DR. MARIA DOLORES GARCÍA COSÍO CARMENA (Orcid ID : 0000-0002-9330-9896)

DR. SONIA MIRABET (Orcid ID : 0000-0001-5955-2748)

Article type : Original Article

TITLE PAGE

GENDER DIFFERENCES IN HEART TRANSPLANTATION. TWENTY-FIVE YEAR TRENDS IN THE NATIONWIDE SPANISH HEART TRANSPLANT REGISTRY.

List of authors:

María Dolores García-Cosio MD PhD1,2. Francisco González-Vilchez MD PhD 3, Raquel López-Vilella MD4, Eduardo Barge-Caballero MD 5, Manuel Gómez Bueno MD 6, Manuel Martínez-Selles MD PhD 2,7, Jose María Arizón MD 8, Diego Rangel Sousa MD9, José González-Costello MD 10, Sonia Mirabet MD PhD 11, Félix Pérez-Villa MD PhD 12, Beatriz Díaz Molina MD 13, Gregorio Rábago MD 14, Ana Portolés Ocampo MD 15, Luis de la Fuente Galan MD 16, Iris Garrido MD 17 and Juan F Delgado Jiménez MD PhD 1,2,18

Affiliations

1 Department of Cardiology, Hospital 12 de Octubre Madrid, Spain

2 CIBERCV

3 Department of Cardiology, Hospital Universitario Marqués de Valdecilla, Santander, Spain

4 Department of Cardiology, Hospital Universitari I Politecnic La Fe, Valencia, Spain

5 Department of Cardiology, Complejo Hospitalario Universitario de A Coruña, A Coruña, Spain

6 Department of Cardiology, Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/CTR.14096

7 Department of Cardiology, Hospital General Universitario Gregorio Marañón, Universidad Europea, Universidad Complutense, Madrid, Spain

8 Department of Cardiology, Hospital Universitario Reina Sofía, Cordoba, Spain.

9 Department of Cardiology, Hospital Universitario Virgen Del Rocío, Sevilla, Spain

10 Department of Cardiology, Hospital Universitari De Bellvitge, Hospitalet de Llobregat, Spain

11 Department of Cardiology, Hospital Santa Creu I Sant Pau, Barcelona, Spain

12 Department of Cardiology, Hospital Clínic I Provincial, Barcelona, Spain

13 Department of Cardiology, Hospital Universitario Central De Asturias, Oviedo, Spain

14 Department of Cardiac Surgery, Clínica Universidad De Navarra, Navarra, Spain

15 Department of Cardiology, Hospital Universitario Miguel Servet, Zaragoza, Spain

16 Department of Cardiology, Hospital Clínico Universitario De Valladolid, Valladolid, Spain.

17 Department of Cardiology, Hospital Universitario Virgen De La Arrixaca, Murcia, Spain

18 Medicine Department, Universidad Complutense de Madrid, Spain.

Running head: Heart transplant: Gender and evolution

Corresponding author: María Dolores García-Cosio

Hospital Universitario 12 de Octubre, Servicio de Cardiología

Centro de Actividades Ambulatorias 4ª planta Area B

Av Cordoba S/N

28041 Madrid Spain

mariadolores.garcia-cosio@salud.madrid.org

Telephone 91 7792473 Fax 917792953

ABSTRACT PAGE

List of authors: García-Cosio MD, González-Vilchez F, López-Vilella R, Barge-Caballero E, Gómez Bueno M, Martínez-Selles M, Arizón JM, Rangel Sousa D, González-Costello J, Mirabet S, Pérez-Villa F, Díaz Molina B, Rábago G, Portolés Ocampo A, de la Fuente Galan L, Garrido I and Delgado Jiménez JF.

GENDER DIFFERENCES IN HEART TRANSPLANTATION. TWENTY-FIVE YEAR TRENDS IN THE NATIONWIDE SPANISH HEART TRANSPLANT REGISTRY.

Clin Transplant.

Abstract: The study of gender differences may lead into improvement in patient care. We have aimed to identify the gender differences in heart transplantation (HT) of adult HT recipients in Spain and their evolution in a study covering the years 1993-2017 in which 6740 HT (20.6% in women) were performed. HT indication rate per million inhabitants was lower in women, remaining basically unchanged during the 25-year study period. HT rate was higher in men, although this decreased over the 25-year study period. Type of heart disease differed in men vs. women ($p<0.001$): ischemic heart disease 47.6% vs 22.5%, dilated cardiomyopathy 41.3% vs 34.6% or other 36% vs 17.8%, respectively. Men were more frequently diabetics (18 vs 13.1% $p<0.001$), hypertensives (33.1 vs 24% $p<0.001$) and smokers (21.7 vs 12.9% $p<0.001$), respectively. Women had more pre-HT malignancies (7.1 vs 2.8% $p<0.001$) and their clinical status was worse at HT due to renal function and mechanical ventilation. Adjusted survival ($p=0.198$) and most of the mortality-related variables were similar in men and women. Death occurred more frequently in women due to rejection (7.9 vs 5.1% $p<0.001$) and primary failure (18.2 vs 12.5% $p<0.001$) and in men due to malignancies (15.1 vs 6.6% $p<0.001$).

Keywords: heart transplant, gender, women, trend.

Author for requests for offprints: María Dolores García-Cosio

Hospital Universitario 12 de Octubre, Servicio de Cardiología

Centro de Actividades Ambulatorias 4ª planta Area B

Av Cordoba S/N

28041 Madrid Spain

Introduction

Many differences exist in human structure, metabolism and function between men and women[1]. These differences must be considered when evaluating any medical condition or therapy applied due to the variability of clinical presentation, diagnosis and/or response to treatments between genders[2]. Special interest is currently being placed on the study of the differences between men and women as a potential field of improvement in the diagnosis, treatment and likely prognosis of patients[3].

Heart transplant (HT) is the gold standard of treatment for selected heart failure (HF) patients refractory to optimal therapy with poor prognosis in the absence of significant comorbidities [4–6]. Although much research has been done to study different aspects of HT, gender differences have received little attention so far [7–9] and most studies have mainly addressed donor recipient matching[10–12]. It is necessary to have reliable information on the differences in HT by gender and to identify gaps in knowledge and needs of prospective studies.

Spain's public health service provides total population coverage in which HT is offered on an equal opportunity basis for everyone. Moreover, it has a National Transplantation Organization that promotes and coordinates donations all over the country. Spain's model has been highlighted as one of the most efficient in terms of transplants per million inhabitants[13,14]. Furthermore, the quality of the HT information is outstanding due to the Spanish National Registry of Heart Transplantation that includes all the procedures performed since this activity began in 1984[15].

