

# Outcomes and survival following heart retransplantation for cardiac allograft failure: a systematic review and meta-analysis

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**Background:** Long-term efficacy of heart retransplantation (RTx) for end-stage cardiac allograft failure remains unclear given the limited worldwide experience and is an important question to elucidate given the shortage of donor organs. The aim of this systematic review was to examine the outcomes of RTx in patients with cardiac allograft failure.

**Methods:** Electronic search was performed to identify all studies in the English literature assessing RTx for cardiac allograft failure. All identified articles were systematically assessed for inclusion and exclusion criteria.

**Results:** Eleven studies were included for analysis, with a total of 7,791 patients. A total of 7,446 patients underwent primary heart transplantation (HTx) whereas 345 patients underwent RTx with average time from primary HTx to RTx interval of 5.03 years (95% CI: 3.13–6.94 years). There were 35.2% of patients received RTx within 30 days of primary transplant. Early mortality was significantly higher among RTx patients (RTx 28.2% vs. HTx 11.2%,  $P < 0.001$ ) whereas survival was significantly higher among HTx patients when compared to RTx patients at 1 year (HTx 81.8% vs. RTx 59.1%,  $P < 0.001$ ), 2 years (HTx 77.9% vs. RTx 53.6%,  $P < 0.001$ ), 3 years (HTx 76.1% vs. RTx 49.8%,  $P < 0.001$ ), 5 years (HTx 68.8% vs. RTx 41.4%,  $P < 0.001$ ) and 10 years (HTx 53.9% vs. RTx 31.7%,  $P < 0.001$ ). There were no significant differences between HTx and RTx in terms of freedom from rejection at 1 year (HTx 61.0% vs. RTx 53.7%,  $P = 0.43$ ), 2 years (HTx 63.8% vs. RTx 53.7%,  $P = 0.26$ ), 3 years (HTx 62.9% vs. RTx 51.9%,  $P = 0.30$ ) and 5 years (HTx 61.0% vs. RTx 51.9%,  $P = 0.36$ ).

**Conclusions:** Patients who underwent heart RTx had a significant lower survival when compared to those who only underwent primary HTx. There were no significant differences in post-transplantation freedom from rejection. Careful patient selection and perioperative care can make heart RTx a viable option for selected recipients.

**Keywords:** Cardiac allograft failure; heart retransplantation (RTx); systematic review



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## Introduction

Orthotopic heart transplantation (HTx) remains the gold standard treatment for end-stage heart disease (1). The International Society for Heart Lung Transplantation (ISHLT) estimates that over 100,000 heart transplants have

been performed worldwide (2). With the advancement in immunosuppressive agents, heart preservation techniques, surgical techniques, donor and recipient selection and rejection surveillance, survival of primary HTx recipients at 30 days, 1 year and 5 years approach to 90%, 86% and 70%, respectively (3).

With the increasing population of patients who received HTx, there is a steady population of those who develop cardiac allograft failure secondary to acute rejection, primary graft failure and transplant coronary artery vasculopathy. Several therapeutic interventions including aggressive immunosuppressive therapy, percutaneous transluminal coronary angioplasty, laser myocardial therapy, coronary artery bypass grafting, valvular repair and temporary and long term mechanical circulatory assist devices have been proposed; however, heart retransplantation (RTx) remains the only viable long-term treatment for end-stage cardiac allograft failure (4-8). Despite annual RTx rates of as high as 6% as reported by the 2017 ISHLT data (9), the literature on RTx is ambiguous with several studies reporting conflicting findings in regards to the survival and viability of this therapy (10,11).

Long-term efficacy of RTx remains unclear given the limited worldwide experience and is an important question to elucidate given the shortage of donor organs. The aim of this systematic review was to examine the outcomes of RTx in patients with cardiac allograft failure.

## Methods

### Literature search strategy

Thorough electronic searches were performed in August 2017 using Ovid Medline, Embase, Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR), Web of Science, Scopus and CINAHL. To achieve the maximum sensitivity of the search strategy, we combined the terms: “heart retransplantation”, “cardiac retransplantation”, “reoperation”, “graft failure” and “graft survival” as either key words or MeSH terms. The reference lists of all retrieved articles were reviewed for further identification of potentially relevant studies, assessed using the inclusion and exclusion criteria.

