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Women on the liver transplantation waitlist are at increased risk of hospitalization compared to men

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## Retrospective Study

**Women on the liver transplantation waitlist are at increased risk of hospitalization compared to men**

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**Abstract****BACKGROUND**

Hospital admissions are common among patients with cirrhosis, but patient factors associated with hospitalization have not been well characterized. Given recent data suggesting increased liver transplant waitlist dropout among women, we hypothesized that women on the liver transplant waitlist would have increased rates of hospitalization compared with men.

**AIM**

To evaluate the role of gender on risk of hospitalization for patients on the liver transplant waitlist, in order to help explain gender disparities in waitlist outcomes.

**METHODS**

Patients listed for liver transplant at a single center in the United States were prospectively enrolled in the Functional Assessment in Liver Transplantation Study. Patients included in this retrospective analysis included those enrolled between March 2012 and December 2014 with at least 12 mo of follow up and without hepatocellular carcinoma. The primary and secondary outcomes were

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hospitalization and total inpatient days within 12 mo, respectively. Logistic and negative binomial regression associated baseline factors with outcomes.

## RESULTS

Of the 392 patients, 41% were female, with median (interquartile range) age 58 years (52-63) and model for end-stage liver disease 18 (15-22). Within 12 mo, 186 (47%) patients were hospitalized  $\geq 1$  time; 48% were readmitted, with a median of 8 (4-15) inpatient days. More women than men were hospitalized (54% vs 43%;  $P = 0.03$ ). In univariable analysis, female sex was associated with an increased risk of hospitalization [odds ratios (OR) 1.6, 95% confidence interval (CI) 1.0-2.4;  $P = 0.03$ ], which remained significant on adjusted multivariable analysis (OR 1.6, 95% CI: 1.1-2.6;  $P = 0.03$ ). Female gender was also associated with an increased number of inpatient days within 12 mo in both univariable and multivariable regression.

## CONCLUSION

Women with cirrhosis on the liver transplant waitlist have more hospitalizations and inpatient days in one year compared with men, suggesting that the experience of cirrhosis differs between men and women, despite similar baseline illness severity. Future studies should explore gender-specific vulnerabilities to help explain waitlist disparities.

**Key words:** Gender; Cirrhosis; Liver transplantation waitlist; Hospitalization; Readmission; Women

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**Core tip:** In this single-center study of patients on the liver transplant waitlist, women were significantly more likely to be hospitalized than men, and were hospitalized for a more days within one year. Among those who were hospitalized at least once, there was a trend toward higher rates of readmission among women compared to men. These gender differences were independent of underlying severity of illness, as measured by model for end-stage liver disease score, suggesting that perhaps traditional indicators of liver disease severity do not adequately capture all contributors to illness, such as non-hepatic comorbidities or socioeconomic factors, which may require acute inpatient care.

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## INTRODUCTION

Women have been shown to have worse transplant-related outcomes than men<sup>[1]</sup>. Rates of liver transplant are lower for women on the waitlist<sup>[2-6]</sup>, and women are more likely to die or become too sick for transplant than men<sup>[2,7,8]</sup>. In particular, recent studies suggest that women are underserved by the model for end-stage liver disease (MELDNa) score<sup>[2]</sup>, and that female sex is independently associated with a 10% higher risk of delisting<sup>[9]</sup>. The reasons for these disparities are not completely understood.

One hypothesis for the gender disparity in outcomes for patients on the liver transplant waitlist has been that women with cirrhosis have a different disease trajectory than men with cirrhosis, either because they are sicker at baseline or experience more rapid progression of cirrhosis (*i.e.*, from compensated to decompensated cirrhosis)<sup>[4,9]</sup>. In several studies, women appear to have similar or even lower MELDNa scores at listing compared with men and have fewer comorbidities, suggesting that they are not sicker at baseline<sup>[3,4,8]</sup>. However, whether their disease progresses more rapidly has not been previously explored. Hospital admissions may be a surrogate marker for disease progression that more accurately captures differences in the experience of living with cirrhosis for women and men. We therefore aimed to evaluate the role of gender on the risk of hospitalization for

patients with cirrhosis on the liver transplant waitlist.

