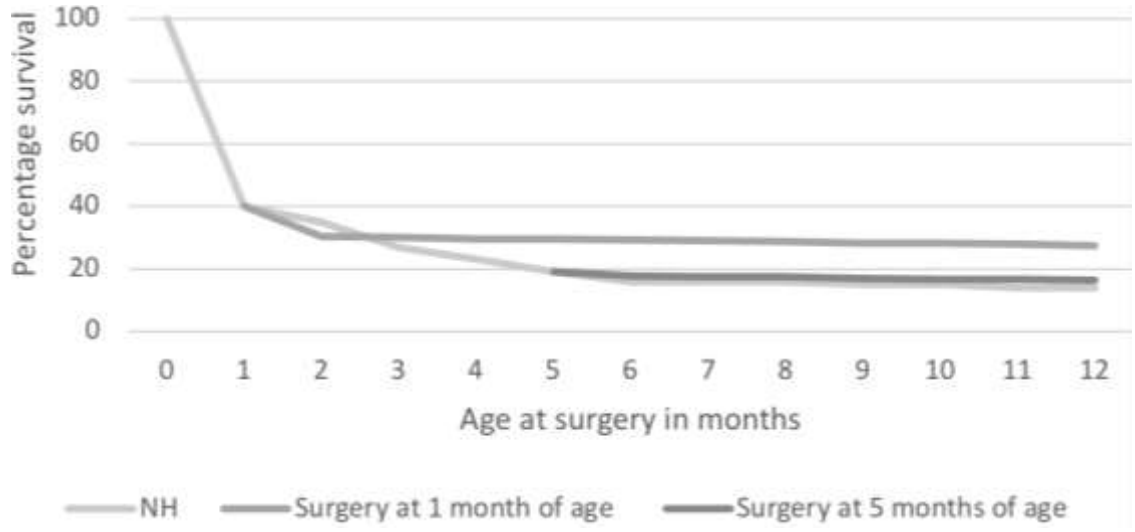

Figure 3. The composite graph for *T. arteriosus.*

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 first 15 years of life. There were 34 patients with *T. arteriosus* in this study (Samánek, 1992; Samánek et al., 1988). From the data, the 10 year natural history mortality was 86% (+/- 11.7%; 95% confidence interval).

The surgical outcome arm of our composite graph for surgeries performed during the neonatal period was created using neonatal surgical outcomes from the most externally valid surgical outcome study (Naimo et al., 2021). It demonstrates clearly what is already known: neonatal surgery improves survival over the natural history. However, the composite graph emphasises the point that the earlier surgery is performed in the neonatal period, the greater the survival advantage.

The surgical outcome arm of the composite graph for repairs performed after the neonatal period was created using the most externally valid outcome data for repairs on non-neonatal patients (Naimo et al., 2021). The graph shows that the surgical outcome curve essentially is superimposed on the natural history survival curve when surgery is performed at 5 months of age. Although not shown by the composite graph, the data used to create this surgical outcome arm confirms that these curves remain superimposed until 15 years of age. This implies that patients repaired after 5 months of age, essentially have the same survival as unoperated patients up to 15 years of age. We do not have sufficient data to compare natural history survival with surgical survival after 15 years of age. Although not the subject of our current study, it is possible that the natural history mortality after 5 months of life is low because patients with unfavourable physiological variants of *T. arteriosus* have died by this age. Favourable physiological variants would have balanced flow through the systemic and pulmonary circulation.

Current practice aims for repair of TA in the neonatal period. Some centres will offer repairs to patients who present later in infancy and even childhood. There is evidence that repair of *T. arteriosus* in late infancy or in childhood can be achieved with a low operative mortality (Naimo et al., 2021). However, our composite graph suggests that offering surgery to patients who are over 5 months of age may not offer a survival advantage over the natural history for the first 15 years of life.

Our search retrieved 3 reports of a patient with *T. arteriosus* living past the age of 40 years. The oldest of these was a lady with type 1 TA who was 52 years old at the time of death (Carter et al., 1973). When these reports are considered together with what our composite graph demonstrates, the rationale for repair of *T. arteriosus* on patients older than 5 months of age must be re-examined. It is entirely possible that the outcome for this group of patients (repair past the age of 5 months of age) could be worse than the natural history. There may well be survival and symptomatic benefits from repair after the age of 5 months of age, however, it cannot be assumed that these benefits exist. Our work cannot answer these questions but it does point to the fact that additional work is required to provide answers.

In conclusion, results suggest that repair of *T. arteriosus* in patients older than 5 months of age offers no survival advantage for the first 15 years if life; existing data is inadequate to determine if surgical survival advantage exists after the first 15 years of life. A survival or symptomatic benefit should not be assumed to exist when repairs are performed after 5 months of age; more work is required to confirm the existence of these benefits.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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