Meta-Analysis of the Effectiveness of Heart Transplantation in Patients With a Failing Fontan

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The Fontan procedure is increasingly being used to palliate univentricular physiology. It is a complex anatomic and physiologic repair that can fail at any age, often leaving heart transplantation as the only remaining solution. A meta-analysis was performed to achieve the aim of systematically evaluating the existing evidence for survival after heart transplantation in patients who have undergone a Fontan palliation. MEDLINE, Embase, PubMed, and Web of Science were searched for original research studies. The primary outcome was mortality at 1 and 5 years after transplantation. Five hundred eighty-two records were screened, after the removal of duplicates, 12 retrospective observational studies were selected for inclusion in our meta-analysis. This encompassed a total of 351 Fontan patients undergoing heart transplantation. Mean age was 14 years (range 7 to 24 years) and 65% were men. One- and 5-year survival rates after heart transplantation were found to be 80.3% (95% CI 75.9% to 84.2%) and 71.2% (95% CI 66.3% to 75.7%), respectively. No significant association was found between age, gender, and pulmonary pressures and 1-year mortality. In conclusion, in the largest analysis to date, we found that heart transplantation in younger patients after Fontan procedure has an acceptable early and mid-term mortality. It is comparable to published mortality data of heart transplantation for other forms of congenital heart disease. Heart transplantation in the younger failing Fontan population appears to be a reasonable option when all other avenues have been exhausted and appropriate screening has taken place. **(Am J Cardiol 2017;119:1269−1274)**

The Fontan procedure creates a unique circulation that separates the systemic venous circulation from the systemic arterial circulation in children born with univentricular physiology. Systemic venous blood is passively directed to the pulmonary circulation, and the single ventricle supplies the systemic circulation. This surgery has substantially decreased mortality and children are now surviving into adulthood.[1,2] The downside is that as a result of the surgically created Fontan circulation, patients are exposed to a high-pressure venous circulation and relative deprivation of cardiac output over a lifetime and complications are frequently encountered in these patients.[3−5] In patients with Fontan failure, cardiac transplantation is often the only option. Several factors are considered to place this population at higher risk of transplant-related morbidity and mortality including difficult assessment of pulmonary vascular resistance, complex anatomy including situs abnormalities, multiple previous operations, allosensitization with preformed antibodies, and increased prevalance of co-morbidities such as hepatic and renal dysfunction.[6] Numerous studies have been published to quantify outcomes in the Fontan population after heart transplantation; however, most characterize single-center experiences and are limited by small sample sizes. The aim of the present meta-analysis was to further quantify outcomes of Fontan patients after heart transplantation.

Methods

A comprehensive literature search of PubMed, MEDLINE, Embase, and Web of Science was conducted in March 2015. Our search strategy included keywords Fontan AND "exp. heart transplantation." In addition to keyword searches, separate title searches were also conducted in MEDLINE, Embase, and Web of Science. No limitations were used for date or publication status. Citations of eligible studies were reviewed for additional references; however, none were identified that were not retrieved already in the primary search.

Selected studies investigated morbidity and mortality after heart transplantation in pediatric and adult patients with a Fontan circulation. Reviews, case reports, and studies not available in English were excluded. Studies were excluded if they did not include any data on survival at 1 year, as this would form the basis of our primary outcome, and if patients underwent multiorgan transplantation. Studies were carefully reviewed for the source of their data and excluded if

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See page 1274 for disclosure information.

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0002-9149/17/$ - see front matter
http://dx.doi.org/10.1016/j.amjcard.2017.01.001

they were found to have reported on the same cohorts. In the event of multiple publications from the same center or single-center data used in multicenter studies, investigators were contacted to confirm if there was overlap of data. Where overlap was confirmed or strongly suspected, the study with the greatest number of patients was selected and the smaller studies were excluded. Numerous large single-center experiences were not included in this meta-analysis due to overlap with a multicenter study using the Pediatric Heart Transplant Study (PHTS) database toward which the individual centers contribute data.

