

# Outcomes of Heart Transplantation Based on Recipient's Clinical Profile: 21-Year Experience

*Resultados del trasplante cardíaco según el perfil clínico del receptor: 21 años de experiencia*

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## ABSTRACT

**Background:** Heart transplantation is still the treatment of choice in patients with severe cardiomyopathies that do not have any therapeutic options. The promising results of heart transplantation in terms of survival have modified the criteria of recipient selection, including more complex patients on the waiting list.

**Objective:** The aim of this report is to analyze the outcomes of heart transplantation performed at the Hospital Universitario Fundación Favaloro over 21 years of follow-up.

**Methods:** Between February 1993 and December 2014, 442 orthotopic heart transplantations were performed at a single center. The clinical records of the recipients, excluding pediatric patients, were retrospectively analyzed, ensuring the confidentiality of the information. Two periods were considered: period 1 (from February 1993 to August 2003) and period 2 (from September 2003 to December 2014).

**Results:** During the second period, the prevalence of recipients with non-ischemic versus ischemic dilated cardiomyopathy was higher, and the indication of heart transplantation in Chagas dilated cardiomyopathy showed a significant increase. The prevalence of pulmonary hypertension increased and more emergency heart transplantations were performed, with requirements of inotropic agents and mechanical circulatory support with intraaortic balloon pump.

**Conclusions:** The clinical profile of heart transplantation recipients has changed and more patients on the waiting list have a greater number of comorbidities. The careful selection of candidates for transplantation needs continuous revision and an individual analysis of the different factors that determine patients' survival and its impact on the outcomes of transplantation programs.

**Key words:** Heart Transplantation – Kidney Transplantation - Chagas disease - Transplant Recipients

## RESUMEN

**Introducción:** El trasplante cardíaco continúa siendo el tratamiento de elección en pacientes con miocardiopatías graves sin otras opciones terapéuticas. Los resultados alentadores del trasplante cardíaco en términos de supervivencia han permitido ampliar los criterios de selección del receptor, lo que ha llevado a la inclusión de pacientes de mayor complejidad en lista de espera.

**Objetivo:** Analizar los resultados del trasplante cardíaco del Hospital Universitario Fundación Favaloro a lo largo de 21 años de seguimiento.

**Material y métodos:** Entre febrero de 1993 y diciembre de 2014 se realizaron 442 trasplantes cardíacos ortotópicos en un único centro. Se analizaron en forma retrospectiva las historias clínicas de los pacientes, excluyéndose los pediátricos y protegiendo la confidencialidad de los datos. Para el análisis se dividió la serie en período 1 (febrero 1993 - agosto 2003) y período 2 (septiembre 2003 - diciembre 2014).

**Resultados:** Se observó durante el segundo período una prevalencia mayor de candidatas con miocardiopatía dilatada no coronaria versus coronaria y un incremento significativo de la indicación de trasplante cardíaco en la miocardiopatía dilatada chagásica. La prevalencia de hipertensión pulmonar aumentó, realizándose un número mayor de trasplantes cardíacos en condición de emergencia, con requerimiento de inotrópicos y soporte circulatorio mecánico con balón de contrapulsación intraaórtico.

**Conclusiones:** Se han observado cambios en el perfil clínico de los receptores de trasplante cardíaco, ingresando en lista de espera pacientes con un número mayor de comorbilidades. La cuidadosa elección de candidatas a trasplante requiere una revisión continua y un análisis individualizado de los diferentes factores que determinan la supervivencia de los pacientes y su impacto en los resultados de los programas de trasplante.

**Palabras clave:** Trasplante de corazón - Trasplante de riñón - Enfermedad de Chagas - Receptores de trasplante

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## Abbreviations

<b>CrCl</b>	Creatinine Clearance	<b>PHTN</b>	Pulmonary hypertension
<b>CCRT</b>	Combined cardio-renal transplantation	<b>PVR</b>	Pulmonary vascular resistance
<b>HTx</b>	Heart transplantation	<b>KT</b>	Kidney transplantation
<b>IABP</b>	Intra-aortic balloon pump	<b>TPG</b>	Transpulmonary gradient
<b>PCR</b>	Polymerase chain reaction		

## INTRODUCTION

The development of new treatments for heart failure has determined an increase in the percentage of patients reaching more advanced stages of this disease with greater rate of comorbidity. The promising results of heart transplantation (HTx) have modified the selection criteria of recipients, including more complex patients on the waiting list, (1, 2) as those with advanced age, kidney failure, severe pulmonary hypertension (PHTN), Chagas disease and cardiogenic shock.

