Sex and Gender Disparities in Liver Disease

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Introduction

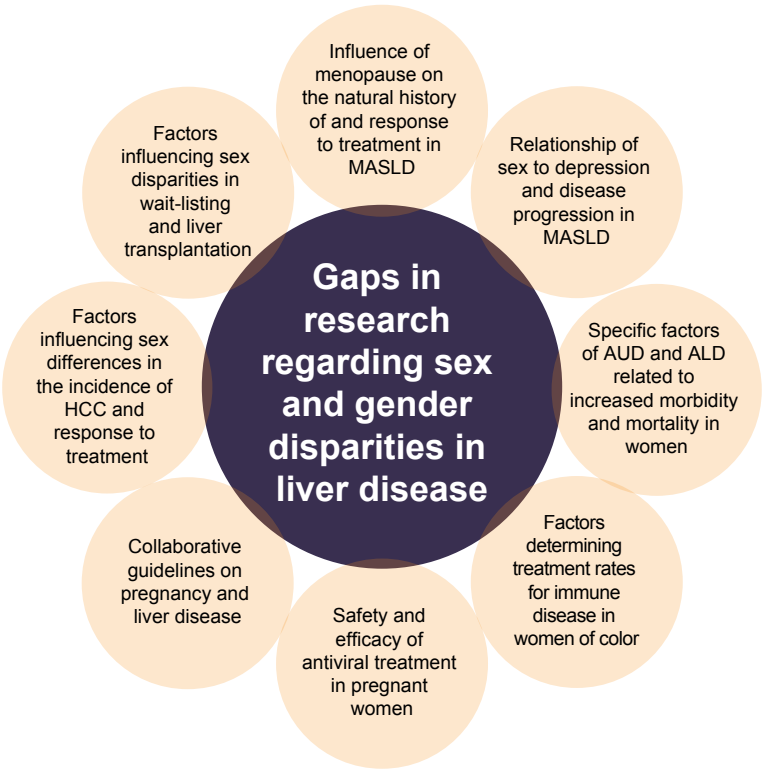
Gender and sex are two terms that are widely used interchangeably but, when pertaining to clinical research and as detailed in Table 1,[1] should be separate and distinct. As shown in the table, sex-based research demonstrates its effect on disease onset, risk factors, prevalence, severity, signs and symptoms, and drug pharmacokinetics and pharmacodynamics. Research on gender has brought to light such important issues as gender inequality, gender stereotypes, and discrimination, which affect patients' lives and well-being.[1]

Table 1. Differences Between Sex and Gender.[1]

Sex	Gender
• Refers to the biological differences between males and females. • Is a biological binary variable that encompasses chromosomal, physiological, and biological differences. • With its associated features, may encompass or affect disease onset, risk factors, prevalence, severity, signs/symptoms, pharmacokinetics, and pharmacodynamics. These factors may be studied in clinical trials for their effect on efficacy or other clinical outcomes.	• Refers to the social and cultural roles, behaviors, and expectations associated with being male or female. • Relates to important issues that research on gender has brought to light, such as gender inequality, gender stereotypes, and discrimination, which affect patients' lives and well-being.

One area of growing interest includes the sex and gender differences, associated disparities, and ultimate consequences in the field of liver disease (see Figure 1). The purpose of the present whitepaper is to discuss sex and gender disparities in clinical research on liver disease and gaps in research, identification, and treatment of liver disease based on sex and gender. This paper was developed out of the efforts of the Women's Committee of the Chronic Liver Disease Foundation (WHISE) and based on a symposium focusing on gender and sex disparities in liver disease presented at the Liver Connect conference in 2023.

Figure 1. Gaps in Research Regarding Sex and Gender Disparities in Liver Disease.[2-27]



ALD, alcohol-related liver disease; AUD, alcohol use disorder; HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease.