The authors of selected studies were contacted to request individual patient data when this was not included in the original publication. Data extracted from each study included the first author, year of publication, source of data, time frame of study, and number of patients. Baseline characteristics of patients at the time of transplant extracted included age, gender, underlying congenital heart disease (CHD) diagnosis, the type of Fontan, previous operations, transplantation wait time, and requirement of mechanical ventilation, ventricular assist device, and extracorporeal membrane oxygenation. Pretransplantation co-morbidities including arrhythmias, protein-losing enteropathy, plastic bronchitis, and renal dysfunction as well as operative factors such as donor ischemia time and bypass time were recorded where available. Outcome measures extracted were mortality at 1 and 5 years, hospital and intensive care unit length of stay.

Pooled estimates of 1-year and 5-year survival rates were calculated separately using fixed effect logistic regression model after applying study sizes as weights. Meta-regression analysis was conducted to examine the association between the 1-year survival rate and mean age, and percentage of male patients separately. Subgroup analysis of 1-year survival rates was carried out after exclusion of studies with a sample size less than 10 patients. Begg's funnel plot and Egger test were used to examine potential publication bias for the 1-year survival rates. For all analyses, 0.05 was considered as the significant level. All the analyses were completed using statistical package rma.glmm in R.3.1.0.

Results

Database searches using the previously described strategy yielded 996 results (Figure 1). Five hundred twenty-six studies irrelevant to the topic were excluded, and 44 were excluded for factors noted in Figure 1 with the use of duplicate data being the main reason for exclusion. A total of 12 studies published between 1995 and 2015 were included in the meta-analysis, with 351 patients undergoing heart transplantation (Table 1).

All the 12 studies selected for inclusion in this meta-analysis are retrospective, observational, largely single-center studies. Of the 12 studies, only 1 study was published before 2000 and the others after 2000. Time frame of heart transplantation ranged from 1984 to 2013. The sample size varied from 3 to 194 subjects, with a median sample size of 9.5 subjects. Information on baseline characteristics specific to the Fontan patients was not consistently available (Table 2). Among 8 studies that reported details regarding age at transplantation, representing 254 patients, 12 patients were older than 18 years (5%). Most Fontan operations were performed using total cavopulmonary connection technique (65.8%) including lateral tunnel and extracardiac conduits. Indication for transplantation was reported in 6 studies, representing a total of 101 patients; these included ventricular failure in 46 patients (45%), protein-losing enteropathy in 26 patients (26%), and arrhythmias in 14 patients (14%).

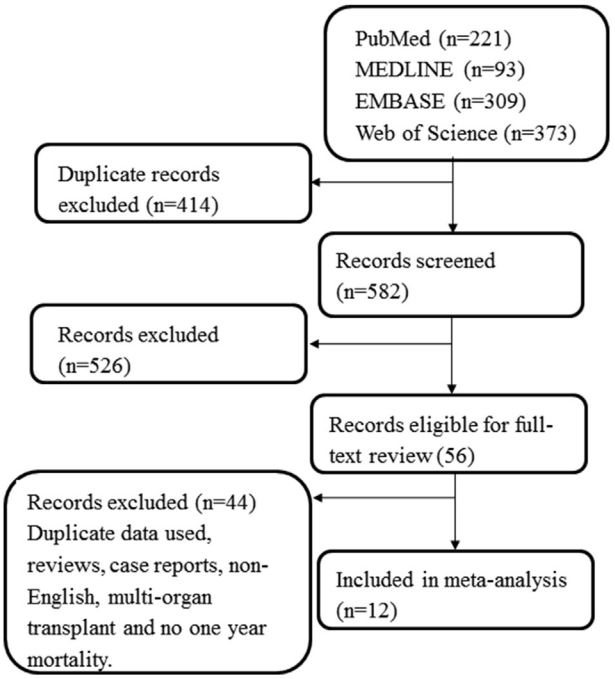

Figure 1. Study selection for studies reporting outcomes after heart transplantation in Fontan patients.

