HHS Public Access

Author manuscript

Clin Gastroenterol Hepatol. Author manuscript; available in PMC 2021 December 01.

Published in final edited form as:

Clin Gastroenterol Hepatol. 2020 December ; 18(13): 3046–3048. doi:10.1016/j.cgh.2019.09.043.

Hospitalized women with cirrhosis have more non-hepatic comorbidities and associated complications than men

Jessica B. Rubin[1], **Yanin T. Srisengfa**[1], **Somaya Albhaisi**[2], **Chathur Acharya**[3], **Gayatri Nangia**[4], **Tahira Shaikh**[5], **Leroy R. Thacker**[6], **K. Rajender Reddy**[4], **Puneeta Tandon**[5], **Jasmohan S. Bajaj**[3], **Jennifer C. Lai**[1]

[1]Division of Gastroenterology and Hepatology, Department of Medicine, University of California-San Francisco, San Francisco, CA

[2]Department of Internal Medicine, Virginia Commonwealth University, Richmond, VA

[3]Division of Gastroenterology and Hepatology, Virginia Commonwealth University and McGuire VA Medical Center, Richmond, VA

[4]Division of Gastroenterology, University of Pennsylvania, Philadelphia, PA

[5]Division of Gastroenterology (Liver Unit), University of Alberta, Edmonton, Alberta, Canada

[6]Department of Biostatistics, Virginia Commonwealth University, Richmond, VA

Introduction

Gender differences in the natural history of chronic liver disease have been well-described. Women have *lower* rates of chronic liver disease and slower fibrosis progression, yet *higher* rates of waitlist mortality.[1,2] While previous studies have identified several clinical factors - including height and creatinine - that explain some of this transplant disparity, most have utilized data from administrative records, which are limited in their ability to identify clinically relevant differences and opportunities for intervention to reduce disparities.[3–5] Additionally, most studies have focused on the period between waitlist and transplant, failing to capture gender differences in access to transplant.[3,6] In the present study, we took advantage of a multicenter inpatient cohort with granular clinical data to characterize how

Correspondence: Jennifer C. Lai, MD, MBA, 513 Parnassus Avenue, UCSF Box 0538, San Francisco, CA 94143, Telephone: 415-476-2777, Fax: 415-476-0659, Jennifer.Lai@ucsf.edu.

Author Contributions:

JBR: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript

YTS, SA, CA, GN, TS: acquisition of data

LRT: statistical analysis

KRR, PT: study supervision

JSB, JCL: study concept and design, acquisition of data, analysis and interpretation of data, critical revision of the manuscript, obtained funding, study supervision

Disclosures:

The authors have no conflicts of interest to disclose.

women and men with cirrhosis differ, in an effort to stimulate future research aimed at reducing the well-established gender disparity in liver transplantation.

Methods

Our prospective cohort included patients with cirrhosis hospitalized non-electively at four North American academic medical centers.[7,8] Additional data were collected on cirrhosis etiology and comorbidities, non-hepatic reasons for admission, and prior to admission medications. Multivariable logistic regression models were developed to determine predictors of mortality and readmission by initially including variables that were significant at the 0.2 level in univariable analysis, then using backwards elimination to exclude co-variates that were not significant at the 0.05 level.

Results

Our cohort included 746 hospitalized patients with cirrhosis; 287 (38%) were women. Women were less likely than men to have cirrhosis from alcohol ($p<0.001$), and more likely to have NASH ($p<0.001$) or autoimmune-related cirrhosis ($p<0.001$) (Table 1). Women and men had similar cirrhosis complications, liver-related medications, admission MELD, and Child-Pugh scores.

Women were more likely to have certain non-liver related comorbidities, including diabetes ($p = 0.05$) and connective tissue disease ($p=0.004$). Women were also more likely to use non-opiate pain medications ($p=0.01$) and antidepressant/sleep aids ($p<0.001$) prior to admission. Overall rates of infection on admission were similar between women and men ($p=0.24$), though women were more likely than men to have urinary tract infections ($p<0.001$) and less likely to have spontaneous bacterial peritonitis ($p=0.03$). Rates of other decompensating events were similar between women and men.

There were no differences between women and men in 30-day (11% vs 12%, $p=0.56$) or 90-day (22% vs 27%, $p=0.13$) mortality, or in 90-day rates of listing for liver transplant (12% vs 11%, $p = 0.88$). In logistic regression, female gender was not associated with increased rates of 30-day mortality (OR 0.87, 95%CI 0.55–1.39, $p=0.56$) or 90-day readmission (OR 1.03, 95%CI 0.74–1.42, $p=0.88$) on univariable or multivariable analysis.

Discussion

Previous studies on gender differences in cirrhosis have only partially elucidated the reasons behind well-documented disparities in liver transplant rates. In the present study, we aimed to understand how important gender differences manifest *throughout* the duration of cirrhosis, regardless of whether patients have been - or will be - listed for transplant. We also captured *detailed* clinical differences during hospitalization, a particularly vulnerable period for cirrhosis patients.

