Persistent Gender Disparities in Liver Transplantation

A discussion of driving factors and potential solutions to equitable access to liver transplantation.

By Pilar Bayona Molano, MD; Nicole Rich, MD; Juan C. Barrera, MD, MPH, PhD; and Koji Hashimoto, MD, PhD

Chronic liver disease accounts for > 44,000 deaths annually and results in a significant burden of disability, hospitalizations, and health care resource utilization in the United States.[1] Liver transplantation affords the chance of a life-saving treatment for patients with end-stage liver disease and liver cancer; however, there remains a disparity between the availability of donor organs and the increasing number of patients in need of transplantation. Despite having similar rates of cirrhosis-related mortality, women are less likely to be wait-listed and less likely to receive liver transplant.[2,3] The United States liver allocation policies have evolved over the past 2 decades with the aim of prioritizing the sickest patients for transplant; however, to date, none of these iterations to allocation policies have addressed this gender disparity.

Health equity is measured through metrics that value the access, opportunity, and resources available to offer the best health care service, independently of race, gender, sexual orientation, socioeconomic status, disability, geographic location, or other societal constructs. These constructs can determine the relationship with the distribution of health care resources, influencing health care outcome. Although sex and gender are interrelated, they are distinct and may impact health outcomes in different ways. Sex by itself may be a biological predictor of morbidity, whereas gender is a social construct that is affected by inequitable distribution and access of health resources, producing less favorable health care outcomes in women and those with other gender identities.

This article briefly reviews gender, ethnicity, and race as they relate to health care disparities and then focuses on factors associated with gender disparities in liver transplantation, as awareness and innovative solutions are necessary to ensure equitable access to liver transplantation for all patients.

GENDER AND ACCESS TO HEALTH CARE

Health care spending in the United States was projected to reach $4.4 trillion by 2018 and is continuing to rise.[4] Because women constitute the majority of Medicare beneficiaries (55.6% vs 44.5% men),[5] achieving equitable use of these services by women and men is paramount. In an analysis of the Health and Retirement Study data, in older adults, the proportion of women with household incomes < 25 percentile was twofold higher than men, and prevalence of chronic conditions such as arthritis, hypertension, and visual problems were higher in women than men.[6] On the other hand, men were more affected by cancer, heart disease, and diabetes than women. In the same study, women aged > 65 years tended to experience mobility limitations and disability at earlier ages than men (ie, 10 years earlier) and used hospital services and preventive health care less frequently than men (odds ratio, 0.91 and 0.89, respectively).[6]

Since 2012, coverage insurance has expanded among young adults.[7] For 2018, private health insurance reached similar coverage for men and women (65.7% vs 65%).[8] However, studies have yielded mixed results about whether improved access to health care has reduced racial and ethnic disparities.[7] Analyzing data from the National Survey of Family Growth, in the population of reproductive age (15-44 years) from 2002 to 2015, the lowest-income group grew from 26% to 33% of the population, whereas the higher income groups shrank. Young adult women showed lower levels of health care utilization and worse sexual and reproductive health outcomes than other age groups.[7]

From 2017 to 2019, the uninsured rate rose by 1.7%.[9] Among uninsured adults aged 18 to 64 years, 16% were men and 13.1% were women.[10] In 2017, the percentage of uninsured Latinas, Black women, Asian women, and non-Hispanic White women was 19.9%, 13.7%, 8.9%,

and 8%, respectively.[11] In 2018, transgender adults were more likely to be uninsured (19% vs 12%) and report cost-related barriers to care than cisgender adults.[12]

RACE, ETHNICITY, GENDER, AND PRIMARY HEALTH CARE

Women have historically been underrepresented in clinical trials, which may result in inequitable access to therapeutics and lack of generalizability of results, increasing health care disparities. As women move through the natural process of changing, such as puberty, adulthood, and menopause, they require special care and attention to monitor their evolving needs.[13]