Mean and median survival rates at 1 year after heart transplantation were 76.3% and 78%, respectively (range 40% to 100%). Mean and median survival rates at 5 years were 71% and 71.5%, respectively (range 40% to 100%). The pooled estimate of 1-year survival rate was 80.3% (95% CI 75.9% to 84.2%), the and 5-year survival rate was 71.2% (95% CI 66.3% to 75.7%). Forest plots of 1-year and 5-year survival rates are presented in Figures 2 and 3. The funnel plot (Figure 4) and the Egger test for publication bias of 1-year survival rates showed the risk of having publication bias were not significant ($p = 0.32$).

There were 6 studies with a sample size of less than 10 (Table 1). After removing these studies from meta-analysis of 1-year survival rates, the pooled estimate of 1-year survival rate was 80.7% (76.0% to 84.7%). Fixed effect univariate logistic regression analysis showed that mean age ($p = 0.17$) at heart transplantation, percentage of male patients ($p = 0.66$) and mean pulmonary artery pressure ($p = 0.64$) were not significantly associated with 1-year survival rate.

Discussion

There are multiple smaller studies that report on outcomes following heart transplantation in the Fontan population. We considered it important to add to the literature a

Table 1
Characteristics of included studies

First Author (reference)	Publication year	Region	Study design	Number of Fontan patients who underwent HT	Study time frame
Hsu [7]	1995	USA	R, SC	9	1984-1993
Gamba [8]	2004	Italy	R, SC	14	1990-2002
Chaudhari [9]	2005	UK	R, SC	6	1985-2003
Simmonds [10]	2008	UK	R, SC	15	1988-2007
Irving [11]	2010	UK	R, SC	3	1988-2009
Kovach [12]	2012	UK, USA, Canada	R, MC	194	1993-2008
Paniagua Martin [13]	2012	Spain	R, MC	10	1984-2009
Seddio [14]	2013	Italy	R, SC	22	1985-2011
Delmo Walter [15]	2013	Germany	R, SC	5	1986-2011
Rungan [16]	2014	New Zealand	R, SC	6	1987-2012
Iyengar [17]	2014	Australia	R, SC	8	1988-2013
Michielon [18]	2015	Europe, USA	R, MC	61	1991-2011

HT = heart transplantation; MC = multicenter; R = retrospective; SC = single-center; UK = United Kingdom; USA = United States of America.

Table 2
Baseline characteristics of patients in included studies

Variable	N patients reported*	Value†	Range
Age	351 (100%)	13.8 years	6.6-23.8 years
Male sex	304 (87%)	65%	50-100
Pre-operative mechanical ventilation	302 (86%)	10%	0-100
Pre-operative protein losing enteropathy	105 (30%)	30.5%	12.5-54.5
Donor ischemic time	89 (25%)	259.5 minutes	184-325 minutes
Pre-transplant pulmonary arterial pressure	87 (25%)	16 mm Hg	13-20 mm Hg
Type of Fontan	79 (23%)		
Right atrial-pulmonary connection		31.6%	
Total caval pulmonary connection		65.8%	
Right atrial-right ventricle connection		2.6%	
Underlying Diagnoses	120 (34%)		
Tricuspid atresia		22.5%	
Pulmonary atresia		15.0%	
Double inlet left ventricle		20.8%	
Double outlet right ventricle		12.5%	
Double inlet right ventricle		1.7%	
Hypoplastic left heart		18.3%	
Heterotaxy		0.8%	
Unbalanced atrio-ventricular septal defect		7.5%	

* The total number of patients for whom the given variable was reported in the meta-analysis and in parentheses the percentage of the total number of patients in the meta-analysis.

† Among the studies for which the given variable was reported, the value of the variable reported as mean for continuous variables or N (% of patients for whom the data were available) for categorical variables.

more global perspective on transplant outcomes in this complex population. Our meta-analysis, inclusive of 351 patients, revealed 1- and 5-year survival rates of 80% and 71%, respectively, in Fontan patients after heart transplantation. This mostly included studies that looked at transplantation performed in a younger population with only a few patients in their early 20s. There are limited published data addressing heart transplantation outcomes in adults with a failing Fontan circulation. However, transplantation is increasingly being performed in the adult Fontan population and data should be forthcoming.

