

# Failures of the Fontan System in Univentricular Hearts and Mortality Risk in Heart Transplantation: A Systematic Review and Meta-Analysis

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**Abstract:** The Fontan procedure (FP) is the standard surgical treatment for Univentricular heart diseases. Over time, the Fontan system fails, leading to pathologies such as protein-losing enteropathy (PLE), plastic bronchitis (PB), and heart failure (HF). FP should be considered as a transitional step to the final treatment: heart transplantation (HT). This systematic review and meta-analysis aims to establish the risk of death following HT according to the presence of FP complications. There was a total of 691 transplanted patients in the 18 articles, immediate survival 88% ( $n = 448$ ), survival from 1 to 5 years of 78% ( $n = 427$ ) and survival from 5.1 to 10 years of 69% ( $n = 208$ ), >10 years 61% ( $n = 109$ ). The relative risk (RR) was 1.12 for PLE (95% confidence interval [CI] = 0.89–1.40,  $p = 0.34$ ), 1.03 for HF (0.7–1.51,  $p = 0.88$ ), 0.70 for Arrhythmias (0.39–1.24,  $p = 0.22$ ), 0.46 for PB (0.08–2.72,  $p = 0.39$ ), and 5.81 for CKD (1.70–19.88,  $p = 0.005$ ). In patients with two or more failures, the RR was 1.94 (0.99–3.81,  $p = 0.05$ ). After FP, the risk of death after HT is associated with CKD and with the presence of two or more failures.

**Keywords:** Fontan procedure; univentricular heart; heart transplantation; risk; mortality

## 1. Introduction

Congenital heart disease (CHD) has an incidence of 8–10 cases per 1000 live births, and its overall survival is over 80% at 45 years [1,2], depending on the complexity of the malformations. In particular, univentricular heart diseases have the most complex spectrum of complications which occur at a high rate and are associated with lower survival.

The Fontan procedure (FP), or total cavopulmonary bypass, is the standard surgical treatment for univentricular heart diseases. It results in the creation of the Fontan System (FS), a circulatory rearrangement characterized by direct passive drainage of the systemic veins to the pulmonary circulation without the support of the subpulmonary ventricle. The cardiac mass is connected in series, dedicating its function as a pump exclusively to the systemic circulation. This is a palliative procedure, avoiding ventricular dysfunction by reducing the overload volume and controlling cyanosis [3,4].

The FP creates a new circuit by joining the systemic venous return and the pulmonary system, this is associated with a sudden lack of active right-heart pumping of blood into the pulmonary arterial tree, resulting in significant venous congestion, reduced ventricular filling, low cardiac output this conditions a pressure overload and a gradual remodeling in the venous vascular and lymphatic system [5], causing plastic bronchitis (PB) [6] and protein-losing enteropathy (PLE) [7,8]. The most frequent complication is ventricular

dysfunction, which leads to death from heart failure (HF). Arrhythmias also develop, conditioned by the malformations of the conduction system and the flow redirection into the cavities [9]. The modified history of end-stage FP heart disease is accompanied by cardiac cirrhosis and cardio-renal syndrome [10]. Recently, there are authors who have investigated solutions to PF failures with venous Fontan ventricular assist such as Pekkan et al. [5]. Nevertheless, the FP is still considered as a transitional step to the final treatment, which is heart transplantation (HT) [11,12].

The proper functioning of the FP is the sum of morphological and hemodynamic variables; although they effectively increase survival, its primary objective is palliative. As time passes, the FP generates organic failures that deteriorate the quality of life, which can decrease the probability of success at the time of HT [13,14].

Analyzing the available scientific evidence is crucial in determining the mortality risk in transplant patients with univentricular physiology [15]. To this end, Tabarsi et al. published a meta-analysis [16] that reported a survival greater than 80% in the first year after HT in patients with FS. However, this study did not separately analyze survival according to the type of failure. Our study therefore aims to establish the risk of death after HT according to the presence of FS failures (PLE, PB, arrhythmias, HF, and chronic kidney disease [CKD]) in patients with univentricular heart disease.

## 2. Materials and Methods

A systematic review and meta-analysis of prognosis was carried based on the PRISMA 2020 statements [17].

### 2.1. Search Strategy and Data Sources

A systematic review of the literature was carried out with no starting date until 1 April 2021. The sources of information used were PUBMED, TRIP Database, International Clinical Trials Registry Platform (WHO), The Cochrane Library, Wiley, LILACS, and Google Scholar. In addition, aim-related systematic reviews were searched (snowball method) [16,18,19]. The reference lists of retrieved full-text articles were also searched to identify additional relevant studies. The search terms used were keywords or MESH terms (Supplementary Material Figure S1).

### 2.2. Eligibility Criteria

The articles and abstracts that fulfilled the PI(C)O criteria were included for further analysis. Population: Patients with HT due to CHD who had undergone FP or its variants; Intervention: Failure of FS; Comparator: PB, PLE, Arrhythmias, HF, CKD, and 2 or more failures; Outcome: death. Retrospective and prospective cohorts were acceptable study designs. Care was taken to select the articles that fulfilled the standards set in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [20].