Race, ethnicity, and gender are often considered separately, which may obscure important differences in how health care is delivered and undermine efforts to eliminate health disparities.[14] Studies have demonstrated how maternal mortality impacts health, education, and economics in women communities.[15] Mexican and Puerto Rican women represent almost 70% of Latinas in the United States.[16] Most of them are younger than 30 years, married, and have children. Despite good indicators in pregnancy-related morbidities for Latinas, the maternal mortality is almost two times higher when compared with Whites. Latinas experience less continuity of health services, less prenatal care, and fewer screening tests for cancer and associated risk factors.[16] In this community, patient-physician interactions, literacy, communication styles, and linguistic and cultural barriers play crucial roles in health care disparities.[16]

GENDER AND ACCESS TO LIVER TRANSPLANT

Ensuring equity in the allocation of deceased donor liver transplant (DDLT) for those with the greatest necessity is a challenge. The Model for End-Stage Liver Disease (MELD) score has been validated as an objective and reliable predictor of outcomes in patients with end-stage liver disease and used for liver organ allocation since 2002. However, there are growing concerns about whether the MELD score may place women at a disadvantage by underestimating their risk of mortality. There are still factors that have not been measured, thus maintaining inequalities in the liver transplant program. The mechanisms behind disparities can be explained by geographic location, lack of understanding of the changes in behaviors and outcomes to adjuvant therapies after liver transplantation, the fact that severity of liver disease may not be accurately reflected in the MELD score, donor-recipient size mismatch, and availability of liver donors.[17]

Unlike some European countries where the majority of donors are women,[18] the distribution of donors by sex in the United States for 2019 was similar, with 49% of donors being women and 51% men.[19] Public health initiatives and patient and provider education are needed to change the culture to improve organ donation rates. In addition, it will be necessary to create policies to widen the criteria of organ donors in all populations (young and older population) to maximize availability of organs for donation and implement presumed consents.

Influence of Geographic Location

Supply and demand for liver allografts in the United States varies according to geographic distribution and has been regulated by allocation policies. Significantly lower rates of gender disparity in liver transplant have been reported in six of 11 Organ Procurement and Transplantation Network regions; the maximum deficit of 35% was found in the Pacific Northwest (region 6), and this gender disparity was magnified among patients with high MELD scores ≥ 15.[17,20]

Behaviors Related to Transplant Access and Liver Transplant Outcomes

In 2008, Moylan et al described differences in incidence of liver disease, etiology of hepatocellular carcinoma (HCC), and the percentages listed for liver transplant, with women having uneven access to transplant before and after the introduction of the MELD score.[21] Bryce et al found that patients were less likely to undergo evaluation, wait-listing, and transplantation if they were women, Black, and lacked health insurance ($P < .001$ for each).[2] In a cohort study using data from the Scientific Registry of Transplant Recipients including 81,357 adults with liver-only listings, between 2013 and 2018, only 36% were women.[22] Women were 8.6% more likely to die while on the waiting list compared with men (hazard ratio [HR], 1.09; 95% CI, 1.05-1.14). After analyzing mediator variables of geographic region, MELD score, and liver size, the HR to die while on the waiting list for female sex increased 25% (HR, 1.25; 95% CI, 1.21-1.29). In the same study, women were 14.4% less likely to receive a DDLT (adjusted HR, 0.86; 95% CI, 0.84-0.88). MELD score and liver size impacted the probability of women receiving DDLT, increasing the inequities in DDLT. Once women are added to the transplant list, they have a greater probability of dying or becoming too sick to receive a transplant.[22] In a small, single-center study of HCC patients, the overall median time for women to receive a transplant was longer than the time for men (236 vs 205 days; $P = .057$), and men had a three times higher probability of being transplanted than women ($P = .002$).[3] In addition, the use of locoregional therapies in HCC was associated with a prolonged stay on the transplant list, likely due to the presence of an aggressive liver tumor.

