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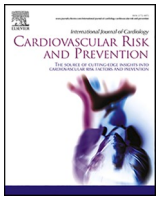

# Impact of biological sex on heart transplant patients admitted to cardiac rehabilitation: A 10-year retrospective cohort study

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ABSTRACT

*Introduction:* Heart transplantation (HTx) serves as the gold-standard therapy for end-stage heart failure, yet patients often experience physical deconditioning and cognitive impairments post-surgery. Cardiac rehabilitation (CR) has shown promise in the HTx context. However, uncertainty surrounds the impact of biological sex. Accordingly, the aim of this paper was to investigate the impact of biological sex in a cohort of patients with HTx early admitted to a residential CR program.

*Methods:* This was a retrospective analysis involving patients who underwent HTx at Niguarda Hospital and who subsequently participated in a CR program at IRCCS Fondazione Don Gnocchi, Milan, Italy, between 2010 and 2022. The primary endpoint was time to event (in months), with an event defined as a composite outcome of whichever occurred first of death, allograft rejection, or cardiac allograft vasculopathy up to 30 months follow-up.

*Results:* In a total of 129 patients, 60 % male, and 40 % female, baseline characteristics presented comparably between the sexes. At 6 months, no significant sex differences were observed for the primary composite outcome. However, at 30 months, females exhibited a significantly lower incidence of the primary composite outcome and an increased survival rate. Multivariable analysis confirmed a protective effect of female sex against mortality (F vs. M, HR 0.164, 95 % CI 0.038–0.716, P = 0.0161).

*Conclusions:* Despite limitations, our findings emphasize that sex affects post-HTx long-term follow-up following CR discharge, with more favorable outcomes for female recipients. In an era of tailored management algorithms, it is imperative to take into account the gender gap even in cardiac rehabilitation.

## 1. Introduction

Heart transplantation (HTx) is the gold-standard therapy for end-stage heart failure (HF) [1]. Patients undergoing HTx often face physical deconditioning and cognitive impairments due to pre-operative inactivity and cerebral hypoperfusion. Common complications include critical polyneuropathy and pressure sores [2]. Cardiac rehabilitation (CR), a multidisciplinary intervention with a track record of enhancing cardiovascular (CV) prognosis and quality of life, has demonstrated effectiveness in various settings, including for patients with ischemic heart disease and chronic HF [3–5]. In the HTx context, previous reports have highlighted the positive impact of early-initiated CR programs, particularly with high intensity interval training (HIIT) proving superior to moderate intensity continuous training (MICT) in functional improvement [6,7]. Moreover, CR has been linked to reduced 1-year readmission risk post-discharge [8]. Sex emerges as a significant factor influencing various aspects of transplantation, from candidate selection to outcomes [9]. Although women constitute a smaller proportion of

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HTx recipients annually, they tend to exhibit better long-term survival and a lower risk of malignancy and cardiac allograft vasculopathy (CAV), but a higher incidence of antibody-mediated rejection (AMR) after HTx [10,11]. Several factors, including allograft ischemic time, donor and recipient sex hormonal and immunologic considerations, and cardiac size mismatch, may also contribute to these outcomes [12]. Surprisingly, the impact of sex differences on HTx-related outcomes in patients who undergo CR remains unexplored. Thus, this study aims to characterize the outcomes of heart transplant patients enrolled in our in-hospital CR program, with a specific focus on sex differences.

## 2. Material and methods

### 2.1. Data collection

We conducted a bicentric, retrospective analysis involving patients aged over 18 who underwent HTx at Great Metropolitan Niguarda Hospital and subsequently participated in a CR program at IRCCS Santa Maria Nascente, Milan – Fondazione Don Gnocchi between 2010 and 2022. Baseline data were extracted from medical records, encompassing pre-HTx demographic and clinical variables, indication for HTx, ischemia time, previous mechanical circulatory support, electrocardiographic/echocardiographic parameters, and pharmacological and laboratory data at admission to CR. Follow-up was exclusively performed at Niguarda Hospital, with data collected during planned/unplanned hospitalization and ambulatory visits. Clinical outcomes were assessed specifically at 6 months and 30 months, using entry into rehabilitation (T0) as the reference point. The HTx patient records were archived in a database for administrative purposes. The study adhered to the principles outlined in the Declaration of Helsinki, and the retrospective data analyses received approval from local institutional review boards. The ethics committee of the IRCCS Santa Maria Nascente, Milan – Fondazione Don Gnocchi granted its approval (protocol no. 2, May 10, 2023, with an amendment to data on June 6, 2023). Owing to the retrospective nature of the study, the requirement for informed consent was waived by our institutional review board.

