REVIEW   **Open Access**

Efficacy of heart transplantation in patients with a failing Fontan: a systematic review and meta-analysis

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Abstract

Background: As the population of patients with Fontan palliation grows, so does the number of patients with Fontan failure, necessitating heart transplantation. However, due to mainly small-sized studies, outcomes after heart transplantation in these patients remain unclear. The objective of this study was to review the available literature and conduct a meta-analysis to provide well-powered and generalizable estimates of outcomes after heart transplantation in patients with a failing Fontan.

Main text: PubMed, Embase, and MEDLINE databases were searched for original studies of patients with a failing Fontan who underwent heart transplantation. The outcomes included were 1-year and 5-year survival, acute rejection, renal dysfunction, sepsis, and multi-organ failure. Proportions were pooled using random effects models to derive pooled proportions (PPs) and corresponding 95% confidence intervals (CIs). Meta-regression analysis was done to study the effects of age and gender on key outcomes. Sixteen retrospective single-center cohort studies with 426 Fontan patients undergoing heart transplantation were included in this meta-analysis. Pooled analysis of this study further revealed that 1-year survival after heart transplantation was 79.9% ([75.8%, 83.7%]; I^2 = 1.92%), and 5-year survival rate was 72.5% ([62.1%, 81.9%]; I^2 = 72.12%). Secondary outcomes after heart transplantation of failed Fontan procedure were acute rejection (PP 20% [7.4%, 36.8%]; I^2 = 72.48%), renal dysfunction (PP 31.3% [10.5%, 57.2%]; I^2 = 75.42%), multi-organ failure (PP 18.6% [2.8 to 43.9%]; I^2 = 69.60%), and sepsis (PP 21.1% [9%, 36.8%]; I^2 = 61.19%).

Conclusion: Cardiac transplantation in patients with a failing Fontan is associated with acceptable interventional success and improved survival rates.

Keywords: Fontan, Adult congenital heart disease, Congenital heart surgery

Background

For over 50 years, procedures like Fontan have been performed for surgical treatment in patients with functionally univentricular hearts [1]. Principally, a Fontan circulation is created when the systemic and pulmonary circulations are placed in series with the single functional ventricle, i.e., redirecting blood from the inferior vena cava (IVC) and superior vena cava (SVC) into the pulmonary artery, bypassing the right ventricle completely. According to the American Heart Association (AHA), the worldwide population of patients with Fontan circulation grew from an estimated 50,000 to 70,000 patients in 2018, with 40% of patients > 18 years of age. The current estimated survival rate following the Fontan procedure is approximately 85% [2]. Although this procedure significantly improves survival and quality of life, Dr. Fontan himself speculated that this procedure imposes a "gradually declining functional capacity and

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premature late death… the Fontan operation is, therefore, palliative but not curative" [3]. By the same token, patients with Fontan failure may present with growth failure, lymphatic failure, ventricular dysfunction, extracardiac organ failure, and decreased functional status (low oxygen consumption VO2) [3].These manifestations may occur early in the postoperative period or late during the long-term follow-up, all indicating towards the need for immediate heart transplantation [4]. Nevertheless, there have been concerns that even after transplantation these patients are at high risk for complications because of multiple prior operations, elevated panel reactive antibody, pre-transplant hepatic dysfunction, coagulopathy, protein-losing enteropathy (PLE), and poor nutrition [5, 6]. However, actual post-transplant outcomes in this population are poorly understood due to mainly small-sized studies with varying findings. Thus, we conducted a meta-analysis to provide well-powered and generalizable estimates of primary survival and other secondary outcomes such as acute rejection, sepsis, renal dysfunction, and multi-organ failure after heart transplantation in patients with a failing Fontan.

Materials and methods

This meta-analysis conforms to the guidelines set by Preferred Reporting Items for Systemic Review and Meta-analysis (PRISMA) [7].