We found that cirrhosis-related clinical characteristics among hospitalized patients are quite similar between women and men, including similar illness severity and cirrhosis-related medication usage. The principle differences we observed were related to non-liver related

illness characteristics, including comorbidities, medication usage, and infectious complications. Women were more likely to have specific comorbidities such as diabetes and connective tissue disease, which likely predispose them to increased rates of chronic pain and physical disability, as evidenced by increased use of pain medication and other neuromodulators among women in our cohort. This patient phenotype - physically deconditioned and dependent on neuropsychiatric medications - is at risk of becoming ineligible for transplant as their comorbidities progress. In addition, increased rates of cirrhosis-unrelated infections, such as urinary tract infections, may further impair their transplant candidacy.

Although gender-based mortality differences were not observed in our cohort, this granular multi-center study allowed us to more thoroughly explore some of the mechanisms by which previously described gender-based disparities might occur. Specifically, our findings suggest that women with cirrhosis may benefit from closer monitoring and more aggressive management of certain non-hepatic comorbidities to prevent progressive physical deconditioning, chronic pain, and comorbidity-related infections. In addition, women in particular may benefit from the development of better algorithms for neuropsychiatric medication use and pain management in order to preserve transplant candidacy with cirrhosis progression. Future studies should further explore these clinical differences between women and men with cirrhosis, seeking to identify additional gender differences across clinical settings, with the ultimate goal of developing targeted interventions to eliminate the national gender disparity in liver transplantation.

Grant Support:

This study was funded by NIA Research Project Grant (R01AG059183, Lai), NIA Paul B. Beeson Career Development Award in Aging (K23AG048337, Lai), and NIDDK National Research Service Award Hepatology Training Grant (T32DK060414, Rubin). Participating institutions have also received research funding from Grifols as part of investigator-initiated grants.

Abbreviations:

CI	confidence interval
MELD	model for end-stage liver disease
NASH	nonalcoholic steatohepatitis
OR	odds ratio

References

1. Ratib S, West J, Crooks CJ, Fleming KM. Diagnosis of liver cirrhosis in England, a cohort study, 1998–2009: a comparison with cancer. Am J Gastroenterol. 2014;109(2):190–198. doi:10.1038/ajg.2013.405. [PubMed: 24419483]
2. Moylan CA, Brady CW, Johnson JL, Smith AD, Tuttle-Newhall JE, Muir AJ. Disparities in liver transplantation before and after introduction of the MELD score. JAMA. 2008;300(20):2371–2378. doi:10.1001/jama.2008.720. [PubMed: 19033587]
3. Lai JC, Terrault NA, Vittinghoff E, Biggins SW. Height contributes to the gender difference in waitlist mortality under the MELD-based liver allocation system. Am J Transplant. 2010;10(12):2658–2664. doi:10.1111/j.1600-6143.2010.03326.x. [PubMed: 21087414]

4. O'Leary JG, Wong F, Reddy KR, et al. Gender-Specific Differences in Baseline, Peak, and Delta Serum Creatinine: The NACSELD Experience. Dig Dis Sci. 2017;62(3):768–776. doi:10.1007/s10620-016-4416-7. [PubMed: 28025746]
5. Allen AM, Heimbach JK, Larson JJ, et al. Reduced Access to Liver Transplantation in Women: Role of Height, MELD Exception Scores, and Renal Function Underestimation. Transplantation. 2018;102(10):1710–1716. doi:10.1097/TP.0000000000002196. [PubMed: 29620614]
6. Rubin JB, Sinclair M, Rahimi RS, Tapper EB, Lai JC. Women on the liver transplantation waitlist are at increased risk of hospitalization compared to men. World J Gastroenterol. 2018;25(8):980–988. doi:10.3748/wjg.v25.i8.980.
7. Bajaj JS, O'Leary JG, Reddy KR, et al. Second infections independently increase mortality in hospitalized patients with cirrhosis: the North American consortium for the study of end-stage liver disease (NACSELD) experience. Hepatology. 2012;56(6):2328–2335. doi:10.1002/hep.25947. [PubMed: 22806618]
8. O'Leary JG, Reddy KR, Garcia-Tsao G, et al. NACSELD acute-on-chronic liver failure (NACSELD-ACLF) score predicts 30-day survival in hospitalized patients with cirrhosis. Hepatology. 2018;67(6):2367–2374. doi:10.1002/hep.29773. [PubMed: 29315693]

Table 1.