Our aim has been to provide updated information on the evolution of the differences in HT by gender over the last 25 years.

Materials and Methods

Data source

The Spanish Heart Transplantation Registry is a prospective database promoted by the Heart Failure Working Group of the Spanish Society of Cardiology. It contains detailed clinical information on all HT procedures performed in Spain from 1984 to the present time. The registry is updated on a yearly basis with data supplied from all the country's transplant centers. This database has been described elsewhere[16]. The Spanish Heart Transplantation Registry has been approved by the Ethics Committees of all the participating centers for investigational purposes.

For the present study, we included all patients aged ≥18 years who underwent HT in Spain from 1 January 1993 to 31 December 2017. Vital status and cause of death as of 31 December 2017 are known for all subjects. Cause of death was locally adjudicated in each participating center. In order to calculate transplantation rate, the number of residents in Spain in each year of the study was obtained from the Spanish National Institute of Statistics.

Statistical analysis

Quantitative and categorical variables are summarized as mean ± standard deviations and percentages, respectively. The annual crude transplantation rate was calculated dividing the number of HT by the total number of residents shown in the statistics of the National Institute for each age span of the study. Transplantation rates adjusted for age were calculated by the direct method using the July 2005 Spanish population as a reference. Trends in transplantation rates (1993-2017) were determined by joinpoint regression analysis and annual percentage change with 95% confidence intervals were calculated. The joinpoint model is a methodology for modeling trends over time using connected linear segments, usually on a logarithmic scale. The joint point refers to the point in which trends change from the previous segment to the next one[17]. Confidence intervals above and below 1 were considered statistically significant ($p<0.05$).

The Kendall's tau-b correlation was used to analyze the trends in the proportion of female recipients during the observation period. Trends in baseline and transplant characteristics for both males and females were visually plotted and analyzed across 5-year intervals (1993-1997, 1998-2002, 2003-2007, 2008-2012, 2013-2017), with year categories regressed as an ordinal variable. Generalized regression models were used to assess the between-gender differences in temporal trends for recipient, donor and transplant characteristics. The models considered time span, gender and interaction time x gender as independent variables. The interaction term provides an estimation of the between-gender differences in the slope of the regression line. Generalized linear regression was used for dependent quantitative variables, negative-binomial regression for dichotomous variables and multinomial logistic regression for categorical variables.

The Chi-squared test was used to analyze the differences between males and females in causes of death. Significance for each individual cause of death was calculated via the standardized corrected residuals (chi-squared equals squared residuals, 1 degree of freedom) using Bonferroni's correction for multiple comparisons. Unadjusted survival for each gender was estimated by the Kaplan-Meier method, and the difference between curves by the Log-rank test.

Multivariate relation with survival, including gender, was evaluated by Cox regression analysis. In the multivariate analysis, all the variables reaching statistical significance in the univariate analysis were included. No imputation was made for missing data.

Significance level was established at a p value of 0.05. All analyses were carried out with SPSS 21.0 package. Joinpoint regression was analyzed with Joinpoint Regression Program. Version 4.0.4. May 2013; Statistical Research and Applications Branch, National Cancer Institute.

Results

In the last 25 years, 6740 HT procedures were performed in 16 centers. Of these, 20.6% were female and 79.4% male recipients. Characteristics of the study population stratified by gender are shown in table 1. Temporal trends in selected variables for both genders and the total population are summarized in table 2.

Transplantation rate in females showed a slight non-significant increase, without joinpoints, throughout the study period (from 3.23 procedures per 10^6 residents in 1993 to 4.98 procedures per 10^6 residents in 2017. On the other hand, transplantation rate in males declined from 18.8 procedures per 10^6 residents in 1993 to 13.1 procedures per 10^6 residents in 2017, overall. Three joinpoints were identified (1996, 1999 and 2011). A significant decrease for the 1999-2011 time span and a significant increase for 2011-2017 time span were observed. Changes in the earlier time spans were not significant (Figure 1). Consequently, the proportion of female recipients significantly increased from 16.9% (1993-1997) to 25.5% (2013-2017) ($p<0.001$) (Table 2).

Gender related differences (table 1)

Female recipients were significantly younger and received combined transplants twice as often as men.

Men had a worse cardiovascular risk profile (with higher rates of diabetes, hypertension and smoking habit) and a twofold prevalence of pulmonary obstructive disease and triple prevalence of peripheral vascular disease.

Women had malignancies pre-HT more frequently, worse renal function and required mechanical ventilation at the time of HT more often.

However, pulmonary vascular resistance, previous cardiac surgery, use of circulatory support, urgent transplant, ischemic time and bicaval technique were similar between genders.

Cerebrovascular disease and other causes of donor's death were more frequently observed in female than in male recipients ($p=0.002$ and $p<0.001$, respectively), while traumatic donor's death was more frequent in male recipients ($p<0.001$).

HT indication was mainly due to ischemic heart disease (IHD) in males ($p<0.001$ compared with females) whereas dilated cardiomyopathy (DCM) and non-ischemic/non-dilated cardiomyopathy (referred as 'other') were the most frequent HT indication in female recipients ($p<0.001$ compared with males). Other etiologies predominant in women included valvulopathies (10% vs 7.1%), congenital heart disease (4.3% vs 1.7%), hypertrophic cardiomyopathy (6.6% vs 2.2%), restrictive cardiomyopathy (7.3% vs 2.1%) and myocarditis (2.3% vs 1%). Re-transplantation accounted for 2.2% of the cases with uniform gender distribution.

Temporal trends (Table 2)

We found significant changes in several baseline characteristics over the 25-year period of the study. Significant increases in the prevalence of diabetes mellitus, pre-HT neoplasia, need of mechanical ventilation, urgent transplant, use of circulatory support Extracorporeal membrane oxygenation (ECMO) and ventricular assist devices (VAD)), donor age, cerebrovascular disease as donor's cause of death, use of bicaval technique and ischemic time were observed in the overall population ($p<0.001$ for all trends). Likewise, transplant indication by non-dilated, non-ischemic cardiomyopathy showed a significant increase over time, mirrored by a significant decrease in IHD as primary indication.