Observational articles (longitudinal, cases and controls, and cohort) of patients with FP and HT, reporting the presence of at least one failure, were included. Publications made by the same author in the same hospital center were included, as long as they did not correspond to the same evaluation period. The exclusion criteria were: history of failure before FP or its takedown, multiorgan transplantation, and coexistence of autoimmune neoplastic diseases or other causes that were directly related to the outcome. Patients with cardiac retransplantation were also excluded. In the event that the articles met the selection criteria, but the data were insufficient to complete the analysis, the corresponding authors were contacted by email to request clarification of said data [21–55] in case that they sent information; it was then included in the review.

Seven investigators (M.H., H.G., D.V.M., Y.L., K.M., A.E., and K.S.) independently reviewed all references identified through the literature search using a predefined protocol. Articles that did not meet inclusion criteria during the title and abstract analysis were excluded. The remaining articles were selected for full text review. When limited

information was available from the abstract, the full text was always obtained. Included articles underwent a quality assessment by all the investigators.

Disagreements regarding the selection and quality assessment of articles were resolved through group discussion, and full consensus was achieved at each stage of review.

### 2.3. Data Extraction

Four investigators (M.H., K.S., H.G., and D.V.M.) independently extracted data from selected studies using a standardized electronic form in Excel. The following information was collected: author, year of publication, country, study design, total number of HT, total number of HT with fontan, deaths, and number of patients with each failure.

### 2.4. Variables

Some variable of interest was death after HT. The exposure variables PLE, PB, arrhythmias, and CKD were identified as the authors refer to the presence of the failure in the articles, authors definition of HF by cardiac catheterization in four articles [56–59], and by Echocardiogram in one [60], the rest of the articles was identified with the presence of HF by the authors. When the authors report the patient's characteristics in a table format and it was possible to identify the presence of two or more failures it was included for the two or more failures analysis.

### 2.5. Bias Control

Bias was evaluated with the GRADE tool (Grading of Recommendations, Assessment, Development, and Evaluation) [61] for observational studies, considering the following biases: adjusted confounders, validity of confounder measurement, analysis control, selection of participants, exposure assessment methods, exposure measurement, change in exposure status, outcome measurement, missing data, and missing exposure data. These were evaluated for each type of failure.

### 2.6. Statistical Analysis

A quantitative synthesis meta-analysis was performed using the Cochrane RevMan version 5.3 software for reviews, processing the data with a random effect method [62]. All outcomes that had at least 2 studies available for meta-analysis were finally reported. Risk of bias was assessed for each study proceeded as mandated by Cochrane standards. The relative risk (RR), confidence intervals (95% CI), and statistical significance were calculated using the Cochrane  $X^2$  test for each exposure variables. The study heterogeneity was assessed with the Tau test (due to small groups) and the  $I^2$  test. A value of  $p < 0.05$  was considered statistically significant.

## 3. Results

From the keyword and Mesh Terms search, a total of 1450 abstracts were identified, of which 731 were removed as duplicates. The full texts of 80 articles were reviewed for their eligibility [6,7,9–16,18,19,21–44,56–60,63–101], and 18 were included in the final analysis [6,7,9,11,12,15,56–60,63,68,69,74,77,83,96] (Figure 1) [17].

There was a total of 691 transplanted patients in the 18 articles (Table 1), with an immediate survival of 88% ( $n = 448$ ), survival from 1 to 5 years of 78% ( $n = 427$ ), survival from 5.1 to 10 years of 69% ( $n = 208$ ), and survival > 10 years 61% ( $n = 109$ ) (Figure 2).

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

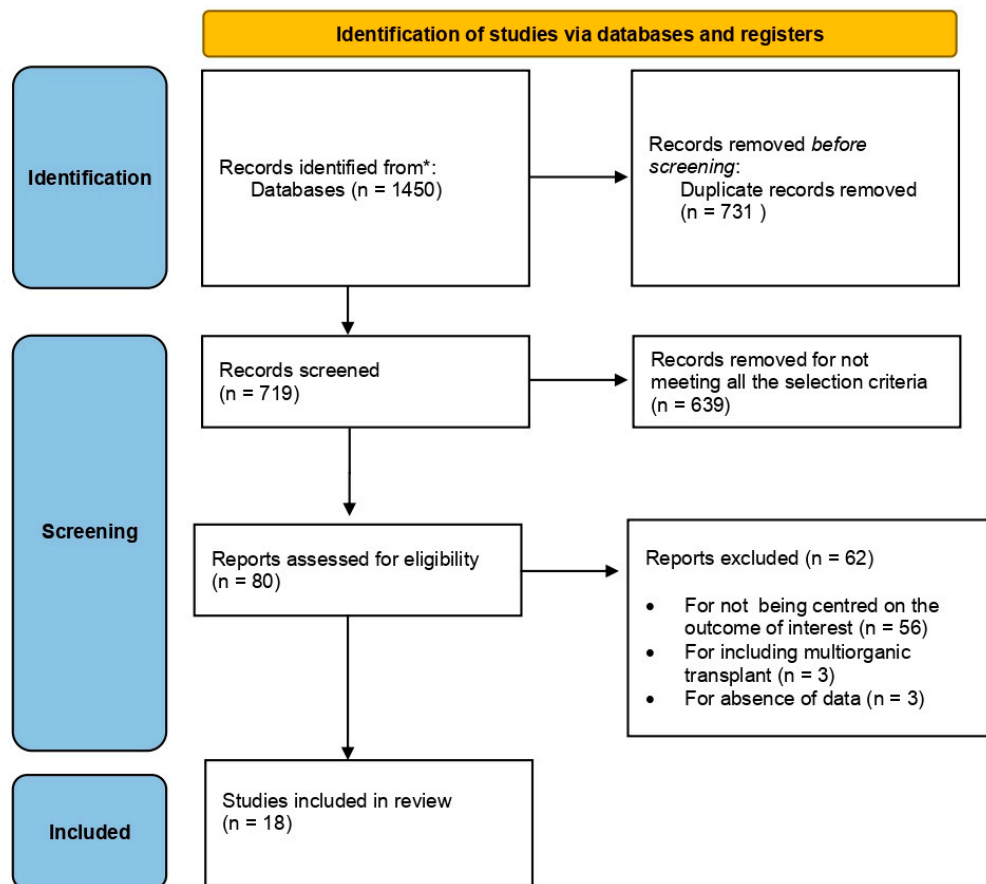


Figure 1. PRISMA flow: Selection of included studies.

