

Editorial

## Sex and Gender Issues in Heart Transplantation

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Heart transplantation (HTx) continues to be the accepted therapy for end-stage heart failure (HF). Although morbidity and mortality continue to decrease, limited donor availability has led to an increase in waiting list times and increases in waiting list mortality [1]. Little attention has been focused on gender differences in post-heart transplant outcomes. Women continue to be underrepresented in clinical trials, and more HF-related deaths occur annually in women as compared to men [2, 3]. The fact remains that women are transplanted less frequently than men, making it critical for researchers to examine why such gender differences continue to exist [4, 5]. In addition, men are more frequently recipients, whereas women are more frequently donors [4].

In a data set of 698 consecutive patients with idiopathic non-ischaemic dilated cardiomyopathy (DCM) referred for HTx to the German Heart Institute, only 15.6% were women, suggesting a referral bias against women. Women were more frequently in NYHA functional class III-IV, had lower exercise tolerance, lower respiratory efficiency, and poorer kidney function but less commonly diabetic than men [6]. Thus, women were referred at a more advanced disease state and relative contraindications such as diabetes appear to be taken more seriously in women [6]. In Spain, women are more likely to be younger, to have a diagnosis of idiopathic dilated



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cardiomyopathy, and to have fewer cardiovascular risk factors [7]. In the USA, heart transplanted men were generally older and had more chronic cardiovascular conditions [5].

International Society of Heart and Lung Transplantation (ISHLT) guidelines for adult HTx suggest a donor to recipient body weight ratio (WR) of greater than 0.8. For female to male transplants, a WR of greater than 0.9 is recommended [8]. According to S.N. Jayarajan et al., HTx can be safely performed using WRL\* donors between sex-matched and male to female transplants [9]. At the same time, in female to male transplants, WRL donors are associated with decreased survival [9]. Reed et al. believed that organ allocation might be improved by avoiding donor organs undersized for their intended recipients [10]. The difference in the predicted total heart mass (pHM) between donors and recipients of orthotopic heart transplants is a risk for decreased survival [10]. Moreover, the male to female ratio for patients who are transplanted in Spain is approximately 5:1. More often they were transplanted in an emergency and with organs from younger males with a body mass index similar to theirs [7].

According to the results of the Spanish Heart Transplantation Groups, no significant correlation between sex and mortality has ever been found [11-15]. At the same time, E.S. Weiss et al. suggested that men receiving organs for same sex donors have significantly improved short- and long-term survival but no survival advantages for women with same sex donors [16]. Unfortunately, female recipients have decreased survival irrespective of whether they receive hearts from male or female recipients [16].

In fact, sensitized patients and other high-risk subgroups may have a disparity in heart allocation, accounting for some of the observed gender differences [17]. Sensitization is the process by which antibodies are formed against human leukocyte antigens; this can occur from a prior pregnancy or exposure to blood products [17] and increases the risk of post-transplant rejection [18]. Thus, female patients who are highly sensitized may remain on the United Network for Organ Sharing (UNOS) list for a longer period of time due to a smaller donor pool for which they are compatible. However, in Canada, sensitization has been recognized as a significant contributor to patient outcomes, especially in women [19]. And sensitized patients have one of the highest priority categories on the heart transplant waiting list [19].

What is important, men had more chronic cardiovascular conditions after HTx, while women were more likely to experience moderate or severe allograft rejection and to be hospitalized for acute rejection [5]. Moreover, donor–recipient gender mismatch is a powerful independent predictor of early and late rejections and long-term major adverse events following HTx [20]. Using the United Network for Organ Sharing, a database containing information on more than 18,000 heart-transplant recipients, Weiss and colleagues have shown that men who received organs from male donors had the highest cumulative survival at 5 years (74.5%), while men receiving female hearts had a 15% increase in the risk of adjusted cumulative mortality [16]. Thus, the cumulative survival-free of major adverse events was significantly higher in male donor–male recipient group compared with the female donor–male recipient groups (5 year rates: 84% vs. 62%, respectively; 10 year rates: 48% vs. 16%, respectively;  $P = 0.001$  for the overall difference during follow-up,  $P = 0.001$  for the overall difference during follow-up) [20]. No significant increase in the relative hazard for death occurred for women receiving opposite sex donor organs. According to another report, female recipients, irrespective of donor sex, had 3.6% lower overall survival at 5 years post-transplant [16]. According to our experience, male gender was associated with poor

survival, complicated time in intensive care unit (ICU) and more frequent development of cardiac allograft vasculopathy (CAV).

In conclusion, the impact of recipients' gender on post-transplant outcomes still remains a matter of debate. Both gender- and sex-related aspects might affect the donation, the access, and the outcome of transplantation. In particular, how sex and gender interact and affect graft success should be taken into account in the management of heart-transplanted patients. We fully agree with F. Puoti et al. [21] that sex and gender issues appears as a mandatory task to be promoted, developed, and regulated.

\* WRL – donor to recipient body weight of 60% to 80%.

### **Author Contributions**

MS – contributed to the editorial concept and design, analysed data and drafted it; PA – analysed data and other contribution.

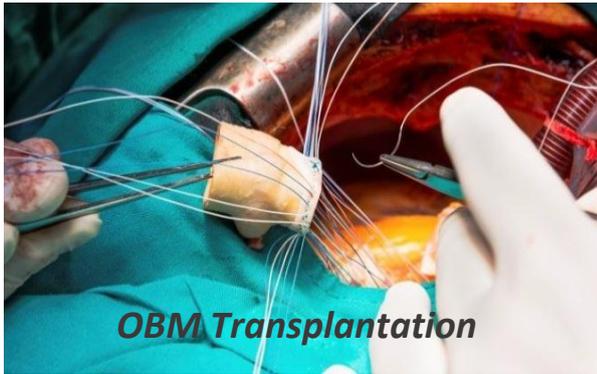
### **Competing Interests**

The authors have declared that no competing interests exist.

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