Search strategy

A systematic literature search was conducted up till December 10, 2020, on PubMed, Embase, and MEDLINE databases with the following subject keywords and their MeSH terms: (heart transplantation, cardiac transplantation, new heart, heart engraftment, heart grafting, heart grafts, heart implantation, heart implants, heart-lung transplantation, heart transplants) AND (failing heart, Fontan procedure failure, Fontan method, Fontan process, Fontan technique, ventricularization of the right atrium, aortopulmonary connection, intracardiac total cavopulmonary connections, extracardiac total cavopulmonary connection).

Two reviewers independently screened the search results. A third reviewer was consulted in case of discrepancies. Studies were initially shortlisted based on title and abstract, after which the full-text was assessed for eligibility. References of the selected studies were also reviewed thoroughly to prevent any risk of selection bias.

Study inclusion and exclusion criteria

Studies were eligible with consideration of the following inclusion criteria: (1) published full text and in the English language, (2) patients with a failing Fontan procedure were included, and (3) 1-year and/or 5-year survival after cardiac transplantation was reported with the inclusion of both adult (age ≥18 years) and pediatric populations. The pediatric population was defined as < 18 years. Moreover, studies were carefully assessed if they had provided the required data for survival and morbidity of failed Fontan patients separately and were excluded if not. Articles were excluded if they were reviews, editorials, or case reports.

Data extraction

Data extraction of the relevant studies included the first author, year of publication, type of study (cohort or randomized controlled trial), study follow-up time, and the total number of patients who underwent heart transplantation. Baseline characteristics and indications for transplantation were also extracted. Primary outcomes of 1-year and 5-year survival rates were extracted by careful screening of Kaplan-Meir survival curves (KM) of the individual studies. Secondary outcomes of acute rejection, sepsis, renal dysfunction, and multi-organ failure were only included if three or more studies reported them. Renal dysfunction was defined as patients requiring renal replacement therapy such as continuous veno-venous hemodialysis and hemodialysis, while multi-organ failure was defined as patients having heart, lung, and liver. The included articles, however, did not mention any specific definition for sepsis; thus, the primary study investigator's definition of sepsis—the body's extreme response to an infection—was accepted.

Assessment of risk of bias

Quality assessment of all the observational studies was done by using the Newcastle-Ottawa reference scale [8].

Data analysis

All the extracted data was statistically analyzed using the OpenMetaAnalyst software (Center for Evidence Synthesis in Health, Brown University). The categorical variables were tabulated in the form of proportions, and arcsine transformation was appertained. Proportions of 1-year and 5-year survival and all the secondary outcomes were pooled using both random and fixed effects models. The I^2 statistic was used to analyze the heterogeneity, with a value of >75% labeled as severe heterogeneity of the data [9]. In addition to that, we also conducted a multivariate meta-regression analysis to assess the association between risk ratio (RR) and age and gender (males) of Fontan patients. A p-value of <0.05 was considered significant.

Ethics committee approval

This is a systematic review that uses publicly available data, therefore, does not require any ethical approval.

Results

The initial search revealed a total of 187 studies. After exclusions, 16 studies [10–25], published between 1995 and 2017, were included in the meta-analysis. The PRISMA figure summarizing the literature search is labeled as Fig. 1. These studies included 426 patients with a failing Fontan who underwent heart transplantation.

Study characteristics and quality assessment

All the studies employed in this meta-analysis were retrospective, observational, and large single-center, covering heart transplantations over 33 years (1955 to 2017) with a sample size ranging from 3 to 194 subjects. Out of the 16 studies, 14 reported details regarding age at transplantation [10–15, 17–20, 22–25], thereby, determining a mean age of 21.4 years from a sample of 426 Fontan patients. Almost three-fourth (72.5%; $N= 309$) of the patients were males. Indications for transplantation reported in some studies were protein-losing

enteropathy (PLE) in 35.6% of patients, tricuspid atresia in 39% of patients, double inlet left ventricle in 27.15% of patients, hypoplastic left heart in 16.8% of patients, and heterotaxy in 18.9% of patients. Table 1 shows the detailed study baseline characteristics. Quality assessment of included studies (Table S1) showed that most studies had a low risk of bias.

