Sex Differences in the Association Between Frailty and Sarcopenia in Patients With Cirrhosis

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OBJECTIVES: Frailty is prevalent in patients with cirrhosis and is hypothesized to result in part from sarcopenia, but the precise contribution of sarcopenia to frailty in this population is poorly understood.

METHODS: Included were patients with cirrhosis from 2011 to 2014 who had an ambulatory frailty assessment and abdominal computed tomography scan within 3 months. Logistic regression assessed the associations between frailty (=Liver Frailty Index ≥4.5), and sarcopenia (=skeletal muscle index of <39 cm²/m² for women and <50 cm²/m² for men).

RESULTS: Two hundred ninety-one participants were included: 33% were female. The median (interquartile range) Liver Frailty Index was 3.7 (3.3–4.2); 19% were frail. The median (interquartile range) skeletal muscle index was 49 cm²/m² (31–69); 36% had sarcopenia. Among the 54 frail participants, 48% had sarcopenia. In univariable logistic regression, sarcopenia was associated with a 1.86³ increased odds of being frail (95% confidence interval [CI], 1.02–3.38). After adjusting for sex, etiology, hepatocellular carcinoma, MELDNa, ascites, encephalopathy, and hypertension, sarcopenia was associated with a 2.38³ increased odds of being frail (95% CI, 1.17–4.85). After stratifying by sex and adjusting for MELDNa, sarcopenia among males was associated with a significantly increased odds of frailty (odds ratio 2.81, 95% CI, 1.19–6.67), whereas sarcopenia among females was not (odds ratio 1.38; 95% CI, 0.45–4.25).

DISCUSSION: In patients with cirrhosis, sarcopenia was associated with a nearly 2-fold increased odds of being frail. Two-thirds of frail men displayed sarcopenia compared with only one-quarter of frail women. Contributors to the frail phenotype may differ by sex and support the need for sex-specific strategies to reduce frailty in this population.

INTRODUCTION

Cirrhosis is characterized by chronic systemic inflammation and undernutrition. These 2 factors have been described as potent and mutual drivers of muscle loss, known as sarcopenia, as well as loss of physiologic reserve, known as frailty (1, 2). Both sarcopenia and frailty are prevalent in patients with cirrhosis and have been shown to be critical determinants of mortality in this population (3, 4). Studies have also shown a differing prevalence, as well as differing impact on outcomes, of frailty and sarcopenia by etiology of cirrhosis (5). Little is known of the overlap between the two.

Conceptually, frailty has been defined as a biologic syndrome of decreased physiologic reserve that results from the derangement of multiple physiologic systems (e.g., inflammatory, endocrine, and cardiac) (6, 7). The cumulative effects of this long-standing derangement lead to a reduction in physical activity, chronic undernutrition, and muscle loss. For patients with cirrhosis, in whom hepatic synthetic dysfunction may accelerate muscle loss, sarcopenia may be the dominant driver of the frailty phenotype.

Recently, we developed the Liver Frailty Index, an objective, performance-based metric derived and validated in patients with cirrhosis, that is reliable, reproducible, and has strong validity for the construct of frailty (4, 8, 9). With this conceptual framework, we aimed to evaluate the relationship between frailty and sarcopenia in patients with cirrhosis. We hypothesized that sarcopenia would be prevalent among those who displayed the frail phenotype.

METHODS

Patients and baseline data collection

We analyzed data from the Functional Assessment in Liver Transplantation (FrAILT) Study, a prospective cohort study of adult patients with cirrhosis who were actively listed for liver transplant at a single center and seen in the ambulatory setting for
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sepsis (17%). Five patients were excluded because their CT scans
included patients were hepatocellular carcinoma (HCC) evaluation
an abdominal computed tomography (CT) scan within 3 months
an institutional review board at the participating site approved this
study.

RESULTS

Characteristics of the entire patient population
A total of 291 patients with cirrhosis were included. Baseline
characteristics of the cohort are shown in Table 1. To summarize
key baseline characteristics, median (IQR) age was 60 years
(54–64), 33% were female, 55% were non-Hispanic white, and
median body mass index (BMI) was 27 kg/m². The primary
etiology of cirrhosis was chronic hepatitis C in 60%, alcoholic liver
disease in 11%, and nonalcoholic steatohepatitis in 8%. Rates of
hypertension were 44% and those of diabetes were 34%. The
median (IQR) MELDNa score was 17 (13–22) and albumin was
3.0 g/dL (2.6–3.4). The proportion with Child-Pugh A, B, and C
was 28%, 51%, and 22%, respectively.