Our results are comparable to a recent study based on 1,851 adult patients with varying types of CHD from the International Society for Heart and Lung Transplantation (ISHLT) registry, which showed postheart transplantation survival rates of 77% and 67% at 1 and 5 years.[19] There have been numerous retrospective cohort studies comparing outcomes of heart transplantation in Fontan patients to those of patients with other indications, yielding conflicting results. Two large-scale studies based on data from the PHTS failed to show a difference in mortality at 1 and 5 years between Fontan and other CHD patients.[12,20] Conversely, a 2009 publication by Lamour et al,[21] which used both PHTS and Cardiac Transplant Research Database data (registry for patients >18 year old), did show significantly lower survival in Fontan patients compared with

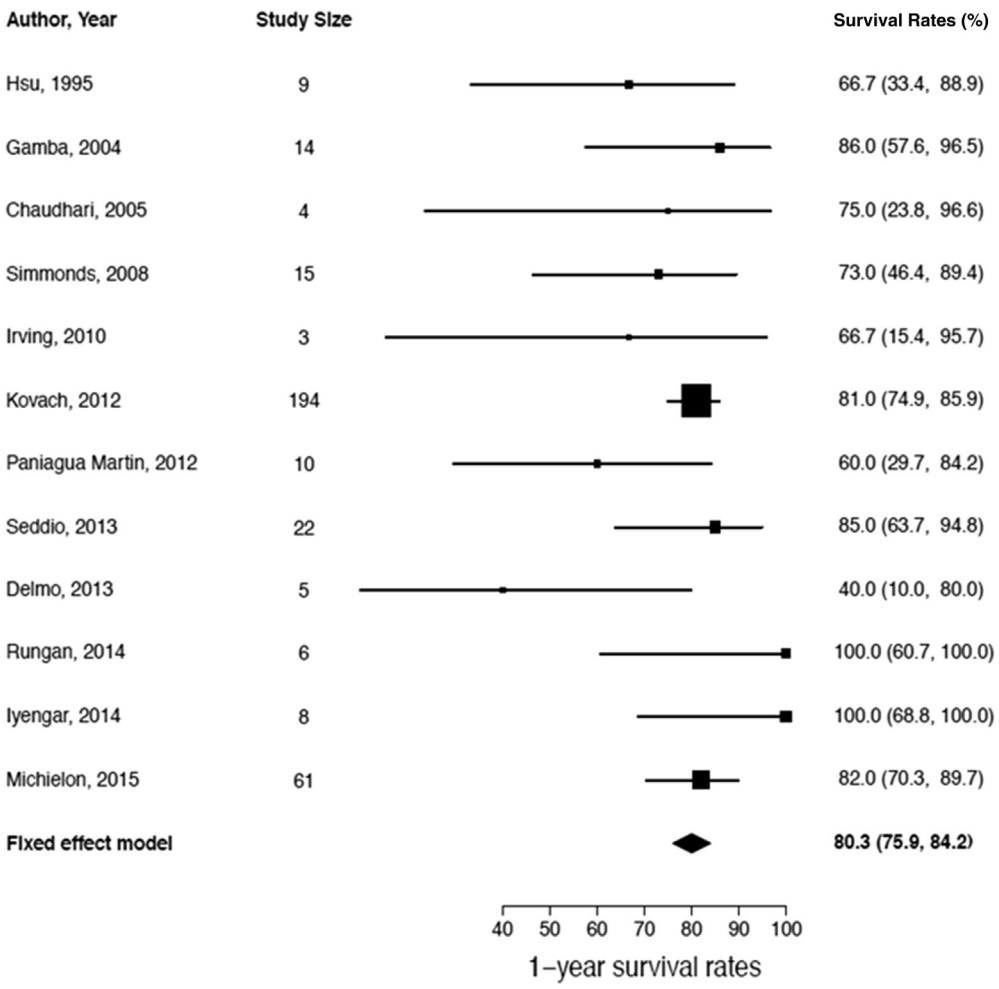

Figure 2. Forest plot of 1-year survival rates using fixed effects model. Studies are arranged by year of publication.

other patients with CHD. The cause of these differences is unclear but may be related to the inclusion of adult Fontan patients after transplant in the Lamour study. Our data taken together with other published data would suggest that outcomes after transplantation in a younger Fontan population are comparable to transplantation outcomes for other forms of CHD. These data are reassuring as it suggests that when screened appropriately, transplantation in at least the younger Fontan population is a reasonable option.