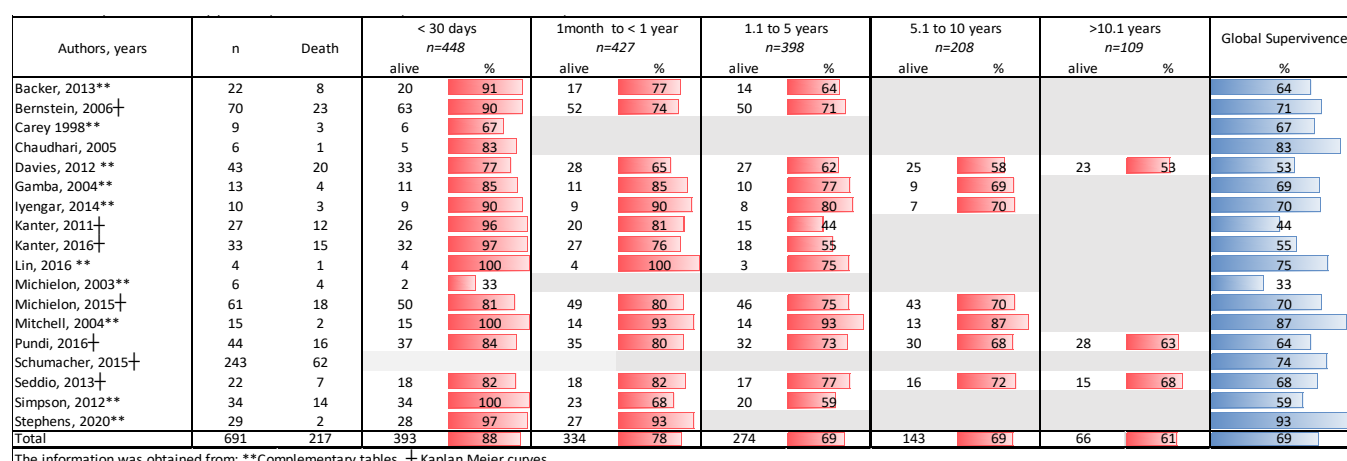
Table 1. Summary of studies included in the meta-analysis.

Author, Year	Country	Design	Overall Results				Outcomes			
			Transplantation	Fontan Population	Death	PLE	Arrythmia	HF	PB	CKD
Backer, 2013 [6]	USA	A retrospective study	206	22	8	5/13 (18%)	N/A	6/13 (46%)	0/2 (0%)	N/A
Bernstein, 2006 [68]	USA	A retrospective, multi- institutional study	1746	70	23	10/25 (40%)	N/A	N/A	N/A	N/A
Carey, 1998 [69]	UK	A retrospective review study in a single center, case series	46	9	3	N/A	2/6 (33%)	2/5 (40%)	N/A	1/2 (50%)
Chaudhar, 2005 [56]	UK	A retrospective review, a case series.	110	6	1	N/A	1/2 (50%)	N/A	N/A	N/A
Davies, 2012 [12]	USA	A retrospective review study	172	43	20	9/17 (53%)	N/A	9/18 (50%)	0/1 (0%)	N/A
Gamba, 2004 [57]	Italy	A retrospective review	575	13	4	2/7 (29%)	2/5 (40%)	4/9 (44%)	N/A	N/A
Iyengar, 2014 [74]	Australia	A retrospective study in a single center	111	10	3	0/1 (0%)	N/A	3/8 (38%)	NA	NA

Table 1. Cont.

Author, Year	Country	Design	Overall Results				Outcomes				
			Transplantation	Fontan Population	Death	PLE	Arrhythmia	HF	PB	CKD	
Kanter, 2011 [77]	USA	A retrospective study in a Single center.	222	27	12	2/12 (17%)	N/A	4/21 (19%)	N/A	N/A	
Kanter, 2016 [59]	USA	A retrospective study in a Single center.	311	33	15	2/13 (15%)	N/A	N/A	N/A	N/A	
Lin, 2016 [60]	Taiwan	A retrospective study in a Single center, cases series.	513	4	1	1/3 (33%)	N/A	0/3 (0%)	N/A	N/A	
Michielon, 2003 [83]	Italy	A Cohort study	25	6	8	1/2 (50%)	N/A	N/A	N/A	N/A	
Michielon, 2015 [15]	Netherlands	A retrospective multicenter review.	61	61	18	11/14 (79%)	N/A	14/28 (50%)	N/A	N/A	
Mitchell, 2004 [58]	USA	A retrospective study in a single center.	15	15	1	1/4 (25%)	1/4 (25%)	2/13 (15%)	N/A	N/A	
Pundi, 2016 [11]	USA	A retrospective review, cohort study in a single center.	44	44	16	5/12 (42%)	6/28 (21%)	N/A	N/A	N/A	
Schumacher, 2015 [7]	USA	A retrospective cohort study	3686	356	62	22/70 (31%)	N/A	N/A	N/A	N/A	
Seddio, 2013 [96]	Italy	A retrospective cohort study	839	22	15	6/11 (55%)	N/A	N/A	N/A	N/A	
Simpson, 2012 [9]	USA	A retrospective review study	34	34	11	5/12 (42%)	N/A	7/17 (41%)	N/A	N/A	
Stephens, 2020 [63]	USA	A retrospective cohort study	153	32	5	N/A	N/A	N/A	N/A	2/3 (67%)	

N/A: Not applicable.