The Evolution of Sex and Gender in Clinical Research: Remaining Issues

From a historical perspective, a guideline issued by the Food and Drug Administration (FDA) in 1977, titled "General Considerations for the Clinical Evaluation of Drugs," recommended that women of childbearing potential, broadly defined as "premenopausal females capable of becoming pregnant," be excluded from participating in phase 1/early phase 2 studies until reproductive toxicology studies were done.[1] This guideline was controversial because it assumed that women of childbearing potential could not have control over avoiding pregnancy in order to be included in studies. It also decided that the protection of the potential fetus outweighed other interests, including the interests of the woman. As the development of experimental therapies accelerated, it was recognized that women needed to be included in earlier studies, especially those related to life-threatening diseases. Thus, in 1993, the FDA reversed the 1977 guideline and, in its place, issued the "Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs."[28] This seminal paper recognized the need for individualized pharmaceutical therapies; called for data to analyze and assess the gender/sex effect, along with age, body size, and hepatic and renal function; and emphasized that rigid sex quotas were not expected in clinical trials, but inclusion in the same trials (not separate trials) was preferred. Furthermore, researchers must also consider the potential for harm to vulnerable populations, such as children, pregnant women, or individuals with mental health disorders, and take appropriate measures to mitigate those risks.[28]

Despite the evolution of the FDA-issued guidelines, sex and gender issues in clinical research continue to be complex, multifaceted, and pose challenges. One main issue is the lack of representation of diverse populations. Historically, research has been conducted mainly on male participants, with the assumption that findings could be generalized to both sexes. This practice has led to the exclusion of women, transgender individuals, and other groups from research studies, limiting our understanding of their experiences and needs and leading to a lack of knowledge on the effectiveness and safety of medications for these populations. For example, through animal studies to early first in-human and phase 1/2 studies in cell-based therapies, 67%-76% of data are acquired in male cells/species or humans.[29] Recent data have demonstrated that appropriate sex participation in clinical trials is still imbalanced. Chen and colleagues examined the demographics of clinical trial participants and the presence of efficacy and safety analyses by sex for new drugs approved by the FDA between 2013 and 2015.[30] Of the 102 newly approved drugs, sex was reported for >99.9% of trial participants, and women accounted for 40.4% of the patients studied. When taking into account the proportion of women in the clinical trials relative to their estimated proportion in the specific disease population, appropriate sex participation

was noted for 83% of new drug indications.[30] As a result, findings from research studies may not be applicable to all individuals in larger global populations or to the general population, leading to health disparities and inequalities.

Sex and gender research can also have ethical implications. Informed consent, confidentiality, and privacy are essential ethical principles that must be upheld in research studies, but sex and gender research can pose challenges in these areas. For example, asking sensitive questions about sexual behavior or identity can be uncomfortable or distressing for participants. Researchers must ensure that participants are fully informed of the risks and benefits of participation and that their privacy and confidentiality are protected.

Addressing these issues requires a commitment to diversity, equity, and inclusion in research, as well as an understanding of the ethical considerations involved. Better regulatory guidance and a better understanding of these issues have yielded positive and significant progress. However, researchers must continue to strive to include diverse populations in their studies, avoid perpetuating gender stereotypes and biases, and uphold ethical principles in all stages of the research process. By doing these things, researchers can enhance the understanding of the complex interactions between gender and sex and promote the well-being of all individuals, regardless of their gender identity or biological sex.

Metabolic Dysfunction-Associated Steatotic Liver Disease and Metabolic Dysfunction-Associated Steatohepatitis

In June 2023, the American Association for the Study of Liver Diseases announced a new nomenclature for fatty liver disease. The terms *metabolic dysfunction-associated steatotic liver disease* (MASLD) and *metabolic dysfunction-associated steatohepatitis* (MASH) replace the terms *nonalcoholic fatty liver disease* (NAFLD) and *nonalcoholic steatohepatitis* (NASH).[31] With a rising global prevalence, MASLD affects millions of people worldwide and has become the leading cause of liver transplant (LT) across many centers.[32] In the US, MASLD still lacks an FDA-approved treatment, and many patients will ultimately progress to cirrhosis, hepatic decompensation, and/or hepatocellular carcinoma (HCC). One area of growing interest is the sex differences associated with MASLD and MASH as they relate to prevalence, disease progression, and treatment approaches. However, there is a paucity of research and publications on gender and sex differences in MASLD.[33] A comprehensive understanding of how these factors affect MASLD would positively influence future drug developments and improve outcomes.

