

EDITORIAL

Sex Equity in Heart Transplant Allocation: What Is Good for the Goose Is Good for the Gander

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Hearth transplantation is the gold standard therapy for advanced (end-stage) heart failure (HF) and substantially improves survival and quality of life. Despite comparable burden of advanced HF, men outnumber women 3 to 1 in listing for and receiving heart transplantation. Further, these trends have not changed substantially over time. The percentage of women on the heart transplant wait-list in the United States was 26% in 2009 and 23% in 2019, and the percentage of women receiving heart transplantation was 24% in 2009 and 28% in 2019.¹ This raises an important question as to why women are less likely to be listed for and to receive heart transplantation compared with men and whether allocation of heart transplant is equitable.

See Article by Breathett et al.

In this issue of the *Journal of the American Heart Association (JAHA)*, Breathett and colleagues explored imbalance in heart transplant/HF mortality ratio in men and women in the United States. The authors examined the sex differences in heart transplant and HF mortality in adults (aged 35–64 years) between 2016 and 2018 nationally and at the state level. The primary outcome was the ratio of heart transplant rate/HF mortality rate. The former data were obtained from the

United Network for Organ Sharing, whereas the latter data were obtained from national mortality data and were used as a surrogate for advanced HF prevalence.

The national ratio of heart transplant rate/HF mortality rate for women versus men was 0.62. Almost all states analyzed had a lower heart transplant/HF mortality rate ratio for women versus men, except for Connecticut. Furthermore, the authors described regional variability in transplantation of women and ranked the regions from the highest to the lowest ratio: the South, the Northeast, the West, and the Midwest.²

The study by Breathett et al provides a high-level overview of heart transplant allocation relative to HF mortality at the national, regional, and state levels. This article addresses a complex issue and is the first step forward in linking sex-specific transplant rate and HF mortality rate in the United States. The findings are thought provoking and raise many questions for us to ponder on potential explanations.

This study has several limitations. Data on ejection fraction and type of HF are missing. The vast majority of heart transplant recipients have HF with reduced ejection fraction. Therefore, the denominator of HF death may overestimate the transplant-eligible population. Similarly, this analysis lacks granular data on demographics, patients' clinical characteristics, comorbidities, eligibility for heart transplantation, and

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factors that precluded referral, listing, and/or heart transplantation. The 2 data sets were from different sources and may not reflect the same population, or account for migration across the states. Furthermore, the data only span a 2-year time frame and are restricted to the ages of 35 to 64 years; secular trend and exclusion of younger and older adults limit generalizability of the findings.

Disparities between men and women in guideline-directed HF therapies are well established. Women receive fewer diuretics, guideline-directed medical therapies, and cardiac resynchronization therapy devices for HF compared with men.³ In contrast, there is a huge knowledge gap in disparities in advanced HF therapies.

Potential explanations for disproportionate share of heart transplantation between men and women are as follows: (1) innate sex differences in epidemiological, biological, and pathophysiological characteristics of HF, (2) underrecognition or underestimation of advanced HF in women, and (3) biases in referrals, evaluation, and listing processes.

INNATE SEX DIFFERENCES IN EPIDEMIOLOGICAL, BIOLOGICAL, AND PATHOPHYSIOLOGICAL CHARACTERISTICS OF HF

Community-level data on prevalence and outcomes of advanced HF in general and sex-specific prevalence in particular are unavailable. Statistics from advanced HF registries and clinical trials do not represent the “real-world” disease epidemiology. Women are less likely to have HF with reduced ejection fraction (wherein most heart transplants occur) and are overrepresented in cardiomyopathies that have better prognosis compared with men. However, contemporary community and multiracial studies suggest that mortality from HF with reduced ejection fraction is comparable in men and women.^{4,5} Data from the national vital statistics showed that of total mortality attributable to HF, 54% occurred in women and 46% occurred in men.⁶

An important biological factor is sex difference in sensitization to the human leukocyte antigens. Women are more likely to be sensitized to human leukocyte antigens, because of prior exposure during pregnancy. Preexisting human leukocyte antigen antibodies may preclude heart transplantation, limit the compatible donor pool, and increase wait-list time; hence, an increased risk of wait-list mortality.³ Even if women represent a lower percentage of patients who are potential heart transplantation candidates, the ratio of 1:3 is large and is not entirely explicable on the basis of sex differences in epidemiological, biological, and pathophysiological characteristics.

UNDERRECOGNITION OR UNDERESTIMATION OF ADVANCED HF IN WOMEN

Women with HF have greater symptom burden, greater impairment of physical activities, and worse health-related quality of life than men.^{7,8} Nonetheless, women are less likely to recognize and attribute their symptoms to heart disease, and they may manifest different symptoms.⁷ Identifying patients with HF is challenging in and of itself, because of lack of single diagnostic criteria for advanced HF. Physicians not attuned to different symptoms in women may face greater challenges diagnosing advanced HF in women.⁹ Timely diagnosis and referral are key to provision of heart transplantation and to improved outcomes. Conversely, data from 2 decades ago showed that women with advanced HF are less willing to pursue heart transplantation when offered.¹⁰ Whether acceptance of heart transplantation by women with advanced HF has changed in the contemporary era is unclear.