Heart transplantation in older recipients is controversial, with dissimilar results according to different transplant groups. (3) Kidney failure in HTx recipients is a well-known predictor of short and long-term adverse outcome, (4) severe and fixed PHTN is one of the main causes of graft dysfunction in the immediate post-operative period after HTx, (5) patients with Chagas dilated cardiomyopathy are at increased risk of reactivation of the disease after HTx, (6) and recipients with refractory cardiogenic shock have greater risk during HTx, but the mortality rate associated with medical treatment is unacceptable. (7)

The aim of this report is to analyze the outcomes of these subgroups of patients undergoing HTx at the Hospital Universitario Fundación Favaloro over 21 years of follow-up.

## METHODS

Between 1993 and 2014, 442 orthotopic HTx were performed at a single center (Figure 1). The clinical records of the patients were retrospectively analyzed excluding pediatric recipients and ensuring the confidentiality of the information. The surgical technique, follow-up after HTx and immunosuppressive treatment were performed following the institutional protocol. (8) Recipients' profile and its impact on survival were analyzed.

To perform the analysis, the series was divided into period 1 (February 1993- August 2003) and period 2 (September 2003-December 2014).

Recipients >65 years were analyzed, considering their biological status and family support. (9)

Combined cardio-renal transplantation (CCRT) was indicated in the presence of kidney failure in HTx recipients with two creatinine clearance (CrCl) assessments  $\leq 40$  ml/min or requirement of dialysis in HTx candidates. (9) Immediately after HTx, once the chest was closed, the kidney was implanted in the iliac fossa according to standard extraperitoneal technique.

Pulmonary hypertension secondary to heart disease was defined as transpulmonary pressure gradient (TPG)  $\geq 12$  mm Hg, pulmonary capillary pressure  $> 15$  mm Hg and/or pulmonary vascular resistance (PVR)  $\geq 2.5$  UW during right heart catheterization. (10) Vasodilator agents were titrated to test

vasoreactivity. Non- responders to acute vasoreactivity tests were considered either candidates to mechanical circulatory assistance or to HTx using a donor- to-recipient weight ratio  $> 1.2$ .

Recipients with Chagas dilated cardiomyopathy with megaesophagus or megacolon and severe functional impairment were excluded from HTx. Triple immunosuppressive scheme consisted in cyclosporine or tacrolimus associated with azathioprine and corticosteroids. The diagnosis of reactivation was based on clinical manifestations, parasitological methods (Strout test) or polymerase chain reaction PCR for early detection of parasite genome. All the patients with reactivation of the disease were treated with benznidazole 5 mg/kg/day for 60 days. (11)

Patients with cardiogenic shock or under inotropic drugs received mechanical cardiovascular support with intra-aortic balloon pump (IABP) or ventricular assist devices. Emergency HTx was performed when the patient was stable and without evidence of multiple organ failure. (9)

## Statistical analysis

Continuous variables with normal and non Gaussian distribution are presented as mean  $\pm$  standard deviation, or median and confidence intervals, respectively. Categorical variables are presented as proportions and frequencies.

Survival curves were built using the Kaplan-Meier method and were compared with the log-rank test. A p value  $< 0.05$  was considered statistically significant.

## Ethical considerations

An informed consent was signed by all patients to perform the procedures in accordance with the Institutional Ethics Committee guidelines.

