REVIEW

OPEN

Gender disparities in transplantation

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Purpose of review
Transplantation is the life-saving therapy for patients suffering from end-organ failure, and as such, equitable access to transplantation (ATT) is of paramount importance. Unfortunately, gender/sex-based disparities exist, and despite the transplant community's awareness of this injustice, gender/sex-based disparities have persisted for more than two decades. Importantly, no legislation or allocation policy has addressed inequity in ATT that women disproportionately face. In fact, introduction of the model for end-stage liver disease-based liver allocation system in 2002 widened the gender disparity gap and it continues to be in effect today. Moreover, women suffering from kidney disease are consistently less likely to be referred for transplant evaluation and subsequently less likely to achieve a kidney transplant, yet they comprise the majority of living kidney donors.

Recent findings
Acknowledging gender/sex-based disparities in ATT is the first step toward interventions aimed at mitigating this long-standing injustice in healthcare.

Summary
This article provides a background of end-stage liver and kidney disease in women, summarizes the existing literature describing the issue of gender disparity in ATT, and identifies potential areas of intervention and future investigation.

Keywords
disparity, gender, kidney, liver, transplantation

INTRODUCTION

Transplantation is the life-saving therapy for patients suffering from end-organ failure. The organ shortage has always been the limiting factor in access to this treatment option, and as a result, equitable allocation of a precious national resource has been a focus of extensive study. Women have been recognized as a disadvantaged population and despite considerable efforts, they continue to experience injustice in access to transplantation (ATT). This article will review the current literature on gender disparities in access to liver and kidney transplantation and identify potential areas of intervention and future investigation.

Liver

Background

End-stage liver disease (ESLD) is a chronic debilitating illness with a tremendous economic impact. The approximate annual cost of medical care is $81.1 billion [1]. It is the 12th leading cause of death overall in the United States, and the 5th leading cause of death for patients aged 45–54 [2]. The prevalence of ESLD continues to rise due to the aging hepatitis C cohort and rise in fatty liver disease [3,4,5]. Medical therapies and minimally invasive interventions can only mitigate symptoms and complications, but cannot reverse the severity of the illness. Liver transplantation (LT) is the only curative option with the potential to increase both quantity and quality of life [6,7,8,9].

Despite strict eligibility criteria for LT, multiple enhancements in the liver allocation system, and efforts to increase the donation process, thousands of people die every year on the liver transplant waitlist as the supply of high-quality organs remains

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KEY POINTS

- Gender/sex-based disparities in access to transplantation have existed for more than two decades.
- Despite multiple iterations to the allocation policies, none have addressed the inequity that women face.
- Disparities are introduced at every step in the complex process of acquiring an organ transplant.
- It is critical for physicians to be aware of this disparity and thus allow them to advocate for their patients suffering from end-organ failure.
- The role of implicit bias is severely understudied in transplantation and can potentially improve our understanding of the factors driving these disparities.

inadequate to serve the need [10]. Women are disproportionately impacted by the supply-and-demand gap, and have consistently been shown to experience greater waitlist mortality than men [11▪▪,12–15].

The most recent major revision in the allocation system was the adoption of the model for end-stage liver disease (MELD) score in 2002. Data suggest that the percentage of women transplanted has declined since this change came into effect. Several other adjustments have been made, mostly revolving around geography and organ sharing, however, none have addressed the issue of gender inequity, which is now a well-established concern for almost two decades. This section examines how inequity persists at every step of this complex process and concludes with possible interventions that might narrow this gap or perhaps even eliminate it.

Etiology of end-stage liver disease

The most common causes of ESLD include viral hepatitis, alcohol and nonalcoholic fatty liver disease (NAFLD), accounting for 53.5% of cases [3]. Additional etiologies include primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), hereditary hemochromatosis (HHC), autoimmune hepatitis (AIH), alpha 1 antitrypsin deficiency (A1AT). The predominant etiology of ELSD differs by gender as described below.