Previous studies that primarily included patients aged <65 years showed a higher prevalence of MASLD among men than among women.[33-36] As women age, however, the prevalence of MASLD increases.[37] A cross-sectional study suggested that the prevalence of MASLD might be influenced by estrogen, with a greater prevalence observed in postmenopausal (57.9%) than in premenopausal (32.2%) women.[38] Furthermore, the severity of MASH fibrosis also increases as women age beyond menopause. In an analysis of 244 Italian women (74 premenopausal and 170 postmenopausal) and 244 age-matched men, a nonsignificant trend was observed between menopausal status and F2-F4 fibrosis, but no association was seen between male sex and fibrosis.[39] In another study, women who experienced menopause before the age of 40 years (N = 143) had a 90% increased risk of more severe fibrosis (ACOR = 1.9; [95% CI: 1.3-2.7]; p = 0.001) compared with women with an age of menopause ≥40 years (N = 345).[40] These data suggest that estrogen protects against hepatic steatosis and fibrosis, as has been observed in other metabolic disorders[2-5]; this illustrates the importance of including not only women but also women at various hormonal stages (i.e., reproductive, menopausal transition, and postmenopause[41]) in such studies.

Younossi and colleagues identified an association between MASLD and increased anxiety and depression.[8] The correlation of impaired mental health and metabolic syndrome has also been well described as intimately connected to the hypothalamic pituitary adrenal axis.[42] Despite the known associations between them, it is less known how sex and, more specifically, hormone differences between the sexes play a role. Xiao and colleagues identified female sex as an important risk factor for having underlying depression in MASLD.[43] In addition, as the severity of depression increases, so does the severity of steatosis and fibrosis. This correlation is more frequent in females than males.[6,7] A more sophisticated understanding of the potential bidirectional effect of mental health and MASLD in females will allow for a more tailored patient care approach with current and future therapies.

Emerging data regarding MASLD in pregnancy suggests a prevalence of 14% among pregnant individuals screened

during early pregnancy; this rate has nearly tripled in the last decade.[44,45] MASLD during pregnancy appears to increase risks for both mother and baby, including the risks of hypertensive complications, bleeding after delivery, and preterm birth.[45] Further research on the identification and management of women with MASLD during pregnancy is warranted.

Autoimmune Hepatitis and Primary Biliary Cholangitis in Women of Color

Autoimmune liver diseases, such as autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC), disproportionately affect women. Although both AIH and PBC are considered rare diseases, they are both rising in prevalence,[46,47] partly because of factors associated with increases in all autoimmune conditions that are not fully understood and partly because of increased diagnosis and life-prolonging treatments. Both AIH and PBC were initially described and studied in Caucasian women, and despite the growth of a multiracial and multiethnic US population, most studies and therapeutic trials continue to underrepresent racial and ethnic minorities.[9] Minorities with AIH and PBC often present with cirrhosis and advanced fibrosis, and they are less responsive to treatment; moreover, they have higher rates of hospitalization and worse outcomes compared with Caucasian women.[10,48-50]

The incidence of PBC in women of color is increasingly being recognized. Latinx patients have higher odds of hospitalization for PBC, a decreased response to ursodeoxycholic acid (UDCA), and a higher incidence of PBC-AIH variant syndrome.[9,10] Older studies have suggested that PBC is rare in Asian women; however, recent studies suggest the prevalence of PBC in the Asia-Pacific region is 11.9/100,000 persons, with the highest prevalence among Japanese and Chinese women.[9] Furthermore, PBC is underdiagnosed in Black women. In the largest cohort study of PBC in the US, which used data from the Fibrotic Liver Disease (FOLD) consortium, the prevalence of PBC in Black patients was greater than previously reported, at 19.7/100,000 persons.[12] Black patients with PBC presented at a younger age and had a lower likelihood of receiving UDCA.[12] A follow-up study on the same cohort showed that although the untreated Black PBC patients had increased all-cause mortality (HR 1.34; 95% CI 1.08-1.67), this risk was reversible with UDCA.[11] Similar findings were reported for Asian Americans and Pacific Islanders; when untreated, they had higher rates of LT and death.[11] UDCA improves LT-free survival; therefore, it is evident that a correct and early diagnosis leading to prompt treatment is essential to improve outcomes.