However, we have found significant gender differences in some of the time spans with more of the HT being done due to "other" heart diseases (i.e. restrictive cardiomyopathy, congenital heart disease, hypertrophic cardiomyopathy, etc.). This increase in the indication of heart transplant under the category of "other" was due to a decrease in IHD in men and a decrease in DCM in women. Males showed a more striking increase in urgent transplant, mainly due to the use of ventricular assist devices. Females showed a reduction in the presence of moderate to severe renal dysfunction while a slight increase was observed in males. A significant decrease in recipient/donor gender mismatch was only found in female recipients.

Outcomes

Median follow-up was 5.71 years (interquartile range, 11.3 years) in females and 4.74 years (interquartile range, 11.25 years) in males (p=0.007). Results of the univariate and multivariate Cox regression analysis are summarized in table 3. The univariate analysis showed that there was a significant improvement in survival over the 25 years. After multivariate adjustment, only the 2013-2017 period reached statistical significance compared with 1993-1998 period. Female gender was associated with better survival by Kaplan-Meier analysis (Figure 2A). However, the multivariate analysis found a similar survival rate for women and men (Figure 2B). Variables related independently with impaired survival were recipient age (>40 compared with <40 years), primary diagnosis (other etiologies compared with DCM), presence of pretransplant diabetes and peripheral vascular disease, glomerular filtration rate <45 mL/min/1.73 m^2, need of ventilatory support prior to HT, cancer diagnosis prior to HT, use of pretransplant circulatory support (ECMO compared with no mechanical support), donor age (>40 years compared to <40 years), gender mismatch (male recipient/female donor) and ischemic time (>240 minutes compared with <120 minutes). We also analyzed variables independently related to mortality segregated by gender (table 4). A bad outcome of female recipients was related to hypertension and mechanical ventilation while in men it was related to diabetes, pre-HT ECMO, donor age, donor recipient mismatch, longer ischemic time and a protective effect of HT in recent years. Both genders had worse survival related to recipients age (older than 60 yr. in females and older than 40 yr in males), etiology (non-DCM in females and other etiologies in males), glomerular filtration rate <45 mL/min/1.73 m^2 and pre-HT malignancies.

Cause of death differed significantly between genders. Female recipients died more frequently due to primary graft failure and acute rejection than male recipients. On the other hand, males died more frequently than females by end-stage malignancy (figure 3).

Discussion

Although gender differences have been studied in some medical conditions and have led to the proposal of improvements in the assessment of the diagnosis and treatment of, for example, ischemic heart disease[18], up to now, little attention has been given to gender differences in HT so that good quality information is lacking. At the time we began to write this article, we could only find one substudy within a study in the literature in which the patients had been screened for another reason [8]. Another study compared post-transplanted men and women, and provided an analysis of patients. However, it did not include many variables so that its statistical significance is poor[7]. In October 2019, more information became available with an analysis from the International Registry of Heart and Lung transplant. This analysis discussed the differences between men and women and focused on the long-term outcome analysis through a propensity score matching[9]. Our study may serve as a complement to the available information on gender differences in HT as it provides extensive statistical data on the evolution of HT over a 25-year period.

The main findings of our study are that there are fewer HT in women than in men. Women show different heart diseases, clinical profile and post-HT morbidity and mortality. Nonetheless, the long-term prognosis does not differ between genders.

Women account for less than one third of HT[16,19], a similar proportion being described in studies of patients on the waiting list[20] and in patients receiving a ventricular assist device[21]. Women represent 40% of HF with reduced ejection fraction, have a better cardiovascular risk profile and less IHD at younger ages[18]. These factors may result in a lower need of HT in women in the most frequent etiologies due to a lower incidence of the disease but also because the clinical course of HF seems to be less aggressive in women[22–24]. HF in women at advanced ages typically occurs with preserved ejection fraction, which affects the age in which women are considered for HT. In our series, HT in women was more frequent in the 40-59 year group (54.1%) but not in recipients above 60 years (26.6%), which is probably not old enough to reflect the higher HF incidence shown in general population[25,26]. The increase in the percentage of HT in women over the years is due to unusual etiologies and reflects a general trend to expand HT indication to any advanced stage heart failure patient independently of the underlying heart disease as has been recommended[27]. In fact, an increase in other heart conditions as a cause of HT is also seen in men. However HT indication per million inhabitants has remained stable for women throughout the 25 years of the study and the increase in the percentage of HT in women reflects a lower HT indication per million inhabitants in men attributable to improvements in IHD prognosis due to the systematic revascularization strategy in acute myocardial infarction through this time frame[28].

There are significant differences between the clinical profile of men and women. The cardiovascular risk profile in men is worse than in women as could be expected due to the higher rate of IHD etiology as well as higher peripheral vascular disease and Chronic Obstructive Pulmonary Disease (COPD). The decrease of IHD over the years can be easily explained as has been pointed out previously. Women have lower IHD rate because of protective estrogenic hormones that delay coronary disease development to older ages[18].

It stands out that all the factors that were related to the treatment indications such as use of circulatory support, immunosuppression regimen, priority of HT and re-transplantation rate were similar and had a similar evolution over time in regards to both woman and men. In contrast to other therapies in Cardiology[18], this suggests that this procedure could be applied equally to both genders in any advanced stage HF patient with poor short term prognosis.

HT indication must be considered according to type and severity of underlying cardiac disease, but also in regards to significant comorbidities associated to a poorer HT prognosis[4–6]. In our study, the men were older and had more cardiovascular risk factors and significant comorbidities (COPD and peripheral vascular disease) while women more frequently had mechanical ventilation and renal failure. The sum of these comorbidities resulted in a similar adjusted long-term survival, this being a good indicator of a balanced indication of HT between genders. However, future studies are still needed to determine if the management of women should be handled differently to avoid a worse clinical status and renal function at the time of HT.

Previous publications have focused their attention on mortality associated to donor and recipient gender mismatch[7,12,29,30]. Our study has shown the gender mismatch proportion to be stable over time in the overall population. Females have a higher proportion of donor-recipient gender discrepancy that diminishes over time and males have a lower proportion that increases over the 25 years. The reason may be that since the onset of the heart transplant activity, results have been worse in male recipients who have received a heart transplant from a female donor, a fact that must be considered as a key factor in donor-recipient matching. Furthermore, the shortage of donors in the last decade and increase of female donors has made it necessary to accept higher risk combinations to ameliorate HT demand in sicker patients as reflected in the increase of urgent HT, increased use of mechanical circulatory support and increase in ventilatory support at the time of HT.