One-year and 5-year survival rate

Fifteen studies reported survival rate at 1 year and 5 years. The pooled prevalence (PP) of 1-year survival rate among Fontan patients was 79.9% ([75.8%, 83.7%]; $I^2 =$ 1.92%), and 5-year survival rate was 72.5% ([62.1%, 81.9%]; $I^2 =$72.12%) as shown in Fig. 2 a and b, respectively.
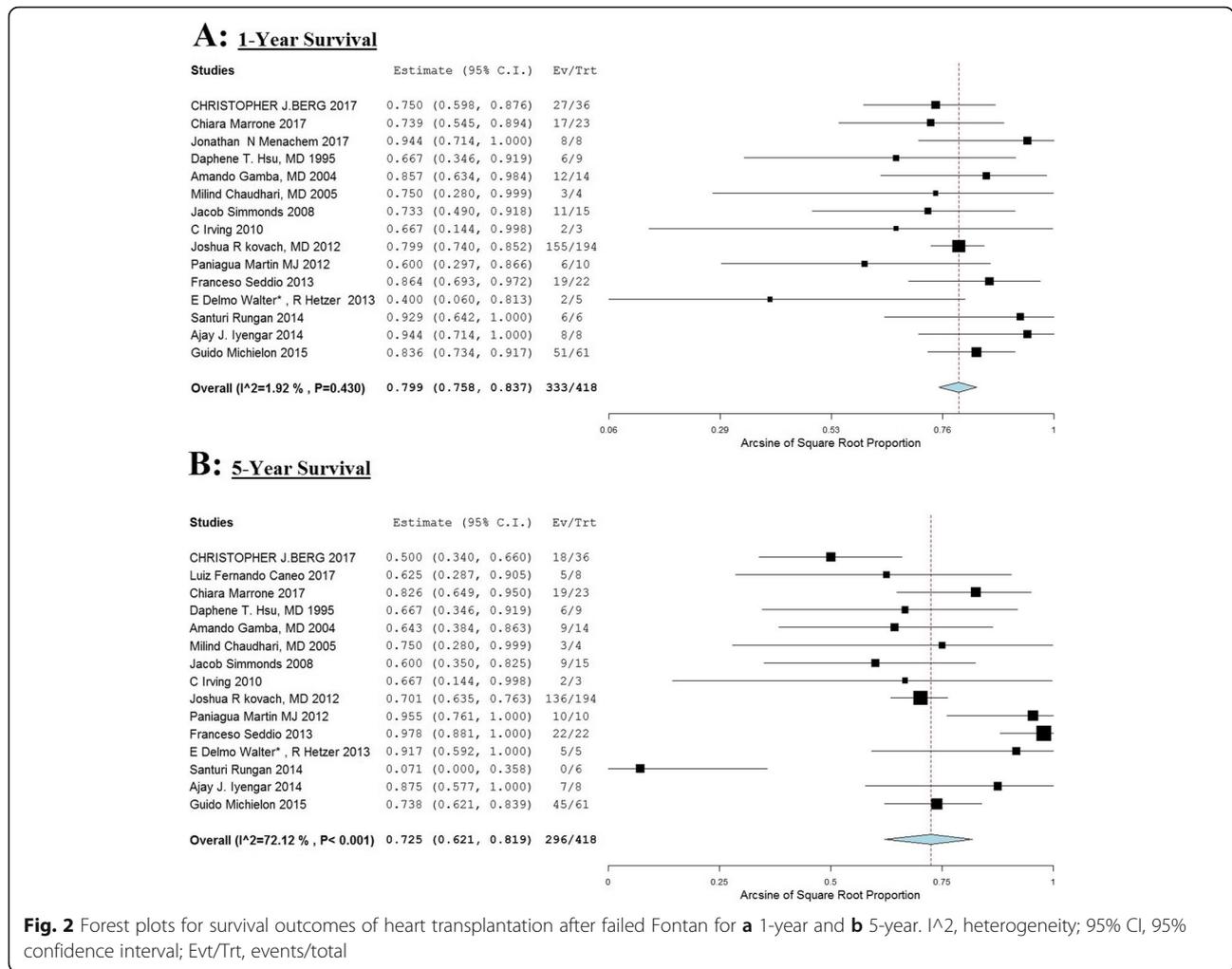
Multivariate meta-regression analysis revealed that age [1-year survival rate (RR= −0.02; p=0.288), 5-year survival rate (RR= −0.017; p=0.447)] and male gender [1-year survival rate (RR= −0.002; p=0.770), 5-year survival