Alcoholic liver disease

Worldwide, approximately 2.3 billion people abuse alcohol, and in the US the use continues to increase [16,17]. Women have seen a rise of nearly 60% in high-risk drinking and 80% in the prevalence of alcohol use disorder diagnosis [18,19]. Even though women consume lower quantities of alcohol, they are at a higher risk of developing ALD more rapidly [20]. This has been attributed to a smaller volume of distribution, reduced gastric metabolism of alcohol, increased gut permeability, and a lower threshold of Kupffer cells to oxidative damage [21]. Furthermore, half of the cirrhosis-related deaths are attributed to ALD, with an increase of 18% and 31% for women ages 25–44 years and 45–64 years between 2000 and 2015, respectively [2]. A recent retrospective review noted that among patients evaluated for ALD, men were 95% more likely to be listed and 105% more likely to be transplanted. In addition, significantly more women were not listed for LT due to active substance use (42% vs 35% $P < 0.05$) which is counterintuitive given studies suggest that lifetime abstinence from alcohol is more common among women than men [22▪].

Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis

Nonalcoholic steatohepatitis (NASH) is the fastest growing indication for LT in the US and projected to become the most common indication for LT in the near future [23]. Although in the younger age group NAFLD is more prevalent in men, after menopause, women are more likely to suffer from NASH and NASH-related cirrhosis [23] due to increased rate of insulin resistance, hyperlipidemia, visceral obesity, and loss of the protective effect of estrogen. As a result, women were 50% more likely to be listed for NASH cirrhosis however men were more likely to be transplanted for NASH (64.3% vs 52.4%, $P < 0.001$). Women were more likely to experience alternate outcomes including remaining on the waitlist without LT (13.3% vs 10.6%, $P = 0.006$), death on the waitlist (17.1% vs. 11.4%, $P < 0.001$) and removal from the waitlist due to clinical deterioration (12.7% vs 10.6%, $P = 0.04$)[24]. Given the expected rise in NASH as the leading cause of OLT, this gender/sex-based disparity will only worsen.

Viral hepatitis

Despite a similar prevalence, men are more likely to be affected by severe chronic Hepatitis C virus (HCV), as they experience a linear progression of fibrosis over time compared to women. The disease severity is very low in women of reproductive and premenopausal age with a rapid rise in the severity of fibrosis among the menopausal group [25,26].

Cholestatic and autoimmune liver disease

Classic examples of autoimmune and cholestatic liver diseases include AIH, PSC and PBC. Although overall a less likely cause of ESLD, AIH and PBC note a female preponderance.

Liver transplant referral

Obtaining a liver transplant is a complicated, multistep process with potential for disparity in access at each step. It most often needs to be initiated by a primary care physician or other provider who must make the diagnosis and identify liver transplant as a therapeutic option followed by referral to a gastroenterologist/hepatologist or a transplant center. The evaluation can begin if and when the patient arrives to the transplant center. For the patient with a chronic, debilitating illness, the comprehensive nature of this process can be daunting and confusing to say the least. If the patient passes the rigorous evaluation, then only do they ever make it to the liver transplant waitlist. United Network for Organ Sharing (UNOS), while responsible for providing national oversight for the equitable access to transplant, can only monitor patients once they are placed on the waitlist. Currently, there is no national standard or criteria by which ESLD patients are referred or waitlisted.

More recent data on the early steps of diagnosis and referral are limited. A retrospective analysis of Pennsylvania-specific data reviewed patients hospitalized for liver-related cause/conditions between 1994 and 2001. They demonstrated that the demographics and clinical characteristics of patients reaching different stages of the transplantation process were most dissimilar in moving from the stage of diagnosis to evaluation. Female patients had a lower probability of being evaluated, listed or transplanted than men [27]. The earlier stages of the transplantation process continue to remain understudied and have a great potential for intervention and improvement.

Candidacy for transplant and concept of frailty

The evaluation process for LT seeks to define patients who will obtain the most benefit from transplantation, have the best chance for survival, and will value and take care of the precious resource (the organ graft) afforded to them [28]. This requires intense medical, surgical, psychiatric, social, and financial screening to identify those who may have contraindications to LT. A more novel concept, not traditionally included in the work up is a measure of frailty.