### Selection criteria

Eligible studies for the present systematic review and meta-analysis included those that addressed heart RTx amongst HTx recipients. Articles were excluded if they did not contain information about post heart RTx outcomes and survival. When institutions published duplicate studies with accumulating numbers of patients or increased lengths of follow-up, only the most complete reports were included

for quantitative assessment with no overlapping time intervals. We excluded studies on patients <18 years of age, studies not published in the English language and those not involving human subjects. Furthermore, abstracts, case reports, conference presentations, editorials, reviews and expert opinions were also excluded.

### Data extraction and critical appraisal

Data was extracted from article texts, tables and figures (JH Choi, JG Luc). Discrepancies between the two reviewers were resolved by discussion and consensus.

### Statistical analysis

A meta-analysis of proportions was conducted for the available main perioperative and postoperative variables with logit transformation. Heterogeneity was evaluated using Cochran Q and  $I^2$  test. Meta-regression was conducted using HTx and RTx as subgrouping variables. All analyses were performed using the metafor package for R version 3.01. P values <0.05 were considered statistically significant.

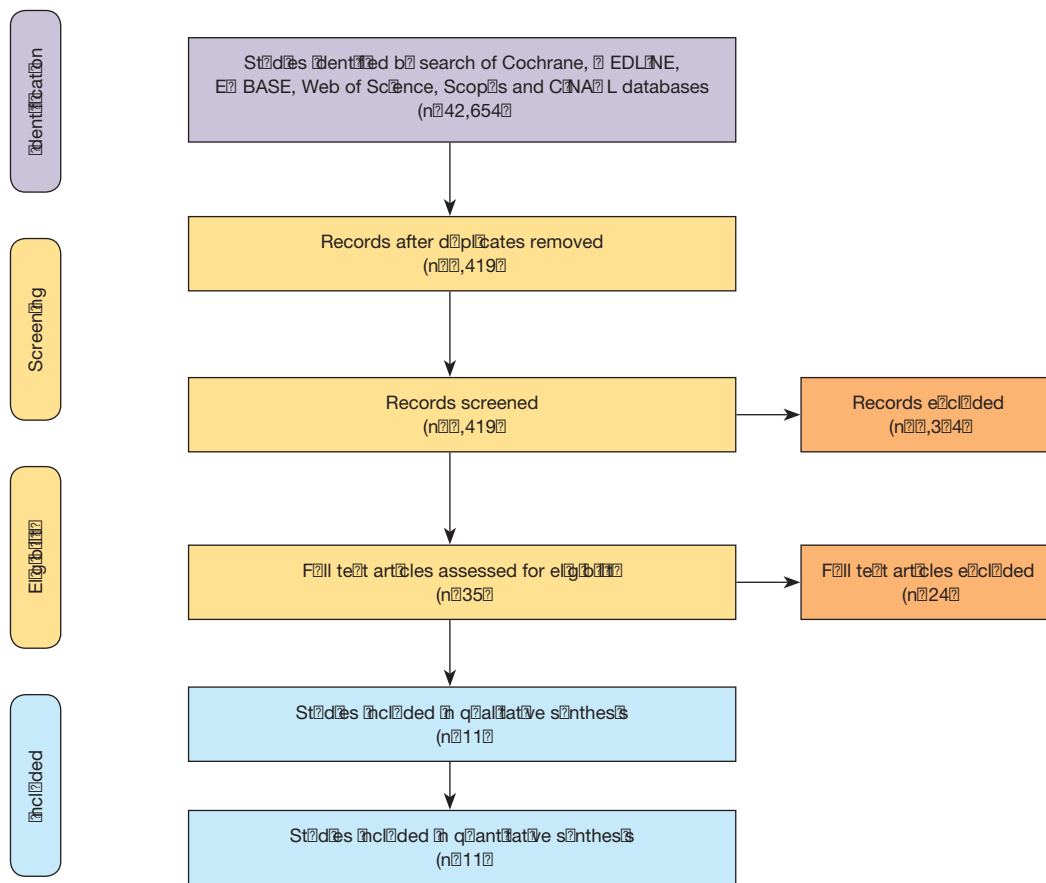
## Results

### Study characteristics

Overall, 8,419 records were identified in the literature search from 1968 to 2011. Following application of the inclusion and exclusion criteria, 11 studies were included for analysis, with a total of 7,791 patients out of which 7,446 patients underwent primary HTx and 345 patients underwent RTx. A PRISMA flow diagram depicting the overall search strategy is provided in *Figure 1*. Manual search of references did not yield further studies. All studies included in the review were single-center retrospective studies.