Although gender differences in mortality for patients on the waiting list for HT have recently been highlighted[31], our study has shown that mortality in men and women after HT is similar, as shown in the study by Moayedi Y, Fan CPS, Cherikh WS, *et al.* [9].) Although it has been suggested that transplant prioritization criteria should account for gender disparity due to a higher mortality of women on the waiting list [20], we have not found any gender differences in post-HT follow-up. Post-HT survival in women and men is similar when evaluated within a scenario that reduces socioeconomic factors (due to public health global system) and registry selection bias (due to Nationwide Registry).

As some of the HT prognosis variables differ between genders, this must be considered when approaching the study of gender differences in HT. This is important, for example, in the management of HF worsening with mechanical ventilation and mechanical circulatory support by gender.

A biological explanation may exist for the differences in causes of death between men and women. There are gender disparities in the immune system with more intense response in women[32]. Beyond this and as a consequence of motherhood, women have a higher risk of sensitization that requires a specific approach in the pre-transplant study[33,34]. Furthermore, gene expression, found to differ between men and women, seems to play a role in prediction of future clinical events in HT recipients [35]. This biological variability also explains the higher percentage of malignancy in men and rejection in women. It may be of interest to include a study on gender-adjusted immunosuppressive strategy from now on.

We cannot explain why we found that primary graft failure was more frequent as a cause of death in women than in men Thus, future studies would be necessary to analyze what the difference in risk factors and treatment of primary graft failure by gender are in order to improve outcome in one of the worse HT complications.

Among the limitations of our study are that it is based on a retrospective analysis and the particular HT scenario in our country (with less VAD use for example) that may lead to different results available from other countries. We have focused this study on HT outcomes, and we have not assessed mortality on the waiting list. This fact prevents the extrapolation of the results to advanced stage HF patients whose mortality has not been addressed. The segregated analysis of mortality predictors could have led to a loss in statistical power, especially for female gender.

Heart transplant is performed less frequently in women with similar long-term results. A better knowledge on the impact of gender disparity in clinical practice would help to understand the need to adjust therapies or to develop different strategies in men and women. More research is needed to fully understand why HT is less frequent in women, if adjusted results differ by gender and how observed biological variabilities translate to clinical changes in HT in men and women.

Acknowledgements

We thank Javier Muñiz for his statistical assistance and Barbara Shapiro for her excellent work of translation and English revision of the paper.

Authorship

María Dolores García-Cosio, Beatriz Díaz Molina and Raquel Lopez Vilella have contributed to the conception and design of the work.

María Dolores García-Cosio, Francisco González-Vilchez and Juan F Delgado Jiménez have contributed to the analysis and interpretation of data.

María Dolores García-Cosio and Francisco González-Vilchez have contributed to drafting the work.

Eduardo Barge-Caballero, Manuel Gómez Bueno, Manuel Martínez-Selles, José María Arizón, Diego Rangel Sousa, José González -Costello, Sonia Mirabet, Félix Pérez Villa, Gregorio Rábago, Ana Portales Ocampo, Luis de la Fuente and Iris Garrido have contributed to critically revising the article.

Funding sources

This investigation was funded by the Centro de Investigación en Red de Enfermedades Cardiovasculares (CIBERCV), Instituto de Salud Carlos III, Spanish Ministry of Economy and Competitiveness.

References

1. Beale AL, Meyer P, Marwick TH, Lam CSP, Kaye DM. Sex Differences in Cardiovascular Pathophysiology. *Circulation*. 2018;138(2):198-205.

2. Tamargo J, Rosano G, Walther T, et al. Gender differences in the effects of cardiovascular drugs. *Eur Hear J - Cardiovasc Pharmacother*. 2017;3(3):163-182.

3. Rosano GMC, Lewis B, Agewall S, et al. Gender differences in the effect of cardiovascular drugs: A position document of theworkinggroup on pharmacology and drug therapy of the ESC. *Eur Heart J*. 2015;36(40):2677-2680.

4. Mehra MR, Canter CE, Hannan MM, et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: A 10-year update. *J Hear Lung*

Transplant. 2016;35(1):1-23.

5. Mehra MR, Kobashigawa J, Starling R, et al. Listing Criteria for Heart Transplantation : International Society for Heart and Lung Transplantation Guidelines for the Care of Cardiac Transplant Candidates — 2006. *J Heart Lung Transplant*. 2006:1024-1042.
6. Crespo Leiro MG, Almenar Bonet L, Alonso-Pulpón L, et al. Conferencia de Consenso de los Grupos Españoles de Trasplante Cardiaco. *Rev Española Cardiol*. 2007;7(Supl.B):4-54.
7. Kaczmarek I, Meiser B, Beiras-Fernandez A, et al. Gender does matter: Gender-specific outcome analysis of 67,855 heart transplants. *Thorac Cardiovasc Surg*. 2013;61(1):29-36.
8. Hickey KT, Doering L V, Chen B, et al. Clinical and gender differences in heart transplant recipients in the NEW HEART study. *Eur J Cardiovasc Nurs*. 2017;16(3):222-229.
9. Moayedi Y, Fan CPS, Cherikh WS, et al. Survival Outcomes After Heart Transplantation: Does Recipient Sex Matter? *Circ Heart Fail*. 2019;12(10):e006218.
10. Khush KK, Kubo JT, Desai M. Influence of donor and recipient sex mismatch on heart transplant outcomes: Analysis of the International Society for Heart and Lung Transplantation Registry. *J Hear Lung Transplant*. 2012;31(5):459-466.
11. Reed RM, Netzer G, Hunsicker L, et al. Cardiac Size and Sex-Matching in Heart Transplantation Size Matters in Matters of Sex and the Heart. *JACC Hear Fail*. 2014;2(1):73-83.
12. M M-S, L A, MJ P-M, et al. Donor/recipient Sex Mismatch and Survival After Heart Transplantation: Only an Issue in Male Recipients? An Analysis of the Spanish Heart Transplantation Registry. *Transpl Int*. 2015;28(3):305-313.
13. Alonso-Pulpón L, Segovia J, Gomez-Bueno M, Garciá-Pavía P. Heart transplantation: Organisational aspects and current trends in immunosuppression - A view from Spain. *Heart*. 2012;98(11):878-889.
14. Stehlik J, Stevenson LW, Edwards LB, et al. Organ allocation around the world: Insights from the ISHLT international registry for heart and lung transplantation. *J Hear Lung Transplant*. 2014;33(10):975-984.
15. González-Vílchez F, Almenar-Bonet L, Crespo-Leiro MG, et al. Registro Español de Trasplante Cardiaco. XXIX Informe Oficial de la Sección de Insuficiencia Cardiaca de la

Sociedad Española de Cardiología (1984-2017). *Rev Española Cardiol*. 2018;64(12):1154-1167.