The information was obtained from: \*\*Complementary tables, †Kaplan Meier curves

Figure 2. Analysis of survival by years in patients with the Fontan procedure and heart transplantation.

For the effect of PLE (Figure 3), 15 articles were included [6,7,9,11,12,15,57–60,68,74, 77,83,96], with a total population of 647 patients (216 with PLE) of whom 205 died (76 with PLE). The RR was 1.12 (95% CI = 0.89–1.40,  $p = 0.34$ ). The heterogeneity test showed a value of  $I^2 = 34\%$ . Authors Kanter [59,77] and Michielon [15,83] published studies from the same



center which were included as there was an interval greater than five years between studies. This translates that the presence of PLE is not a risk factor for death in these patients.

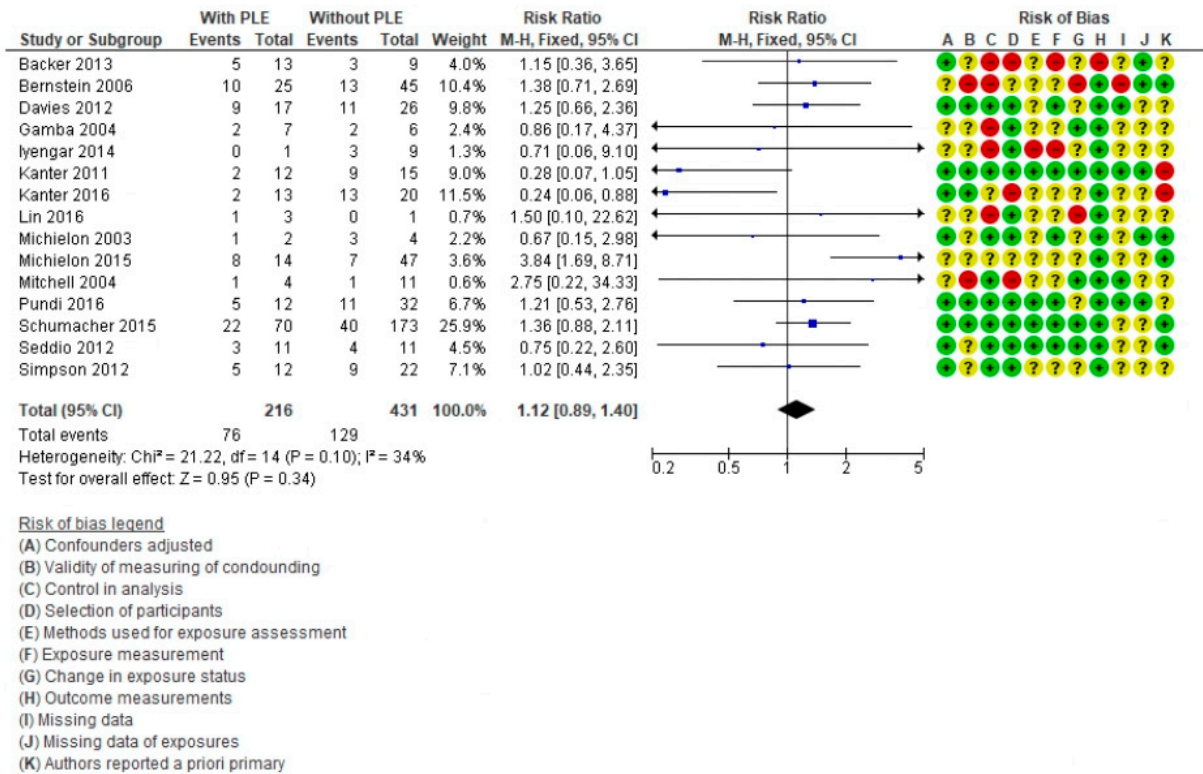


Figure 3. Forest plot comparing Fontan patients with protein-losing enteropathy (PLE) vs. without PLE for mortality post-cardiac transplant.

Regarding HF (Figure 4), 10 articles were included [6,9,12,15,57,58,60,69,74,77], with a total population of 239 patients (135 with HF) of whom 75 died (41 with HF). The RR was 1.03 (95% CI = 0.70–1.51, p = 0.88). The heterogeneity test showed a value of I<sup>2</sup> = 0%. The presence of HF is not a risk factor for death in these patients.