### 2.2. Rehabilitation program

Rehabilitation in the transplanted recipient presents distinct challenges arising from respiratory deconditioning, pleural effusion, reduced average peak oxygen consumption, muscle atrophy, and physical deconditioning linked to prolonged intensive care unit (ICU) stays, bed rest, and complications tied to drug effects and immunosuppression. Over the last decade, the rehabilitation strategy for HTx patients has evolved significantly. At the commencement of our study in 2010 patients engaged initially in a subthreshold endurance training program. As the literature expanded on the effects and safety of various exercises for HTx patients, CR protocols were modified to incorporate strength training and respiratory muscle exercises alongside endurance training, in either intervals or continuous modalities [13–19]. Additionally, patient care increasingly embraced an interdisciplinary approach, involving physiotherapists, dieticians/nutritionists, speech therapists, and psychologists, and facility physicians and nurses. Rehabilitation objectives encompass respiratory reconditioning, restoration of muscle tone and strength, and reintegration into exercise. Addressing post-cardiac surgery complications, such as wound complications and deficits from peripheral neuropathy or myelopathy, is crucial. CR in HTx patients is structured in multiple phases.

The initial CR phase, spanning from immediate postoperative to clinical stability, occurs in an acute-care hospital. Inpatient rehabilitation involves early postoperative activities, weaning from ventilation, respiratory physiotherapy, adequate nutrition balancing the patient's caloric need, early passive or active mobilization, recovery of standing and walking, activities of daily living (ADL) training, and patient/family education with promotion of adherence to these activities [20,21]. A subsequent phase, conducted in inpatient CR institutions, includes a multifunctional approach of medical surveillance of rejection and immunosuppressive drugs; monitoring of blood pressure to avoid the risk of posterior reversible encephalopathy syndrome; dyslipidemia management; monitoring for cytomegalovirus infection (and treatment if required); counseling on nutrition and psychological stress; nurse care of pressure sores and the surgical wound; overcoming of any kind of neuropathy, if present; and physical training to enhance exercise tolerance and muscle strength. During rehabilitation at our CR facility, patients engage in approximately 90 min of daily physical activity, divided into supervised sessions involving continuous aerobic activity, interval training, or resistance training [18]. Initially, short sessions lasting about 15 min are repeated three or four times in the morning and afternoon. As clinical conditions stabilize and exertion improves, the time of each session is increased and the frequency decreased to two training sessions per day. Endurance, resistance, and strength exercises, utilizing a variety of equipment (exercise bikes, treadmills, walking training), are adapted based on perceived fatigue and/or oxygen consumption. Heart rate during physical training is targeted at between 70 % and 85 % (for continuous training) and 90 % (for interval training) of peak $VO_2$ achieved during cardiopulmonary exercise testing (CPET) [14,22]. Resistance sessions aim for three or four sets of 10 repetitions per muscle group, monitored for intensity, duration, load, and speed. Resistance exercises involve the use of natural loads and/or overload exercises, with the goal of reaching a muscle fatigue level of 4 on the OMNI-RES scale. Besides supervised exercise, counseling during CR covers nutrition, stress management, and social and psychological support. Following completion, patients are encouraged to maintain a lifelong exercise regimen [2].

In the case of ICU-acquired weakness or critical illness polyneuropathy, three phases are considered. During the first phase, intervention is provided in the form of speech therapy, motor rehabilitation, occupational therapy, and neuropsychology, based on the particular rehabilitation needs. In the intermediate phase, moderate-intensity aerobic exercise of at least 30 min/day is progressively introduced for 5 days a week, favoring the reacquisition of anti-gravity control. In the third phase, exercises are provided with a progressive increase in loads accompanied by a decrease in repetitions, with counter-resistance exercises to increase muscle mass. The work environment expands. Occupational therapy intervention becomes prominent at this stage, involving the global care of the person to establish a one-to-one therapeutic relationship between the occupational therapist and the CR patient. These rehabilitation sessions are designed to increase individual autonomy in the daily living environment and community by promoting, through personally significant activities, the recovery, and optimization of present and potential procedural and executive functions.

### 2.3. Outcomes and statistical analysis

The primary endpoint was time to event (in months), with event defined as time to a composite outcome of whichever occurred first of death, allograft rejection, or CAV within the first 6 months of admission to the rehabilitation facility and, after this time, during the following 30 months of follow-up. Each component of the composite outcome was evaluated as a secondary endpoint. We estimated an overall cohort of about 130 patients of whom approximately 60 % were male and 40 % were female. According to the approach of Schoenfeld and Richter, this sample allowed detection, with a level of significance of $\alpha = 5$ % and a power of 80 %, of a 20 % difference in composite outcome-free survival probability between males and females at the end of the follow-up time included in the survival analyses, using the log-rank test to compare the Kaplan–Meier curves and assuming a survival probability of 75 % for male subjects. The descriptive statistics included proportions for categorical variables and median values and interquartile range (IQR) for continuous variables. The baseline demographic and clinical-epidemiological characteristics of females and males were compared using $\chi^2$ or