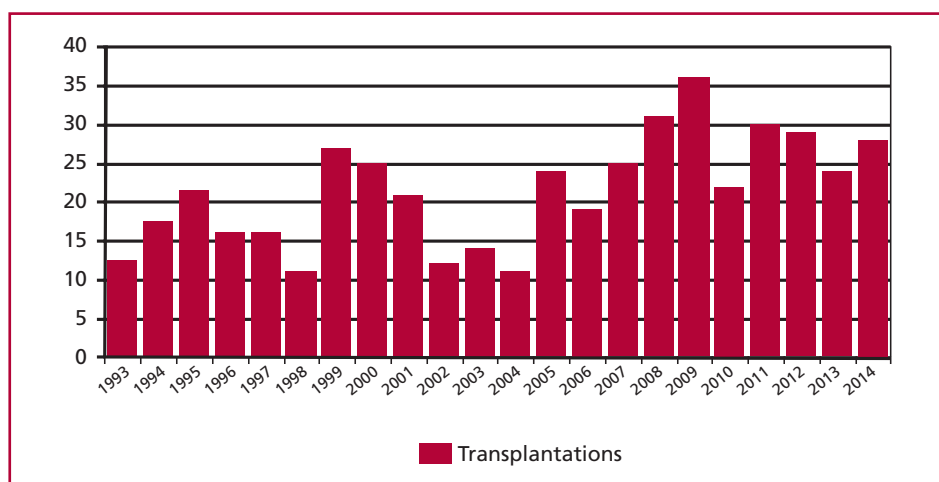
## RESULTS

Among the 442 orthotopic HTx in this series, 418 procedures corresponded to de novo HTx, 20 to CCRT, 2 to combined liver-HTx and 2 to retransplantation. The annual trend of transplants performed in the center show an increase in the second period (Figure 1). Baseline population characteristics are detailed in Table 1.

During the second period, the prevalence of HTx in older recipients with non-ischemic dilated cardiomyopathy was higher, and there was a significant increase in the indication of HTx in Chagas dilated cardiomyopathy. The prevalence of heart transplant recipients with PHTN requiring inotropic agents and mechanical circulatory support with IABP also increased. Mean recipient survival was 12 years (95% CI, 11-12.6) and in-hospital mortality was 9%. Overall survival at 1, 5, 10 and 15 years was 80%, 66%, 53% and 44%, respectively.

Table 2 shows the outcomes according to the clinical

**Fig. 1.** Number of heart transplantations performed per year at Hospital Universitario Fundacion Favaloro since 1993



**Table 1.** Baseline characteristics of the general population

Variable	n=442	Period 1 n=191	Period 2 n=251	p
Age, years	50±13	49±13	50±13	0.1
Body mass index	25±4	24±3	25±4	0.0001
Baseline etiology				
*Ischemic	52%	84%	31%	0.0001
*Dilated	22%	6%	32%	0.0001
*Chagas disease	6%	2%	9%	0.0001
Diabetes mellitus	11%	12%	10%	0.8
Pulmonary hypertension	49%	36%	58%	0.0001
Creatinine >1.5 mg/dl before HTx	42%			
Elective Tx	36%	52%	26%	0.0001
Urgent Tx	22%	12%	28%	0.001
Emergency Tx	42%	31%	46%	0.03

HTx: Heart transplantation. Tx: Transplantation

profile of HTx recipients. The following list describes some specific characteristics of each group.

- Thirty-eight patients >65 years underwent HTx. Four patients had diabetes, 12 patients presented chronic kidney failure not requiring dialysis and 22 had PHTN. The survival rate of patients <65 years vs. those >65 years at 1, 5 and 10 years was 82%, 67% and 54% vs. 71%, 55% and 30%, respectively (p=0.001) (Figure 2). There were no significant differences in the survival rate at 30 days (p=0.8) but in this group mortality was higher after the first year of HTx, mainly due to sepsis.
- Twenty patients underwent CCRT. Three patients required dialysis before CCRT and 4 were under chronic dialysis. The etiology of cardiomyopathies were ischemic heart disease in 10 patients, non-ischemic heart disease in 9, and heart retransplantation in 1 patient, and that of kidney diseases included nephroangiosclerosis in 5 patients, cardio-renal syndrome in 10, diabetes in 2, glomerulopathy

in 1, polycystic kidney disease in 1, and toxic nephritis in 1 patient. Mean creatinine level and CrCl before transplantation were 3.1±2.5 mg/dl and 27.5±10 ml/min, respectively. In-hospital mortality was 15% (n=3/20), due to sepsis in 2 patients and to primary cardiac graft failure in 1 patient.