16. González-Vílchez F, Gómez-Bueno M, Almenar-Bonet L, et al. Spanish Heart Transplant Registry. 28th Official Report of the Spanish Society of Cardiology Working Group on Heart Failure (1984-2016). *Rev Esp Cardiol*. 2017;70(12):1098-1109.
17. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med*. 2000;19(3):335-351.
18. Mehta LS, Beckie TM, DeVon HA, et al. Acute Myocardial Infarction in Women : A Scientific Statement from the American Heart Association. *Circulation*. 2016;133(9):916-947.
19. Chambers DC, Cherikh WS, Goldfarb SB, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-fifth adult lung and heart-lung transplant report—2018; Focus theme: Multiorgan Transplantation. *J Hear Lung Transplant*. 2018;37(10):1169-1183.
20. Hsich EM, Starling RC, Blackstone EH, et al. Does the UNOS Heart Transplant Allocation System Favor Men Over Women? *JACC Hear Fail*. 2014;2(4):347-355.
21. Magnussen C, Bernhardt AM, Ojeda FM, et al. Gender differences and outcomes in left ventricular assist device support: The European Registry for Patients with Mechanical Circulatory Support. *J Hear Lung Transplant*. 2018;37(1):61-70.
22. Gómez-Martínez L, Orozco-Beltrán D, Quesada JA, et al. Trends in Premature Mortality Due to Heart Failure by Autonomous Community in Spain: 1999 to 2013. *Rev Esp Cardiol*. 2018;71(7):531-537.
23. Aimo A, Vergaro G, Castiglione V, et al. Effect of Sex on Reverse Remodeling in Chronic Systolic Heart Failure. *JACC Hear Fail*. 2017;5(10):735-742.
24. Cannatà A, Fabris E, Merlo M, et al. Sex Differences in the Long-term Prognosis of Dilated Cardiomyopathy. *Can J Cardiol*. 2020;36(1):37-44.
25. Fernández Gassó ML, Hernando-Arizaleta L, Palomar-Rodríguez JA, Soria-Arcos F, Pascual-Figal DA. Trends and Characteristics of Hospitalization for Heart Failure in a Population Setting From 2003 to 2013. *Rev Española Cardiol (English Ed*. 2017;70(9):720-

726.

26. Go AS, Mozaffarian D, Roger VL, et al. Heart Disease and Stroke Statistics—2014 Update. *Circulation*. 2014;129(3):431-434.

27. Crespo-Leiro MG, Metra M, Lund LH, et al. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2018;20(11):1505-1535.

28. Cequier Á, Ariza-Solé A, Elola FJ, et al. Impact on Mortality of Different Network Systems in the Treatment of ST-segment Elevation Acute Myocardial Infarction. The Spanish Experience. *Rev Española Cardiol (English Ed*. 2017;70(3):155-161.

29. Eifert S, Kofler S, Nickel T, et al. Gender-based analysis of outcome after heart transplantation. *Exp Clin Transplant*. 2012;10(4):368-374.

30. Jalowiec A, Grady KL, White-Williams C. Mortality, rehospitalization, and post-transplant complications in gender-mismatched heart transplant recipients. *Hear Lung J Acute Crit Care*. 2017;46(4):265-272.

31. Hsich EM, Blackstone EH, Thuita L, et al. Sex Differences in Mortality Based on United Network for Organ Sharing Status while Awaiting Heart Transplantation. *Circ Hear Fail*. 2017;10(6).

32. Klein SL, Flanagan KL. Sex differences in immune responses. *Nat Rev Immunol*. 2016;16(10):626-638.

33. Kobashigawa J, Mehra M, West L, et al. Report From a Consensus Conference on the Sensitized Patient Awaiting Heart Transplantation. *J Hear Lung Transplant*. 2009;28(3):213-225.

34. Kobashigawa J, Colvin M, Potena L, et al. The management of antibodies in heart transplantation: An ISHLT consensus document. *J Hear Lung Transplant*. 2018;37(5):537-547.

35. Crespo-Leiro MG, Stypmann J, Schulz U, et al. Performance of gene-expression profiling test score variability to predict future clinical events in heart transplant recipients. *BMC Cardiovasc Disord*. 2015;15(1):120.

Table1

	Female (n=1386)	Male (n=5354)	P Value
Age (years)[a]	54.0 (44, 61)	56 (49, 62)	<0.001
Etiology (%)			< 0.001
Dilated	41.3	34.6	
Ischemic	22.5	47.6	
Others	36.2	17.8	
Diabetes (%)	13.1	18.0	< 0.001
Hypertension (%)	24.1	33.1	< 0.001
COPD (%)	6.7	12.3	< 0.001
Peripheral vascular disease (%)	2.5	7.4	< 0.001
Pre-transplant malignancy (%)	7.1	2.8	< 0.001
GFR (ml/min/1.73 m^2) [a]	64.0 (48.7, 83.8)	68.7 (52.3, 86.7)	0.01
Pulmonary vascular resistance (WU) [a]	2.0 (1.3, 3.0)	2.0 (1.3, 2.9)	0.10
Pre-transplant cardiac surgery (%)	26.0	28.1	0.25
Pre-transplant infection (%)	9.8	11.5	0.041

Pre-transplant mechanical ventilation (%)	14.8	11.1	0.004
Combined organ transplantation (%)	3.3	1.8	0.01
Pre-HT circulatory support (%)			0.26
None	78.0	77.8	
IABP	12.5	13.8	
ECMO	4.3	3.1	
VAD	5.2	5.3	
Urgent transplant (%)	30.5	29.5	0.88
Cold ischemic time (min) [a]	200 (147, 240)	195 (145, 237)	0.26
Surgical technique (bicaval) (%)	49.9	46.7	0.97
Donor age (years) [a]	39 (24, 49)	37 (25, 47)	0.07
Donor Cause of death (%)			< 0.001
Trauma	32.5	41.1	
Cerebrovascular disease	42.0	37.7	
Other	25.5	21.2	

Gender donor/recipient mismatch (%)	47.5	26.3	< 0.001

COPD, Chronic Obstructive Pulmonary Disease; ECMO, extracorporeal membrane oxygenation; GFR, glomerular filtration rate; IABP, intra-aortic balloon pump; VAD, ventricular assist device; WU = Wood units.

