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Authors

Fozouni, Laila
Wang, Connie W
Lai, Jennifer C

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

Laila Fozouni, MPH[1], Connie W. Wang, MD[2] and Jennifer C. Lai, MD, MBA[2]

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 1.86× 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 2.38× 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.**

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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

[1]School of Medicine, University of California San Francisco, San Francisco, California, USA; [2]Department of Medicine, University of California-San Francisco, San Francisco, California, USA. **Correspondence:** Jennifer C. Lai, MD, MBA. E-mail: Jennifer.lai@ucsf.edu.

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a clinic visit. Patients enrolled from November 1, 2011, through November 30, 2014, were eligible for inclusion in this study.

For inclusion in the study, all candidates must have undergone an abdominal computed tomography (CT) scan within 3 months of frailty testing. Indications for undergoing CT scans among the included patients were hepatocellular carcinoma (HCC) evaluation or follow-up (51%), HCC screening (22%), preliver transplant evaluation (5%), evaluation for portal vein thrombosis (4%), and the remaining for acute indications including abdominal pain and sepsis (17%). Five patients were excluded because their CT scans did not adequately capture abdominal wall musculature.

At initial visit, data regarding demographics and medical comorbidities (e.g., hypertension and diabetes) were collected from the patient's electronic health record. Hepatic encephalopathy was categorized as none/mild, moderate, or severe based on a Numbers Connection Test time of ≤60 seconds, 60–120 seconds, or >120 seconds, respectively.

Muscle mass and quality assessment

On axial CT images, skeletal muscles were identified at the third lumbar (L3) vertebral level and quantified within standard Hounsfield units thresholds of −29 to +150. Sarcopenia was defined as a skeletal muscle index (SMI) of <50 cm^2/m^2 for men and <39 cm^2/m^2 for women (3).

All CT images were analyzed by a single trained researcher using a CT scan postprocessing workstation (Advantage Windows 2.2, Volume Viewer software, GE Healthcare, Waukesha, WI). We have previously reported that interobserver correlation was 98% for muscle mass measurements using this technique (3).

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 categorical variables and compared by frailty status using Wilcoxon rank-sum or χ^2 tests. Logistic regression was used to assess associations 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, hypertension, 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 associated 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.

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/m^2. 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.

The median SMI in this cohort was 49 (31–69) cm^2/m^2. One hundred five (36%) patients met the criteria for having sarcopenia. Compared with patients without sarcopenia, patients with sarcopenia were less likely to be female (19% vs 42%) or Hispanic white (20% vs 29%) and had a lower median BMI (26 vs 28 kg/m^2). However, patients with and without sarcopenia had similar etiologies of liver disease, similar rates of HCC, and similar MELDNa and median albumin.

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 sarcopenia. 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 hypertension, 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 between frailty and sarcopenia by sex (Figure 1). Among the 193 men, a total of 20 (10%) men met the criteria for both frail and sarcopenia. 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

		Comparison by frailty			Comparison by sarcopenia		
	All	Not frail (n = 163)	Frail (n = 30)	*P* value	No sarcopenia (n = 74)	Sarcopenia (n = 24)	*P* value
Female	34%	31%	44%	0.06	42%	19%	<0.001
Age, yr	60 (54–64)	61 (55–64)	59 (50–65)	0.34	60 (54–64)	61 (56–65)	0.26
Follow-up time, mo	15 (9–23)	15 (9–23)	17 (10–23)	0.47	15 (9–23)	15 (9–23)	0.70
Race/ethnicity							
Non-Hispanic white	55%	55%	54%	0.35	53%	60%	0.10
Black	5%	6%	0%		6%	3%	
Hispanic white	26%	24%	31%		29%	20%	
Asian/Pacific Islander	8%	8%	7%		5%	11%	
Other	6%	6%	7%		6%	6%	
Body mass index, kg/m^2	27 (24–31)	28 (24–31)	27 (23–32)	0.45	28 (25–33)	26 (24–29)	<0.001
Etiology of liver disease							
Chronic hepatitis C	60%	62%	50%	0.10	60%	59%	0.93
Alcohol	11%	11%	11%		11%	10%	
Nonalcoholic steatohepatitis	8%	7%	13%		9%	7%	
Hepatitis B virus	7%	7%	7%		6%	9%	
Autoimmune/cholestatic	10%	11%	7%		10%	10%	
Other	5%	3%	11%		4%	6%	
HCC	46%	50%	30%	0.007	47%	45%	0.74
Medical comorbidities							
Hypertension	44%	44%	43%	0.82	48%	37%	0.08
Diabetes	34%	32%	43%	0.16	35%	33%	0.78
Laboratory tests							
MELDNa	17 (13–22)	16 (13–20)	22 (17–26)	<0.001	17 (14–21)	18 (13–23)	0.64
Total bilirubin, mg/dL	2.3 (1.5–3.8)	2.2 (1.5–3.5)	3 (1.8–6.8)	0.002	2.3 (1.6–3.6)	2.1 (1.5–4)	0.82
Creatinine, mg/dL	0.9 (0.7–1.2)	0.9 (0.7–1.1)	1.1 (0.8–1.5)	<0.001	0.9 (0.7–1.1)	1 (0.8–1.3)	0.01
International Normalized Ratio	1.4 (1.2–1.6)	1.3 (1.2–1.5)	1.4 (1.3–1.7)	0.02	1.4 (1.2–1.6)	1.4 (1.2–1.5)	0.45
Sodium, mEq/L	136 (134–139)	137 (134–139)	135 (132–138)	0.01	137 (134–139)	135 (134–138)	0.12
Albumin, g/dL	3 (2.6–3.4)	3 (2.6–3.5)	2.7 (2.4–3.2)	0.004	2.9 (2.6–3.4)	3.1 (2.6–3.6)	0.15
Ascites	31%	25%	59%	<0.001	28%	37%	0.11
Encephalopathy	18%	15%	33%	0.001	20%	14%	0.19
Child-Pugh score							
A	28%	32%	8%	<0.001	27%	29%	0.82
B	51%	50%	51%		52%	48%	
C	22%	17%	42%		21%	23%	
Waitlist outcome							
Waiting	33%	38%	11%	<0.001	34%	31%	0.37
Died/delisted	21%	17%	37%		20%	23%	
Transplanted	41%	39%	48%		39%	44%	
Other	5%	5%	4%		7%	2%	