Fig. 1 PRISMA flow chart summarizing the literature search
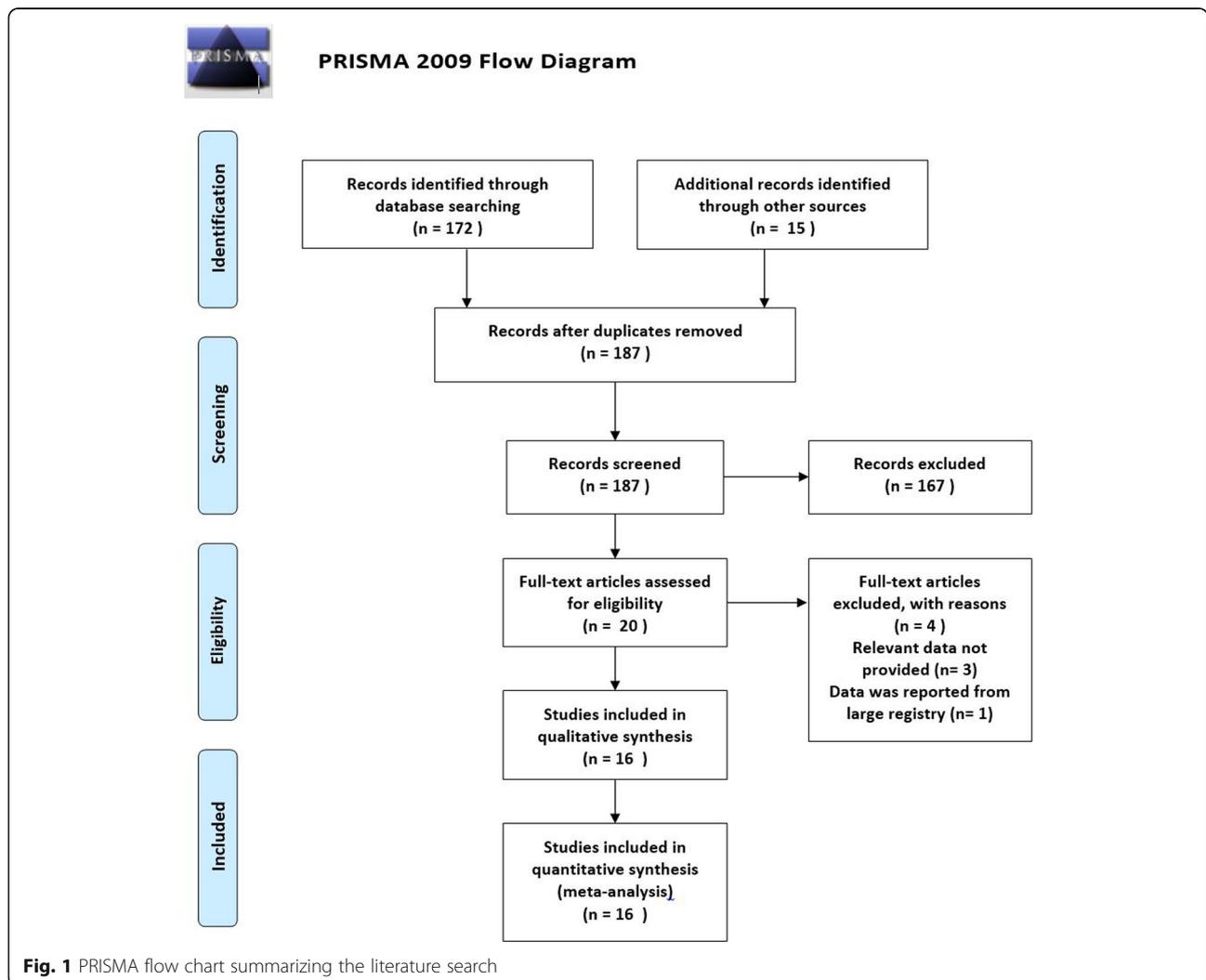
Table 1 General characteristics and outcomes of included studies