[a] Data expressed as median (25th, 75th quartiles)

Table 2

	1993-1997 (n = 1375)	1998-2002 (n = 1604)	2003-2007 (n = 1297)	2008-2012 (n = 1187)	2013-2017 (n = 1277)	Total (n = 6740)	P Time	P Gender	P Time*Gender
Recipient Gender (%)							< 0.001	< 0.001	
Female	16.9	17.9	19.3	24.5	25.5	20.6			
Male	83.1	82.1	80.7	75.5	74.5	79.4			
Recipient Age (yr.)[a]							0.25	0.003	0.15
Female	55.0 (13.7)	54.0 (16.0)	53.0 (17.0)	54.0 (17.0)	51.5 (19.2)	54.0 (17.0)			
Male	55.0 (11.0)	55.0 (13.0)	55.0 (14.0)	57.0 (14.0)	56.0 (15.0)	56.0 (13.0)			
Total	55.0 (12.0)	55.0 (13.0)	55.0 (15.0)	56.0 (14.0)	56.0 (16.0)	55.0 (14.0)			
Etiology (%)							<0.001	<0.001	<0.001
Female									
Dilated	52.2	41.8	36.4	40.5	37.4	41.3			
Ischemic	22.0	26.5	16.4	22.7	23.9	22.5			
Others	25.9	31.7	47.2	36.8	38.7	36.2			
Male									
Dilated	32.7	34.9	35	34.9	35.9	34.6			
Ischemic	52.5	50.0	44.7	46.3	42.7	47.6			

Others	14.8	15	20.3	18.8	21.5	17.8			
Total									
Dilated	36.0	36.2	35.2	36.3	36.3	36.0			
Ischemic	47.3	45.8	39.2	40.5	37.9	42.4			
Others	16.7	18	25.5	23.2	25.8	21.6			
Diabetes (%)							<0.001	<0.001	0.056
Female	10.5	15.4	10.9	11.8	15.5	13.1			
Male	10.7	15.1	18.5	20.8	27.1	18.0			
Total	10.7	15.1	17.0	18.6	24.1	17.0			
Glomerular Filtration Rate < 45 mL/min/1.73 m^2 (%)							0.117	0.01	0.015
Female	21.7	11.7	28.6	17.5	15.9	18.4			
Male	13.0	13.7	13.3	14.2	15.7	14.2			
Total	14.3	13.4	16.2	15	15.8	15.1			
Hypertension (%)							0.15	<0.001	0.095
Female	23.1	26.0	23.0	26.6	21.9	24.1			
Male	28.3	27.9	31.8	40.6	40.4	33.1			
Total	27.4	27.6	30.1	37.1	35.7	31.3			
COPD (%)							0.04	<0.001	0.30
Female	10.9	6.9	4.1	5.3	6.8	6.7			
Male	13.1	12.2	11.5	10.5	14.0	12.3			
Total	12.8	11.2	10.1	9.2	12.1	11.1			

Peripheral vascular disease (%)							0.49	<0.001	0.51
Female	1.4	1.4	2.4	3.1	3.5	2.5			
Male	7.4	7.5	7.5	7.4	7.5	7.4			
Total	6.4	6.4	6.5	6.3	6.5	6.4			
Pulmonary Vascular Resistance > 2.5 (%)							0.66	0.42	0.71
Female	37.4	34.6	35.2	40.4	32.5	35.9			
Male	36.5	31.2	36.5	32.9	33.9	34.1			
Total	36.6	31.8	36.3	34.7	33.5	34.5			
Pretransplant infection (%)							<0.001	0.041	0.223
Female	3.4	10.9	11.8	10.8	10.8	9.8			
Male	5.8	10.4	11.3	13.7	17.7	11.5			
Total	5.4	10.5	11.4	13.0	16.0	11.2			
Pretransplant cardiac surgery (%)							0.129	0.25	0.65
Female	30.2	21.6	27.4	25	26.8	26			
Male	29.9	26	25.9	26.6	33.1	28.1			
Total	29.9	25.2	26.2	26.2	31.5	27.7			
Mechanical ventilation (%)							0.001	0.004	0.478
Female	11.4	13.1	14.9	20.4	13.6	14.8			
Male	8.2	9	12	13.7	14	11.1			
Total	8.7	9.7	12.6	15.4	13.9	11.9			
Combined organ transplant (%)							0.99	0.84	1.0

Female	0.0	4.2	4.4	4.1	3.4	3.3			
Male	0.9	2.6	2.4	1.7	1.5	1.8			
Total	0.7	2.9	2.8	2.3	2.00	2.1			
Pretransplant malignancy (%)							<0.001	< 0.001	0.43
Female	6.2	3.5	6.5	9.6	9.3	7.1			
Male	1.5	2.1	2.5	3.7	4.8	2.8			
Total	2.3	2.3	3.3	5.2	6.0	3.7			
Urgent transplant (%)							< 0.001	0.88	0.012
Female	21.7	26.1	28	35.7	37.7	30.5			
Male	19.5	22.8	30.5	31.9	47.3	29.5			
Total	19.9	23.4	30	32.9	44.9	29.7			
Circulatory support prior to HTx (%)									
Female							<0.001	0.26	0.01
None	88.2	85.8	81.0	72.3	67.5	78.0			
IABP	9.9	11.7	14.9	14.2	11.3	12.5			
ECMO	0.9	0.0	2.8	5.9	10.1	4.3			
VAD	0.9	2.5	1.2	7.6	11.0	5.2			
Male									
None	89.4	87.0	77.7	72.0	57.6	77.8			
IABP	9.7	12.0	20.3	17.0	11.1	13.8			
ECMO	0.2	0.1	0.7	5.1	11.1	3.1			

VAD	0.6	1.0	1.4	5.9	20.3	5.3			
Total									
None	89.2	86.8	78.3	72.1	60.1	77.9			
IABP	9.8	11.9	19.2	16.3	11.1	13.5			
ECMO	0.3	0.1	1.1	5.3	10.8	3.3			
VAD	0.7	1.3	1.3	6.3	17.9	5.3			
Donor age (yr.) [a]							< 0.001	0.22	0.16
Female	25.0 (18.0)	33.0 (24.0)	38.0 (23.3)	42.0 (18.8)	49.0 (16.3)	39.0 (25.0)			
Male	29.0 (19.0)	32.0 (22.0)	35.0 (21.0)	43.0 (19.0)	47.0 (17.0)	37.0 (22.0)			
Total	28.0 (19.0)	33.0 (22.0)	35.0 (21.0)	43.0 (19.0)	48.0 (17.0)	37.0 (23.0)			
Gender Recipient/Donor mismatch (%)							0.39	< 0.001	<0.001
Female	59.5	53.0	51.2	44.0	34.7	47.5			
Male	25.5	25.0	23.9	25.3	32.5	26.3			
Total	31.3	30.0	29.1	29.9	33.0	30.7			
Donor cause of death (%)							< 0.001	< 0.001	0.56
Female									
Trauma	47.8	38.3	38.8	22.3	20.6	32.5			
CVD	33.2	34.5	36.8	54.6	47.5	42.0			