Frailty is a complex syndrome characterized by functional decline and reduced physiological reserve. The prevalence of frailty in patients with ESLD awaiting LT ranges from 17% to 43% [29]. It increases proportionately with worsening severity of liver disease as depicted by the MELD score (with each point in the MELD-sodium score having a 0.04 coefficient with the Liver Frailty Index (LFI) ($P < 0.001$). Frailty is also a poor prognostic factor predictive of increased morbidity, mortality, and delisting in patients with cirrhosis. Frail patients are more likely to be hospitalized for cirrhosis-related complications. Such admissions exacerbate their frailty, decrease their physiological reserve to withstand additional/subsequent events and lead to a vicious cycle of deterioration. Women have been demonstrated to have a greater degree of frailty compared to men (as indicated by their higher LFI scores) that partially explains their higher waitlist mortality [11▪▪]. In addition, frailty occurs more frequently in NASH vs viral hepatitis or alcoholic liver disease (ALD) [30]. The combination of greater frailty and NASH in the female population with NASH being the projected leading indication for LT in the next decade, one can predict widening of the existing gender/sex-based gap in access to LT.

Model for end-stage liver disease

The MELD score was employed by the Organ Procurement and Transplantation Network (OPTN) in February 2002 [31] to objectively determine the severity of illness in ELSD patients and allocate lifesaving organs accordingly. This was in accordance with the OPTN Final Rule that called for equitable allocation of deceased donor organs among potential recipients based on medical urgency [32]. The previous allocation system placed great emphasis on waiting time and included subjective assessments of the illness including ascites and encephalopathy (CTP score) [14]. Although the introduction of the MELD score greatly reduced biases such as access to care and racial disparity in LT, the gender disparity unfortunately worsened [14]. A large database study found women experienced 30% increased odds of death or becoming too sick for liver transplant in the post-MELD era. Women were also less likely to receive a LT within three years of listing in both the pre-MELD and post-MELD era. Subsequent research demonstrated that the gender gap in liver transplant rates actually widened in the post-MELD era [33,34]. Several mechanisms have been proposed to explain this finding including the use of serum creatinine in the MELD, donor-recipient size mismatch, and geography.

Model for end-stage liver disease and renal function

Creatinine is a product of muscle metabolism. Serum creatinine is an easily measured laboratory value used in the MELD score calculation as a surrogate marker of renal function. Given that renal

dysfunction is an independent predictor of mortality in patients with ESLD [35], it carries significant weightage in the MELD calculation. However, serum creatinine inaccurately estimates renal dysfunction in cirrhotic patients [36]. This can be explained by several reasons. First, creatinine production is reduced in ESLD due to decreased hepatic creatine synthesis. Next, renal tubular secretion of creatinine is increased leading to lower serum creatinine levels. Lastly, cirrhotic patients often suffer from malnutrition and sarcopenia. This issue is particularly amplified in women as they have overall decreased muscle mass and, for a given creatinine level, women have a lower glomerular filtration rate (GFR) than men [37,38].

Research has been conducted to investigate if including an estimation of GFR in the MELD calculation can mitigate the disadvantage women experience [34]. The study concluded that not only were women less likely to be transplanted within ninety days of waitlisting, they also had worse renal function at the time, reflected in their lower Modification of Diet in Renal Disease (MDRD)-derived eGFR. The authors also found that since serum bilirubin and INR were part of the MELD calculation, for any given MELD category, women tended to have greater hepatic dysfunction. Although the differences were small, the combination of worse renal and hepatic function may explain the reduced survival among women. They were unable to, however, improve discrimination for waitlist mortality by substituting the serum creatinine with the MDRD-derived eGFR. This negative finding can be explained in several ways. First, the MDRD equation was originally derived in patients with primary renal dysfunction and patients with ESLD were excluded. Additionally, the MDRD equation is based on serum creatinine which we have established, is an inaccurate predictor of renal function, especially in this population. Another study utilized direct measures of renal function (iothalamate clearance) and this model incorporating the calculated GFR slightly outperformed MELD in predicting waitlist mortality. However, due to the highly labile nature of renal function in patients with decompensated cirrhosis and the cumbersome/invasive nature of the nuclear medicine study, this might be too difficult to update in real time to reflect the current severity of illness [37].

