

## Clinical characteristics and long-term outcomes of patients undergoing combined heart-kidney transplantation: a single-center experience

Á. López-Sainz<sup>a,b,f</sup>, E. Barge-Caballero<sup>a,b,f</sup>, M.J. Paniagua-Martin<sup>a,b,f</sup>, R. Marzoa Rivas<sup>a,b,f</sup>, G. Sánchez-Fernández<sup>a,b,f</sup>, L. Fernández Arias<sup>b,c,f</sup>, M. García-Vieites<sup>b,c,f</sup>, Á. Alonso-Hernández<sup>b,d,f</sup>, J.J. Rodríguez-Rivera-García<sup>b,e,f</sup>, and M.G. Crespo-Leiro<sup>a,b,f</sup>

<sup>a</sup> Servicio de Cardiología, Complejo Hospitalario Universitario A Coruña, Servicio Galego de Saúde (SERGAS), A Coruña, Spain

<sup>b</sup> Complejo Hospitalario Universitario A Coruña, Servicio Galego de Saúde (SERGAS), A Coruña, Spain

<sup>c</sup> Servicio de Cirugía Cardíaca, A Coruña, Spain

<sup>d</sup> Servicio de Nefrología, A Coruña, Spain

<sup>e</sup> Servicio de Urología, A Coruña, Spain

<sup>f</sup> Instituto de Investigación Biomédica de A Coruña (INIBIC), A Coruña, Spain

### Abstract

**Background.** The purpose of the study was to describe clinical characteristics and long-term survival of patients undergoing combined heart-kidney transplant in a single center.

**Methods.** We conducted a retrospective analysis of 22 consecutive patients who underwent combined heart-kidney transplant at our institution between 1995 and 2013. Long-term outcomes were analyzed by means of the Kaplan-Meier method.

**Results.** Four patients underwent re-do transplant (2 cardiac re-transplants, 1 kidney re-transplant, and 1 combined heart-kidney re-transplant). Most frequent underlying cardiac conditions were coronary artery disease (54%), dilated cardiomyopathy (23%), and chronic rejection of a previous heart graft (18%). Known causes of chronic renal dysfunction were nephroangioesclerosis (23%), drug-related toxicity (14%), and Wegener granulomatosis (5%). Non-specified chronic renal dysfunction was present in 50% patients. In-hospital postoperative mortality rate was 5 of 22 (23%). Causes of early death were directly related to kidney transplant surgery in 4 of 5 (80%) patients. Among the remaining 17 patients who surmounted the postoperative period, long-term survival rates 1 year, 5 years, and 10 years after HKT were 88%, 82%, and 65%, respectively. Over a mean follow-up of  $6.7 \pm 6.4$  years, cumulative incidences of cytomegalovirus infection, coronary allograft vasculopathy, malignancy, and acute cardiac graft rejection were 41%, 6%, 24%, and 41%, respectively. There was no episode of acute renal graft rejection. At the end of follow-up, all survivors ( $n = 11$ ) were in functional New York Heart Association class I. Mean creatinine serum level was 1.68 mg/dL.

**Conclusions.** In our experience, combined heart-kidney transplant is a feasible therapeutic option that yielded favorable long-term outcomes, with a low cumulative incidence of cardiac graft dysfunction. These results were obtained at the expense of a significant risk of early postoperative mortality, which was mainly related to complications of kidney transplant surgery.

Combined heart-kidney transplantation (HKT) has become an accepted therapy for selected patients with refractory heart failure who are candidates for heart transplantantion and present concurrent advanced renal disease. However, it is not a frequent indication, and data on long-term follow-up are lacking. There have been several case reports and small series along with United Network of Organ Sharing Database registry [1] and a multicenter French study [2], with diverse results regarding survival and outcomes. Our aim was to describe the clinical characteristics and long-term survival of patients undergoing combined HKT in our center.

## Methods

### *Description of the Study*

We conducted a retrospective study that was based on the historic cohort of adult patients who underwent HKT at the Complejo Hospitalario Universitario de A Coruña (A Coruña, Spain) between January 1995 and December 2013. Patient demographics, clinical characteristics, and follow-up data were retrospectively collected from our computerized database.

### *Follow-Up Protocol*

Patients were treated and followed according local protocols. Induction therapy was administered with muronab-CD3, thymoglobulin, or basiliximab. Maintenance immunosuppressive therapy consisted of different combinations of steroids, calcineurin inhibitors (tacrolimus or cyclosporine A), an antiprolipherative agent (azathioprine or mophetil mycophenolate), or a mammalian target of rapamycin inhibitor (everolimus or sirolimus).