Comparison of baseline characteristics by frailty and sarcopenia
The median (IQR) Liver Frailty Index was 3.7 (3.3–4.2). Fifty-four
(19%) patients were classified as frail. Compared with nonfrail
patients, frail patients were more likely to be female (44% vs 31%)
and Hispanic white (31% vs 24%). Frail patients were less likely
to have chronic hepatitis C (50% vs 62%) and HCC (30% vs 50%).
Frail patients had higher median MELDNa (22 vs 16), higher
median total bilirubin (3 vs 2.2 mg/dL), and lower median albumin
(2.7 vs 3 g/dL). Frail patients had higher incidence of ascites (61% vs
25%), hepatic encephalopathy (33% vs 15%), and waitlist death
(37% vs 17%). However, frail and nonfrail patients had similar
median age, BMI, and incidence of hypertension and diabetes.

Frailty assessment
Frailty was assessed at an outpatient clinic visit using the Liver
Frailty Index, which consists of 3 performance-based tests (4):

1. Grip strength: the average of 3 trials, measured in the patient’s
dominant hand using a hand dynamometer;
2. Timed chair stands: measured as the number of seconds it takes to
do 5 chair stands with the patient’s arms folded across the chest;
3. Balance testing: measured as the number of seconds that the patient
can balance in 3 positions (feet placed side to side, semitandem, and tandem) for a maximum of 10 seconds each.

With these 3 individual tests of frailty, the Liver Frailty Index
was calculated using the following equation (calculator available
at: http://liverfrailtyindex.ucsf.edu):

\[
(- 0.330 \times \text{gender-adjusted grip strength}) \\
+ (- 2.529 \times \text{number of chair stands per second}) \\
+ (- 0.040 \times \text{balance time}) + 6.
\]

Patients were categorized as frail based on previously established
cutoffs if they had a Liver Frailty Index score of ≥4.5 at the time of
their last assessment before liver transplant (4). We have established
the reliability and reproducibility of these cut-points (8).

Statistical analysis
Baseline demographics were presented as medians (interquartile
ranges [IQR]) for continuous variables or percentages for cate-
gerical variables and compared by frailty status using Wilcoxon
rank-sum or χ² tests. Logistic regression was used to assess asso-
ciations between frailty and sarcopenia. All variables associated
with the outcome of interest with a P value of <0.2 in univariable
analysis or that differed significantly by sex (etiology, HCC, hy-
pertension, and MELDNa) were evaluated for inclusion in the final
model. Backward stepwise regression was then performed to derive
the final multivariable model, which included only variables as-
sociated with a P value of <0.05.

Statistical analyses were performed using Stata (v15, SE). The
institutional review board at the participating site approved this
study.

Relationship between frailty and sarcopenia
A total of 54 patients met the criteria for frail, and 105 patients met
the criteria for sarcopenia; 26 met the criteria for both frail and sar-
copenia. Among the 54 patients who were frail, 48% also had sarcopenia.
Among the 105 patients who had sarcopenia, 25% were also frail.

In univariable logistic regression, sarcopenia was associated
with a 1.86 times increased odds of being frail (95% CI, 1.02–3.38, 
P = 0.04). In multivariable regression, after adjusting for sex, etiology, HCC, MELDNa, ascites, encephalopathy, and hyper-
tension, sarcopenia was associated with a 2.38 times increased
odds of being frail (95% CI, 1.17–4.85; P = 0.02) (Table 2).

We observed significant differences in the relationship be-
tween frailty and sarcopenia by sex (Figure 1). Among the 193
men, a total of 20 (10%) men met the criteria for both frail and sar-
copenia. Among the 30 (16%) men who met the criterion for
frail, 67% also met the criterion for sarcopenia. Among the 85
(44%) men who met the criterion for sarcopenia, 24% also met
Table 1. Baseline characteristics of the 291 patients with cirrhosis, categorized by frailty and by sarcopenia