However, liver-directed therapies allow the patient to remain active on the liver transplant list, increasing their chances of undergoing transplantation.[3]

It is well known that HCC is more common in men, and the incidence rate is two to four times higher than in women.[23] This difference in incidence has been hypothesized to be related to sex hormones (ie, estrogen being protective and testosterone being deleterious) and a higher prevalence of known behavioral risk factors in men (eg, alcohol use, tobacco use, hepatitis C virus infection related to intravenous drug use).[23]

Effect of MELD Scoring on Gender-Related Organ Allocation

Although the introduction of the MELD score as a marker for the severity of liver function impairment aimed to achieve an equitable distribution of donor livers, its use may result in unequal distribution of livers in relation to women. The bias seems based on the fact that creatinine is 30% higher in males as compared with females. In other words, comparing men and women with chronic liver disease of the same age, ethnicity, and creatinine, the estimated glomerular filtration rate is lower in women compared to men. This difference is not considered when calculating the MELD score, causing systematic bias against women when grading severity of chronic liver disease, increasing time in waiting list and decreasing access to liver transplant.[15] The use of glomerular filtration rate to replace creatinine level in the MELD score calculation has been proposed as a step toward rectifying this bias.[22] Most recently, the MELD 3.0 has been introduced as a new model to more accurately predict mortality and address the sex disparity in wait-list outcomes.[24] The MELD 3.0 model incorporates additional variables including female sex, serum albumin, and an upper bound for creatinine at 3.0 mg/dL, in addition to interactions between bilirubin and sodium and bilirubin and creatinine.[24] Kim et al demonstrated that the MELD 3.0 model had better discrimination than MELD-Na (C statistic, 0.869 vs 0.862; $P < .01$) and resulted in the reclassification of 16.7% of women decedents to a higher MELD tier, which would have provided them with a meaningfully higher chance of receiving an organ.[24] The MELD 3.0 has been proposed for consideration to replace the current MELD-Na in determining organ allocation in the United States and will be the subject of future discussion and debate.

Influence of Recipient/Donor Body and Donor Size Mismatch

One of the factors associated with the decreased rate of liver transplantation in women is body size. Height is one of the factors studied to explain this disparity.[25] In the study by Lai et al of 12,585 female and 22,126 male patients listed for liver transplant, the mean height was 1.6 versus 1.8 meters, respectively. The focus of interest in this study was the association between gender and the risk of death or becoming too sick for transplant. At listing, females were older, shorter height, lower weight, and more likely to be African American or Hispanic. After adjusting by MELD score, women had 19% more probability of death while on the waiting list or becoming too sick for transplant than men ($P = .001$). Mortality was 24% higher when height was < 1.65 cm (60% women and 5% men were in this group), and 8% higher in the group of 1.65 to 1.80 cm (38% women and 56% men) when compared with patients taller than 180 cm. Using competing risk analysis, the probability of receiving a transplant was 17% lower in women and 11% lower after adjustment by height.[25]

Another hypothesis that explains lower liver transplant rates in women is the liver donor size mismatch. Mindikoglu et al determined the effect of transplant candidate-donor liver size mismatch on monthly transplantation rates. The median estimated liver volume and liver weight were significantly lower in women than in men on the liver transplant waiting list ($P < .0001$). After considering region (geographic distribution), blood type, MELD scores, and estimated liver weight of the transplant candidate, liver transplant rates in women were still 13% lower than in men.[26] In other words, if women and men with similar estimated liver weight are compared, women would be transplanted at a lower rate than men and would have to wait longer for a size-appropriate allograft.

Availability of Liver Donors

Living donor programs can decrease disparities overcoming the critical organ shortage. Living donor liver transplantation (LDLT) studies showed a similar proportion of donors by gender in the United States (49% men vs 51% women). In addition, a small variation in liver transplant recipients was identified (54% male vs 46% female).[27] LDLT has a great potential to overcome a lower transplant rate in female candidates. In liver transplantation using partial allografts, graft-recipient size mismatch can cause functional graft failure, or so-called small-for-size syndrome. One of the solutions to prevent graft failure in LDLT is to transplant small recipients. When small women are recipients, a concern of size mismatch is less likely to be an issue to avoid small-for-size syndrome. Similarly, a single-center study demonstrated that recipients in split liver transplantation were more likely to be female to avoid graft-size mismatch.[28]

CONCLUSION

The implementation of continued research in geographic areas with higher gender disparity will be necessary. Promoting education of the population to create a culture of organ donation and initiating policies and even legal reform to increase organ donors in all populations (young and older people) may maximize availability of organs for donation using presumed consent. Awareness is the necessary first step to reduce gender disparities in liver transplantation and improve equitable access to transplant for all patients with end-stage liver disease. ■

