

Dear Editors and Reviewers,

Thank you for your thoughtful feedback on our manuscript, “WJG 43338. Women on the Liver Transplantation Waitlist Are at Increased Risk of Hospitalization Compared to Men”. A point-by-point response to editor and reviewer comments is included below. The revisions are described in detail in this response document with new text highlighted in ***bold, italics, and underline*** below, and are highlighted in the manuscript.

Based on your thoughtful feedback, we have edited the manuscript, which we believe has enhanced its quality. We hope that you agree.

Sincerely,

Jennifer C. Lai, MD, MBA

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Comments to Author:

Editor:

Sorry to inform you that your copyright form is not meet our requirements, please download the Copyright License Agreement form and upload the PDF version of the Copyright License Agreement Form that has been signed by all authors. Note: Please keep the author order consistent.

RESPONSE:

We have resubmitted the Copyright License Agreement form that has been signed by all authors in consistent order with how they are listed in the manuscript.

Please provide the department.

RESPONSE:

We have added the department for Dr. Sinclair at the University of Melbourne:

“Marie Sinclair, Department of Medicine, The University of Melbourne, Melbourne, VIC 3010, Australia”

A copy of the full approved grant application form(s), consisting of the information section and body section, should be provided to the BPG in PDF format.

RESPONSE:

Grant application forms have been submitted in PDF format.

Please provide the primary version (PDF) of the Informed Consent Form that has been signed by all subjects and investigators of the study, prepared in the official language of the authors’ country, and state it on the title page.

RESPONSE:

The primary version of the Informed Consent Form is attached and we have added the following statement to the title page:

“Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.”

Please download the Conflict of Interest (PDF), fill it in, and then upload the completed PDF version to the system. Note: The Corresponding Author is responsible for filling out a Conflict-of-Interest Form.

RESPONSE:

Dr. Lai (the Corresponding Author) has completed a Conflict-of-Interest form which has been uploaded in PDF format (Note: this was completed and submitted with previous version of manuscript as well).

BACKGROUND. This section should clearly describe the rationale for the study. It should end with a statement of the specific study hypothesis.

RESPONSE:

The following Background section has been added to the Abstract:

“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.”

Please offer the audio core tip, the requirements are as follows:

In order to attract readers to read your full-text article, we request that the first author make an audio file describing your final core tip. This audio file will be published online, along with your article.

RESPONSE:

An audio core tip has been uploaded.

Similar sentences with other articles, please rephrase.

RESPONSE:

Three sections of Materials and Methods section were highlighted as being similar to sentences in other manuscripts. These sections were reworded, as follows:

1.

“Our cohort included adult (> 18 years) patients seen at 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.”

2.

“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.”

3.

“Two-sided p-values <0.05 were considered statistically significant. All analyses were performed using Stata 15.1 statistical software (College Station, Texas). 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 University of California – San Francisco.”

The guidelines for writing and formatting Article Highlights are as follows...

RESPONSE:

An Article Highlights section was added to the manuscript – worded as follows:

“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 (≥ 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 MELD exception points for hepatocellular carcinoma were excluded, as were patients lost-to-follow up at 12 months 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 months from study enrollment, and the secondary outcome was the number of inpatient days within 12 months. 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 (IQR) age of 58 years (51 – 63). During the 12-month 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-month study period (54% vs 43%, $p=0.03$). In univariable logistic regression, the odds of being hospitalized at least once within 12 months 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 OR 1.6, 95% CI 1.1 – 2.6; $p=0.03$). Female gender was also associated with a higher number of total inpatient days within 12 months on univariable (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 disparity 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.”

Reviewer #1:

This is an interesting study, and all the limitations have been stated. There are several typing mistakes that need to be corrected.

RESPONSE:

We appreciate this review. We have made a few small wording changes in the manuscript to address possible “typing mistakes”, but are happy to make additional changes if requested. These minor changes are highlighted in the revised manuscript.

Reviewer #2:

This is a valuable study with important results proving significant differences in hospitalization rates between men and women. The authors hypothesize as to what might be the reasons for these disparities and that aspect deserves further study. However, even though the reasons for differences in hospitalization rates are not entirely elucidated, I think that this study deserves publication.

RESPONSE:

We agree that further studies should investigate specific reasons behind differences in hospitalization rates between women and men, as is stated in our manuscript.

Reviewer #3:

This is a good paper. It highlights an important point. It can be accepted.

RESPONSE:

Thank you for this review – no revisions were made based on these comments.