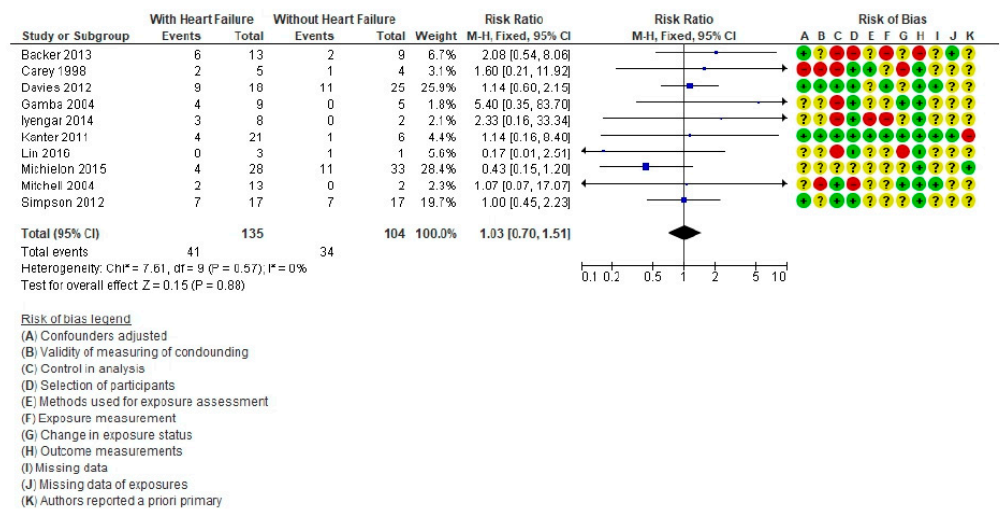


Figure 4. Forest plot comparing Fontan patients with cardiac failure vs. without cardiac failure for mortality post-cardiac transplant.

Five publications including arrhythmias were analyzed (Figure 5) [11,56–58,69], with a total of 87 patients (45 with arrhythmia) of whom 26 died (12 with arrhythmia). The RR was 0.70 (95% CI = 0.39–1.24,  $p = 0.13$ ). Heterogeneity presented a value of  $I^2 = 44\%$ . The presences of arrhythmias are not a risk factor for death in these patients.

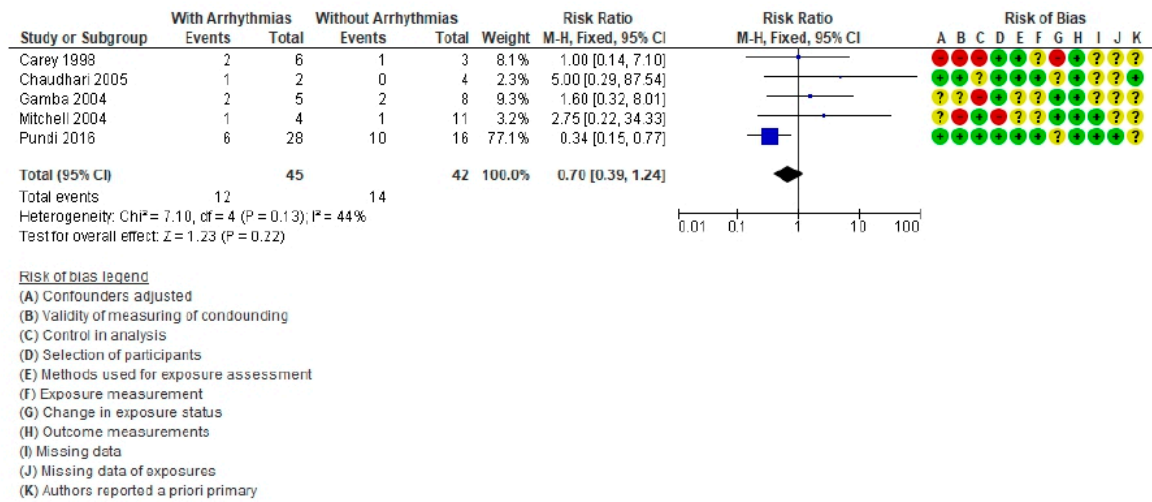


Figure 5. Forest plot comparing Fontan patients with arrhythmias vs. without arrhythmias for mortality post-cardiac transplant.

For the effect of CKD (Figure 6), two articles [63,69] were included, with a population of 38 patients (five with CKD) and a total of five deaths (three with CKD). The RR was 5.81 (95% CI = 1.70–19.88,  $p = 0.005$ ). The heterogeneity test had an  $I^2$  value of 68%. The presence of CKD is a risk factor for death in patients with HT after FP.