1. Moon AM, Singal G, Tapper EB. Contemporary epidemiology of chronic liver disease and cirrhosis. Clin Gastroenterol Hepatol. 2020;18:2650-2666. doi: 10.1016/j.cgh.2019.07.060
2. Bryce CL, Angus DC, Arnold RM, et al. Sociodemographic differences in early access to liver transplantation services. Am J Transplant. 2009;9:2092-101. doi: 10.1111/j.1600-6143.2009.02737.x
3. Molano MDPB, Garza L, Selvaggi G, et al. Impact of liver-directed therapy and non-therapy on the waiting time list of patient candidates for liver transplantation: retrospective survival analysis. Clin Exp Hepatol. 2020;6:304-312. doi: 10.5114/ceh.2020.102175
4. The Healthcare Imperative. In: Institute of Medicine (US) Roundtable on Evidence-Based Medicine, Yong PL, Saunders RS, Olsen L, eds. The Healthcare Imperative: Lowering Costs and Improving Outcomes. Washington (DC): National Academies Press (US); 2010.
5. Kaiser Family Foundation. Distribution of Medicare beneficiaries by sex: state health facts. Accessed November 29, 2021. https://www.kff.org/medicare/state-indicator/medicare-beneficiaries-by-sex/?currentTimeframe=0&selectedDistributions=male--emale&sortModel=%7B%22colId%22:%22Location%22,%22sort%22:%22asc%22%7D
6. Cameron KA, Song J, Manheim LM, Dunlop DD. (2010). Gender disparities in health and healthcare use among older adults. J Womens Health (Larchmt). 2010;19:1643-1650. doi: 10.1089/jwh.2009.1701
7. Murray Horwitz ME, Pace LE, Ross-Degnan D. Trends and disparities in sexual and reproductive health behaviors and service use among young adult women (aged 18-25 years) in the United States, 2002-2015. Am J Public Health. 2018;108(S4):S336-S343. doi: 10.2105/AJPH.2018.304556
8. Yang J. Persons in the US population with private health insurance coverage from 1984-2019, by gender. Statista. Published September 8, 2021. Accessed November 29, 2021. https://www.statista.com/statistics/188323/persons-in-the-us-with-private-health-insurance-by-gender-since-1984/
9. Finegold K, Conmy A, Chu RC, Bosworth A, Sommers, BD. Trends in the US Uninsured Population, 2010-2020. Issue Brief No. HP-2021-02. Washington, DC: Office of the Assistant Secretary for Planning and Evaluation; US Department of Health and Human Services; 2021. https://aspe.hhs.gov/sites/default/files/private/pdf/265041/trends-in-the-us-uninsured.pdf
10. Cha AE, Cohen RA. Reasons for being uninsured among adults aged 18-64 in the United States. NCHS data brief no. 382. Accessed November 29, 2021. https://www.cdc.gov/nchs/products/databriefs/db382.htm
11. US Census Bureau. Current population survey tables for personal income. PINC-05: work experience—people 15 years old and over, by total money earnings, age, race, hispanic origin, sex, and disability status. Accessed November 29, 2021. https://www.census.gov/data/tables/time-series/demo/income-poverty/cps-pinc/pinc-05.2017.html
12. Koma W, Rae M, Ramaswamy A, et al. Demographics, insurance coverage, and access to care among transgender adults. Accessed November 29, 2021. https://www.kff.org/health-reform/issue-brief/demographics-insurance-coverage-and-access-to-care-among-transgender-adults/
13. Zephyrin L, Suennen L, Viswanathan P, et al. Transforming primary health care for women—part 1: a framework for addressing gaps and barriers. Accessed November 29, 2021. https://www.commonwealthfund.org/publications/fund-reports/2020/jul/transforming-primary-health-care-women-part-1-framework
14. Warner DF, Brown TH. Understanding how race/ethnicity and gender define age-trajectories of disability: an intersectionality approach. Soc Sci Med. 2011;72:1236-1248. doi: 10.1016/j.socscimed.2011.02.034