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## MATERIALS AND METHODS

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### Patients

Our cohort included adult ( $\geq 18$  years) patients seen as outpatients at the University of California - San Francisco (UCSF) Liver Transplant Clinic, who were listed for liver transplantation at UCSF from March 2012 to December 2014, and subsequently enrolled prospectively in the Functional Assessment in Liver Transplantation (FrAILT) Study<sup>[10,11]</sup>. Ninety-seven percent of invited participants enrolled in this study<sup>[11,12]</sup>. Patients with time to complete a Numbers Connection Test (NCT) of  $> 120$  s were excluded because of concerns about their ability to provide informed consent<sup>[13]</sup>. For the purposes of this study, patients listed for transplant with MELD exception points for hepatocellular carcinoma were excluded, as their reasons for hospitalization (*e.g.*, complications of locoregional therapy) may differ compared to patients solely listed for decompensated cirrhosis. Patients lost-to-follow up at 12 mo were also excluded.

### Baseline variables

At the time of study enrollment, patient demographics including age, gender, race, etiology of cirrhosis, as well as medical comorbidities (*e.g.*, diabetes and hypertension) and baseline laboratory values were collected from the patient's electronic health record. All patients underwent frailty assessment using the Liver Frailty Index (LFI), which is composed of hand grip, chair stands, and balance. "Frail" was defined as LFI  $\geq 4.5$ <sup>[10]</sup>. Clinical information regarding the presence of ascites, ascertained by the patient's primary hepatologist, was recorded as absent, mild/moderate, or severe, then further classified as absent or present for the current study. Hepatic encephalopathy was classified as none/mild versus moderate/severe based on the patient's performance on the NCT Score of  $<$  or  $> 45$  s, respectively<sup>[13]</sup>.

### Outcomes

The primary outcome was any hospitalization within 12 mo from study enrollment. The secondary outcome was the number of inpatient days within 12 mo. Information on number of hospitalizations and inpatient days were obtained from manual review of medical records at UCSF and review of external medical records in the case of hospital admissions elsewhere<sup>[14]</sup>. As part of their listing agreement for liver transplant at our center, all patients were required to report hospitalizations to outside institutions at time of admission. Patients who died or were transplanted within 12 mo were censored at the time of their waitlist event ( $n = 82$ ). A 12-mo study period was selected to minimize confounding from women remaining on the waitlist longer than men due to lower rates of transplant.

### Statistical analysis

Categorical data were presented as percentages; groups were compared using chi-square tests. Continuous variables were presented as medians and interquartile ranges (IQR); groups were compared using Wilcoxon Rank-Sum tests. Univariable logistic regression with odds ratios (OR) evaluated the association of all listed covariates with the primary outcome of hospitalization within 12 mo. Univariable negative binomial regression with incidence rate ratios (IRR) evaluated the association of all listed covariates with the secondary outcome of number of hospitalized days within 12 mo. Variables significant at a  $P$ -value  $< 0.2$  were included in the multivariable models. Backward elimination ( $P > 0.05$  for removal) was used to develop the final multivariable models. Two-sided  $P$ -values  $< 0.05$  were considered statistically significant. All analyses were performed using Stata 15.1 statistical software (College Station, TX, United States). The statistical methods of this study were reviewed by multiple individuals with biomedical statistical training. This study was approved by the institutional review board at the UCSF.

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## RESULTS

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### Baseline characteristics

A total of 392 patients were enrolled between March 2012 and December 2014. Women comprised 41% of the cohort, 61% were non-Hispanic Caucasian, and median (IQR) age was 58 years (51-63). The etiology of cirrhosis was chronic hepatitis C in 43% of the cohort; median (IQR) MELDNa was 18 (15-22) and median (IQR) albumin

was 3.0 mg/dL (2.6-3.4). Thirty-four percent of patients had ascites and 42% had moderate or severe hepatic encephalopathy. Sixteen percent of the patients were characterized as frail. Baseline demographics, comorbidities and cirrhosis complications by gender are shown in [Table 1](#). Men were more likely than women to have cirrhosis due to Hepatitis C (48% *vs* 35%,  $P < 0.01$ ) and alcohol (23% *vs* 14%,  $P = 0.02$ ) and more likely to have coronary artery disease (6% *vs* 2%,  $P = 0.05$ ); women were more likely to have cirrhosis due to autoimmune liver disease (24% *vs* 9%,  $P < 0.01$ ).