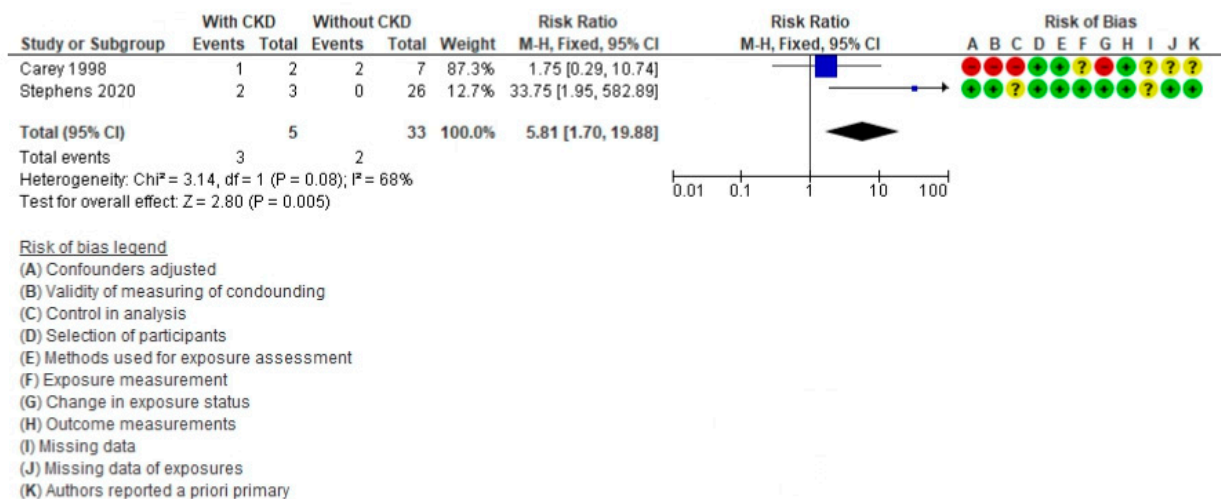


Figure 6. Forest plot comparing Fontan patients with chronic kidney disease (CKD) vs. without CKD for mortality post-cardiac transplant.

Two publications [6,12] were analyzed for PB, including 65 patients (three with PB) and no deaths (Figure 7). The estimated RR was 0.46 (95% CI = 0.08–2.72,  $p = 0.39$ ), and the  $I^2$  heterogeneity was 0%. The presence of PB is not a risk factor for death in these patients.

A subanalysis was carried out (Figure 8) including seven articles [6,9,56–58,60,69] with additional information on the coexistence of the failures. The total population was 104 subjects (28 with two or more failures) and there were 33 deaths, including 12 patients with two or more failures. The RR was 1.94 (95% CI = 0.99–3.81,  $p = 0.05$ ) and

the  $I^2$  heterogeneity was 0%. The coexistence of the failures are a risk factor for death in these patients .

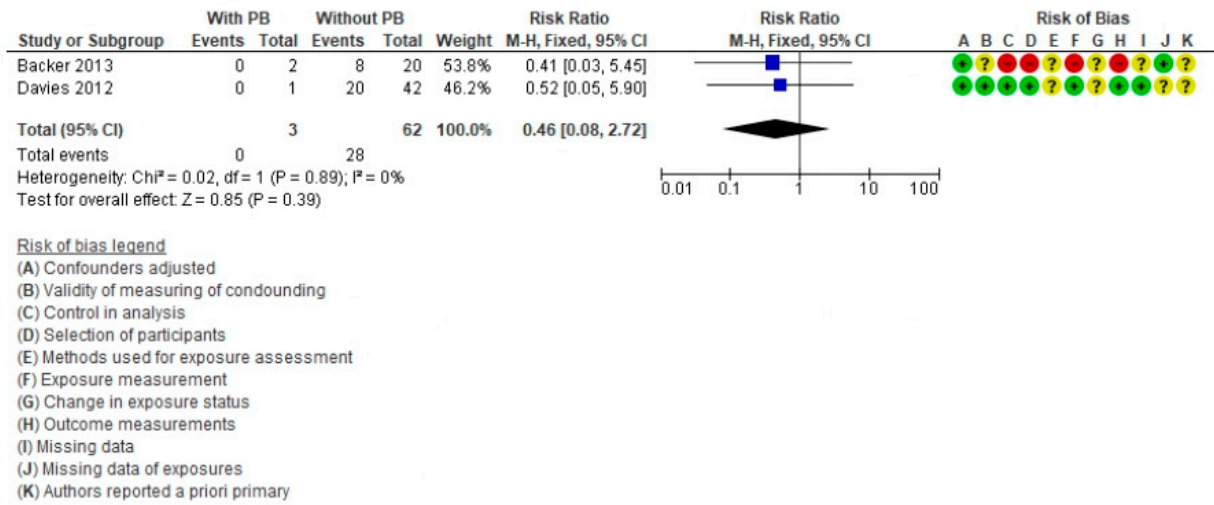


Figure 7. Forest plot comparing Fontan patients with plastic bronchitis (PB) vs. without PB for mortality post-cardiac transplant.

