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# Life After Surviving Fontan Surgery: A Meta-Analysis of the Incidence and Predictors of Late Death

Q1 C.L. Poh<sup>a,b,c</sup>, Y. d’Udekem, MD, PhD<sup>a,b,c\*</sup>

Q2 <sup>a</sup>Department of Cardiac Surgery, The Royal Children’s Hospital, Melbourne, Vic, Australia

Q3 <sup>b</sup>Department of Paediatrics, University of Melbourne, Melbourne, Vic, Australia

Q4 <sup>c</sup>Heart Research, The Murdoch Childrens Research Institute, Melbourne, Vic, Australia

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## Aim

We now know that 20–40% of patients with a single ventricle will develop heart failure after the second decade post-Fontan surgery. However, we remain unable to risk-stratify the cohort to identify patients at highest risk of late failure and death. We conducted a systematic review of all reported late outcomes for patients with a Fontan circulation to identify predictors of late death.

## Methods

We searched MEDLINE, Embase and PubMed with subject terms (“single ventricle”, “Hypoplastic left heart syndrome”, “congenital heart defects” or “Fontan procedure”) AND (“heart failure”, “post-operative complications”, “death”, “cause of death”, “transplantation” or “follow-up studies”) for relevant studies between January 1990 and December 2015.

Variables identified as significant predictors of late death on multivariate analysis were collated for meta-analysis. Survival data was extrapolated from Kaplan-Meier survival curves to generate a distribution-free summary survival curve.

## Results

Thirty-four relevant publications were identified, with a total of 7536 patients included in the analysis. Mean follow-up duration was 114 months (range 24–269 months). There were 688 (11%) late deaths. Predominant causes of death were late Fontan failure (34%), sudden death (19%) and perioperative death (16%). Estimated mean Kaplan-Meier survival at 5, 10 and 20 years post Fontan surgery were 95% (95%CI 93–96), 91% (95%CI 89–93) and 82% (95%CI 77–85). Significant predictors of late death include prolonged pleural effusions post Fontan surgery (HR1.18, 95%CI 1.09–1.29,  $p < 0.001$ ), protein losing enteropathy (HR2.19, 95%CI 1.69–2.84,  $p < 0.001$ ), increased ventricular end diastolic volume (HR1.03 per 10 ml/BSA increase, 95%CI 1.02–1.05,  $p < 0.001$ ) and having a permanent pacemaker (HR12.63, 95% CI 6.17–25.86,  $p < 0.001$ ).

## Conclusions

Over 80% of patients who survive Fontan surgery will be alive at 20 years. Developing late sequelae including protein losing enteropathy, ventricular dysfunction or requiring a pacemaker predict a higher risk of late death.

Q5 \*Corresponding author at: Department of Cardiac Surgery, The Royal Children’s Hospital, 50 Flemington Road, Parkville, Vic 3052, Australia.

Tel.: (03) 9345 5200, Fax: (03) 93456001. Email: [Yves.Dudekem@rch.org.au](mailto:Yves.Dudekem@rch.org.au)

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## Introduction

Q6 As we head towards the fifth decade of Fontan surgery, there is a new optimism towards the long-term survival of these patients. Late follow-up studies report survival rates between 60 and 80%, 20 years after Fontan surgery [1–3]. With population projections predicting this cohort to double in the next 20 years, we will soon face a large population of adult patients living with a Fontan circulation requiring long-term surveillance. However, till today, we still lack reliable criteria to risk-stratify this cohort, so as to identify those at highest risk of late failure and death. Improving our standard of care requires the identification of those most at risk of seeing the demise of their circulation. The small size of patients' cohorts in existing studies limit the relevance of prognostic factors identified. Therefore, we conducted a systematic review of all reported outcomes of patients with a Fontan circulation to identify predictors of late death in this Q7 population.

## Methods

MEDLINE, Embase and PubMed were searched with subject terms ("single ventricle", "Hypoplastic left heart syndrome", "congenital heart defects" or "Fontan procedure") AND ("heart failure", "post-operative complications", "death", "cause of death", "transplantation" or "follow-up studies") for relevant studies published from January 1990 to December 2015. Reference lists of eligible studies were also hand searched for additional articles. All relevant abstracts were screened. Selected reports were then appraised in the full text with consideration of the following inclusion criteria: 1) All patients included were beyond the stage of Fontan completion, 2) follow-up data was available beyond the immediate perioperative period (within 30 days post Fontan completion), 3) the incidence of late mortality was described. There were no limitations to the type of Fontan surgery. Serial studies with duplicate data from the same cohort were excluded from the survival analysis. However, all independent predictors of death were identified to ensure a comprehensive review.

## Data Extraction

Relevant study data was extracted from the selected studies. This included publication-related details, baseline patient characteristics, Fontan surgery related details, morbidity and mortality at latest follow-up, and all significant predictors of late death identified on multivariate analysis. All selected studies were screened to identify Kaplan-Meier (KM) survival curves for the combined analysis of overall survival for the pooled cohort. Only survival curves from studies with follow-up longer than 5 years were included in the analysis to generate the final summary survival curve. For the systematic review of predictors of late death, only variables identified as statistically significant on multivariate analysis were included. Variables identified by three or more

studies to be significant predictors of the endpoint were included in the final meta-regression analysis. Studies focusing on the review of single predictors of late death or failure were excluded from this review as they were limited by their methodology to overestimate their value of prediction [4]. This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [5] and The Cochrane Collaboration and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [6].

## Data Analysis

Continuous variables were reported as mean  $\pm$  standard deviation. For the purpose of the meta-analysis of continuous data, medians and interquartile ranges reported in Q8 individual studies were converted to the form of mean  $\pm$  standard deviation as per the methodology proposed by Wan et al. [7]. For the purpose of generating a distribution-free summary survival curve, all studies with follow-up data beyond a mean of 5 years were reviewed to identify KM survival curves. Conditional survival probabilities were re-constructed from published survival curves using the DigitizeIt software and the algorithm previously described [8]. The conditional survival probabilities extracted were then pooled at fixed time intervals (second yearly till final time-point on KM curve) with consideration for between-study variance. The summary KM survival curve was generated with final time cut-off at 22 years post Fontan surgery, being the last time-point with at least two studies contributing to the meta-analysis. Summary survival probabilities were then derived via Stata, Version 14.0 (Metacorp Q9 package) using the product-limit estimator, as the product of the pooled estimates [9]. Confidence intervals of the summary survival probabilities were derived using the log-log transformation. Independent predictors of late mortality were identified as described above, and analysed using Review Manager (RevMan), Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

## Results

The search strategy identified 1570 journal articles. Additional hand searches of reference lists found nine additional reports, resulting in a total of 1579 citations. All articles were screened via review of their abstracts. A total of 64 relevant manuscripts for late mortality were identified. For late mortality, eight studies reported on duplicate patient cohorts without additional relevant survival analysis and were excluded [10–17]. An additional 15 studies were excluded on further review: follow-up of all single ventricle patients of different stages of surgical palliation (7) [18–24]; late outcomes not clearly described (2) [25,26]; and subject cohort not representative of actual cohort (6) [27–32]. Forty-one studies satisfied inclusion criteria. Of these, seven studies reported on duplicate cohorts [33–39]. These were excluded from

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