### Hospitalizations

During the 12-mo study period, 186 (47%) patients were hospitalized at least once. Of these 186 patients, 89 (48%) were readmitted at least once and 47 (25%) were readmitted more than once. Among patients hospitalized at least once, median (IQR) number of hospitalizations within 12 mo was 1 (1-3), median (IQR) number of inpatient days was 8 (4-15), and median (IQR) length of stay was 5 d (3-8).

In univariable analysis, the factors associated with at least one hospitalization within 12 mo were female gender [OR 1.6, 95% confidence interval (CI) 1.0-2.4;  $P = 0.03$ ], MELDNa (OR 1.1; 95% CI 1.1-1.2;  $P < 0.01$ ), albumin (OR 0.4; 95% CI: 0.3-0.6;  $P < 0.01$ ), ascites (OR 2.3; 95% CI: 1.5-3.5;  $P < 0.01$ ), and frailty (OR 3.6; 95% CI: 2.0-6.5;  $P < 0.01$ ).

### Gender and hospitalization

More women than men were hospitalized at least once within the 12-mo study period (54% *vs* 43%,  $P = 0.03$ ). As noted above, in univariable logistic regression, the odds of being hospitalized at least once within 12 mo were 1.6 times higher among women compared to men ( $P = 0.03$ ). In multivariable analysis, female gender remained significantly associated with hospitalization after adjusting for MELDNa, albumin, ascites, and frailty (adjusted OR 1.6, 95% CI: 1.1-2.6;  $P = 0.03$ ) ([Table 2](#)).

Women also had a higher median (IQR) number of total inpatient days within 12 mo compared with men [2.5 (0-10) *vs* 0 (0-6.5),  $P = 0.02$ ]. On univariable negative binomial regression, female gender was associated with a higher number of total inpatient days within 12 mo (IRR 1.7, 95% CI 1.1-2.6,  $P = 0.02$ ). This association persisted in multivariable analysis after adjusting for MELDNa and albumin (adjusted IRR 1.9, 95% CI: 1.2-3.0,  $P < 0.01$ ) ([Table 3](#)). Among the 186 patients hospitalized at least once, there was a trend toward women being readmitted more often than men (54% *vs* 42%), but this did not reach statistical significance ( $P = 0.11$ ).

## DISCUSSION

Hospital admissions are common among patients with cirrhosis due to portal hypertensive complications<sup>[15]</sup>. Hospitalizations in patients with cirrhosis are also associated with high mortality, and account for a large proportion of the cost of end-stage liver disease. In 2012, liver disease accounted for nearly 250000 hospitalizations at an estimated cost of \$3-12 billion each year<sup>[15-17]</sup>, and rates of hospitalization as well as costs have been increasing over time<sup>[15]</sup>. A 2014 study also showed that pre-transplant spending increased exponentially with severity of illness for patients on the liver transplant waitlist, likely due in large part to increased number and complexity of hospitalizations<sup>[16]</sup>. In light of the increased mortality and high costs associated with hospitalizations in patients with cirrhosis, we wondered whether differential rates of hospitalization could help explain the gender disparity on the liver transplant waitlist.

Consistent with previous studies on hospitalizations in patients with cirrhosis, we observed that hospitalizations were quite common: Nearly half of patients on the liver transplant waitlist in our study were hospitalized at least once within one year, and approximately one half of those were readmitted at least once. But our analyses investigating gender differences in hospitalizations expand upon prior work. Specifically, in the current study, we found that in one year, women on the liver transplant waitlist were significantly more likely to be hospitalized than men. They also were hospitalized for a higher number of days within one year. Among those who were hospitalized at least once, there was a trend toward higher rates of readmission among women in comparison to men.