Fisher's exact test where necessary for categorical variables and Wilcoxon's rank-sum test for continuous variables. Kaplan–Meier curves were derived to assess the time-dependent probability of the composite outcome in males and females and were compared using the log-rank test. The 3-year study period was divided into two intervals: the first 6 months after admission to the rehabilitation facility and the following 30 months (*adapted follow-up considering the initial critical phase and the benefit of CR expected early compared to the usual 5-year follow-up*). In the first case, the survival analysis was performed by censoring the patients at 6 months of follow-up; in the second case, the analysis included the subjects who were still outcome-free at the start of the second interval. The same analyses were performed for the secondary outcomes. Univariable and multivariable Cox proportional hazard models were applied to estimate the relationship between sex and the study endpoint. The effect of sex was adjusted for the transplant year (before or after 2019) as a potential confounder in the multivariable model. The results were expressed as hazard ratios (HRs) with 95 % confidence intervals (CIs). The statistical analyses were performed using SAS software, version 9.4, and P-values of less than 0.05 were considered statistically significant.

## 3. Results

### 3.1. Characteristics of the patients at baseline

In total, 129 HTx recipients enrolled in the CR program at IRCCS Santa Maria Nascente, Milan–Fondazione Don Gnocchi from January 2010 to June 2022 were included in the analysis for sex differences. Nine patients below 18 years of age or with re-transplantation were excluded (Fig. 1). Detailed baseline (T0) data are presented in Table 1. Of the 129 patients, 52 (40 %) were female, and 77 (60 %) were male. At the time of admission to CR, the median age was equivalent between women and men (female [F] median age 53, IQR 45–59 years, male [M] median age 53, IQR 42–59 years; P = 0.973). No statistically significant differences were observed between the two groups for major risk factors such as hypertension (F 44.2 % vs. M 46.8 %; P = 0.858), smoking (F 9.6 % vs. M 13.0 %; P = 0.78), diabetes (F 17.3 % vs. M 16.9 %; P = 0.99), and dyslipidemia (F 36.5 % vs. M 38.2 %; P = 0.99). Female recipients were shorter in stature (F 160.5 cm vs. M 174.0 cm; P < 0.001) and had lower body mass index BMI (21.26 kg/m$^2$ vs. 23.42; P < 0.001). Women also exhibited a different distribution of HF etiology (P = 0.048) with a higher prevalence of non-ischemic (80.8 % vs. 63.2 %) and a lower prevalence of ischemic (19.2 % vs. 36.8 %) cardiomyopathy. Regarding medication, women had a higher probability than men of receiving tacrolimus as a calcineurin inhibitor (34.6 % vs. 13.0 %, P = 0.005), while more men were treated with cyclosporin (87.0 % vs 65.4 %, P = 0.005). No significant differences were found between the two groups for other baseline characteristics including New York Heart Association (NYHA) class, renal disease, chronic obstructive pulmonary disease, anemia, year of HTx and time passed since HTx, laboratory tests, number of myocardial biopsies prior to the inpatient CR, and infections on admission to rehabilitation (Table 1).

### 3.2. Course after transplantation

Table 2 provides a summary of the clinical course of patients following admission to CR. At 6 months follow-up, there was no significant difference in the primary endpoint between males and females (M 15.6 % vs. F 17.3 %, P = 0.795). Similarly, when evaluating each component of the primary endpoint individually, no significant differences were observed between the two sexes (death F 3.8 % vs. M 0 %, P = 0.083; rejection M 14.3 % vs. F 13.5 %, P = 0.895; CAV F 0 % vs. M 3.9 %, P = 0.15; Table 2A). Furthermore, according to the Kaplan–Mayer curves, there were no survival probability differences (M 0.84 [0.74–0.91] vs F 0.83 [0.69–0.91], P = 0.777) at this follow-up point (Fig. 2). During long-term follow-up (median follow-up 29.3 months, 95 % CI 28.5–29.5 months), the primary composite outcome was significantly lower in females (7.0 % vs 25.4 %, P = 0.015; Table 2B) and survival analysis confirmed statistically significant differences in favor of females (M 0.79 [0.67–0.87] vs. F 0.95 [0.82–0.99], P = 0.006; Fig. 2). When univariable and multivariable Cox proportional hazard models were employed to assess the relationship between sex and the study endpoint, female sex demonstrated a protective effect against the primary outcome (F vs. M, HR 0.164, 95 % CI 0.038–0.716, P = 0.0161;