Study ID (author, year)	Region	Type of study and design	Study follow-up time	Number of patients who underwent heart transplantation (n)	Mean age[a] (years)	Males (%)	1-year survival (n)	5-year survival (n)	Acute rejection (n)	Sepsis (n)	Renal failure (n)	Multi-organ dysfunction (n)
Christopher J. Berg, 2017 [10]	USA	Retrospective, single center	1991–2014	36	21.3 (7.2–48.1)	61	27	18	5	-	7	-
Luiz Fernando Caneo, 2017 [11]	Brazil	Retrospective, single center	1984–2015	8	8 (6-12)	-	-	5	-	-	8	-
Chiara Marrone, 2017 [12]	Italy	Retrospective, single center	8.7 years	23	17.6 (11–33)	65	17	19	2	1	-	1
Jonathan N Menachem, 2017 [13]	USA	Retrospective, single center	2010–2016	8	40 (23–57)	50	8	-	-	-	-	-
Daphne T. Hsu, 1995 [14]	USA	Retrospective, single center	1984–1993	9	13.6	-	6	6	1	4	-	-
Amando Gamba, 2004 [15]	Italy	Retrospective, single center	1990–2002	14	17.6 (5.3–33.8)	50	12	9	6	1	-	1
Milind Chaudhari, 2005 [16]	UK	Retrospective, single center	1985–2003	4	6.78	83.30	3	3	1	1	-	-
Jacob Simmonds, 2008 [17]	UK	Retrospective, single center	1988–2007	15	-	-	11	9	-	-	-	-
C Irving, 2010 [18]	UK	Retrospective, Single center	1988–2009	3	23.8 (20.8–27)	-	2	2	-	1	-	1
Joshua R Kovach, 2012 [19]	UK/USA/Canada	Retrospective, multi-center	1993–2008	194	10.3 (0.4–18.2)	64	155	136	-	-	15	-
Paniagua Martin, 2012 [20]	Spain	Retrospective, multi-center	1984–2009	10	19 (10)	50	6	-	-	-	-	-
Franceso Seddio, 2013 [21]	Italy	Retrospective, single center	1985–2011	22	-	-	19	0	1	1	-	1
E Delmo Walter, 2013 [22]	Germany	Retrospective, Single center	1986–2011	5	6.6 (2–14)	-	2	0	1	-	-	-
Santuri Rungan, 2014 [23]	New Zealand	Retrospective, single center	1987–2012	6	16 (6–33)	100	6	6	4	0	0	-
Jay J. Iyengar, 2014 [24]	Australia	Retrospective, single center	1988–2013	8	12.37	53.80	8	7	-	-	-	-
Guido Michielon, 2015 [25]	Europe, USA	Retrospective, multi-center	1991-2011	61	15 ± 9.7	63.90	51	45	1	22	-	5

[a]The numbers in brackets for mean age show minimum to maximum

Fig. 2 Forest plots for survival outcomes of heart transplantation after failed Fontan for **a** 1-year and **b** 5-year. I^2, heterogeneity; 95% CI, 95% confidence interval; Evt/Trt, events/total

rate (RR=0.00; *p*=0.99)] had an insignificant negative correlation with both the survival rates respectively.