What might explain this gender disparity in hospitalizations? Here, we explore several possible explanations. While the most obvious hypothesis would be that the women in our cohort were sicker than the men, we found that traditional markers of illness severity for cirrhosis, including MELD and hepatic decompensation (presence of ascites or hepatic encephalopathy), did not differ at baseline by gender, confirming findings from prior studies<sup>[3,4,8]</sup>. Perhaps, then, these traditional indicators of liver disease severity do not adequately capture all contributors to illness, such as non-

**Table 1** Baseline characteristics by gender<sup>1</sup>

Characteristics	Total (n = 392)	Men (n = 231, 59%)	Women (n = 161, 41%)	P value
Age, yr	58 (51-63)	57 (50-63)	58 (52-63)	0.51
Race				0.64
Non-Hispanic Caucasian	240 (61)	142 (62)	98 (61)	
Black	9 (2)	4 (2)	5 (3)	
Hispanic	105 (27)	59 (26)	46 (29)	
Asian	16 (4)	11 (5)	5 (3)	
Other	22 (6)	15 (7)	7 (4)	
Etiology				< 0.01
HCV	168 (43)	112 (49)	56 (35)	
Alcohol	75 (19)	53 (23)	22 (14)	
NAFLD/NASH	55 (14)	24 (10)	31 (19)	
Autoimmune <sup>2</sup>	59 (15)	21 (9)	38 (24)	
HBV	3 (1)	3 (1)	0 (0)	
Other	32 (8)	18 (8)	14 (9)	
BMI, kg/m <sup>2</sup>	28.5 (25.0-33.7)	28.8 (25.3-34.1)	28.0 (24.2-33.0)	0.13
Diabetes mellitus	115 (29)	71 (31)	44 (27)	0.47
Coronary artery disease	17 (4)	14 (3)	3 (2)	0.05
Hypertension	153 (39)	98 (42)	55 (34)	0.10
Stroke	7 (2)	4 (2)	3 (2)	0.92
Dialysis	16 (4)	7 (3)	9 (5)	0.21
MELDNa	18 (15-22)	18 (15-22)	19 (15-23)	0.13
Albumin, g/dL	3.0 (2.6-3.4)	3.0 (2.6-3.4)	3.1 (2.7-3.4)	0.30
Presence of ascites	133 (34)	77 (33)	56 (35)	0.77
Numbers connection test, s	41 (30-58)	42 (32-58)	40 (29-58)	0.30
Moderate/severe HE	165 (42)	98 (42)	67 (42)	0.87
Frail	62 (16)	26 (16)	26 (17)	0.88

<sup>1</sup>Data presented as n (%) or median (IQR).

<sup>2</sup>Combined autoimmune hepatitis, primary sclerosing cholangitis, and primary biliary cholangitis.

IQR: Interquartile range; HCV: Hepatitis C; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; HBV: Hepatitis B; BMI: Body mass index; MELDNa: Model for end-stage liver disease with serum sodium; HE: Hepatic encephalopathy.

hepatic comorbidities or socioeconomic factors, that may affect an individual's vulnerability to adverse events that necessitate acute inpatient care. Our study also raises the possibility of systematic differences in the management of women and men with cirrhosis - either there exists a lower threshold for admission in women or a gap in coordination of care from the inpatient setting to outpatient recovery. Interestingly, among those who were hospitalized at least once, women were re-admitted almost 30% more frequently than men, though this did not reach statistical significance. It is also possible that differences in etiology of cirrhosis may contribute to differences in disease progression that lead to this gender disparity. Men were more likely to have cirrhosis due to Hepatitis C and alcohol, which are often no longer active by the time of listing for liver transplant. Women, in contrast, are more likely to have autoimmune hepatitis, which often continues to cause liver injury until the time of transplant.