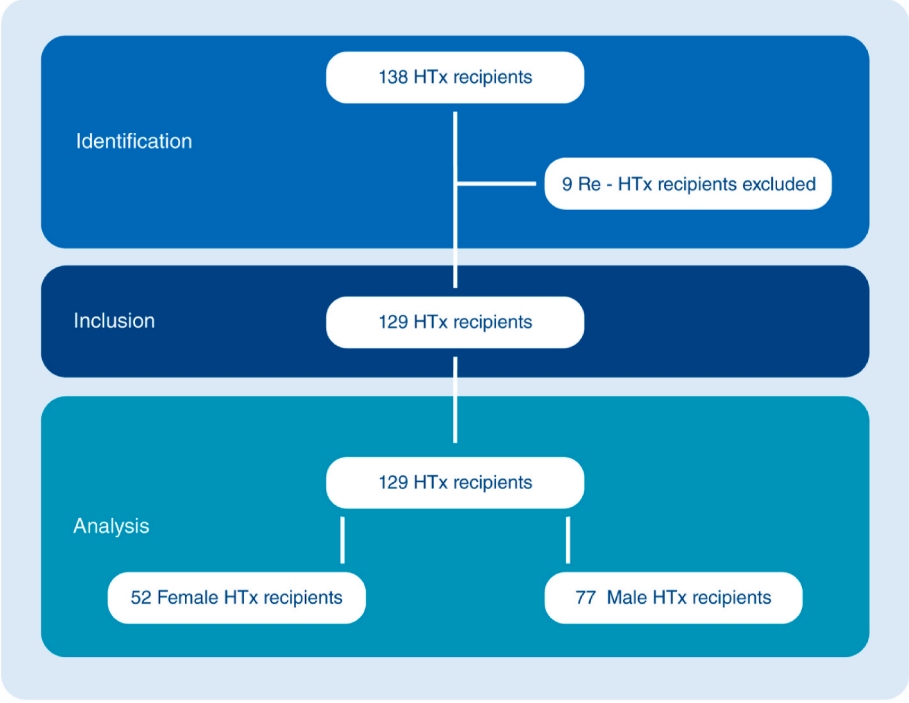


**Fig. 1.** Flow diagram illustrating the selection of the study population.

**Table 1**
Patient characteristics at baseline with comparison between males and females.

| | Overall N = 129 | Female n = 52 (40 %) | Male n = 77 (60 %) | P-value |
|---|---|---|---|---|
| **General characteristics** | | | | |
| Age (years) | 53.00 (43.00, 59.00) | 53.00 (45.00, 59.00) | 53.00 (42.00, 59.00) | 0.973 |
| Height (cm) | 169.50 (160.75, 175.00) | 160.50 (158.00, 165.25) | 174.00 (169.00, 178.00) | < **0.001** |
| Weight (kg) | 65.00 (56.00, 75.00) | 55.50 (48.00, 65.50) | 72.00 (65.00, 80.00) | < **0.001** |
| BMI (kg/m$^2$) | 22.62 (20.66, 25.41) | 21.26 (19.35, 24.08) | 23.42 (21.69, 25.70) | **0.002** |
| Hypertension, n (%) | 59 (45.7) | 23 (44.2) | 36 (46.8) | 0.858 |
| Smoking, n (%) | 15 (11.6) | 5 (9.6) | 10 (13.0) | 0.78 |
| Diabetes, n (%) | 22 (17.1) | 9 (17.3) | 13 (16.9) | 0.999 |
| Dyslipidemia, n (%) | 48 (37.5) | 19 (36.5) | 29 (38.2) | 0.999 |
| Renal disease, n (%) | 58 (46.0) | 20 (40.0) | 38 (50.0) | 0.281 |
| Chronic renal disease—stage, n (%) | | | | |
| 1 | 68 (52.7) | 32 (61.5) | 36 (46.8) | 0.349 |
| 2 | 32 (24.8) | 10 (19.2) | 22 (28.6) | |
| 3 | 28 (21.7) | 10 (19.2) | 18 (23.4) | |
| 4 | 1 (0.8) | 0 (0.0) | 1 (1.3) | |
| 5 | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| COPD, n (%) | 6 (4.7) | 3 (5.8) | 3 (3.9) | 0.685 |
| Anemia, n (%) | 87 (68.5) | 33 (64.7) | 54 (71.1) | 0.559 |
| Year of transplant ≥2019, n (%) | 29 (22.5) | 9 (17.3) | 20 (26.0) | 0.287 |
| Time from transplant (days) | 22.00 (18.00, 30.00) | 22.00 (18.75, 29.25) | 21.00 (18.00, 30.00) | 0.831 |
| Ischemic time (min) | 180.00 (137.50, 214.00) | 180.00 (146.25, 200.75) | 180.00 (135.00, 227.00) | 0.678 |
| Etiology, n (%) | | | | |
| Ischemic | 38 (29.7) | 10 (19.2) | 28 (36.8) | **0.048** |
| Non-ischemic | 90 (70.3) | 42 (80.8) | 48 (63.2) | |
| NYHA class, n (%) | | | | |
| 1 | 39 (30.5) | 15 (29.4) | 24 (31.2) | 0.842 |
| 2 | 18 (14.1) | 8 (15.7) | 10 (13.0) | |
| 3 | 47 (36.7) | 17 (33.3) | 30 (39.0) | |
| 4 | 24 (18.8) | 11 (21.6) | 13 (16.9) | |
| Ejection fraction (%) | 60.00 (58.00, 63.00) | 60.00 (56.75, 63.00) | 60.00 (58.75, 63.00) | 0.773 |
| Mitral regurgitation—grade, n (%) | | | | |
| I | 118 (94.4) | 45 (90.0) | 73 (97.3) | 0.115 |
| II | 7 (5.6) | 5 (10.0) | 2 (2.7) | |
| III | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| Sinus rhythm, n (%) | 123 (98.4) | 49 (100.0) | 74 (97.4) | 0.519 |
| Septum thickness (mm) | 11.00 (10.00, 12.00) | 11.00 (10.00, 12.00) | 11.00 (10.00, 12.00) | 0.984 |