During the first year of follow-up no significant acute cellular rejection or humoral rejection were observed. Mean creatinine level at 30 days and 1 year was 1.2±0.4 mg/dl and 1.1±0.2 mg/dl, respectively. Long-term mortality was 29% (n=5/17): in 4 patients due to sepsis and in 1 patient due to hepatic sarcoma. Survival at 1 and 3 years was 76% and 72%, respectively. There were no significant differences in patients with isolated HTx or CCRT (Figure 2).

- The prevalence of group 2 PHTN in HTx recipients was 218 patients. In all cases, drug therapy with vasodilators and/or mechanical support with IABP were used to reduce PHTN values guided by invasive

monitoring with Swan Ganz catheter. A ventricular assist device (Berlin Heart®) was implanted in 4 patients as bridge to HTx until pulmonary artery pressure reduction. In this subgroup of patients,

donor- to-recipient weight ratio >1.2 was the strategy used for HTx. The survival rates of patients with PHTN vs. those without PHTN at 1, 5 and 10 years were 76%, 60% and 47% vs. 85%, 71% and

Variable	> 65 years	CCRT	PHTN	Chagas	Emergency HTx
Prevalence	38 (9%)	20 (4.5%)	218 (50%)	28 (6%)	185 (42%)
Age, years	69 ± 4	58 ± 7	56 ± 8	50 ± 11	50 ± 13
Male sex	89%	85%	86%	79%	82%
Ischemic etiology	63%	50%	54%	-	51%
Elective Tx	5 (13%)	8 (40%)	12 (5%)	6 (36%)	-
Urgent Tx	15 (40%)	8 (40%)	86 (40%)	8 (16%)	-
Emergency Tx	18 (47%)	4 (20%)	120 (55%)	15 (48%)	-
1-year survival	71%	76%	76%	83%	77%
5-year survival	55%	72%	60%	83%	66%
10-year survival	30%	-	47%	75%	59%

CCRT: Combined cardio-renal transplantation. PHTN: Pulmonary hypertension. HTx: Heart transplantation. Tx: Transplantation.