HCC, hepatocellular carcinoma.

Table 2. Univariable and multivariable logistic regression evaluating characteristics associated with frailty, as defined by a Liver Frailty Index ≥4.5

	Univariable			Multivariable		
Characteristics	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Sarcopenia	1.86	1.02–3.38	0.04	2.38	1.17–4.85	0.02
Female	1.76	0.96–3.22	0.07	2.34	1.14–4.80	0.02
Etiology[a], reference group chronic hepatitis C						
Alcohol	1.31	0.49–3.48	0.59	—	—	—
Nonalcoholic steatohepatitis	2.38	0.90–6.34	0.08	—	—	—
Hepatitis B virus	1.36	0.42–4.39	0.61	—	—	—
Autoimmune/cholestatic	0.87	0.28–2.70	0.81	—	—	—
Other	4.08	1.31–12.71	0.02	—	—	—
HCC[a]	0.42	0.22–0.80	0.008	—	—	—
Diabetes	1.54	0.84–2.82	0.16	—	—	—
MELDNa, per point[a]	1.13	1.07–1.19	<0.001	1.09	1.03–1.16	0.002
Ascites	4.39	2.37–8.14	<0.001	3.00	1.64–5.51	<0.001
Encephalopathy	2.89	1.48–5.64	0.002	2.35	1.34–4.11	0.003
Hypertension[a]	0.93	0.51–1.69	0.819	—	—	—

Only variables associated with a *P* value <0.2 in univariable analysis or that differed significantly by sex are presented in this table.
HCC, hepatocellular carcinoma.
[a]Differed significantly by sex ($P < 0.05$).

the criterion for frail. 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 ($P = 0.28$).

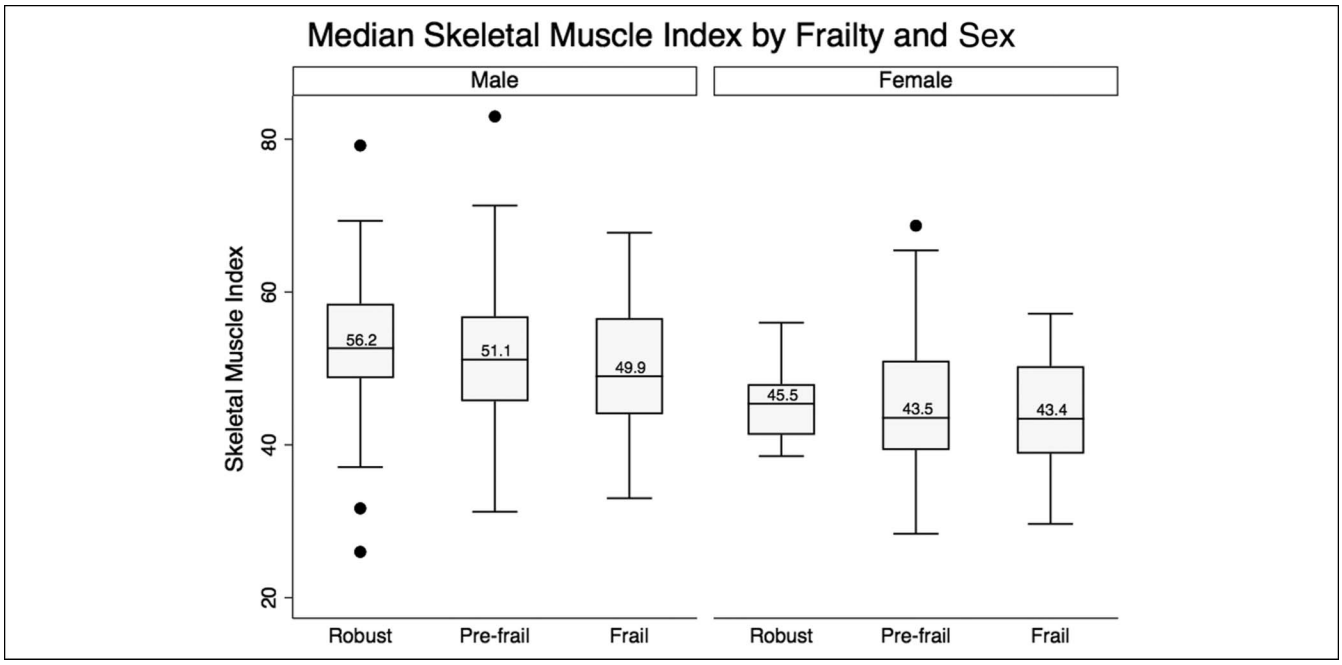

Figure 1. Box and whisker plot of the median skeletal muscle index by frailty status and sex.

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) (i.e., sarcopenia contributes to the frail phenotype), 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.

LIVER

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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