Scheduled endomyocardial biopsies for rejection surveillance were performed during the first 6 to 12 months after transplantation and thereafter on any clinical suspicion of rejection. Biopsy specimens were graded according to the classification of the International Society for Heart and Lung Transplantation [3]. Acute rejection was treated with high-dose intravenous steroids if graded 2R or greater or if accompanied by cardiac graft dysfunction. Renal biopsies were only performed in the case of a clinical suspicion of kidney graft rejection. Coronary angiographies were performed in the case that coronary allograft vasculopathy was clinically suspected, and, beyond 2003, in all asymptomatic patients, barring contraindications, 1 month, 1 year, 5 years, and 10 years after transplantation.

### *Statistical Analysis*

Statistical analyses were conducted with the use of SPSS software, version 18 (SPSS Inc, Chicago, Ill, United States). Continuous variables are summarized by use of mean  $\pm$  standard deviations; categorical variables are presented as percentages. Actuarial survival was described by means of the Kaplan-Meier method. Statistical significance was set as a value of  $P < .05$ .

## Results

### *Study Population*

Nineteen men and 3 women were studied. The mean age of the population was  $56 \pm 9$  years. Prevalence of hypertension, diabetes, and hypercholesterolemia was, respectively, 77%, 18%, and 55%. Seven patients were receiving chronic dialysis at the time of HKT. Four procedures consisted in a re-do transplant (2 cardiac re-transplant, 1 kidney re-transplant, and 1 heart-kidney re-transplant).

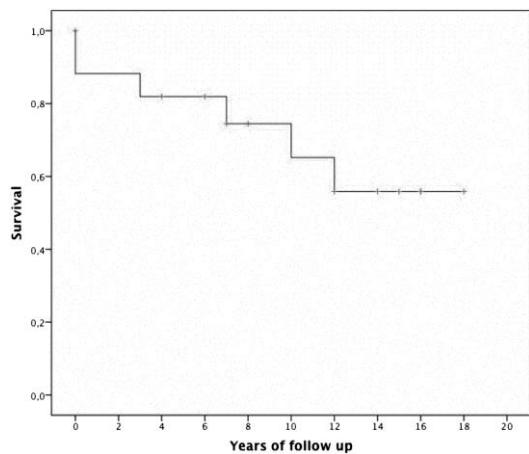
The mean waiting list time was 117 days ( $\pm 148$ ). Donor allocation was based exclusively on ABO compatibility; HLA matching was not investigated. Heart and kidney harvesting, preservation, and transplantation were performed through the use of standard surgical techniques. All transplants were performed simultaneously with the use of the same donor for both organs. Induction therapy with OKT3

antibodies (mean, 4 days) or basiliximab was administered in all cases. Maintenance immunosuppression included cyclosporine A (68%) or tacrolimus (32%), mofetil mycophenolate (91%), and azathioprine (9%) and steroids (100%).

Most frequent underlying cardiac conditions that motivated cardiac transplant were coronary artery disease (54%), dilated cardiomyopathy (23%), and chronic rejection of a previous cardiac graft (18%). The majority of the patients (68%) were in New York Heart Association (NYHA) functional class III to IV, with a mean ejection fraction of 25%. Renal dysfunction was attributable to nephroangioesclerosis (23%), drug-related toxicity (14%), and Wegener granulomatosis (5%). Non-specified chronic renal dysfunction was present in 50% patients. The mean serum creatinine level before HKT was  $3.51 \pm 2.15$  mg/dL.