15. Davidson PM, McGrath SJ, Meleis AI, et al. The health of women and girls determines the health and well-being of our modern world: a white paper from the International Council on Women's Health Issues. Health Care Women Int. 2011;32:870-886. doi: 10.1080/07399332.2011.603872
16. Ramos BM, Jurkowski J, Gonzalez BA, Lawrence C. Latina women: health and healthcare disparities. Soc Work Public Health. 2010;25:258-271. doi: 10.1080/19371910903240605
17. Oloruntoba OO, Moyla CA. Gender-based disparities in access to and outcomes of liver transplantation. World J Hepatol. 2015;7:460-467. doi: 10.4254/wjh.v7.i3.460
18. Puoti F, Ricci A, Nanni-Costa A, et al. Organ transplantation and gender differences: a paradigmatic example of intertwining between biological and sociocultural determinants. Biol Sex Differ. 2016;7:35. doi: 10.1186/s13293-016-0088-4
19. Elflein J. Number of donors in the U.S. by gender 1988-2020. Statista. Published November 19, 2021. Accessed November 29, 2021. https://www.statista.com/statistics/398450/number-of-us-organ-donors-by-gender/
20. Mathur AK, Schaubel DE, Gong Q, et al. Sex-based disparities in liver transplant rates in the United States. Am J Transplant. 2011;11:1435-1443. doi: 10.1111/j.1600-6143.2011.03498.x
21. Moylan CA, Brady CW, Johnson JL, et al. Disparities in liver transplantation before and after introduction of the MELD score. JAMA. 2008;300:2371-2378. doi: 10.1001/jama.2008.720
22. Locke JE, Shelton BA, Olthoff KM, et al. Quantifying sex-based disparities in liver allocation. JAMA Surg. 2020;155:e201129. doi:10.1001/jamasurg.2020.1129
23. Shaw JJ, Shah SA. Rising incidence and demographics of hepatocellular carcinoma in the USA: what does it mean? Expert Rev Gastroenterol Hepatol. 2011;5:365-370. doi: 10.1586/egh.11.20
24. Kim WR, Mannalithara A, Heimbach JK, et al. MELD 3.0: the Model for End-Stage Liver Disease updated for the modern era. Gastroenterology. 2021;161:1887-1895.e4. doi: 10.1053/j.gastro.2021.08.050
25. Lai JC, Terrault NA, Vittinghoff E, Biggins SW. Height contributes to the gender difference in wait-list mortality under the MELD-based liver allocation system. Am J Transplant. 2010;10:2658-2664. doi: 10.1111/j.1600-6143.2010.03326.x
26. Mindikoglu AL, Emre SH, Magder LS. Impact of estimated liver volume and liver weight on gender disparity in liver transplantation. Liver Transpl. 2013;19:89-95. doi: 10.1002/lt.23553
27. Hermann HC, Klapp BF, Danzer G, Papachristou C. Gender-specific differences associated with living donor liver transplantation: a review study. Liver Transpl. 2010;16:375-386. doi: 10.1002/lt.22002
28. Hashimoto K, Quintini C, Aucejo FN, et al. Split liver transplantation using Hemiliver graft in the MELD era: a single center experience in the United States. Am J Transplant. 2014;14:2072-2080. doi: 10.1111/ajt.12791

Pilar Bayona Molano, MD
Associate Professor
Division of Vascular and Interventional Radiology
Department of Radiology
UT Southwestern Medical Center
Dallas, Texas
pilarbayonam16@gmail.com
Disclosures: None.

Nicole Rich, MD
Assistant Professor of Medicine
UT Southwestern Medical Center
Dallas, Texas
nicole.rich@utsouthwestern.edu
Disclosures: None.

Juan C. Barrera, MD, MPH, PhD
Kent State University
Kent, Ohio
jucarlosb@gmail.com
Disclosures: None.

Koji Hashimoto, MD, PhD
Director of Living Donor Transplantation
Director of Pediatric Liver Transplantation
Department of General Surgery
Digestive Disease & Surgery Institute
Cleveland Clinic
Cleveland, Ohio
hashimk@ccf.org
Disclosures: None.