### Baseline demographics

Baseline demographic of recipients undergoing primary HTx and RTx are shown in *Tables 1,2*, respectively. Mean age of patients undergoing primary HTx and RTx was 50.2 and 49.0 years, respectively, with >81% of patients being male in both groups. The indications for HTx include dilated cardiomyopathy (51.3%), ischemic cardiomyopathy (39.1%), congenital heart disease (4.4%), valvular cardiomyopathy



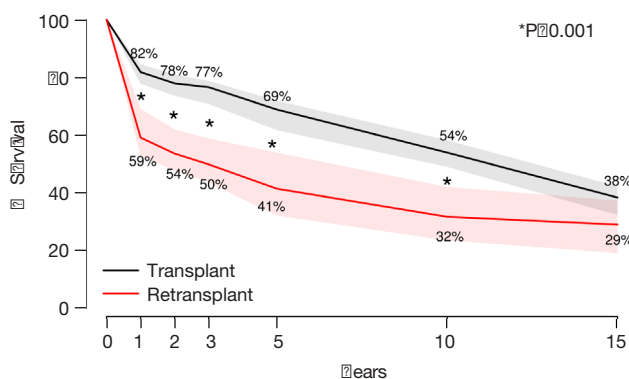
**Figure 1** PRISMA schematic of search strategy. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

**Table 1** Baseline demographics of primary heart transplant recipients

Variables	Studies (n)	Events (n)	Total (n)	Mean
Age (years)	4	0	3,512	50.2
Males (%)	4	2,537	3,115	81.4
<b>Indications for primary transplant (%)</b>				
DCM	3	951	1,253	51.3
ICM	3	724	1,253	39.1
Valvular disease	2	35	1,117	3.1
Hypertrophic heart disease	1	12	723	1.7
Congenital heart disease	2	49	1,117	4.4
DCM, dilated cardiomyopathy; ICM, ischemic cardiomyopathy.				

**Table 2** Baseline demographics of heart retransplant recipients

Variables	Studies (n)	Events (n)	Total (n)	Mean
Age (years)	4	0	137	49.0
Males (%)	4	103	127	81.1
<b>Indications for retransplant (%)</b>				
Graft vascular/coronary artery disease	10	127	304	61.5
Acute rejection	7	55	223	24.7
Early graft failure	6	36	122	19.1
Unspecified graft failure	2	13	42	27.1
Early retransplant (30 days from primary)	3	32	91	35.2



**Figure 2** Survival amongst primary heart transplant and retransplantation recipients. Survival was significantly higher among primary heart transplant patients at 1, 2, 3, 5 and 10 years. No significant differences in survival between the two groups were found at 15 years post-transplantation.

(3.1%) and hypertrophic cardiomyopathy (1.7%).

### RTx

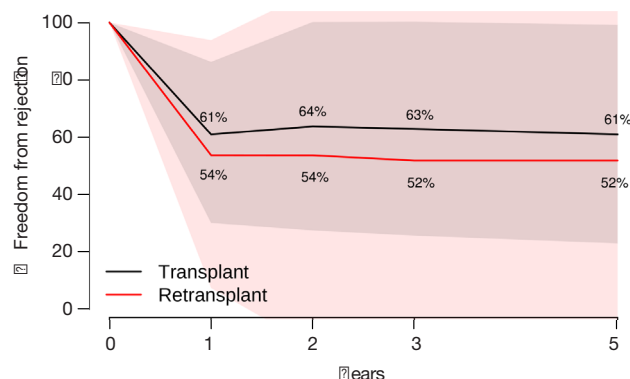
The indications for RTx include allograft vasculopathy (61.5%), acute rejection (24.7%), early graft failure (19.1%). Graft failure etiology was unspecified in 27.1%. In total, 35.2% of patients received RTx within 30 days of getting primary HTx. Mean time interval between primary HTx to RTx was 5.03 years (95% CI: 3.13–6.94).