In our larger analysis, we confirmed that there is no association between transplant recipient gender or age and 1-year mortality, which is consistent with previous smaller studies.[12,22] We reported a mean pulmonary arterial pressure of 16 mm Hg before transplantation and did not find an association with 1-year mortality. Previous smaller studies have not demonstrated a significant relation between mean pulmonary arterial pressure and early postheart transplantation mortality in the Fontan population.[5] The pulmonary arterial pressures (Fontan pressure) in this particular patient cohort are not increased. However, those with an increase in Fontan pressure predominantly as a result of an increase in systemic atrial pressures would certainly be considered for heart transplantation. In the future, it would be interesting to analyze the effect of pulmonary hypertension therapy on pulmonary/Fontan pulmonary vascular resistance as it may increase the number of Fontan patients who become eligible for transplantation. Although improved outcomes have been demonstrated with the total cavopulmonary conduit variant of the Fontan procedure,[23] it is unknown if these patients would have improved outcomes after heart transplantation.

An additional factor that has been considered as an adverse predictor of outcomes after heart transplantation in the Fontan population is mechanical ventilation. Mechanical ventilation reflects a critically ill patient and transplantation in this scenario regardless of underlying diagnosis is associated with poorer outcomes.[12] In our analysis, we found that 10% of patients were on mechanical ventilation at the time of transplantation. This may be attributable to the general tendency to delay heart transplantation in this complex population given the perceived increased procedural risk, despite the risks associated with progression of disease.

In both our analysis and other cohort studies, it has been difficult to ascertain the relationship of other factors with outcomes due to the heterogeneous nature of the population. Previous findings show a difference in early mortality after heart transplantation between patients with CHD and those