Baseline demographic and clinical characteristics by gender for hospitalized cirrhosis patients[1]

	Total n = 746	Men n = 459, 62%	Women n = 287, 38%	p-value
Age, years	56.27 (10.47)	56.06 (10.28)	56.61 (10.77)	0.68
Race				
White	75% (559/745)	76% (351/459)	73% (208/286)	
Black	14% (106/745)	13% (59/459)	16% (47/286)	0.37
Asian	3% (21/745)	3% (15/459)	2% (6/286)	
Other	8% (59/745)	7% (34/459)	9% (25/286)	
Body Mass Index	29.27 (7.22)	28.76 (6.81)	30.09 (7.79)	0.05
Etiology of cirrhosis				
Hepatitis C	22% (167/746)	22% (102/4590)	23% (65/287)	
Alcohol	33% (243/746)	36% (163/459)	28% (80/287)	
Hepatitis C + alcohol	15% (110/746)	18% (82/459)	10% (28/287)	
NASH/Cryptogenic	18% (135/746)	15% (69/459)	23% (66/287)	<0.001
Hepatitis B	1% (7/746)	2% (7/459)	0% (0/287)	
Autoimmune[2]	8% (57/746)	4% (19/459)	13% (38/287)	
Other	4% (27/746)	4% (17/459)	3% (10/287)	
Complications of cirrhosis				
Prior ascites	73% (544/744)	73% (333/458)	74% (211/286)	0.75
Variceal bleed history	24% (172/729)	24% (106/449)	24% (66/280)	0.99
History of hepatic encephalopathy	12% (84/719)	12% (54/440)	11% (30/279)	0.54
History of hyponatremia	52% (357/690)	53% (223/422)	50% (134/268)	0.47
Comorbidities				
Hypertension	45% (336/746)	45% (207/459)	45% (129/287)	0.97
Congestive heart failure	8% (65/746)	10% (45/459)	7% (20/287)	0.18
Coronary artery disease	12% (86/746)	13% (59/459)	9% (27/287)	0.15
Diabetes mellitus	38% (282/746)	35% (161/459)	42% (121/287)	0.05
Insulin use	44% (125/282)	39% (62/161)	52% (63/121)	0.02
Stroke	4% (29/746)	3% (14/459)	5% (15/287)	0.13
COPD	9% (70/746)	11% (50/459)	7% (20/287)	0.07
Connective tissue disease	2% (16/746)	1% (5/459)	4% (11/287)	0.01
Chronic kidney disease	11% (84/746)	11% (52/459)	11% (32/287)	0.94
Psychiatric illness	36% (267/746)	34% (155/459)	39% (112/287)	0.15
Prior to admission medications				
Opiates	30% (226/746)	30% (139/459)	30% (87/287)	0.99
Benzodiazepines	12% (86/746)	11% (51/459)	12% (35/287)	0.65
Neuropathic pain medications	10% (71/746)	7% (34/459)	13% (37/287)	0.01
Antidepressants or sleep aids	32% (235/746)	27% (124/459)	39% (111/287)	<0.001
Admission Labs				
Serum sodium	134 (6)	134 (6)	134 (6)	0.28
Serum creatinine	1.55 (1.37)	1.60 (1.38)	1.46 (1.34)	0.09

	Total n = 746	Men n = 459, 62%	Women n = 287, 38%	p-value
White blood cell count	8.1 (5.4)	7.8 (5.0)	8.5 (6.0)	0.26
Serum albumin	2.9 (0.7)	2.9 (0.7)	2.9 (0.8)	0.66
Admission MELD	20.01 (8.04)	20.18 (7.93)	19.74 (8.22)	0.52
Admission Child-Pugh Score	9.68 (2.26)	9.78 (2.28)	9.52 (2.21)	0.15
NACSELD-ACLF Score	14% (102/746)	14% (63/459)	14% (39/287)	0.96
Infection on admission				
Urinary tract infection	8% (57/746)	4% (19/459)	13% (38/287)	<0.001
Spontaneous bacterial peritonitis	9% (65/746)	10% (48/459)	6% (17/287)	0.03
Bacteremia	3% (26/746)	3% (12/459)	5% (14/287)	0.10
Respiratory	4% (30/746)	4% (18/459)	4% (12/287)	0.86
Skin/soft tissue infection	3% (19/746)	3% (14/459)	2% (5/287)	0.27
Clostridium difficile infection	2% (15/746)	2% (8/459)	2% (7/287)	0.51
Any infection	23% (173/743)	22% (100/458)	26% (73/285)	0.24
Outcome				
Discharged home	76% (551/721)	76% (337/445)	78% (214/276)	
Discharged to hospice	6% (42/721)	6% (27/445)	5% (15/276)	
Discharged to nursing home	7% (48/721)	7% (30/445)	7% (18/276)	0.99
Transplanted	5% (35/721)	5% (22/445)	5% (13/276)	
Died during this admission	6% (45/721)	7% (29/445)	6% (16/276)	

[1] Data presented as mean (standard deviation) or percent (number).

[2] Includes autoimmune hepatitis, primary sclerosing cholangitis, and primary biliary cirrhosis

Nonalcoholic steatohepatitis (NASH); Chronic obstructive pulmonary disease (COPD); Model for End-Stage Liver Disease (MELD); North American Consortium for the Study of End-Stage Liver Disease Acute-On-Chronic Liver Failure (NACSELD-ACLF)