The data on racial and ethnic minorities with AIH also point toward disparities in this disease. The odds of hospitalization for AIH are much higher for patients of color compared with White patients. Black patients with AIH present at a younger age, with more severe disease. They are more difficult to treat; furthermore, they have increased rates of cirrhosis on liver biopsy and higher mortality.[13,14] Latinx patients with AIH have more severe disease and more cirrhosis at presentation.[9] Notably, given the high female predominance of disease, it is not surprising that 75%-80% of patients of color in these retrospective AIH cohorts are women.

Overall, AIH and PBC are underrecognized and undertreated in women of color, and this affects outcomes. Although HLA associations have been noted for these diseases, which may be influenced by race and ethnicity, the more prominent issue seems to be the role of the environment and social determinants of health in women of color.[9] Such factors as access to healthcare, health literacy, a physical environment free of pollutants, toxins, exposure to xenobiotics, and economic factors can all affect these autoimmune disorders and should be systematically studied.

The "Pinking" of Drinking: The Rise in Women's Alcohol Consumption and Alcohol-Related Liver Disease

From 2002 to 2012, rates of AUD rose more rapidly for women compared with men (80% increase vs. 30% increase).[15] In a meta-analysis of 6 large population-based national surveys, rates of any past-year drinking and past-year binge drinking (consumption of 5 or more drinks for men or 4 or more drinks for women in 2 hours) increased more rapidly among women compared with men.[16] The increases in overall population-level drinking observed in many of these datasets appeared to be driven almost entirely by drinking increases among women. This finding has been mirrored in studies of age cohorts, which demonstrated that from age 26 onward, drinking increased much more rapidly among women than among men.[51]

The effects of the COVID-19 pandemic worsened many of the trends described above, with the US experiencing a 25% increase in overall alcohol consumption in the earliest days of the pandemic; since this time, there has been some decline, but no return to pre-pandemic baseline drinking.[52-54] One study used online surveys to assess pandemic effects on alcohol consumption and found that men drank more

than women did at the beginning of the pandemic. By later in the pandemic, men's consumption of alcohol had declined, while women's had continued to rise, with women drinking as much as men.[55] In addition, while both men and women experienced alcohol-related problems, only men appeared to reduce their drinking over the pandemic in response to those problems, whereas women's drinking continued to rise in spite of a self-reported increase in alcohol-related problems.[55] One potential reason for this may be that marketing targeted to women often portrays alcohol use as key to important features of women's lives, such as friendships and relationships, and casts alcohol use as an element of "girl power" and part of women's self-care.[56] In particular, alcohol advertising aimed at women also uses parenting themes (e.g., "mommy juice"), again making reference to alcohol consumption as a normal part of relaxation (e.g., "wine-down Wednesdays" or "rosé all day" themes).

As a consequence of these trends, alcohol-related liver disease (ALD) rates have increased more rapidly among women compared with men in recent years. Mortality data from WONDER, a system for disseminating public health data and information from the Centers for Disease Control and Prevention (CDC), shows that annual death rates for liver disease have risen most rapidly among women, especially young women aged 25-34 (13% for women vs. 9% for men in the same age group).[17] For women, similar doses of alcohol are more likely to cause physical harm and liver disease because of differences in alcohol metabolism. These differences are attributed to body water content differences, changes in first-pass metabolism, and hormonal differences that appear to moderate the effects of alcohol on body tissues.[57] As a consequence, women with preexisting cirrhosis who consume alcohol at levels equivalent to men have a greater likelihood of progression to cirrhosis and liver-related mortality.[58-60] For example, at a daily consumption of 24-36 g of alcohol (approximately 2-3 drinks per day), women with cirrhosis have a 7.7-fold increased relative risk of liver-related mortality (95% CI 6.4-9.6, $p < 0.001$), compared with a 2.8-fold increased relative risk for men (95% 2.3-3.4, $p < 0.001$).[58]

Despite the increased risk of cirrhosis progression and mortality because of alcohol use in women compared with men, proportional rates of wait-listing and transplants for alcoholic hepatitis for women remained steady in 2016-2021, at 36.1%-37.3%.[61,62] However, in a single-center retrospective study of 949 patients with ALD, McElroy and colleagues found that men with ALD were 95% more likely to be listed and 105% more likely to undergo transplantation compared with women with ALD.[63]

Efforts to reduce alcohol consumption and ALD rates among both women and men will need to involve multiple levels. Such efforts should include policy-level solutions, individual interventions that can be delivered at the bedside, and integrated care initiatives at the organizational level.