The literature concluded that renal dysfunction is an important prognostic factor and should be included in models predicting the severity of ESLD. However, serum creatinine is an inaccurate marker of renal function in women and thus contributes to the gender disparity issue. No alternative measures have been identified thus far to replace serum creatinine.

Donor-recipient size mismatch

Recipient height plays an important role in LT rates [38]. In a recent study, recipients 165 cm or less were found to be approximately 10–15% less likely to undergo LT. More than half of the women listed for LT fell into that category. However, even the small percentage of tall women experienced LT at rates much lower than those of men with similar height [38]. Similarly, another study demonstrated that while small stature impacts both genders, small women were far more likely to have an organ offer declined than small men. The implication of an organ offer decline can be fatal; women with even 1 organ declined on their behalf were 26% more likely than men to die or be removed from the waitlist [39]. A study looking at OPTN data found the median estimated liver volume (eLV) and the median estimated liver weight (eLW) were significantly lower for women vs men. As consistent across the literature, women were 25% less likely to undergo LT after controlling for factors including region, blood type, and MELD. Once the model was adjusted for eLV and eLW, LT rates were still lower for women (13%), concluding that stature and liver size did contribute to the gender disparity to some extent, however other factors yet undiscovered may be at play [15,39,40▪▪,41]. The role of implicit bias, studied to some extent in other fields, remains unexplored in LT and may hold the answer to why women continue to disproportionately experience disparities in access to life-saving transplantation compared to men.

Geography

Geographic location has been shown to be associated with disparities in waitlist mortality and LT [40▪▪,42–44]. Multiple studies demonstrated regional variation in the median allocation MELD score by up to 10 points [42,43]. In response, the transplant community implemented a policy to replace the regions and donor service areas with fixed concentric circles around the donor hospital effectively redefining the local organ supply [45]. However, a recent study quantifying factors contributing to sex-based disparities found that while geographic location was indeed associated with increased wait list mortality, candidate anthropometric and liver measurements and MELD scores had the strongest associations [40▪▪]. Although the new allocation policy may relieve some disparities in access, it still relies on the MELD score to determine medical urgency and does not appear to offer a solution to the persistent gender inequities driven by the plethora of reasons discussed herein.

CONCLUSION (LIVER)

For patients with ESLD, LT is the only life-saving therapy. Given the ongoing shortage of donor organs, the liver allocation system has undergone several iterations, with the most significant being the introduction of the MELD-based system in 2002. The gender disparity gap in access to LT, present for decades, has only widened with the current MELD-based policies. The scientific literature clearly highlights this concern, yet none of the proposed policies have aimed to mitigate this disparity. Several factors potentially responsible for the inequity have been identified including use of serum creatinine as a marker of renal dysfunction in the MELD score, donor-recipient size mismatch, issues around referral and completion of the evaluation process, especially frailty.

Kidney

Background

Chronic kidney disease (CKD) is a massive public health problem affecting approximately 10% of the world's adult population [46]. It has significant economic implications with total Medicare spending over $120 billion on CKD and end-stage renal disease (ESRD) in 2017 [47]. The disease process disproportionately affects women yet they are less likely to be initiated on renal replacement therapy (RRT) [48]. Furthermore, despite the well-established survival benefit of transplant over dialysis [49], which is even slightly better in women [50], there exists a gender disparity in access to this superior treatment option. Women are further disadvantaged as they constitute the majority of the living kidney donors, yet are less likely to be a recipient of a living donor kidney transplant (LDKT) [51–53]. This section examines where gender/sex-based disparities have been introduced along the continuum of kidney transplant care.