Secondary outcomes

Figure 3 shows forest plots for secondary outcomes of heart transplantation after failed Fontan procedure. The prevalence of acute rejection was 20% ([7.4%, 36.8%]; I^2 = 72.48%) (Fig. 3a), renal dysfunction was 31.3% ([10.5%, 57.2%]; I^2 =75.42%) (Fig. 3b), multi-organ failure was 18.6% ([2.8 to 43.9%]; I^2= 69.60%) (Fig. 3c), and sepsis was 21.1% ([9.0%, 36.8%]; I^2 = 61.19%) (Fig. 3d).

Sensitivity analysis of pediatric population

Furthermore, a sensitivity analysis was also conducted to identify the survival rate among the pediatric population separately who underwent heart transplantation for failed Fontan. The analysis yielded a pooled prevalence of 74.5% ([65.4%, 82.5%]; I^2 =14.85%) for 1-year survival rate (Figure S1) and 69.2% ([63.1%, 75%]; I^2=0%) for 5-year survival rate (Figure S2) in pediatric population.

Sensitivity analysis of low bias studies

To assess the risk of bias, a sensitivity analysis was done for 1-year and 5-year survival rate by excluding studies that had a medium risk of bias (Figure S3-S4). The new pooled prevalence for 1-year survival was 80.3% ([75.3%, 84.8%]; I^2=11.83%) and for 5-year survival was 73.6% ([62.3%, 82.6%]; I^2=75.62%).
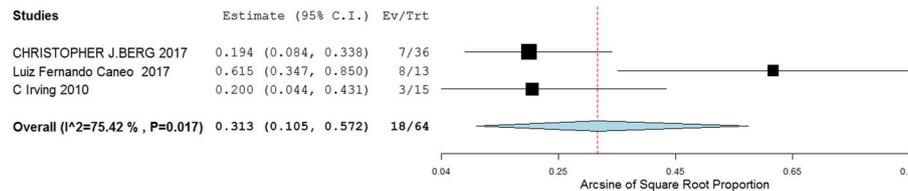
Sensitivity analysis of studies with ≥10 patients

Another sensitivity analysis was done to find the effect of sample size on heterogeneity by including only those studies that had ≥10 patients (Figure S5-S6). The 1-year survival rate was 79.6% ([75.4%, 83.6%]; I^2=0%), and 5-year survival rate was 75.8% ([64.2%, 85.7%]; I^2=77.6%). Sample size (≥10 patients) sensitivity analysis was able to reduce heterogeneity to 0% in 1-year survival rate. Furthermore, leave-one-out sensitivity analyses were done for 5-year survival rate outcome, but no study was found whose removal reduced heterogeneity.
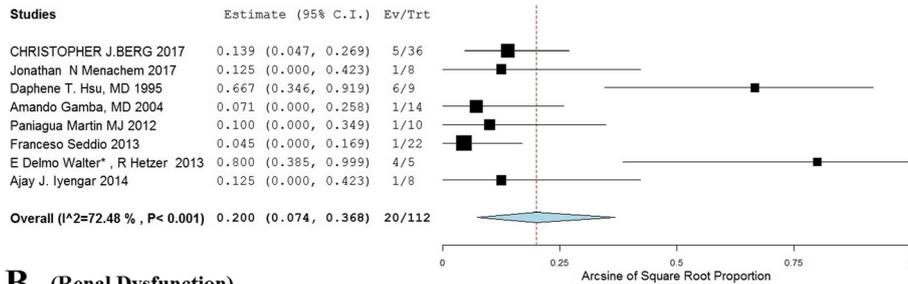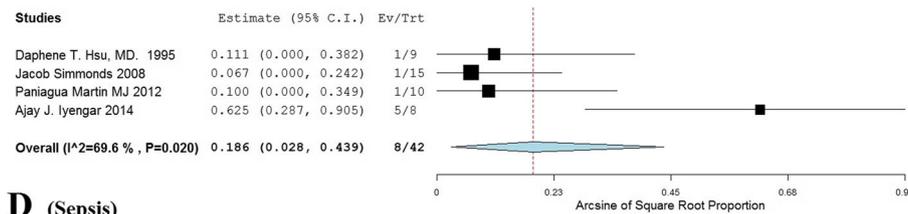
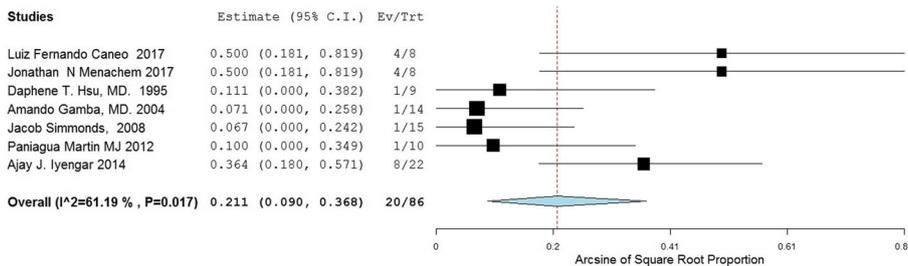**Fig. 3** Forest plots for safety outcomes: **a** acute rejection, **b** renal dysfunction, **c** multi-organ failure, and **d** sepsis. I^2, heterogeneity; 95% CI, 95% confidence interval; Evt/Trt, events/total