Table 2. Outcomes of heart transplantation based on recipient clinical profile

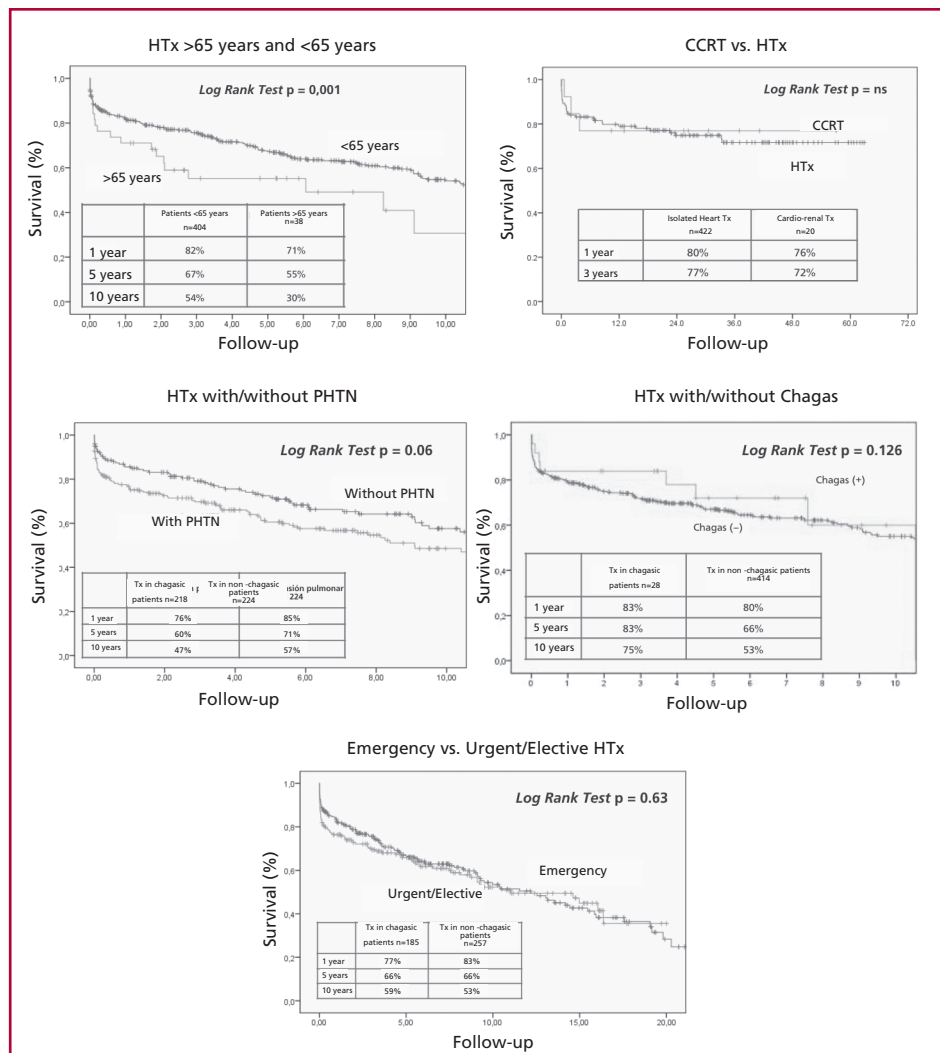


Fig. 2. Survival curves according to recipient characteristics. Tx: Transplantation. HTx: Heart transplantation. KT: Kidney transplantation. CCRT: Combined cardio-renal transplantation. PHTN: Pulmonary hypertension.

57%, respectively ( $p=0.06$ ) (Figure 2).

- Twenty eight patients with Chagas dilated cardiomyopathy underwent orthotopic HTx. Reactivation of Chagas disease by *T. cruzi* after HTx occurred in 12 (41%) cases. The diagnosis was made in 7 patients with panniculitis, 3 patients with Chagas disease myocarditis detected in surveillance endomyocardial biopsy without heart failure symptoms, and 1 patient with a positive Strout test. In all cases, the parasite was detected by PCR and the patients were treated with benznidazole. Acute cellular rejection  $>2R$  was diagnosed in 9/11 patients with reactivation vs. 9/17 patients without disease reactivation (cellular rejection rate 2.2% vs. 0.8%). In 89% of cases, reactivation was associated with cellular rejection that had been treated with pulses of methylprednisolone. The incidence of graft vascular disease was 12% at 5 years. In-hospital mortality was 7% due to sepsis and primary graft failure. Long-term mortality was 22% (6 patients). The causes of death were acute cellular rejection in 3 patients, pneumonia, acute abdomen and car accident. The survival of patients who underwent HTx with Chagas disease vs. those without Chagas disease at 1, 5 and 10 years was 83%, 83% and 75% vs. 80%, 66% and 53%, respectively ( $p=0.126$ ) (Figure 2).
- Emergency HTx was performed in 185 patients. Sixty-three percent of the patients presented moderate to severe PHTN. Intra-aortic balloon pump was the mechanical support device most widely used and was indicated in 165 recipients. Advanced ventricular assist devices were used in only 20 patients as bridge to transplantation: 90% were paracorporeal devices for short-term support, of which 78% were continuous-flow left ventricular assist devices (centrifugal pump). Table 3 describes the different devices used. In-hospital mortality was 12% in patients with emergency HTx vs. 7% ( $p=0.06$ ) in patients with urgent/elective HTx. The leading cause of death at 30 days was primary graft failure in 13/23 patients (56%), sepsis and multi organ failure in 7 patients, humoral rejection in 1 patients, perioperative bleeding in 1 patient and sudden death in 1 patient. Overall survival in patients with emergency vs. urgent/elective HTx at 1, 5, 10 and 15 years was 77%, 66%, 59% and 45% vs. 83%, 66%, 53% and 42%, respectively ( $p=0.63$ ) (Figure 2).