Hepatitis B and C and Pregnancy

It is estimated that in women of childbearing age (WOCA) across the globe, 65 million have hepatitis B virus (HBV) and 15 million have hepatitis C virus (HCV). The World Health Organization (WHO) Global Strategy for Viral Hepatitis Elimination has identified pregnant individuals as a priority population.[62,64] Pregnancy provides the opportunity to implement many of the WHO's proposed interventions, including primary prevention (i.e., vaccination of the mother and infant), prevention of mother-to-child transmission (MTCT), integrated testing approaches, and strategies to minimize stigma/discrimination in the healthcare setting. However, over the past decade, there has been a 3-fold increase in the incidence of HCV diagnosed among all US births.[61] Although there has been an overall decline in HBV, a study evaluating HBV specifically among WOCA found increases in HBV infections in such states as Kentucky and West Virginia, which are heavily affected by the opioid epidemic. This suggests that injection drug use may also be contributing to new HBV infections among women.[65]

The care of women during pregnancy involves screening, considering antiviral therapy, and addressing the risk of MTCT. The AASLD recommends that all women be screened for HBV and HCV during each pregnancy.[66,67] However, recent data have shown that among pregnant women, only ~85% and ~40% undergo screening for HBV and HCV, respectively.[68,69] Approaches for the prevention of HBV MTCT are defined as neonatal HBV vaccine and hepatitis B immune globulin, as well as maternal antiviral therapy. The AASLD guidance recommends HBV treatment for women with immune-active disease or those who have HBV DNA ≥200,000 IU/mL.[67] Despite these recommendations, studies demonstrate that antiviral therapy for HBV is often not initiated during pregnancy.[18] With regard to HCV, the baseline risk of MTCT of HCV is lower than that of HBV, but it still exists (around 5.8%, reaching 10.8% with HIV coinfection); however, there are no defined methods to decrease the risk.[19] Fortunately, emerging data have demonstrated the efficacy and safety of using direct-acting antivirals (DAAs) in pregnancy.[70] New developments include an ongoing phase 4 study of sofosbuvir/velpatasvir

in pregnancy[71] and the recently developed Treatment in Pregnancy for Hepatitis C registry, which is part of the CDC Coalition for Global Hepatitis Elimination, to collect data on exposure to DAAs during pregnancy.[72]

Despite advances in research on women with HBV/HCV during pregnancy, significant challenges remain. Women living with HBV/HCV face stigma that may be exacerbated during pregnancy care. Hesitancy on the part of healthcare providers to offer medication during pregnancy is still apparent. In addition, maintaining engagement after pregnancy delivery is challenging, with high rates of loss to follow-up. Interdisciplinary communication is needed among obstetricians, liver specialists, and pediatricians, who all play key roles in the pregnancy care cascade. Strategies are required to increase the uptake of screening during pregnancy and the use of antiviral therapy when indicated. Policies should also be implemented to increase rates of HBV vaccinations in primary care and obstetrical/gynecological offices. These approaches are critical to improving health outcomes and contributing to viral hepatitis elimination.