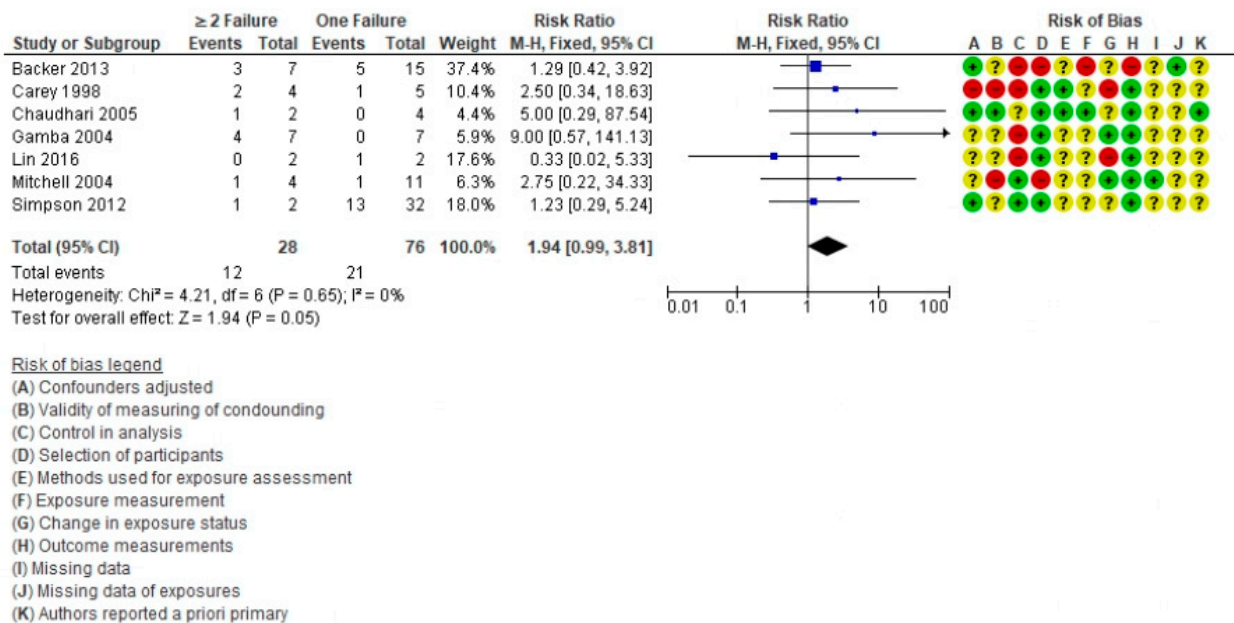


Figure 8. Forest plot comparing Fontan patients with a single failure vs. ≥2 failures for mortality post-cardiac transplant.

#### 4. Discussion

This systematic review and meta-analysis focuses on the effect of each failure of the FS as risk factors for mortality at the time of HT in different periods. It is the first meta-analysis that evaluates the individual risk of each failure for HT, the results are important since the findings showed that there is no association of death for failures of PLE, PB, HF, and arrhythmias, while the presence of Renal failure and the set of two failures if they represent risk and lower survival for patients who underwent HT after Fontan. In the 18 articles reviewed, these patients had a first-year survival of 79%, consistent with the findings of a 2017 meta-analysis by Tabarsi et al. which analyzed survival after HT in the presence of failures of the FS and found 80% survival at one year [16].

In the updated International Society for Heart and Lung Transplantation (ISHLT) database (as of 2020), there were a total of 30,130 patients with HT between 2004 and



2014. Of these, 1839 were related to CHD (one-year survival 78.3%), 16,444 to dilated cardiomyopathy (one-year survival 86.2%) and 12,247 to ischemic heart disease (survival of 84.3%) [102]. In this regard, patients with FP demonstrated 1.7-times higher risk of death from complications in the immediate postoperative period. The overall survival of HT performed from 5 to 10 years of age is greater than 60%, with a decrease after the first decade secondary to HF, which implies the need for retransplantation [103,104]. In the case of patients with FP, transplantation is useful to reverse the effects of failures, especially PLE and PB [13].

PLE is the consequence of increased pressure at different sites, such as the liver and splanchnic beds and the mesenteric network, which favors protein leakage into the intestinal lumen. Generally, patients who present with PLE also have other complications such as malnutrition, recurrent infections, and capillary leakage into the interstitial space. The present meta-analysis did not demonstrate a difference in mortality in the group of HT patients with PLE, which may be due to the fact that it is reversible when the etiological mechanism is removed.

PB occurs after FP with a frequency of 1–4%. Its etiological mechanism is similar to that of PLE, as well as lymphatic flow also being increased [105]. In this meta-analysis, the presence of PB was not associated with higher mortality. In the two articles analyzed, this complication was not reversible with HT as the lymphatic circulation does not fully improve; it is also associated with greater complications during immediate postoperative ventilatory support and pulmonary pressures are at high levels according to transplant criteria.

Of the patients included in this meta-analysis, 55.7% were classified with some of the criteria for HF. No differences in mortality were demonstrated in these patients at the time of transplantation. While the morphology of the systemic ventricle is associated with immediate mortality at the time of cavopulmonary bypass, no differences in the presentation of HF or other failures have been demonstrated when comparing a right or left morphology of the single ventricle [106,107]. Variables such as hospitalizations due to HF or sudden death events are directly associated with mortality in transplant patients [108], and these variables were not controlled in the meta-analysis.

Rhythm disorders are a frequent complication of FP. The most frequent are supraventricular tachyarrhythmias (approximately 60%) which include atrial fibrillation (40%), atrial flutter (17.2%) and atrial ectopic tachycardia (17.2%) [109]. The second most frequent group are second and third degree blocks; these are mostly treated with epicardial pacemakers, and can be accompanied by ventricular failure secondary to desynchrony [110]. In this work there was no association between death and the presence of arrhythmia, probably because the mechanism is completely resolved once the transplant has been performed, but complicated by the fact that in this analysis all rhythm disorders were grouped together [111].

The only failure associated with a statistically significant risk of death was CKD (RR = 5.8), which is conditioned by a mixed mechanism: first the pre-renal origin associated with HF and the distribution of fluid to the interstitial space and second by the intrarenal component due to prolonged diuretic intake [10,112]. Unlike PLE and PB [68,96], this lesion is irreversible and can become more acute in the immediate postoperative period, during ischemia and the postsurgical low-output syndrome.

Hollander et al. reported that after HT in patients with univentricular hearts with CKD, the 8% progressed to the renal stage [113], and during follow-up, 10% were expected to die in the next 5 years [114]. In the sub-analysis of this work, the two included articles did not specify the diagnostic method and stage of CKD, which may represent a misclassification bias. In this study, the analyses are based on comparing the failures with each other, which is likely the reason for the lack of significance in mortality differences. However, when focusing the analysis on the coexistence of two simultaneous failures, a value of RR = 1.94 was found, mostly explained by the coexistence of PLE and HF. It is important to consider the potential biases caused by the temporality of this phenomenon and the reference bias.