Other	19.0	27.2	24.4	23.0	31.9	25.5			
Male									
Trauma	55.5	47.2	42.1	32.9	22.2	41.1			
CVD	30.3	32.3	33.8	43.4	52.8	37.7			
Other	14.3	20.5	24.1	23.7	25.0	21.2			
Total									
Trauma	54.2	45.6	41.5	30.3	21.8	39.4			
CVD	30.8	32.7	34.4	46.2	51.4	38.5			
Other	15.1	21.7	24.1	23.5	26.8	22.1			
Bicaval surgical technique (%)							< 0.001	0.97	0.71
Female	29.4	39.9	51.5	57.7	64.4	49.9			
Male	25.7	36.8	45.9	64.3	68.2	46.7			
Total	26.3	37.4	47	62.7	67.3	47.3			
Cold ischemic time (min)							< 0.001	0.97	0.71
Female	180 (86)	183 (97)	200 (92)	210 (79)	210 (96)	200 (93)			
Male	185 (89)	188 (97)	200 (90)	210 (83)	205 (94)	195 (92)			
Total	185 (88)	188 (97)	200 (90)	210 (81)	208 (94)	192 + 64			

Temporal trends of baseline characteristics across 5-year intervals for the total population and stratified by gender. P Time, p value for temporal trend of the whole population; P gender, p value for gender differences; P time*gender, p value for time * gender interaction. COPD, Chronic obstructive pulmonary disease.

a Data expressed as median (interquartile range)

Table 3.

	Univariate			Multivariate		
	HR	CI (95%)	P Value	HR	CI (95%)	P Value
Female gender	0.89	0.82-0.97	0.01	0.93	0.79-1.10	0.42
Recipient age			<0.001			<0.001
< 40 years	1			1		
40-59 years	1.39	1.23-1.56	<0.001	1.25	1.05-1.48	0.01
> 60 years	1.81	1.60-2.04	<0.001	1.74	1.45-2.09	<0.001
Etiology			<0.001			0.006
Dilated	1			1		
Ischemic	1.27	1.18-1.37	< 0.001	1.10	0.99-1.24	0.08
Other	1.22	1.11-1.34	< 0.001	1.26	1.09-1.45	0.002
Diabetes	1.26	1.16-1.38	< 0.001	1.18	1.05-1.34	0.007
Hypertension	1.14	1.06-1.23	<0.001	1.03	0.93-1.14	0.55
COPD	1.16	1.05-1.29	0.004	1.13	0.98-1.30	0.09
PVD	1.34	1.18-1.52	<0.001	1.38	1.15-1.65	<0.001
GFR < 45 mL/min/1.73 m2	1.51	1.35-1.69	< 0.001	1.34	1.18-1.52	<0.001
PVR > 2.5 WU	1.03	0.95-1.10	0.49			
Pretransplant infection	1.16	1.04-1.29	0.007	1.16	0.99-1.34	0.16
Pretransplant cardiac surgery	1.27	1.18-1.37	< 0.001	1.09	0.97-1.22	0.17
Mechanical ventilation	1.33	1.20-1.47	< 0.001	1.32	1.10-1.58	0.002
Pretransplant neoplasia	1.4	1.18-1.66	< 0.001	1.50	1.21-1.86	<0.001
Pretransplant circulatory support			0.037			0.02

None	1			1		
IABP	1.03	0.93-1.14	0.58	0.93	0.80-1.09	0.40
ECMO	1.35	1.09-1.68	0.007	1.55	1.13-2.14	0.007
VAD	1.12	0.93-1.34	0.24	1.12	0.86-1.46	0.39
Urgent transplant[a]	1.07	1.0-1.16	0.057			
Combined organ transplant	1.32	1.07-1.64	0.01	1.08	0.77-1.51	0.65
Donor age			0.001			<0.001
< 40 years	1			1		
41-50 years	1.15	1.07-1.25	<0.001	1.24	1.11-1.40	<0.001
> 50 years	1.13	1.03-1.25	0.015	1.21	1.05-1.39	0.009
Recipient/Donor gender mismatch			<0.001			0.09
None	1			1		
Recipient female/Donor male	0.89	0.79-0.99	0.046	1.02	0.82-1.26	0.89
Recipient male/Donor female	1.14	1.05-1.24	0.001	1.14	1.01-1.28	0.03
Donor cause of death			0.016			0.79
Trauma	1			1		
CVD	1,11	1.03-1.20	0.004	0.97	0.87-1.09	0.66
Other	1.07	0.98-1.16	0.15	0.96	0.84-1.09	0.50
Bicaval surgical technique	0.92	0.86-0.99	0.02	0.96	0.87-1.06	0.40
Cold ischemic time			<0.001			0.06
< 120 min	1			1		
120-239 min	1.01	0.91-1.11	0.895	1.08	0.94-1.23	0.26
> 240 min	1.21	1.08-1.35	0.001	1.19	1.02-1.38	0.02

Transplant time span			<0.001			0.02
1993-1998	1			1		
1999-2002	0.91	0.83-0.99	0.03	0.94	0.81-1.09	0.45
2003-2008	0.83	0.75-0.91	<0.001	0.97	0.83-1.14	0.74
2009-2012	0.85	0.76-0.96	0.008	0.94	0.78-1.12	0.48
2013-2017	0.73	0.64-0.84	<0.001	0.72	0.58-0.89	0.003

HR, Hazard ratio; CI, Confidence interval; COPD, Chronic obstructive pulmonary disease; CVD, cerebrovascular disease; ECMO extracorporeal membrane oxygenation; GFR glomerular filtration rate; IABP intra-aortic balloon pump, PVD, Peripheral vascular disease; PVR, Pulmonary vascular resistance; VAD ventricular assist device.