### Primary endpoint: post-transplant survival

Actuarial survival was significantly higher among HTx patients when compared to RTx patients at 1 year (HTx 81.8% vs. RTx 59.1%,  $P < 0.001$ ), 2 years (HTx 77.9% vs. RTx 53.6%,  $P < 0.001$ ), 3 years (HTx 76.1% vs. RTx 49.8%,  $P < 0.001$ ), 5 years (HTx 68.8% vs. RTx 41.4%,  $P < 0.001$ ) and 10 years (HTx 53.9% vs. RTx 31.7%,  $P < 0.001$ ). This was principally due to a high early mortality of amongst RTx patients (RTx 28.2% vs. HTx 11.2%,  $P < 0.001$ ). Differences in survival were no longer statistically significant between HTx and RTx patients when the survival timepoint was extended to 15 years (Figure 2).

### Secondary endpoint: freedom from rejection

There were no significant differences between HTx and RTx in terms of freedom from rejection at 1 year (HTx 61.0% vs. RTx 53.7%,  $P = 0.43$ ), 2 years (HTx 63.8% vs.



**Figure 3** Freedom from rejection between primary heart transplant and retransplant patients at 1, 2, 3 and 5 years.

RTx 53.7%,  $P = 0.26$ ), 3 years (HTx 62.9% vs. RTx 51.9%,  $P = 0.30$ ) and 5 years (HTx 61.0% vs. RTx 51.9%,  $P = 0.36$ ) (Figure 3).

### Discussion

Although outcomes following orthotopic HTx have improved, allograft loss is a problem ultimately confronted by many recipients. Although different surgical and medical options have been proposed to overcome allograft failure such as revascularization, valvular repair, mechanical assistance and new pharmacological regimens (8,12-15), heart RTx remains the only definitive management for these patients. Previous studies have demonstrated that outcomes following RTx are inferior to those for primary HTx (10,16-25). Given the limited number of available donor hearts, the long-term results of this treatment option need to be evaluated.

In this systematic review and meta-analysis, the three major indications for heart RTx (coronary allograft vasculopathy, early graft failure and acute rejection) mirror those seen in other heart RTx experiences (20,23). We demonstrate that patients who underwent RTx had a significantly lower survival than those who only underwent primary HTx, principally due to a high early mortality amongst RTx patients. There were no significant differences between HTx and RTx patients in terms of freedom from rejection.

In an analysis of 364 heart RTx reported to the Scientific Registry of Transplant Recipients from 2000 to 2005 (18), 1-, 3- and 5-year unadjusted graft survival was lower in RTx than primary HTx (82% vs. 86%, 70% vs. 80% and 58% vs. 73%, respectively, all  $P < 0.001$ ). However, following

adjustment for donor and recipient factors, the relative risk (RR) for graft loss after RTx were comparable to primary HTx at 1-year (RR, 1.34;  $P=0.151$ ) and 3-years (RR, 1.16;  $P=0.426$ ) after transplantation. In an analysis of the ISHLT Registry of 1,125 RTx from 1982 to 2003, survival at 1, 3, 5 and 10 years was significantly lower for RTx compared to HTx. An early study of RTx at 13 centers revealed a 1-year survival of only 60% (17). Another study reporting on the outcomes from the Cardiac Transplant Research Database of 106 RTx recipients also confirm that survival after RTx was inferior to primary HTx with a survival of 56% at 1 year and 38% at 5 years (20).