| Posterior wall thickness (mm) | 10.00 (9.00, 11.00) | 11.00 (9.00, 11.00) | 10.00 (9.00, 11.00) | 0.52 |
| Pericardic effusion, n (%) | 64 (52.5) | 24 (49.0) | 40 (54.8) | 0.581 |
| CIED, n (%) | | | | |
| ICD | 1 (0.8) | 0 (0.0) | 1 (1.4) | 0.999 |
| PM | 5 (4.1) | 2 (3.9) | 3 (4.2) | |
| None | 117 (95.1) | 49 (96.1) | 68 (94.4) | |
| **Laboratory tests** | | | | |
| Total cholesterol (mg/dL) | 215.00 (191.50, 244.50) | 231.00 (198.00, 260.50) | 210.50 (188.75, 236.00) | 0.06 |
| LDL cholesterol (mg/dL) | 125.00 (99.00, 154.00) | 129.50 (107.25, 156.25) | 120.00 (96.50, 147.00) | 0.301 |
| Triglycerides (mg/dL) | 167.50 (123.50, 200.50) | 170.00 (150.00, 200.50) | 164.00 (111.00, 200.00) | 0.289 |
| eGFR (ml/min) | 80.00 (62.25, 100.00) | 90.00 (68.00, 100.00) | 80.00 (59.50, 99.00) | 0.217 |
| Potassium (mEq/L) | 4.51 (4.11, 4.79) | 4.46 (4.12, 4.71) | 4.58 (4.11, 4.83) | 0.347 |
| Sodium (mEq/L) | 139.00 (137.00, 141.00) | 139.50 (138.00, 142.00) | 139.00 (137.00, 141.00) | 0.33 |
| Blood urea (mg/dL) | 41.00 (33.75, 55.50) | 39.00 (34.00, 50.00) | 42.00 (33.50, 60.00) | 0.398 |
| Hemoglobin (g/dL) | 11.00 (10.20, 11.70) | 11.10 (10.40, 11.70) | 11.00 (10.07, 11.80) | 0.98 |
| MCV (fL) | 91.45 (89.00, 95.00) | 91.00 (89.00, 95.75) | 91.70 (89.00, 94.70) | 0.689 |
| White blood cell count (n) | 4770.00 (7.92, 8050.00) | 4950.00 (9.28, 8250.00) | 4630.00 (7.87, 7932.50) | 0.59 |
| AST/GOT (U/L) | 17.00 (13.00, 24.00) | 17.00 (14.00, 23.25) | 17.50 (13.00, 24.25) | 0.786 |
| ALT/GPT (U/L) | 25.00 (16.00, 40.50) | 23.00 (17.50, 34.00) | 27.00 (16.00, 48.00) | 0.559 |
| Bilirubin (mg/dL) | 0.75 (0.56, 1.10) | 0.62 (0.41, 0.90) | 0.78 (0.61, 1.12) | **0.014** |
| **Therapy** | | | | |
| Beta blockers, n (%) | 16 (12.5) | 4 (7.7) | 12 (15.8) | 0.276 |
| ACE inhibitors, n (%) | 57 (44.2) | 24 (46.2) | 33 (42.9) | 0.722 |
| ARB, n (%) | 4 (3.1) | 3 (5.8) | 1 (1.3) | 0.302 |
| MRA, n (%) | 4 (3.1) | 1 (2.0) | 3 (3.9) | 0.999 |
| Statin, n (%) | 7 (5.4) | 5 (9.6) | 2 (2.6) | 0.117 |
| Anticoagulane, n (%) | 12 (9.3) | 5 (9.6) | 7 (9.1) | 0.999 |
| Insulin, n (%) | 20 (15.6) | 9 (17.6) | 11 (14.3) | 0.627 |
| Tacrolimus, n (%) | 28 (21.7) | 18 (34.6) | 10 (13.0) | **0.005** |
| Mycophenolic acid, n (%) | 126 (97.7) | 52 (100.0) | 74 (96.1) | 0.273 |
| Cyclosporin, n (%) | 101 (78.3) | 34 (65.4) | 67 (87.0) | **0.005** |
| Corticosteroid, n (%) | 128 (99.2) | 51 (98.1) | 77 (100.0) | 0.403 |
| Everolimus, n (%) | 1 (0.8) | 0 (0.0) | 1 (1.3) | 0.999 |
| **Infection after HTx** | | | | |
| CMV infection, n (%) | 92 (71.3) | 39 (75.0) | 53 (68.8) | 0.552 |
| Other infections, n (%) | 47 (36.4) | 16 (30.8) | 31 (40.3) | 0.351 |