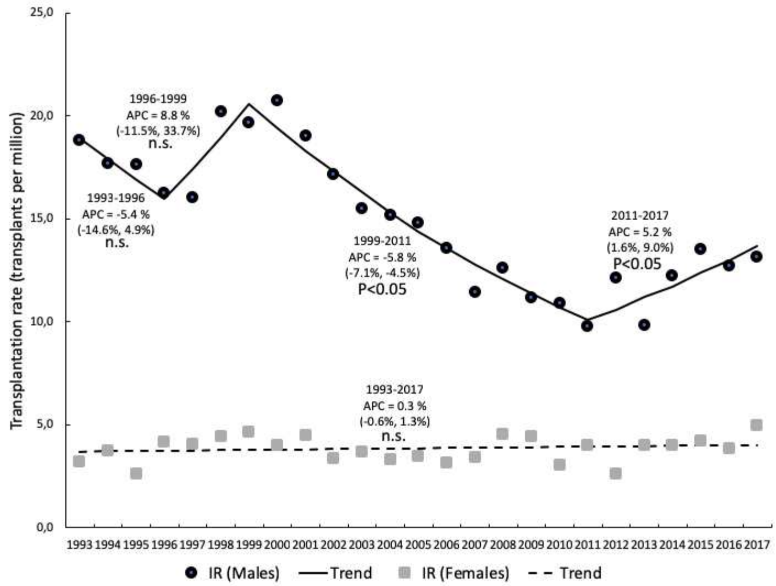
[a] Urgent transplant was not included in the multivariate model due to collinearity with Pretransplant Circulatory Support

Table 4

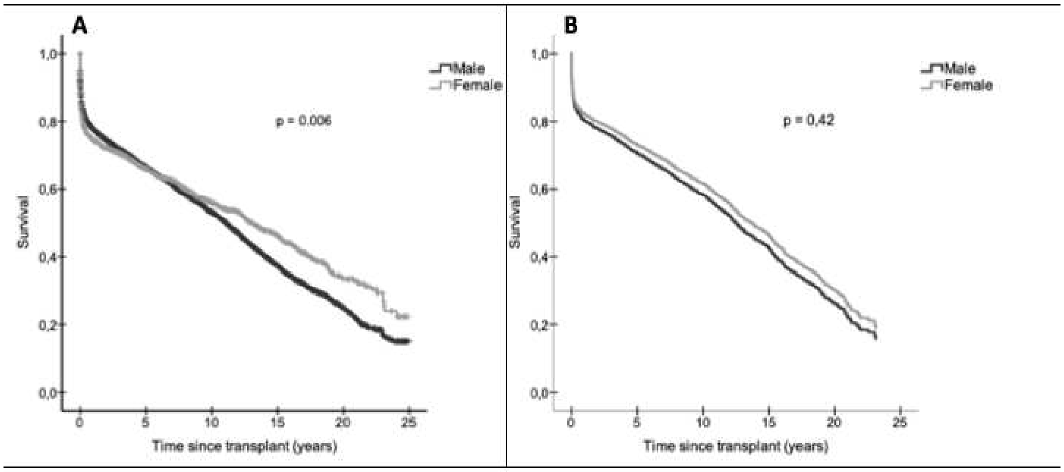
	Females			Males		
	HR	CI (95%)	P Value	HR	CI (95%)	P Value
Recipient age 40-59 yr. vs < 40 yr.				1.32	1.08-1.61	0.006
Recipient age > 60 yr. vs < 40 yr.	1.46	1.04-2.48	<0.03	1.87	1.53-2.30	<0.001
Ischemic vs. Dilated Etiology	1.38	1.05-1.81	0.02			
Other vs. Dilated Etiology	1.33	1.04-1.71	0.02	1.24	1.05-1.47	0.01
Diabetes				1.23	1.08-1.40	0.002
Hypertension	1.32	1.04-1.66	0.02			
GFR < 45 mL/min/1.73 m2	1.43	1.11-1.82	0.005	1.34	1.16-1.54	<0.001
Mechanical ventilation	1.96	1.51-2.55	<0.001			
Pretransplant neoplasia	1.93	1.36-2.75	<0.001	1.38	1.05-1.81	0.02
Pretransplant ECMO				2.09	1.47-2.97	<0.001
Donor age 41-50 years Donor age > 50 years				1.23 1.28	1.08-1.39 1.10-1.49	0.001 0.001
Recipient/Donor gender mismatch				1.14	1.01-1.27	0.03
Cold ischemic time > 240 min				1.20	1.01-1.42	0.04
Transplant span 2013-2017				0.67	0.53-0.85	<0.001

HR, Hazard ratio; CI, Confidence interval; ECMO extracorporeal membrane oxygenation; GFR glomerular filtration rate.

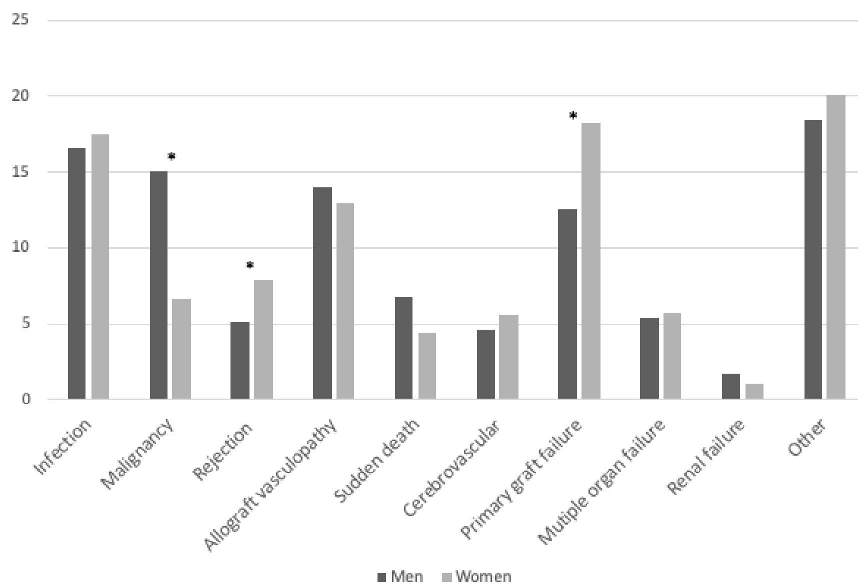
In order to improve the understanding of the results, only the factors with statistically significant association are shown. The analysis of the variables of 3 categories was carried out in the same way as in the total population.



ctr_14096_f1.tiff



ctr_14096_f2.tiff



ctr_14096_f3.tiff