Discussion

This updated meta-analysis provides a reliable evaluation of heart transplantation outcomes in patients with a failing Fontan. Although the Fontan procedure has been a symbolic contribution to the field of congenital heart surgery, it has its debacles. Many of the patients with Fontan will ultimately develop its failure [3]. Management of a failing Fontan consists of prolonging the state of Fontan circulation with the primary intention of making the patients better candidates for transplantation. Fontan failure is historically resistant to medical therapy, although the use of standard heart failure vasodilators and pulmonary anti-hypertensive drugs is part of the clinical management to help bridge patients to a more

definitive surgical solution [26]. Mechanical circulation can be considered an option in cases of primary systemic ventricular dysfunction, predominantly the right side as the preeminent cause of Fontan failure [27, 28]. Surgical options for a failing Fontan are Fontan conversion and heart transplantation [29]. Fontan conversion usually consists of the construction of a bi-directional Glenn anastomosis, right atrial reduction, and placement of an extracardiac inferior vena cava to pulmonary artery conduit [30, 31]. Although the total cavopulmonary connection (TCPC) has provided better early and intermediate outcomes for Fontan conversion [32], patients are at increased risk of heart failure or end-organ dysfunction during long-term follow-up [33–36]. On the other hand,

the results of heart transplantation have improved significantly over the past decade [37–39].

Our study inclusive of 426 patients revealed 1- and 5-year survival rates of 79.9% and 76.7% respectively. In this study, we confirmed that there is no association between transplant recipient age or gender and survival, revealed by multivariate meta-regression which showed that age (RR= −0.014; *p*=0.196) and male gender (RR= −0.003; *p*=0.694) had a nonsignificant negative correlation with 1-year survival rate whereas male gender had a significant negative correlation (RR= −0.014; *p*=0.002) with 5-year survival rate. In addition to these results, this study revealed that the incidence of PLE was considerably high among patients with a failing Fontan, but no significant association was found between PLE and 1- and 5-year survival. However, PLE patients have been shown to have a high systemic venous pressure, low cardiac index, high pulmonary vascular resistance, decreased left ventricular systolic function, and elevated systemic ventricular end-diastolic pressure [40, 41], thus leading to an increase in Fontan pressure. Therefore, patients with PLE should be considered for heart transplantation. Furthermore, our analysis prompted that tricuspid atresia and double inlet left ventricle were found to present in a large number of Fontan patients requiring heart transplantation.