BIASES IN IDENTIFICATION, REFERRALS, EVALUATION, AND LISTING PROCESSES

Most of the patients with HF are cared for in the community. Distinguishing the role of bias in identification or referrals versus underrecognition or underestimation of advanced HF in women is difficult. In advanced HF centers, a multidisciplinary selection committee evaluates candidates and decides on listing after extensive review. The selection process involves medical, surgical, and psychosocial factors (psychosocial stability, caregiver support, and adequate insurance). The psychosocial assessment for heart transplantation varies across institutions and is more prone to subjectivity than the medical and surgical assessments. The authors' prior qualitative research has demonstrated bias against women, particularly Black women; however, bias did not significantly impact allocation recommendations.¹¹ This underscores the complexity of sex-race interaction.

FUTURE DIRECTIONS

A multifaceted approach is needed to define and tackle sex-related disparities in advanced HF and heart transplantation. The first step is to improve our understanding of the following: (1) sex differences in epidemiological, biological, and pathophysiological characteristics of advanced HF, (2) recognition and estimation of advanced HF in men and women, and (3) biases in identification, referrals, evaluation, and transplant listing processes. Second, education is necessary for physicians on

disease recognition and early referrals and engagement of patients and communities. Lastly, accountability from physicians in the community, members of the multidisciplinary transplant selection committee, and national organizations is necessary to determine and track barriers to identification, referral, and transplant listing of women versus men.

ARTICLE INFORMATION

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Disclosures

None.

REFERENCES

- Colvin M, Smith JM, Ahn Y, Skeans MA, Messick E, Goff R, Bradbrook K, Foutz K, Israni AK, Snyder JJ, et al. OPTN/SRTR 2019 annual data report: heart. *Am J Transplant*. 2021;21:356–440. DOI: 10.1111/ajt.16492.
- Breathett K, Knapp SM, Carnes M, Calhoun E, Sweitzer NK. Imbalance in heart transplant to heart failure mortality ratio by sex. *J Am Heart Assoc*. 2021;10:e020146. DOI: 10.1161/JAHA.120.020146.
- Hsich EM. Sex differences in advanced heart failure therapies. *Circulation*. 2019;139:1080–1093. DOI: 10.1161/CIRCULATIONAHA.118.037369.
- Gerber Y, Weston SA, Redfield MM, Chamberlain AM, Manemann SM, Jiang R, Killian JM, Roger VL. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. *JAMA Intern Med*. 2015;175:996–1004. DOI: 10.1001/jamainternmed.2015.0924.
- Chang PP, Wruck LM, Shahar E, Rossi JS, Loefer LR, Russell SD, Agarwal SK, Konety SH, Rodriguez CJ, Rosamond WD. Trends in hospitalizations and survival of acute decompensated heart failure in four US communities (2005–2014): ARIC study community surveillance. *Circulation*. 2018;138:12–24. DOI: 10.1161/CIRCULATIONAHA.117.027551.
- Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Cheng S, Delling FN, et al. Heart disease and stroke statistics-2021 update: a report from the American Heart Association. *Circulation*. 2021;143:e254–e743. DOI: 10.1161/CIR.0000000000000950.
- Eisenberg E, Di Palo KE, Piña IL. Sex differences in heart failure. *Clin Cardiol*. 2018;41:211–216. DOI: 10.1002/clc.22917.
- Dewan P, Rørth R, Jhund PS, Shen L, Raparelli V, Petrie MC, Abraham WT, Desai AS, Dickstein K, Køber L, et al. Differential impact of heart failure with reduced ejection fraction on men and women. *J Am Coll Cardiol*. 2019;73:29–40. DOI: 10.1016/j.jacc.2018.09.081.
- Prichard RA, Zhao FL, McDonagh J, Goodall S, Davidson PM, Newton PJ, Farr-Wharton B, Hayward CS, et al. Discrepancies between proxy estimates and patient reported, health related, quality of life: minding the gap between patient and clinician perceptions in heart failure. *Qual Life Res*. 2021;30:1049–1059. DOI: 10.1007/s11136-020-02722-z.
- Aaronson KD, Schwartz JS, Goin JE, Mancini DM. Sex differences in patient acceptance of cardiac transplant candidacy. *Circulation*. 1995;91:2753–2761. DOI: 10.1161/01.CIR.91.11.2753.
- Breathett K, Yee E, Pool N, Hebdon M, Crist JD, Yee RH, Knapp SM, Solola S, Luy L, Herrera-Theut K, et al. Association of gender and race with allocation of advanced heart failure therapies. *JAMA Netw Open*. 2020;3:e2011044. DOI: 10.1001/jamanetworkopen.2020.11044.