It should also be noted that articles reporting multiorgan transplantation were excluded from the analysis.

There are some systemic diseases in which it is not yet clear whether they will benefit from a heart transplant such as: Kearns–Sayre syndrome that belongs to a group of neuromuscular disorders known as mitochondrial encephalomyopathies that typically involves the central nervous system, eyes, skeletal muscles, and heart [115]. Acute onset of congestive HF possible expression of a rare form of dilated cardiomyopathy; Fabry disease that is an X-linked lysosomal storage disorder caused by mutations in the  $\alpha$ -galactosidase A gene (GLA) that leads to reduced or undetectable  $\alpha$ -galactosidase A (AGAL) enzyme levels and progressive accumulation of glycolipids—primarily globotriaosylceramide (Gb3) and its deacylated form, lysoGb3, in cells throughout the body including vascular endothelial and smooth muscle cells and cardiomyocytes. Heart disease is present in all forms of Fabry disease, with different grades of organ involvement, and the concentric left ventricular (LV) hypertrophy [116]. Systemic sclerosis that is a systemic autoimmune disease of heterogeneous pathogenesis in which vascular, cutaneous, and internal organ fibrosis are prominent [117], in the literature there are reports of successful HT [115–117]; however, each case should never fail to be evaluated individually, for patients with PF and specifically for patients with Failing Fontan, there is no doubt that the treatment is HT and the fact of knowing that the presence of a single fault that could be PLE, PB, HF, and arrhythmias are not associated with a greater risk of death. It is new information in the literature since failures have never been evaluated in this way and it is very useful for patient care.

In patients with congenital heart disease, survival of HT is lower compared to other cardiomyopathies, much due to the fact that the clinical state is compromised, this occurs more frequently in patients with PF and its failures. In this meta-analysis we could identify that mortality is very similar to that reported by ISHLT. Most of the failures are not associated with mortality, except for CKD, which is not reversible. At the same time, we also found that the association of the presence of two or more failures has significant risk. These results are a first approach to having more information for the discrimination of patients who present greater risk and the selection of patients than if would benefit after the HT.

In this work, the random effect analysis was carried out, unlike the meta-analysis published by Tabarsi et al. [16], finding greater heterogeneity in the analysis of arrhythmias ( $I^2 = 44$ ), probably conditioned by the clinical diversity of the spectrum of electrical disorders considered as “rhythm disturbances” and CKD ( $I^2 = 68\%$ ) explained by the methodological variability in its definition in the studies that included it.

We meta-analyzed the effect of five different failures in the risk of mortality in FP transplant patients, it is important to mention that some of the sub-analyses were carried out with a limited number of articles and patients, for example, CKD with just three events and BP without deaths, these results demonstrate the need to carry out research studies focused on the standardization and follow-up of these failures. Also, misclassification bias is present in most of the included studies, for example for the PB the diagnosis information was obtained from the reference in the article by the authors not from medical records or from confirmatory tests such as  $\alpha$ -1 antitrypsin in stool. Another example: an MRI or bronchoscopy study is required for the diagnosis of PB, which are not declared in the included studies, so there may be diagnostic confirmation bias. Another risk of bias in the included articles was the incomplete follow-up of the cohorts limiting the analysis to the first year after the HT, and in the case of publications by the same author who analyzed different periods it was not possible to identify whether there was patient repetition.

Other limitation of the study was that there are determining variables that intervene in the development of the disease, such as age at the time of the FP, pulmonary pressure, surgical technique, the type of treatment used, among others, that have not been weighted in this work because the variables measured in the included items are different from each other.

Another weakness to answer the objective is that the failure that is evaluated is compared with the group with the other failures; however, it cannot be performed in another way since if the patient does not present failure, there would be no indication for heart transplantation.

## 5. Conclusions

In conclusion, heart transplant in patients with a failing FP showed an immediate survival of 88%. PB, PLE, HF, and arrhythmias were not found to be associated with a greater risk of death, but the sum of two or more failures had an RR of 1.94 (95% CI = 0.99–3.81). The presence of CKD had an RR value of 5.81 (95% CI = 1.70–19.88). To fully understand the contribution of failures of FS to mortality, further studies with greater follow-up and clarity around the detection of failures is required.

**Supplementary Materials:** The following are available online at <https://www.mdpi.com/article/10.3390/life11121363/s1>, Figure S1: Search terms used.

**Author Contributions:** Conceptualization, H.M.-G. and L.Y.-G.; methodology, H.M.-G. and S.G.K.; software, H.M.-G. and S.G.K.; validation, L.Y.-G., M.K.-K., and E.A.-G.; formal analysis, H.M.-G. and S.G.K.; investigation, H.M.-G., J.G.H.-V., M.D.V.-L., S.G.K.; resources, H.M.-G. and L.Y.-G.; data curation, H.M.-G., J.G.H.-V., M.D.V.-L. and S.G.K.; writing—original draft preparation, H.M.-G. and S.G.K.; writing—review and editing, L.Y.-G., M.K.-K. and E.A.-G.; visualization, L.Y.-G., M.K.-K. and E.A.-G.; supervision, L.Y.-G., M.K.-K. and E.A.-G. All authors have read and agreed to the published version of the manuscript.

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