Compared to the previous study [42], which included a total of 351 patients, a significant number of patients and four observational studies have been added. The results of our analysis are consistent with the previous analysis, which revealed 1- and 5-year survival rates of 79.9% and 72.5%, respectively, with no significant association of age and gender with survival rates. The high heterogeneity in pooled results at 1-year and 5-year survival rate after exclusion of medium risk of bias studies can be attributed to many small studies with varying numbers of patients (from 4 to 194). In both our analysis and previous study, it has been difficult to ascertain the relationship of other factors with outcomes due to the heterogeneous nature of the population.

This study also revealed that the incidence of renal dysfunction after heart transplant was found to be significantly high (31.3%) among our included Fontan patients. Post-transplant renal dysfunction has a multifactorial etiology, the most common being the calcineurin inhibitor-induced nephrotoxicity [43], which could be aggravated in patients with a poor pre-transplant renal reserve [44]. Other non-immunosuppression-related risks include impaired renal function before heart transplant, age at transplant, female gender, pre-transplant diabetes, hypertension, hyperlipidemia, atherosclerosis, and surgical factors (i.e., prior cardiac surgery, use of cardiopulmonary mechanical support) [45]. Therefore, kidney function should be assessed prior to a heart transplant, so that appropriate measures could be taken to prevent the renal function from deteriorating. Other than renal dysfunction, acute rejection (20%), multi-organ failure (18.6%), and sepsis (21.1%) were also reported among our post-transplant population.

Limitations

This study has potential limitations. The effect estimates in the model are based on retrospective observational, single-center studies with a few multi-center studies. Therefore, they are subject to biases and confounding that may have influenced our results. We excluded patients with any underlying comorbidity like diabetes, hypertension, and patients with a history of prior transplantation. Most of the studies included in our study did not report data related to baseline characteristics of Fontan patients specifically. Despite trying to pursue the investigators of respective studies, we could not get access to the data related to prompting the need for heart transplantation in the Fontan population; a definite relationship could not be established. Therefore, more studies should be conducted in the future to determine the role of underlying heart conditions in the failure of Fontan. The relationship of other factors with outcomes could not be ascertained in our analysis due to the heterogeneity of the population. In addition to these, the data available was mostly related to the pediatric Fontan population, with only a few studies, including adult patients. Consequently, outcomes of heart transplantation in the adult population could not be determined. Furthermore, due to limited data available on the underlying heart conditions in adult Fontan patients, more studies should be conducted in the future.

Conclusions

As the results of this study exhibit increased survival rates among post-transplant patients, heart transplantation can be regarded as a standard option for patients with a failing Fontan. To further gauge the effectiveness of heart transplantation among patients with a failing Fontan, future researches should focus on the effects of underlying heart conditions on post-transplant outcomes and heart transplantation in the adult population with a failing single ventricle. Efforts should be made to optimize patient selection and the timing of transplantation in the hope of decreasing the significant early mortality and morbidity seen in this group.

Supplementary Information

Additional file 1 : **Table S1**. Quality assessment of cohort studies by Newcastle-Ottawa scale. **Figure S1**. Sensitivity analysis of 1-year survival

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rate including only pediatric population. **Figure S2**. Sensitivity analysis of 5-year survival rate including only pediatric population. **Figure S3**. Sensitivity analysis of 1-year survival rate including only low bias studies. **Figure S4**. Sensitivity analysis of 5-year survival rate including only low bias studies. **Figure S5**. Sensitivity analysis of 1-year survival rate including only studies with ≥10 patients. **Figure S6**. Sensitivity analysis of 1-year survival rate including only studies with ≥10 patients.

Abbreviations
IVC: Inferior vena cava; SVC: Superior vena cava; AHA: American Heart Association; PP: Pooled proportions; RR: Risk ratio; PLE: Protein-losing enteropathy; TCPC: Total cavopulmonary connection

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