Continuous variables are expressed as median and inter-quartile range (Q1, Q3). Categorical variables are expressed as n (%) or n/n available (%).
ALT, Alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; CIED, cardiac implantable electronic device; CMV, cytomegalovirus; eGFR, estimated glomerular filtration; CRT, cardiac resynchronization therapy; HTx, heart transplantation; ICD, internal cardioverter defibrillator; MRA, mineralocorticoid receptor antagonist; PM, pace-maker.

**Table 2A**
Outcomes between T0 (entry into rehabilitation) up to 6 months in rehabilitation: descriptive analysis.

| | Overall N = 129 | Female n = 52 (40 %) | Male n = 77 (60 %) | P-value |
|---|---|---|---|---|
| Composite outcome, n (%) | 21 (16.3) | 9 (17.3) | 12 (15.6) | 0.795 |
| Death, n (%) | 2 (1.6) | 2 (3.8) | 0 (0.0) | 0.083 |
| Allograft rejection, n (%) | 18 (14.0) | 7 (13.5) | 11 (14.3) | 0.895 |
| CAV, n (%) | 3 (2.3) | 0 (0.0) | 3 (3.9) | 0.15 |

Table 3). Additionally, the influence of sex was adjusted for the transplant year (before or after 2019) as a potential confounder in the multivariable model (F vs. M, after adjustment for HTx ≥2019 vs. <2019, F vs. M, HR 0.166 95 % CI 0.038–0.723, P = 0.0168; Table 3). Female sex also appeared to be protective against CAV development, although this was not statistically significant (HR 0.288, 95 % CI 0.062–1.334, P = 0.1114). *The further adjustment for age did not substantially change the results.*