|                                | All            | Comparison by frailty | Comparison by sarcopenia | Pvalue |
|--------------------------------|-----------------|-----------------------|--------------------------|--------|
|                                | All            | Not frail (n = 163)   | Frail (n = 30)           | Pvalue |
|                                |                |                       |                          |        |
| Female                         | 34%            | 31%                   | 44%                      | 0.06   |
| Age, yr                        | 60 (54–64)     | 61 (55–64)            | 59 (50–65)               | 0.34   |
| Follow-up time, mo             | 15 (9–23)      | 15 (9–23)             | 17 (10–23)               | 0.47   |
| Race/ethnicity                 |                |                       |                          |        |
| Non-Hispanic white             | 55%            | 55%                   | 54%                      | 0.35   |
| Black                          | 5%             | 6%                    | 0%                       | 6%     |
| Hispanic white                 | 26%            | 24%                   | 31%                      | 29%    |
| Asian/Pacific Islander         | 8%             | 8%                    | 7%                       | 5%     |
| Other                          | 6%             | 6%                    | 7%                       | 6%     |
| Body mass index, kg/m²         | 27 (24–31)     | 28 (24–31)            | 27 (23–32)               | 0.45   |
| Etiology of liver disease      |                |                       |                          |        |
| Chronic hepatitis C            | 60%            | 62%                   | 50%                      | 0.10   |
| Alcohol                        | 11%            | 11%                   | 11%                      | 11%    |
| Nonalcoholic steatohepatitis   | 8%             | 7%                    | 13%                      | 9%     |
| Hepatitis B virus              | 7%             | 7%                    | 7%                       | 6%     |
| Autoimmune/cholestatic         | 10%            | 11%                   | 7%                       | 10%    |
| Other                          | 5%             | 3%                    | 11%                      | 4%     |
| HCC                            | 46%            | 50%                   | 30%                      | 0.007  |
| Medical comorbidities          |                |                       |                          |        |
| Hypertension                   | 44%            | 44%                   | 43%                      | 0.82   |
| Diabetes                       | 34%            | 32%                   | 43%                      | 0.16   |
| Laboratory tests               |                |                       |                          |        |
| MELDNa                         | 17 (13–22)     | 16 (13–20)            | 22 (17–26)               | <0.001 |
| Total bilirubin, mg/dL         | 2.3 (1.5–3.8)  | 2.2 (1.5–3.5)         | 3 (1.8–6.8)              | 0.002  |
| Creatinine, mg/dL              | 0.9 (0.7–1.2)  | 0.9 (0.7–1.1)         | 1.1 (0.8–1.5)            | <0.001 |
| International Normalized Ratio | 1.4 (1.2–1.6)  | 1.3 (1.2–1.5)         | 1.4 (1.3–1.7)            | 0.02   |
| Sodium, mEq/L                  | 136 (134–139)  | 137 (134–139)         | 135 (132–138)            | 0.01   |
| Albumin, g/dL                  | 3 (2.6–3.4)    | 3 (2.6–3.5)           | 2.7 (2.4–3.2)            | 0.004  |
| Ascentes                       | 31%            | 25%                   | 59%                      | <0.001 |
| Encephalopathy                 | 18%            | 15%                   | 33%                      | 0.001  |
| Child–Pugh score               |                |                       |                          |        |
| A                              | 28%            | 32%                   | 8%                       | <0.001 |
| B                              | 51%            | 50%                   | 51%                      | 52%    |
| C                              | 22%            | 17%                   | 42%                      | 21%    |
| Waitlist outcome               |                |                       |                          |        |
| Waiting                        | 33%            | 38%                   | 11%                      | <0.001 |
| Died/delisted                  | 21%            | 17%                   | 37%                      | 20%    |
| Transplanted                   | 41%            | 39%                   | 48%                      | 39%    |
| Other                          | 5%             | 5%                    | 4%                       | 7%     |

HCC, hepatocellular carcinoma.
A total of 6 (6%) women met the criteria for both frail and sarcopenia. Among the 98 women, 24 (24%) met the criterion for frail, of whom 25% had sarcopenia. Among the 20 (20%) women who met the criterion for sarcopenia, 30% also met the criterion for frail. After stratifying by sex and adjusting for MELDNa, sarcopenia among males was associated with a 2.81 times increased odds of frailty (95% CI 1.19–6.67, \( P = 0.02 \)), whereas sarcopenia among females was not significantly associated with frailty (odds ratio 1.38; 95% CI 0.45–4.25, \( P = 0.55 \)). A test of homogeneity demonstrated no evidence of effect measure modification by sex on the relationship between sarcopenia and frailty (\( P = 0.28 \)).

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![Figure 1](image-url)
DISCUSSION

It is now well established that both frailty and sarcopenia are prevalent in patients with cirrhosis, and studies have shown that frailty is a more reliable predictor of adverse outcomes in this population (10). Conceptually, sarcopenia has been described as an integral component of the frail phenotype, as operationalized by the classic Fried Frailty Phenotype for community-dwelling older adults (6). By this framework, multiple systemic derangements resulting from aging, undernutrition, and chronic disease lead to sarcopenia, which then predispose an older adult to the clinical manifestation of frailty. Whether this conceptual pathway applies to patients with cirrhosis—who experience undernutrition and muscle wasting predominantly from the liver disease itself rather than chronologic aging—has not been characterized.