Furthermore, it is possible that women are hospitalized for different reasons than men. Specifically, women may be more susceptible to complications of sarcopenia, such as infection or hepatic encephalopathy, which may lead to increased risk of hospitalization. Although proportion of "frail" patients did not differ between men and women in our cohort, more subtle differences in muscle mass could lead to differences in cirrhosis complications. Unfortunately, given the complexity of ascertaining cause of hospitalization (as many patients with cirrhosis have multiple - such as acute kidney injury, hepatic encephalopathy, worsening ascites), we were not able to accurately capture indications for hospitalization, which is a limitation of this study. Other factors that could contribute to hospitalization were also not captured in this study, such as medication complexity and adherence, diuretic resistance in patients with ascites, and social support. Future studies should evaluate such predictors, though some, such as social support or adherence, may be difficult to

Table 2 Logistic regression for hospitalization within 12 mo

Characteristics	Univariable			Multivariable		
	OR	95%CI	P value	aOR	95%CI	P value
Female gender	1.57	1.05-2.35	0.03	1.64	1.05-2.56	0.03
Non-Hispanic Caucasian	0.81	0.54-1.22	0.31			
Age per year	1.00	0.98-1.02	0.95			
Hypertension	1.26	0.84-1.89	0.26			
Diabetes mellitus	1.31	0.85-2.02	0.23			
Coronary artery disease	0.98	0.37-2.60	0.97			
Stroke	0.83	0.18-3.75	0.81			
Dialysis	1.89	0.67-5.31	0.22			
BMI per 1 kg/m <sup>2</sup>	1.02	0.99-1.05	0.24			
Autoimmune <sup>1</sup>	0.61	0.35-1.08	0.09			
MELDNa per 1 point>	1.13	1.07-1.18	< 0.001	1.08	1.03-1.13	0.001
Albumin per 1 mg/dL	0.44	0.31-0.63	< 0.001	0.53	0.36-0.78	0.001
Ascites	2.28	1.49-3.50	< 0.001	1.61	1.00-2.57	0.05
> NCT per 1 s	1.01	1.01-1.02	0.006			
Moderate/severe HE	1.17	0.78-1.75	0.45			
Frail	3.59	1.97-6.55	< 0.001	2.37	1.24-4.54	0.009

<sup>1</sup>Combined autoimmune hepatitis, primary sclerosing cholangitis, and primary biliary cholangitis. OR: Odds ratio; CI: Confidence interval; aOR: Adjusted odds ratio; BMI: Body mass index; MELDNa: Model for end-stage liver disease with serum sodium; NCT: Numbers connection test; HE: Hepatic encephalopathy.

collect on a large scale. Another limitation is that this is a US-based single center study serving a large catchment area within an open hospital network, so it is possible that we did not capture all hospitalizations for every patient. However, all of the patients enrolled in this study were waitlisted at our center and were required to report outside hospitalizations. Therefore, we believe that our ascertainment of hospitalizations was reliable, but validation of our gender-based findings in a larger, closed health system is warranted. It is also possible that rates of and reasons for hospitalization for patients on the liver transplant waitlist differ in countries with different healthcare systems, so our findings should be replicated outside of the United States as well.

Despite these limitations, this study describes significant gender differences in hospitalizations for patients on the liver transplant waitlist and thus, takes us one step closer to understanding the gender disparity in liver transplant waitlist mortality and dropout. Our finding that women are more likely to be hospitalized than men suggest that the experience of cirrhosis differs between women and men despite similarities in traditional measures of severity of illness. As the hepatology community moves toward developing cirrhosis-specific models of care, our data strongly suggest that these models may need to consider gender-specific vulnerabilities. Future studies are needed to evaluate gender-specific interventions in order to truly optimize the management of women and men living with cirrhosis.

**Table 3** Binomial regression for number of hospitalized days within 12 mo

Characteristics	Univariable			Multivariable		
	IRR	95%CI	P value	aIRR	95%CI	P value
Female gender	1.68	1.08-2.60	0.02	1.92	1.23-2.99	0.004
Non-Hispanic Caucasian	0.86	0.55-1.35	0.52			
Age per year	1.00	0.98-1.03	0.80			
Hypertension	1.31	0.84-2.04	0.24			
Diabetes mellitus	1.05	0.65-1.69	0.85			
Coronary artery disease	0.52	0.18-1.55	0.28			
Stroke	0.20	0.03-1.16	0.13			
Dialysis	1.63	0.55-4.87	0.34			
BMI per 1 kg/m <sup>2</sup>	1.01	0.98-1.05	0.42			
Autoimmune <sup>1</sup>	0.59	0.32-1.09	0.11			
MELDNa per 1 point	1.09	1.04-1.14	< 0.001	1.08	1.03-1.13	0.001
Albumin per 1 mg/dL	0.58	0.39-0.84	0.005	0.47	0.31-0.70	< 0.001
Ascites	1.72	1.09-2.70	0.02			
NCT per 1 s	1.00	1.00-1.01	0.13			
Moderate/severe HE	1.28	0.82-1.98	0.28			
Frail	2.12	1.17-3.81	0.007			