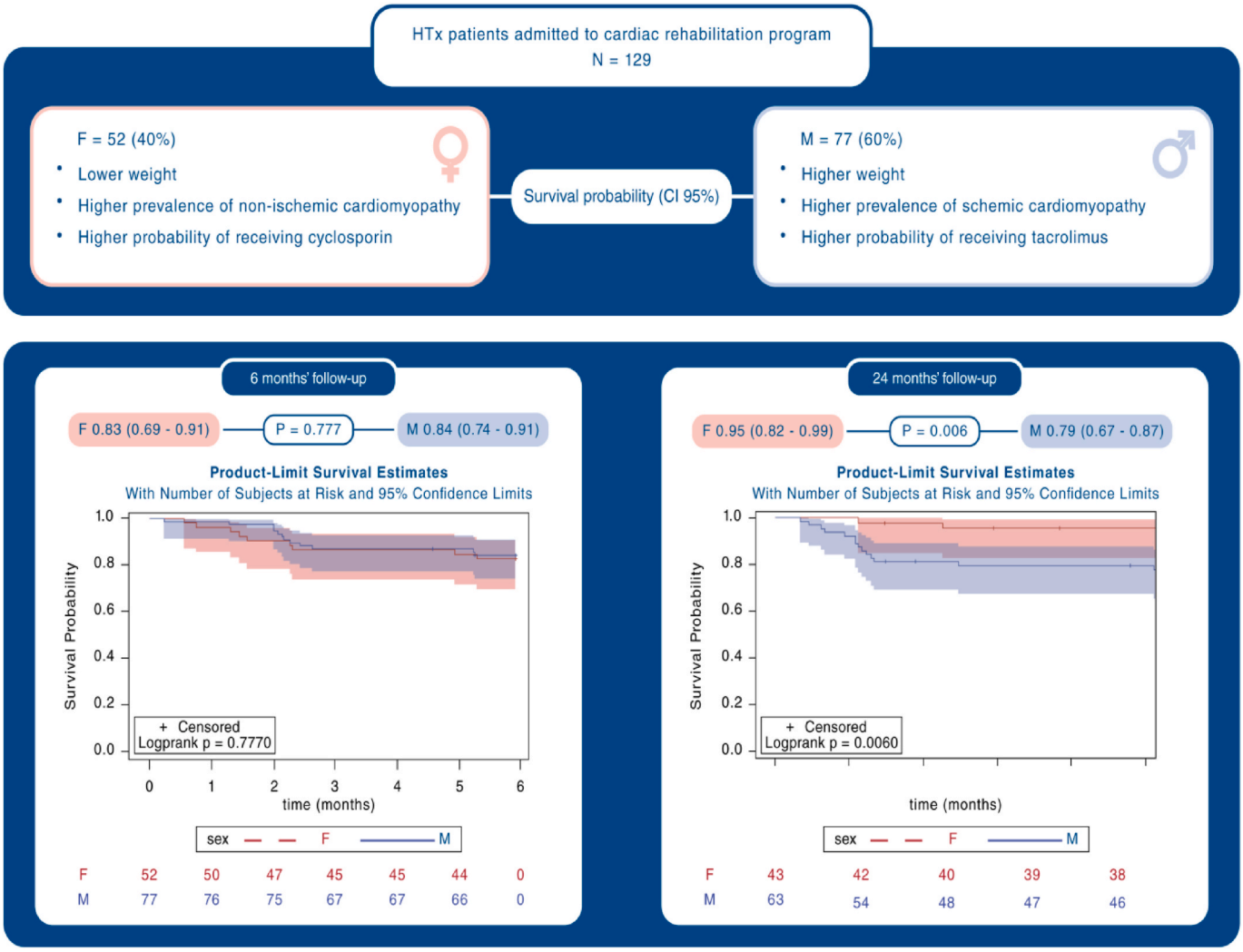


**Fig. 2.** Comparison between male and female sex in terms of population characteristics and of survival probabilities at 6 and 24 months of follow-up.

**Table 2B**
Outcomes between 6 months from T0 and long-term follow-up: descriptive analysis.

| | Overall N = 106 | Female n = 43 (41 %) | Male n = 63 (59 %) | P-value |
|---|---|---|---|---|
| Composite outcome, n (%) | 19 (17.9) | 3 (7.0) | 16 (25.4) | **0.015** |
| Death, n (%) | 4 (3.8) | 0 (0.0) | 4 (6.3) | 0.092 |
| Allograft rejection, n (%) | 6 (5.7) | 1 (2.3) | 5 (7.9) | 0.219 |
| CAV, n (%) | 11 (10.4) | 2 (4.7) | 9 (14.3) | 0.11 |
| Time of long-term follow-up (months, calculated as beginning 6 months after admission to the rehabilitation facility) | 29.3 (28.9, 29.5) | 29.4 (29.2, 29.5) | 29.3 (28.6, 29.5) | 0.194 |

Continuous normally distributed variables are expressed as median and interquartile range (Q1, Q3). Categorical variables are expressed as n (%) or n/n available (%).
CAV, Coronary allograft disease.

**Table 3**
Composite outcome using Cox model to estimate the effect of sex, unadjusted and adjusted for time of transplantation.

| Unadjusted | Hazard ratio (HR) | 95 % Lower confidence limit for HR | 95 % Upper confidence limit for HR | P-value |
|---|---|---|---|---|
| Female vs. male | 0.164 | 0.038 | 0.716 | **0.0161** |
| **Adjusted for the time of HTx** | | | | |
| Female vs. male | 0.166 | 0.038 | 0.723 | **0.0168** |
| HTx year ≥2019 vs. <2019 | 1.102 | 0.354 | 3.431 | 0.8668 |

HTx, Heart transplantation.

## 4. Discussion

To the best of our knowledge, this study represents the first examination of the influence of biological sex on long-term outcomes in HT patients admitted to an early CR program. Previously published research in the field has focused only on HTx patients admitted to CR 6 months post-HTx.

The key findings of our study can be summarized as follows: (1) despite a higher male admission rate to CR, the program is equally accessible to both sexes; (2) female recipients exhibit baseline characteristics comparable with males; and (3) sex affects post-HTx long-term follow-up following CR discharge, with more favorable outcomes for female recipients.

Previous studies indicate that CR is underutilized among HTx recipients, particularly in women [8,23,24]. However, it is crucial to note

that the Italian healthcare system differs significantly from the US system, which is the primary focus of many reports. Given the public nature of healthcare access, the CR program in Italy is offered to every patient undergoing HTx. The rehabilitation process begins in the ICU, progresses through the cardiology department, and concludes in conventional clinics where patients are housed in a specialized unit. Although some patients may perceive admission to the rehabilitation department as an unwelcome delay in their anticipated return home, we strongly emphasize that CR plays a pivotal role in their clinical journey. We find ourselves in an era where the challenge of the disparity between the demand and supply of heart for HTx poses a significant therapeutic barrier in advanced HF, a condition with growing incidence.