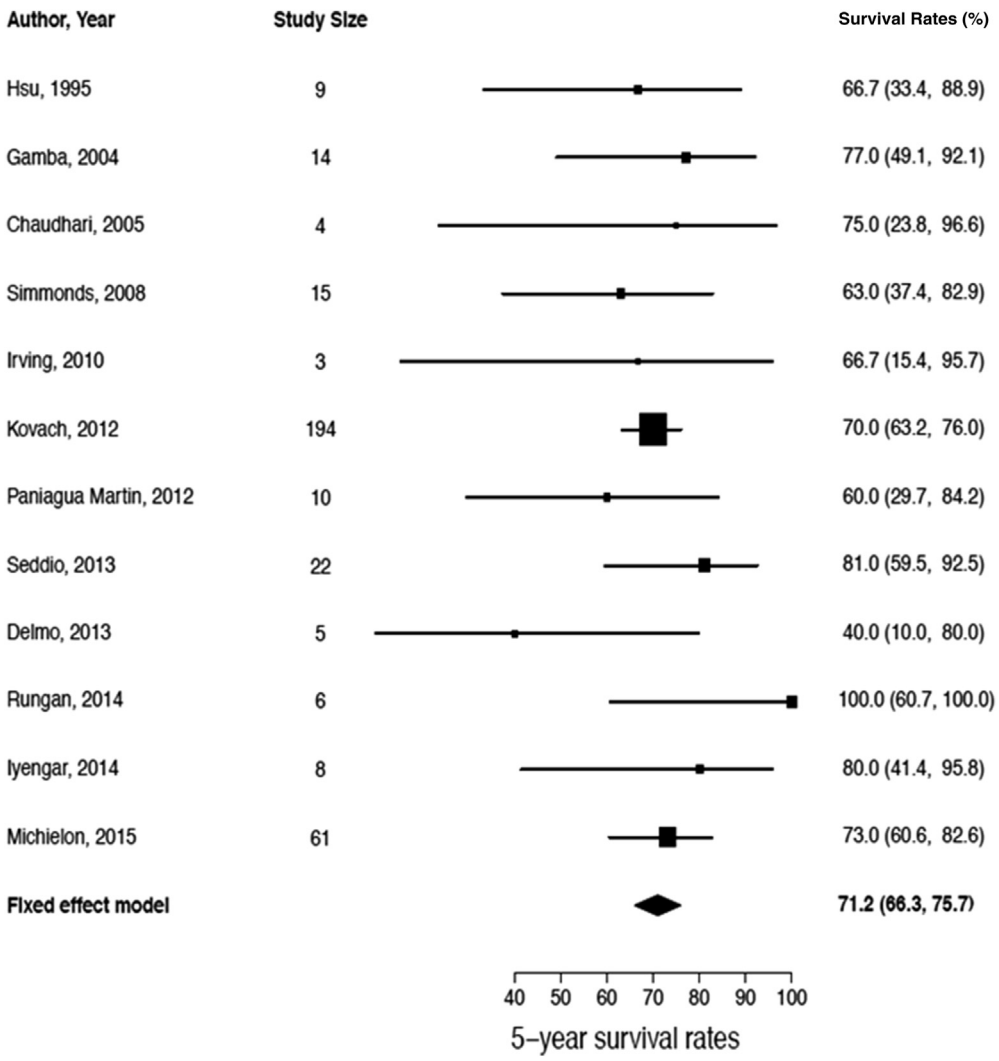

Figure 3. Forest plot of 5-year survival rates using fixed effects model. Studies are arranged by year of publication.

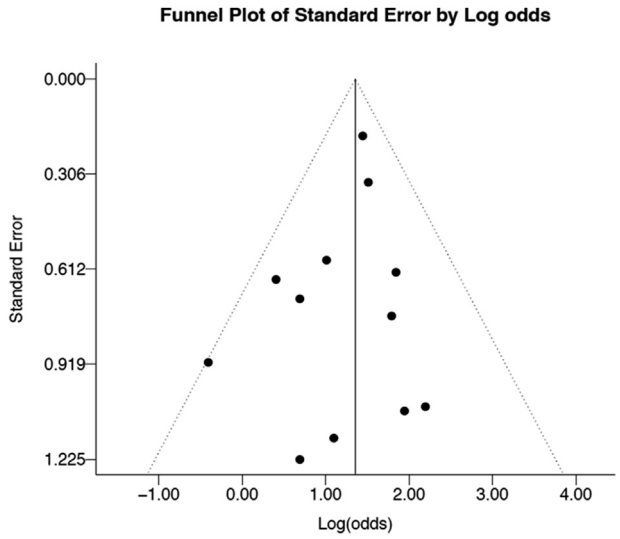

Figure 4. Funnel plot of standard error by log odds—1-year survival rates.

with other forms of heart disease but comparable long-term survival.[21] This is most likely the direct result of technical complexities related to individual anatomic variations, multiple earlier palliative procedures, aortopulmonary collaterals, and increased propensity to bleeding in the CHD population.[6,21,24,25] Additional considerations in the Fontan population include chronic sluggish blood flow to the pulmonary arteries increasing the risk for thrombus, changes in the distribution of flow to the right and left lung and an increased risk of infection.[26–28]

According to the registry of the ISHLT, children with CHD account for 40%, 32%, and 23% of pediatric patients undergoing cardiac transplantation among the 1- to 5-year-old, 6- to 10-year-old, and 11- to 17-year-old age groups, respectively.[29] Although transplantation for adults with end-stage heart failure due to acquired heart disease is increasingly common, the experience with transplantation in adults with CHD is limited with only 3% of adult heart transplantation attributed to CHD.[30] As survival among patients

with Fontan circulation continues to improve, more patients and specifically adults can be expected to present for consideration of heart transplantation.

Most studies were single-center studies with a small absolute number of patients. We excluded patients who had undergone multiorgan transplantation due to limited patient numbers; therefore, our results cannot be extrapolated to that population. Our study included one relatively large publication which compiled data from the PHTS.[13] Despite our attempts to contact investigators for individual patient data when this was not present in the original publication, our response rate was low. Therefore, we were limited in the examination of variables associated with mortality after transplantation. In addition, the heterogeneity of the studies prevented us from being able to conduct a thorough risk analysis.

Disclosures

The authors have no conflicts of interest to disclose.

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