Society Guidelines on Pregnancy and Liver Disease

Numerous guidelines have been published in recent years for the diagnosis and management of liver disease in pregnancy. However, several major discrepancies exist among the guidelines, reflecting the limitations in our understanding of the diagnosis and management of liver disease in pregnancy. One example of such a discrepancy in recommendations is the diagnosis of intrahepatic cholestasis of pregnancy (ICP). ICP is characterized by pruritus and elevation in serum bile acid concentrations in the late second and/or third trimester. While all societies agree that pruritus must be present, guidelines vary on the total serum bile acid concentration used for the diagnosis of ICP. Further, the AASLD,[20] American College of Gastroenterology (ACOG),[21] and European Association for the Study of the Liver[27] do not specify whether serum bile acid measurements should be fasting levels. In contrast, the Society for Maternal-Fetal Medicine (SMFM) recommends fasting levels, while the Royal College of Obstetricians and Gynecologists[24] recommends postprandial or nonfasting levels. A recent study showed that bile acid concentrations increase postprandially and reach levels of 19 μmol/L in women with ICP.[73] Given that peak levels are more clinically relevant in predicting pregnancy outcomes, it may be more valuable to measure serum bile acid levels postprandially. Ultimately, larger prospective studies in pregnant women are needed to better understand serum bile acid cutoffs and the ideal timing of measurements for the diagnosis of ICP.

Controversies in screening strategies for HCV in pregnancy not only provide another example of major discrepancies in society guidelines but also show how they have the potential to impact the management of liver disease in pregnancy. Prior to 2018, most obstetrics and gastrointestinal societies recommended risk-based screening for high-risk women—that is, women at high risk for contracting HCV. Given the rising prevalence of HCV infection among pregnant women because of increases in injection drug use among childbearing women, the AASLD and Infectious Diseases Society of America (IDSA) modified their recommendations to universal HCV screening for all pregnant women.[74] However, the CDC and obstetric societies (SMFM, ACOG) did not change their recommendations to universal screening until 2020 and 2021, respectively.[75,76] The positive effects on expanding screening were not seen until after the obstetric societies changed their recommendations, highlighting the importance of adoption of recommendations by obstetric societies, as pregnancy may be the only time when WOCA engage with the healthcare system.

Future research agendas in pregnancy and liver disease should include comparative effectiveness trials for preeclampsia prevention to identify specific aspirin dosing, length of continuation, and which populations are most likely to benefit; larger-scale clinical trials of DAA therapy in pregnant women with chronic HCV; studies determining the safety and efficacy of tenofovir alafenamide in pregnant women with chronic HBV; and prospective cohort trials to better understand pregnancy outcomes among women with MASLD.

Hepatocellular Carcinoma

HCC is a major cause of morbidity and mortality in patients with chronic liver disease and cirrhosis worldwide. HCC is projected to surpass breast and colorectal cancers to become the third leading cause of cancer-related death in the United States by 2035.[77] Sex disparities in incidence and survival exist for most cancers,[78] and HCC is no exception; it has a consistent male-to-female predominance in its burden and mortality observed throughout all regions of the world, across time periods, and in all racial and ethnic groups.[79,80] Despite this consistent observation, the specific driving factors underlying this sex disparity remain unclear. In animal models, sex-related biological factors

(i.e., sex hormones) have been demonstrated to have a role in HCC pathogenesis, with androgens promoting tumorigenesis (e.g., via signaling pathways resulting in the upregulation of vascular endothelial growth factor [VEGF]) and estrogens protecting against it (e.g., via suppression of proinflammatory cytokines, such as IL-6).[81] However, researchers have suggested that this hormone hypothesis has been overemphasized; in humans, data are limited and discordant, with only a weak to no association observed between circulating sex hormones and HCC risk.[82] The prevalence of some established HCC risk factors (e.g., alcohol use, smoking, diabetes, and viral hepatitis) does differ by gender[83]; however, major challenges in determining specific driving factors underlying this disparity (and to what extent behavioral vs. biological factors each play a role) include the following: 1) most published studies have relied on large administrative databases and cancer registries (which lack granular data on key confounders, including liver function, cirrhosis etiology, and behavioral factors); 2) most are limited to small sample sizes when it comes to women; and 3) studies have often failed to distinguish between the distinct concepts of sex (i.e., biological factors) and gender (i.e., social, behavioral, and cultural factors).