## DISCUSSION

The last report of the International Society for Heart & Lung Transplantation (ISHLT) has changed the clinical profile of HTx recipients. (12) The results of Hospital Universitario Fundación Favaloro series have been previously reported, but not the detailed analysis of the outcomes according to the different profiles of recipients and their follow-up. (13)

The survival of patients with stage D advanced heart

**Table 3.** Type of ventricular assist devices used as bridge to heart transplantation

Device	Patients (n=185)
Intraaortic balloon pump	169
Biomedicus® Centrifugal pump	5
Novacor®	2
ECMO	3
Polvad®	1
CentriMag® Centrifugal pump	9
Berlin Heart – Excor®	2

ECMO: Extracorporeal membrane oxygenation

failure has increased due to optimal medical treatment, advances in surgical and endovascular procedures for myocardial revascularization, antiarrhythmic devices and cardiac resynchronization therapy. This has led to consider HTx as a therapeutic option for older patients (14-16) with controversial results according to the series analyzed. (15)

In our series, and unlike other reports, in-hospital mortality was not greater in recipients  $>65$  years, but survival was lower after the first year following transplantation. Thus, in this subgroup of patients, biological age and the use of scores of frailty should be used for decision-making and inclusion in the waiting list. During follow-up, these patients presented a high rate of infections, in accordance with the results of a multicenter study. (17) In these patients, immunosuppressive scheme could be minimized.

The natural history of kidney function after HTx shows progressive impairment of glomerular filtration rate aggravated by chronic nephrotoxicity secondary to the use of calcineurin inhibitors. (18) The requirement of dialysis after HTx or KT is associated with higher mortality compared with CCRT. (19, 20) In 2006, the Hospital Universitario Fundación Favaloro started the CCRT program. Our results coincide with those previously published and allow considering CCRT as an effective therapeutic option in a selected subgroup of patients. (20-22) A thorough evaluation of recipients and an adequate selection of donors should be carried out in candidates for multi-organ transplantation due to the shortage of donors.

Severe and fixed PHTN is one the main causes of graft failure after HTx and is associated with high in-hospital morbidity and mortality due to lack of graft adaptation to a preexistent elevated right ventricular afterload. (12) Different reports of multicenter studies differ in defining the unacceptable values of systolic pulmonary artery pressure, PVR and TPG to perform HTx. (5, 23) The prognostic value of pulmonary vasoreactivity in candidates for HTx is controversial. (24, 25) There is evidence of PHTN reversibility with continuous or pulsatile-flow left ventricular assist device support as bridge to transplantation or transplantability.

(26, 27) In our series, the prevalence of patients with PHTN in HTx recipients was high, showing a subpopulation of patients with advanced cardiomyopathy. The strategy selected was the use of vasodilators, ventricular assist devices and donors weighing more than recipient. (28) Severe and fixed PHTN was the main cause for not including patients on the waiting list, indicating that PHTN should be detected at earlier stages.

The significant experience with HTx and Chagas disease achieved by Bocchi and Fiorelli has allowed considering HTx a safe and effective approach for patients with end-stage Chagas cardiomyopathy. (29) The HTx program in recipients with Chagas disease started at Hospital Universitario Fundación Favaloro in 1998. Our group reported the usefulness of PCR strategies for early diagnosis of Chagas disease reactivation, follow-up and response to treatment in 2000, and after an initial experience with 10 patients in 2007 this technique was incorporated to the follow-up protocol after transplantation. (30, 31) Discontinuation or severe reduction of immunosuppression due to an episode of reactivation was associated with higher mortality due to graft rejection. The incidence of allograft vascular disease and neoplasms was low. (32, 33)

Patients with hemodynamic instability or refractory cardiogenic shock require optimization of tissue perfusion with vasoactive drugs or short-term mechanical support devices. (34) These measures improve patients' conditions before HTx preventing organ dysfunction. (35, 36)

The use of mechanical circulatory assist devices for intermediate or long-term support has not been established in our country, and the experience with short-term devices is still limited. The incorporation of these devices to the therapeutic scheme as bridge to HTx or transplantability in a rational and effective fashion is pending.

Currently, the use of risk scores associating multiple prognostic variables allows the identification of subgroups of patients at higher risk and greater morbidity and mortality in the waiting list and after transplantation. Recently, the INTERMACS scale, the CARRS score and the IMPACT score have been shown to be useful tools to optimize the selection of HTx recipients. (37-39)

## CONCLUSIONS

The criteria for the selection of orthotopic HTx recipients have evolved over the last decade, and patients with more comorbidities are now included. The careful selection of candidates for HTx needs continuous revision and an individual analysis of the different factors that determine patients' survival, the adequate distribution of donors and its impact on the outcomes of transplantation programs.

## Conflicts of interest

None declared. (See authors' conflicts of interest forms in the website/Supplementary material).

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