*Over the 13 years observed in our study, the number of HTx in Italy remained stable, with an average of 248.1 transplants* per *year. However, this represents a significant decline compared to the previous 13-year period (1997–2009), when the average number of transplants was 329.1* per *year. Several factors may contribute to this decline, including a decrease in the number of organ donors,* an aging population and the enhanced efficacy of pharmacological HF treatment capable of slowing disease progression necessitates that HF specialists handle progressively more complex cases [25]. In this context, CR emerges as a crucial opportunity for optimizing the management of these high-complexity cardiac patients. CR should be regarded as a comprehensive, multidisciplinary chronic disease management program. It not only facilitates intervention in motor reactivation and functional improvement but also serves as a distinct opportunity to address nutritional, psychological, and educational aspects, particularly emphasizing adherence to prescribed pharmacological therapies. Over the long term, counseling and exercise rehabilitation may also play a significant role in managing CV risk factors [26]. All these elements undoubtedly contribute to enhanced outcomes, as previously evidenced in individuals participating in CR programs [8]. The immediate post-transplant period is the phase of utmost vulnerability, with both physical and psychological challenges for patients, who are often in a fragile state due to prolonged hospitalization. Although a lack of direct data comparing various CR models hinders conclusive determination of the optimal strategy for these patients, commencing a rehabilitation program in tandem with hospitalization appears to be the most effective approach for impactful and sustained long-term benefit. Indeed, the care paradigm inherent in the context under scrutiny in this study facilitates a seamless continuation of the rehabilitation trajectory, effectively averting early complications linked to HTx. The model's strength lies in its ability to provide uninterrupted care. However, even in a public system such as the Italian one, healthcare constraints hinder the best care of the patient. Reimbursements are suboptimal and may not cover the entire process of cardiac care. Accordingly, extending the care of patients in the appropriate way will always be difficult.

Regarding the sex comparison data in our analysis, women exhibited lower weight and a higher prevalence of non-ischemic cardiomyopathy compared with men. Additionally, women had a higher probability than men of receiving tacrolimus as a calcineurin inhibitor. No other significant differences in terms of CV risk factors, comorbidities, or therapies were observed between the two groups upon admission to CR. Analyzing outcomes, the female population demonstrated a significant reduction in the incidence of the primary composite outcome (death/allograft rejection/CAV) and an increased survival rate in long-term follow-up (Fig. 2). The impact of sex on outcomes after HTx remains unclear. Although previous studies yielded inconsistent results regarding sex as an independent risk factor for survival after HTx [27–29], our findings align with data from the International Society of Heart and Lung Transplantation (ISHLT), which reported a trend toward improved survival in women [28]. However, differences in baseline characteristics in the heterogeneous population of advanced HF patients make outcome comparison challenging, particularly regarding mortality. Despite no statistically significant gender difference in CAV incidence, female sex appears to be protective against the development of this complication. CAV is a significant contributor to the long-term mortality of HTx recipients, constituting about 10 % [28]. Consistent with our results, previous research indicated higher CAV incidence in men compared with women [30]. Gender differences in immunological response, influenced by factors such as hormones, metabolism, and other variables unexplored in our analysis, may contribute to variations in CAV incidence. We postulate that adherence to structured CR programs may amplify these sex differences, especially by addressing the control of CV risk factors, well-established for their correlation with CAV development [31]. Notably, Nytrøen et al. [32] reported that HIIT among maintenance HTx recipients significantly impeded CAV progression, prompting further studies on this intriguing intervention. *Although functional outcomes are not the focus of this study, the role of CR in improving functional status in both sexes after HTx has been previously documented.* [6,7] *Given that CR is less frequently prescribed in the female population, it is essential to develop tailored programs to maximize functional recovery by restoring normal respiratory and muscle function and addressing the factors contributing to the frailty that typically characterizes these patients.* Our study has limitations, including its retrospective nature preventing control for all potential confounding variables. Additionally, the sample size, reflective of recent HTx experiences at Niguarda Hospital, is limited for a 1-year follow-up. The absence of a control group not undergoing CR prevents the exploration of additional benefits related to rehabilitation programs after HTx. In conclusion, among HTx recipients engaging in an in-hospital CR program, we observed a reduced incidence of the primary outcome (death, rejection, and CAV) and an increased survival probability in female patients at a median follow-up of 29 months post-CR discharge. These findings underscore the importance of offering admission to well-structured CR programs to all patients and tailoring the program according to sex, particularly in an era of high-complexity cardiac patients. Our results encourage further research on the long-term benefits of CR in HTx recipients and optimal practical approaches.

## CRediT authorship contribution statement

**Andrea Tedeschi:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Ignazio Cusmano:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Francesca Di Salvo:** Data curation. **Letizia Oreni:** Formal analysis. **Anastasia Toccafondi:** Methodology, Conceptualization. **Monica Tavanelli:** Writing – review & editing. **Paola Grati:** Writing – review & editing. **Luca Mapelli:** Writing – original draft. **Luisa Arrondini:** Writing – original draft. **Gianmarco Cannadoro:** Writing – original draft. **Matteo Gonella:** Writing – original draft. **Chiara Barcella:** Writing – original draft. **Leone Stilo:** Writing – original draft. **Alessandro Verde:** Writing – review & editing. **Gabriella Masciocco:** Writing – review & editing. **Giacomo Ruzzenenti:** Data curation. **Marco Biolcati:** Data curation. **Andrea Garascia:** Writing – review & editing. **Nuccia Morici:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization.

## Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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## Declaration of competing interest

The authors of this manuscript have no conflicts of interest to disclose.

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