Disparities in HCC also extend beyond incidence; indeed, they reach across the entire cancer care continuum, from early detection to tumor stage at diagnosis and treatment receipt. No gender-specific recommendations exist for HCC surveillance (other than the difference in age to begin surveillance, at 50 years old in women vs. 40 in men with chronic hepatitis B);[84] however, as observed in other cancers, women appear to be more likely to receive the recommended HCC surveillance than men are.[85] Surveillance receipt is associated with early detection, curative treatment receipt, and survival in patients with cirrhosis.[86] This may partly explain why women are more likely to present with earlier tumor stages and have better overall survival compared with men.[85] Women with HCC appear to receive some curative treatments (e.g., resection, local ablation) at similar or higher rates compared with men,[87] but they are less likely than men to undergo LT, the definitive treatment for both HCC and the underlying cirrhosis.[88,89] In studies examining tumor doubling time, tumor biology did not appear to differ significantly by sex.[90] However, while not specifically studied in HCC, some data suggest sex differences in the efficacy of immune checkpoint inhibitors, with women having a higher risk of experiencing immune-mediated adverse events compared with men.[91] Sex differences in body composition (i.e., women having more subcutaneous fat and men having higher metabolically active fat-free body mass than women) impact drug metabolism and toxicity, and they are associated with prognosis in some cancers.[92] Although the sex gap in HCC incidence is narrowing (in part because of the significant increase in MASLD-HCC cases among women),[93] women remain underrepresented in HCC clinical trials,[25] and published studies often fail to provide sex-stratified analyses and/or subgroup analyses by sex on efficacy, safety, and risk-benefit ratios. Ultimately, the inclusion of women in all aspects of HCC research (including clinical trials) is needed to move toward more equitable care and better outcomes for both women and men with HCC.

Liver Transplantation and Sex

LT has been an area in which sex disparities have been known for some time. Liver allocation has long been a topic considered when discussing sex and gender disparities in transplant opportunities. The Model for End-Stage Liver Disease (MELD) score, which was introduced in 2002, contributes to the disparity, given the reliance on renal function as part of the equation. It has long been recognized that the reliance on creatinine as part of the MELD score places women at a disadvantage because of their lower muscle mass.[94,95] Biological differences in muscle mass result in the underestimation of renal function in women compared with men at any given creatinine level. As such, MELD and MELD-Na underestimate the mortality risk in women compared with men. The use of creatinine leads to underestimation of the mortality risk in women by up to 2.4 MELD-Na points.[96] This disparity appears to increase the risk of mortality while waiting for transplant by 25% for women compared with men.[97] In response, MELD 3.0 has been introduced, which includes a coefficient assigned for female sex.[98]

Further disparities in LT occur as a result of the difference in stature between men and women, which results in less access to size-appropriate livers. In fact, women are more likely to have livers declining because of size,[96,97] resulting in further worsening of wait-list mortality for women.

Disease etiology likely plays a role in the disparity as well. Following menopause, women are more likely to develop MASH and MASH-related cirrhosis compared with men, resulting in a 50% greater likelihood that women will be listed for this diagnosis. However, men are more likely to undergo transplantation for MASH (64.3% vs. 52.4%).[99] Women are also more likely to die while waiting (17.1% vs. 10.6%) or to be removed from the wait list because of

clinical deterioration (12.7% vs. 10.6%).[26] Furthermore, as discussed above, it may be that men are more likely to be listed and undergo transplantation compared with women with ALD.[63] Patients with PBC are at an overall disadvantage with respect to LT, and they experience higher wait-list mortality than do patients with other diagnoses.[100] Given the predominance of female patients with PBC, with historic female:male ratios of 10:1 and more recent ratios of 4:1, this further amplifies the sex disparities present in LT.

Policies around transplantation should always strive for equity. The current allocation and distribution policies for LT fall short when considering sex and gender. Although MELD 3.0 strives to address one aspect of the differences between men and women, further policy changes are needed to ensure that the disparities in listing, allocation, and transplant opportunity are the same for men and women.

Conclusions

It is critical for our understanding of liver disease that we acknowledge the known differences between the sexes. Clinical research should include diverse populations, encompassing both men and women, and consider the additional effects of hormones on both disease progression and treatment response. By conducting such research, we can enhance our understanding of the complex interactions between gender and sex and promote the well-being of all individuals, regardless of their gender identity or biological sex. Opportunities for research into these areas occur with every liver disease, and a focus on these differences will allow improved recognition, management, and treatment of liver disease in our patients.

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