Referral

Men are more likely to be initiated on RRT despite the higher prevalence of CKD in women [48]. Given that referral for a transplant evaluation is usually prompted by initiation of RRT, this is an important point of discussion [54]. Women also start dialysis at eGFR levels that are slightly lower than men [48] and are more likely to receive a low dialysis dose. Although the rate of decline in renal function is faster in men these differences are not entirely explained by the rate of CKD progression alone.

According to the latest report from the US Renal Data System (USRDS), the proportion of men and women receiving pre-ESRD nephrology care is remarkably similar. There are no gender differences in the modality of dialysis used (hemodialysis vs peritoneal dialysis), although women are more likely to use catheters at the initiation of dialysis vs arteriovenous fistulas. Despite the apparent equity in pre-ESRD care, there exists a marked disparity in access to therapy for ESRD, be it RRT or transplantation.

Differences in referral patterns specifically between genders have not been studied in recent years, however, Patzer *et al.* examined overall referrals for kidney transplantation and start of the actual evaluation process in dialysis patients in the Southeastern United States [55▪]. They found that the median proportion of patients referred within 1 year was 33.7% (range 0–100%). However, fewer than half of the referred patients started the evaluation process within 6 months of the referral, representing 16.1% of all incident dialysis patients. They also reported that older age, female sex, Medicaid insurance, and higher neighborhood poverty were associated with lower referral and evaluation start [54,55▪]. These results suggest barriers continue to exist even after referral is initiated and remain an important area of study and intervention. An important policy aimed at eliminating the differences in referral patterns for transplant evaluation in ESRD patients was the 'Advancing American Kidney Health' Executive Order issued in 2019 [56]. To achieve this goal, the Centers for Medicare and Medicaid Services will adjust dialysis facility and nephrologists' payments based on home dialysis and kidney transplantation rates. Although this can improve access to transplant centers, subsequent barriers continue to remain a point of concern.

Effect of age and comorbidities

Age is an important variable; studies have found women over 60 years of age are 2–3× more likely to choose conservative care instead of RRT or transplant [48]. A national cohort study using data from the USRDS evaluated ATT and the survival benefit. They found that overall women had 11% less ATT than men. However, when adjusted for age, they discovered that women aged 18–55 have equivalent ATT, however, for older women, the ATT disparity widened exponentially (age 56–65, 15% less ATT; age > 75, 59% ATT). This persisted for both deceased-donor and live-donor kidney transplantation. Although social factors such as education level were associated with ATT overall, they did not sufficiently account for the observed gender difference.

Women in all age brackets with comorbidities including diabetes, coronary artery disease or vascular disease had decreased ATT compared to men with the same comorbidities. However, it is interesting to

note that there was no difference in the survival benefit after transplant between men and women regardless of the comorbidity status.

The finding that disparity was present in older women and magnified in women with comorbidities could suggest that this patient population was seen to be sicker than men; 'perceived frailty'. This could lead providers to incorrectly assume women will not be able to tolerate or benefit from a major surgery and affect the therapy options offered [57]. This ties back in with the earlier observation, that despite equal pre-ESRD nephrology care in both genders, there is a marked difference in the referral and evaluation process, for unclear reasons.

Obesity

Obesity has reached epidemic proportions in the US. It is a prominent risk factor for ESRD and is associated with a reduction in the likelihood of waitlisting and higher likelihood of being bypassed on the waitlist when an organ became available. Not only was the effect magnified as the body mass index (BMI) increased, it was significantly more pronounced in women compared to men at each BMI category [58▪,59,60].

Sensitization

Histocompatibility testing is a critical step in kidney transplantation. Sensitizing events such as pregnancy, which is unique to the female gender, can cause HLA alloimmunization [61]. Resulting HLA incompatibility creates an additional barrier for women to overcome [62]. Furthermore, the prevalence of HLA alloimmunization increased with parity [61]. This effect is magnified in minority women as they are more likely to be multiparous [63▪▪] making it challenging for this population to achieve transplant.