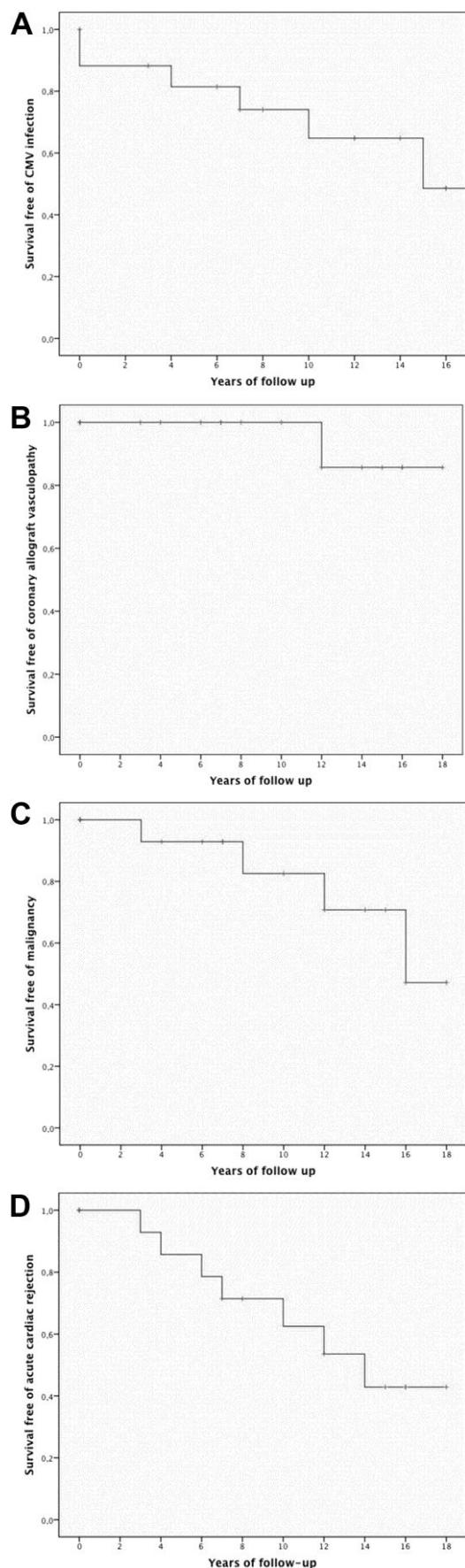
### Outcomes

Five patients (23%) died within the in-hospital postoperative period. Causes of early death were directly related to kidney transplant surgery in 4 (80%) patients (3 of them because of post-surgery abdominal infection, and 1 secondary to major bleeding of the renal graft). Among the remaining 17 patients who survived the postoperative period, long-term survival rates 1 year, 5 years, and 10 years after HKT were 88%, 82%, and 65%, respectively, as shown in Fig 1.



**Fig 1.** Long-term survival after heart-kidney transplantation.

Over a mean follow-up of  $6.7 \pm 6.4$  years, cumulative incidences of cytomegalovirus infection, coronary allograft vasculopathy, malignancy, and acute rejection were 41%, 6%, 24%, and 41%, respectively (Fig 2). There was no episode of renal graft rejection. At the end of follow-up, all survivors ( $n = 11$ ) were in functional NYHA class I and had a left ventricular ejection fraction  $>50\%$ . The mean serum creatinine level at this time was  $1.68 \pm 0.52$  mg/dL.



**Fig 2.** Long-term survival free of cytomegalovirus (CMV) infection (A), coronary allograft vasculopathy (B), malignancy (C), and acute cardiac rejection (D).

## **Discussion**

Advanced renal dysfunction is a common condition among patients awaiting heart transplantation. However, combined HKT has been performed sparingly as compared with isolated cardiac transplantation, as reflected in multicenter registries [4]. Presently, there are no established rules about when HKT should be preferred instead of isolated cardiac transplant; as a result, indications may vary among different centers and countries. Nevertheless, HKT has become an accepted therapeutic solution since 1978, when the first successful procedure was performed [5]. Numerous case reports and small studies have been published, but our study represents one of the largest HKT series described in a single center.

In a multi-institutional study of 82 patients, Narula et al [1] described 1-year and 2-year survival rates of 76% and 67%, respectively, whereas in the Cedars Sinai Medical Center program [6], 87%, 68%, and 51% survival rates 1 year, 5 years, and 10 years after the operation have been reported. Our results are consistent with these previously reported data, but no deaths was observed in one smaller single-center study [7].

Our experience shows that rates of cardiac complications such as acute rejection and coronary allograft vasculopathy, as well as kidney rejection, are low after combined HKT. Previous experimental studies have also shown that heart rejection is infrequent after multi-organ transplant [8]. Several hypotheses have been proposed to explain this tolerance induction, but the crucial mechanism remains unknown. It has been suggested that the donor kidney might supply the migrating donor hematopoietic stem cells, an effect that results in stimulation of suppressor T cells (CD4+CD25+ regulatory T cells). The presence of an immunosuppressive agent at the time of the interaction may lead to the development of immunotolerance [9]. In addition, in HKT patients, a more aggressive immunosuppressive regimen is used compared with isolated kidney transplant, which may make rejection of the kidney allograft a relatively infrequent event.

Most early deaths after HKT in our population were attributable to complications of kidney transplant surgery (infection and bleeding). In our opinion, this fact could be explained by the surgical technique, given that the heart transplant is performed first, and the renal allograft is then placed. This indicates the requirement of a more extensive surgical field, a longer cross-clamping time, and that the ischemic donor kidney graft is exposed to reperfusion under conditions of possible hemodynamic instability and low perfusion pressure in addition to high doses of vasoconstrictive drugs. However, all of the published data concur in showing favorable long-term results, not significantly different from the isolated Cardiac Transplant [2].

Our study has several limitations. First, data were extracted from a single-center database with a relatively small number of patients. In addition, by the nature of its retrospective design, the study has a possible selection bias caused by incomplete retrieval of data. There also have been differences in the immunosuppressive treatment used in the entire cohort that could have influence in the results. Furthermore, detection of renal allograft rejection that is based on worsening renal function rather than on histological criteria may have failed to detect subclinical episodes of rejection. Because of this, our analysis represents only a limited experience in a small number of patients at a single center, and results must be validated by multicenter registries.

In conclusion, HKT is a feasible therapeutic option for selected patients with advanced heart failure and chronic renal failure. In our experience, this intervention yielded favorable long-term outcomes, with a low cumulative incidence of graft-related complications. These results were obtained at the expense of a significant risk of early postoperative mortality, which was mainly related to complications of kidney transplant surgery.

## References

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