<sup>1</sup>Combined autoimmune hepatitis, primary sclerosing cholangitis, and primary biliary cholangitis. IRR: Incidence rate ratio; CI: Confidence interval; aIRR: Adjusted incidence rate ratio; BMI: Body mass index; MELDNa: Model for end-stage liver disease with serum sodium; NCT: Numbers connection test; HE: Hepatic encephalopathy.

## ARTICLE HIGHLIGHTS

### Research background

It is well-established in the literature that women have worse transplant-related outcomes than men, including lower rates of transplant and increased risk of waitlist mortality and dropout. The reasons for these disparities are unclear.

### Research motivation

Hospital admissions are common among patients with cirrhosis, and may be a surrogate marker for disease progression that more accurately captures the differences in experience between men and women living with cirrhosis, and may help explain gender disparities in waitlist outcomes.

### Research objectives

Thus, we aimed to evaluate the role of gender on risk of hospitalization for patients on the liver transplant waitlist.

### Research methods

Our cohort included adults ( $\geq 18$  years) with cirrhosis listed for liver transplant at University of California - San Francisco (UCSF) from March 2012 to December 2014 who were seen as outpatients and enrolled as a part of a prospective trial. Patients listed for transplant with model for end-stage liver disease (MELD) exception points for hepatocellular carcinoma were excluded, as were patients lost-to-follow up at 12 mo and those with severe hepatic encephalopathy. At the time of study enrollment, patient demographics and baseline laboratory values were collected. Clinical information regarding complications of patients' liver disease were assessed by enrolling clinician. The primary outcome was any hospitalization within 12 mo from study enrollment, and the secondary outcome was the number of inpatient days within 12 mo. Logistic regression and negative binomial regression evaluated the association of all listed covariates with the primary and secondary outcomes.

### Research results

A total of 392 patients were enrolled during the study period; 41% were women and 61% were non-Hispanic Caucasian, with median (interquartile ranges) age of 58 years (51-63). During the 12-mo study period, 186 (47%) patients were hospitalized at least once. Of these 186 patients, 89 (48%) were readmitted at least once and 47 (25%) were readmitted more than once. More women than men were hospitalized at least once within the 12-mo study period (54% vs 43%,  $P = 0.03$ ). In univariable logistic regression, the odds of being hospitalized at least once within 12 mo was 1.6 times higher among women compared to men ( $P = 0.03$ ). In multivariable analysis, female gender remained significantly associated with hospitalization after adjusting for MELDNa, albumin, ascites, and frailty [adjusted odds ratios (OR) 1.6, 95% confidence interval (CI) 1.1-2.6;  $P$



= 0.03]. Female gender was also associated with a higher number of total inpatient days within 12 mo on univariable [incidence rate ratio (IRR) 1.7, 95%CI: 1.1-2.6,  $P = 0.02$ ] and multivariable analysis (adjusted IRR 1.9, 95%CI: 1.2-3.0,  $P < 0.01$ ). There was a trend toward women being readmitted more often than men (54% *vs* 42%), but this did not reach statistical significance ( $P = 0.11$ ).

### Research conclusions

Women on the liver transplant waitlist are significantly more likely to be hospitalized than men, and are hospitalized for a higher number of days, even after adjustment for illness severity. Among those who were hospitalized at least once, there was a trend toward higher rates of readmission among women in comparison to men. These findings suggest that the clinical course of cirrhosis among women and men differs despite similarities in traditional measures of severity of illness.

### Research perspectives

Our findings may help explain the gender disparities in liver transplant waitlist mortality and dropout, by highlighting differences in the experience of living with cirrhosis for women and men. Future studies are needed to evaluate gender-specific interventions in order to truly optimize the management of women and men living with cirrhosis and to eliminate waitlist disparities.

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