Living donor kidney transplant

LDKT is the ideal therapy for transplant candidates with ESRD [62]. Recent data suggests a 30% reduced rate of LDKT for women. A closer look at the process of achieving LDKT noted that women fell behind their male counterparts at the step of HLA testing. The rate of incompatibility with a potential living donor was equivalent between both genders sensitized by either a prior blood transfusion or transplant. However, living donor incompatibility was significantly higher in women with history of pregnancy. This created a roadblock disproportionately larger than anticipated as a critical group of the women's living donor pool was comprised of either the spouse or offspring. To make matters more unfair, women actually comprise the large majority of the living donor pool, 63%, yet are less likely to be the recipient of a living donor kidney for transplant [62].

Kidney paired donation

Kidney paired donation (KPD) is a strategy that allows for one incompatible donor-recipient pair to exchange kidneys with another incompatible donor-recipient pair, thus achieving two compatible LDKTs. This method facilitates kidney transplantation in a large number of ESRD patients, notably racial minorities [63▪▪,64] and sensitized women [62,63▪▪]. Ideally more widespread participation and implementation of the KPD programs can improve ATT for this disadvantaged group. However, a declining trend in LDKT has been noted since 2005, particularly in male donors [51]. Although there is no study that examines the effect of this trend on KPD programs, one can hypothesize that this might theoretically further reduce female ATT.

Hepatitis C virus-viremic donors

A major breakthrough in the last decade to battle the organ shortage was the practice of transplanting kidneys from HCV-viremic donors into HCV-negative patients (HCV D+/R-) followed by direct-acting antiviral therapy. Early data were promising demonstrating decreased waitlist times and access to younger donors with excellent allograft function [65–67]. A recent study of the impact of this newly discovered donor pool on racial minorities and women revealed that once again this population continues to be disadvantaged [68▪]. Specifically, women were 20% less likely to receive a kidney from a HCV donor. The authors propose several hypotheses to explain the results, including the possibility of bias (conscious or unconscious/implicit) in the treatment of patients by transplant centers. Education on HCV donors requires great time and effort and perhaps this time was invested on patients thought to be more likely to be interested or benefit from this source of donor kidneys or perhaps more culturally competent education is warranted that focuses specifically on the educational needs of women. These issues of implicit bias and cultural competence are ripe for further investigation.

CONCLUSION (KIDNEY)

Over two decades of research indicate that women continue to experience inequities in access to life-saving treatment options. Ironically, women tend to utilize health services more frequently, be more compliant and have demonstrated equal or better outcomes after transplant [50,57], yet they struggle

to successfully achieve transplantation at comparable rates to men. Efforts to develop incompatible kidney transplant programs to overcome unavoidable biological barriers such as HLA alloimmunization have clearly shown to mitigate these disparities yet no policies on the national level have been enacted. The 'Advancing American Kidney Health' Executive Order is an excellent initiative to improve access to transplant centers, however, it may not translate into improved access to kidney transplantation in isolation as subsequent barriers in the process continue to exist and remain unaddressed. The roles of implicit bias and cultural competence are severely understudied in transplantation and can potentially improve our understanding of the factors driving these disparities.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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The authors found that liver transplant candidate anthropometric and liver measurements has the strongest associated with disparities in wait list mortality and deceased donor liver transplant. They also noted that allocation policies addressing geographic disparities alone may not mitigate sex-based disparities, which are associated with the inability of the MELD score to accurately estimate the disease severity in women.

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The authors found that less than half of the referred patients initiated the transplant evaluation process. They allude to the barriers that exist in the process prior to ever being listed for transplant and highlight the importance of collecting national surveillance data on the early steps in the process to identify barriers to transplant and how we might address them.

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The authors describe the implementation of an incompatible living donor kidney transplant program resulting in the nation's longest single-center kidney chain. As a result, they noted a decrease in the disparity experienced by minorities, specifically sensitized women. The success of this endeavor has great potential to serve the vulnerable population if applied at the national level.

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The authors found that despite an increase in the kidney transplants from HCV NAT + donors, there exists substantial racial/ethnic disparities in access to this novel scientific breakthrough.