In this study of 291 patients with cirrhosis, we report high rates of frailty (19%) and even higher rates of sarcopenia (36%). Sarcopenia was associated with greater than 2 times an adjusted odds of being frail, suggesting a strong relationship between sarcopenia and frailty. However, only 48% of those who met the criterion for frail also met the criterion for sarcopenia. The low prevalence of HCC and higher median MELDNa scores among frail patients, neither of which differed by sarcopenia status, further supports the importance of understanding the frailty phenotype among patients with cirrhosis and reinforces the distinct nature of frailty from sarcopenia. These findings add substantially to our current understanding of frailty and sarcopenia in patients with cirrhosis not only by quantifying the contribution of sarcopenia to the frail phenotype but also by opening the door to new investigations to uncovering other contributors to frailty in this chronic disease state. Such factors that have been proposed in the field of geriatrics (where the construct of frailty originated) that may be particularly relevant to patients with cirrhosis include—but are not limited to—impaired cognition, psychological distress, systemic inflammation, or hormonal imbalance (7).

Of particular interest was the sex difference that we observed in the relationship between frailty and sarcopenia. Although two-thirds of frail men with cirrhosis had sarcopenia, only one-quarter of frail women had sarcopenia. The reason for this finding is unknown, but it is not the first report of sex differences with respect to sarcopenia in patients with cirrhosis. Previous data have demonstrated higher rates of sarcopenia in men compared with women, as well as a stronger association between sarcopenia and waitlist mortality or posttransplant outcomes in men compared with women (3, 11–17). These findings emphasize the importance of developing large cohorts of patients with cirrhosis enriched with women and conducting sex-subgrouped analyses when studying frailty and sarcopenia. Our findings also support further investigation into the use of testosterone in men with cirrhosis and low testosterone, which has been shown to increase lean muscle mass, decrease fat mass, and improve grip strength (18).

Our study used outpatient testing to identify patients who were classified as frail and sarcopenic, but we acknowledge that acute illness, such as acute on chronic liver failure, could substantially impact a patient’s frailty status and/or SMI during the course of their illness. Future studies are necessary to understand the role of acute hospitalization on changes in both frailty and sarcopenia.

We acknowledge the following limitations to our study. Because this study was a cross-sectional study, we were not able to evaluate the causal relationship between frailty and sarcopenia. However, traditional frameworks of frailty firmly situate sarcopenia in the causal pathway of frailty (6), so we elected to present the data in this direction. Second, our cohort had relatively few frail women, so we were unable to fully investigate hypotheses related to the sex differences in the frailty-sarcopenia relationship that we described. Third, because of low numbers, we were relatively underpowered for survival analysis. In addition, because abdominal CT scans are not obtained as part of standard of care in all patients with cirrhosis, our cohort only included those patients who had an abdominal CT scan performed within 3 months of frailty assessment, which may have led to bias toward selecting patients who were, perhaps, sicker (and therefore, requiring an abdominal CT scan for evaluation). However, the median Liver Frailty Index was similar to the median Liver Frailty Index and MELDNa that we reported in our original cohort, suggesting that the patients included in this specific study were not substantially different from the larger population of patients with cirrhosis awaiting liver transplantation. Last, our cohort included only patients with cirrhosis who were seen as outpatients and had a relatively low MELDNa score (and the Liver Frailty Index has only been validated in an outpatient population). Additional studies are necessary to confirm whether our observations apply to higher MELDNa patients and those cared for as inpatients.

Despite these limitations, our study is the first to quantify the contribution of sarcopenia to the frail phenotype using the newly developed Liver Frailty Index and provides further evidence to support the fact that frailty and sarcopenia are not synonymous. The sex differences that we observed in the relationship between frailty and sarcopenia are novel—and highlight the importance of sex-stratified analyses of frailty and sarcopenia in the future. Understanding sex-specific factors that lead to frailty are essential to develop therapeutic interventions targeting the lethal cirrhotic manifestation of frailty, whether they be pharmacologic, activity-based, or environmental. Our data lay the groundwork for this important interventional work.

CONFLICTS OF INTEREST

Guarantor of the article: Jennifer C. Lai, MD, MBA, accepts full responsibility for the conduct of the study.

Specific author contributions: L.F.: analysis and interpretation of data and drafting of the manuscript. C.W.W.: acquisition of data and critical revision of the manuscript. J.C.L.: study concept and design, drafting of manuscript, and critical revision of the manuscript.

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Potential competing interests: None to report.


Study Highlights

WHAT IS KNOWN

✓ Both frailty and sarcopenia are highly prevalent among patients with cirrhosis.
✓ Frailty and sarcopenia are predictors of mortality in this population.

WHAT IS NEW HERE

✓ Sarcopenia is associated with an over 2-fold increased adjusted odds of frailty.
✓ Less than half of the patients who met the criterion for frailty also met the criterion for sarcopenia.
✓ Sarcopenia is far less prevalent in frail women compared with frail men.

TRANSLATIONAL IMPACT

✓ There is a need for sex-specific therapeutic intervention when targeting frailty among patients with cirrhosis.

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