

Does the UNOS Heart Transplant Allocation System Favor Men Over Women?

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ABSTRACT

OBJECTIVES The aim of this paper was to identify sex differences in survival of patients awaiting orthotopic heart transplantation (OHT).

BACKGROUND Women have a higher mortality rate while awaiting OHT than men, and the reason has not been fully determined.

METHODS We included all adult patients in the Scientific Registry of Transplant Recipients (SRTR) placed on the OHT waiting list from 2000 to 2010. The primary endpoint was all-cause mortality before receiving OHT, analyzed using time-to-event analysis. Multivariate Cox proportional hazards models were used to evaluate sex differences in survival, with data stratified by United Network for Organ Sharing (UNOS) status at time of listing.

RESULTS There were 28,852 patients (24% women) awaiting OHT. This cohort included 6,163 UNOS status 1A (25% women), 9,168 UNOS status 1B (25% women), and 13,521 UNOS status 2 (24% women) patients. During a median follow-up of 3.7 years, 1,290 women and 4,286 men died. Female sex was associated with a significant risk of death among UNOS status 1A (adjusted hazard ratio [HR]: 1.20; 95% confidence interval [CI]: 1.05 to 1.37, $p = 0.01$) after adjusting for more than 30 baseline variables. In contrast, female sex was significantly protective for time to death among UNOS status 2 patients (adjusted HR: 0.75; 95% CI: 0.67 to 0.84, $p < 0.001$). No sex differences were noted among UNOS status 1B patients.

CONCLUSIONS There are sex differences in survival between women and men awaiting heart transplantation, and the current UNOS transplant criteria do not account for this disparity. (J Am Coll Cardiol HF 2014;2:347-55) © 2014 by the American College of Cardiology Foundation.

Women in the United States have a higher mortality rate than men while awaiting orthotopic heart transplantation (OHT) (1), which has not been fully evaluated. Based on publicly available Scientific Registry of Transplant Recipients (SRTR) data, the median OHT wait time for women during this same time period was shorter than for men (1), suggesting it was not due to availability of donors. In 1 small European study (58 women, 260 men), more women (17%) than men (12%) died

awaiting OHT during a 12-month follow-up. After adjusting for age, heart failure survival score, serum creatinine, inpatient status, cardiac index, low vocational level, smoking, and low emotional support at time of transplant listing, female sex was still associated with a higher risk of death/deterioration (hazard ratio [HR]: 2.3; 95% confidence interval [CI]: 1.04 to 5.12; $p = 0.04$) (2). What remains unknown is whether sex differences in waitlist mortality also exist in the United States after adjusting for baseline risk factors.

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ABBREVIATIONS AND ACRONYMS

ECMO = extracorporeal membrane oxygenation

GFR = glomerular filtration rate

HF = heart failure

IABP = intra-aortic balloon pump

LVAD = left ventricular assist device

OHT = orthotopic heart transplantation

PCWP = pulmonary capillary wedge pressure

SRTR = Scientific Registry of Transplant Recipients

TAH = total artificial heart

UNOS = United Network for Organ Sharing

VAD = ventricular assist device

The current OHT allocation system in the United States is based primarily on severity of illness (3). However criteria for OHT listing and heart failure (HF) survival models (4-6) do not distinguish women from men despite known sex differences in cause (7-9), cardiac remodeling (10-12), response to therapy (13-16), and prognosis (17-19). Therefore, advanced HF therapies such as OHT or mechanical circulatory support may be recommended with no evidence-based expectations if sex differences in prognostic risk factors are not recognized and utilized. The goal of this study was to further evaluate sex differences in mortality for HF patients awaiting OHT, using our current allocation system

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that stratifies patients into categories based on severity of illness: United Network for Organ Sharing (UNOS) status 1A for high-risk patients; UNOS status 1B for intermediate-risk patients; and UNOS status 2 for lower risk, ambulatory patients. To account for the limited mechanical circulatory support available to rescue women prior to April 2008, when the U.S. Food and Drug Administration approved a smaller device called HeartMate II (Thoratec Corp., Pleasanton, California) that could be implanted in petite patients (body surface area: <1.5 m²), we also assessed the importance of the era before and after that date to look for any sex interaction.

METHODS

SCIENTIFIC REGISTRY OF TRANSPLANT RECIPIENTS.

This study used data from SRTRs. The SRTR database includes data for all donors, waitlisted candidates, and transplantation recipients in the United States submitted by members of the Organ Procurement and Transplantation Network (OPTN) and has been described elsewhere (20). The U.S. Department of Health and Human Services Health Resources and Services Administration provides oversight of the activities of OPTN and SRTR contractors. Human error in collecting data is minimized by edit checks, validation of data at time of entry, and internal verification, when there are outliers.

PATIENT POPULATION AND UNOS STATUS. We included all adult patients in the SRTR database who were placed on the waiting list for OHT from January 1, 2000, to December 31, 2010. Follow-up data were available until November 30, 2011. Patients were excluded if they were <18 years of age because the

UNOS criteria for listing pediatric patients differs from that for patients who are adults, and the donor pools are distinguished by age (3).

Data were stratified according to UNOS status at time of waitlisting. UNOS status 1A includes patients requiring ventricular assist device (VAD), total artificial heart (TAH), extracorporeal membrane oxygenation (ECMO), intra-aortic balloon pump (IABP), mechanical ventilation, continuous intravenous high-dose inotropes, or an exemption for critical illness such as ventricular tachycardia or complications with mechanical circulatory support. UNOS status 1B is the next highest status for OHT and includes patients receiving continuous intravenous doses of inotrope support and stable VAD patients. UNOS status 2 is the least urgent status for patients actively waiting for OHT and is reserved for patients receiving standard medical therapy.

OUTCOME MEASURES. The primary endpoint was all-cause mortality, assessed as a right-censored time to death, with follow-up censored at the time of transplantation. SRTR mortality data are maintained by the transplantation centers and verified with the U.S. Social Security Administration Death Master File which was available until November 30, 2011.

STATISTICAL ANALYSIS. Sex-specific baseline characteristics were reported according to UNOS status at the time of listing for OHT. Continuous variables were expressed as means, and categorical variables were expressed as frequencies. Chi-square and Wilcoxon rank-sum tests were used for group comparisons. Sex-specific survival analysis was performed for UNOS status 1A, 1B, and 2 patients, using the Kaplan-Meier method with censoring for OHT. The primary analysis was based on intent to treat such that deaths following removal from the waiting list were included in the primary analysis. The cumulative incidence of transplantation and death was estimated as competing risks, using the Fine and Gray method (21). Cox proportional hazard models were created to assess for the association between female sex and death according to initial UNOS status at time of listing. Two models were created. Model 1 was adjusted for the following characteristics at time of listing: age, diabetes mellitus status, dialysis, body mass index, previous OHT, race (white, black, Hispanic, Asian, other), history of cerebral vascular accident and tobacco use, inotrope use, glomerular filtration rate (GFR), ventilator status, insurance (private, Medicare/Medicaid, other), type of ventricular assist device (left ventricular assist device [LVAD] or right ventricular assist device with or without LVAD or TAH/unspecified mechanical

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