As survival following heart RTx is inferior to that following primary HTx, it is important for further analysis to determine risk factors for poor outcomes following RTx. A previous analysis of the Joint ISHLT/United Network for Organ Sharing Thoracic Registry suggested that the outcome following RTx was significantly affected by the time between transplants, where an inter-transplant interval of less than 2 years resulted in a 2-year survival less than 60% (19). Furthermore, an analysis of data in the Cardiac Transplant Research Database showed that survival following RTx were lowest for acute rejection (32% and 8% at 1 and 5 years, respectively) and early graft failure (50% and 39% at 1 and 5 years, respectively) (20). In another report from Columbia University, the authors reported that since 1993, when selection criteria for RTx excluded those with primary allograft failure and intractable acute rejection occurring less than 6 months after HTx, 1-, 2- and 4-year survival following RTx was 94%, 94% and 94%, respectively (24). These findings suggest that if appropriate candidates are selected for RTx, outcomes can approximate those following primary HTx.

Our study is consistent with the findings of previous studies (10,16-25) though it reports a lower survival than the international average of RTx survival. Reasons for this discrepancy may be due to the high percentage of early (30 days) RTx in our cohort, which has been demonstrated to significantly predict mortality (19). Other reasons include the lack of detail to allow for differentiation of patients based on etiology of allograft failure, inter-transplant interval, era of RTx and other comorbidities such as pre-operative dependence on ventilation or mechanical circulatory support, factors of which have been shown to affect RTx survival. By highlighting inferior early survival of RTx compared to HTx with similar rates of long-term freedom from rejection, our study raises the question as to why outcomes following RTx are inferior to HTx. As seen

in *Figure 2*, the survival curves diverge early in the first year following transplant and then are nearly parallel. This suggests that the differences in survival likely represent perioperative and early postoperative complications such as multi-organ failure, bleeding, and infection, which deserve further exploration (26,27). If the problem of early mortality can be overcome, long-term survival of heart RTx appears to be good.

Since its first clinical application in 1977 (28), the discussion about the justification of heart RTx in the context of donor organ shortage is still ongoing. The Working Group on Heart Retransplantation has published a consensus statement regarding the indications for heart RTx (26). In the consensus statement, Johnson *et al.* suggest that RTx should be considered in patients with chronic allograft dysfunction, whereas patients with acute rejection and early graft dysfunction should be considered contraindications to RTx (26). Patients on mechanical cardiorespiratory support and those with post-transplant lymphoproliferative disorder should undergo careful consideration on an individual basis (26). Acute graft failure following primary HTx is a clinical dilemma. A widely used salvage strategy for acute graft failure is temporary mechanical circulatory support using venoarterial extracorporeal membrane oxygenation or short-term left or right ventricular assist devices as a bridge to recovery or RTx (8). Recent publications have been encouraging by demonstrating that long-term outcomes for HTx recipients with preoperative left ventricular assist devices were comparable to those without (29-31). Careful patient selection and perioperative care is paramount considering the limited allograft resources.

### Limitations

This meta-analysis has several key limitations and must be interpreted with care. Regional differences exist in patient and donor selection, listing practices, access to transplantation, center experience, HTx techniques, immunosuppressive regimes, and clinical management of heart failure. We acknowledge that this heterogeneity in study population is a fundamental limitation that cannot be addressed due to the inability to extract sufficient detail from the pooled data. Pooled results of heart RTx spanning 1968 to 2011 may not correctly reflect the advancements made during the last five decades of this procedure. Moreover, the heterogeneity in results precludes broad generalization into prognostic terms. Due to a lack of detail

in the data, we were unable to stratify outcomes of RTx based on early versus late allograft failure, transplantation interval and comorbidities, which are known to affect outcomes. Furthermore, etiology of graft failure was unspecified in 27.1% of patients. Despite these limitations, this study systematically assessed the efficacy and safety of heart RTx for cardiac allograft failure and forms a basis for future studies. Additional studies are needed to identify risk factors for poor outcomes following heart RTx to improve patient and donor selection as well as advancement in perioperative care. It is hoped that these will improve the early mortality of patients requiring heart RTx so that their outcomes can approximate those of primary HTx.

## Conclusions

The results of our systematic review of 11 studies consisting of 7,446 patients who underwent primary HTx and 345 patients who underwent RTx demonstrates that patients who underwent RTx had a significantly lower survival than those who only went primary HTx. These were principally due to a high perioperative mortality amongst RTx patients. There were no significant differences between HTx and RTx patients in terms of freedom from rejection. Careful patient selection and perioperative care can make heart RTx a viable option.

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None.

## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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