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Cognitive Function, Sarcopenia, and Inflammation Are Strongly Associated with Frailty: A Framingham Cohort Study

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Abstract

BACKGROUND: Frailty is an important contributor to morbidity and mortality in chronic liver disease. Understanding the contributors to frailty has the potential to identify individuals at risk for frailty and may potentially provide targets for frailty-modifying interventions. We evaluated the relationship among cognitive function, inflammation, and sarcopenia and frailty.

METHODS: Using cohorts from the Framingham Heart Study (2011-2014), we evaluated for factors associated with frailty. Exposures included cognitive tests (combined Trails A/B test, Animal Naming Test, and combined Digit Span Forward/Backward test), inflammation (interleukin-6 and tumor necrosis factor receptor II), and sarcopenia (creatinine-to-cystatin C ratio). We performed linear and logistic regression to identify the relationship between these exposures and the Liver Frailty Index (LFI).

RESULTS: The study population (N = 1208) had a median age of 70 years, was 56% female, and 48.5% had evidence of liver disease. The combined Trails A/B test (β 0.05, $P < .001$), creatinine-to-cystatin C (β −0.17, $P = .006$), and both inflammatory markers, interleukin-6 levels (β 0.16, $P = .002$) and tumor necrosis factor receptor II (β 0.21, $P = .04$), were independently associated with the LFI. Using an LFI cutoff of ≥4.5 to define frailty, Trails A/B (odds ratio [OR] 1.21, 95% confidence interval [CI] 1.07-1.37), Animal Naming Test (OR 0.64, 95% CI 0.42-0.97), sarcopenia (OR 0.10, 95% CI 0.01-0.73), and interleukin-6 (OR 4.99, 95% CI 1.03-15.53) were all associated with frailty. Although liver disease did not modify the relationship between the LFI and the Trails A/B test, interleukin-6 was significantly associated with the LFI only in the presence of liver disease.

CONCLUSIONS: Cognitive performance, inflammation, and sarcopenia, each highly prevalent in cirrhosis, are associated with the LFI in this population-based study of persons without

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cirrhosis. Further research is warranted for interventions aiming to prevent frailty by tailoring their approach to the patient's underlying risk factors.

Keywords

Cirrhosis; Interleukin-6; Liver disease; Psychometrics

INTRODUCTION

Frailty is an emerging determinant of poor outcomes in chronic liver disease.[1–5] The most robust physical performance markers of frailty in liver disease are timed chair stands (in particular),[4,5] handgrip, balance, and their combination as measured by the Liver Frailty Index (LFI).[2,3] The Liver Frailty Index is strongly associated with mortality in patients with end-stage liver disease on the liver transplant waitlist.[6] Despite the importance of frailty as a biomarker of poor outcomes, interventions to improve frailty are lacking. The design of effective interventions for frailty is presently hampered by a limited understanding of the underlying mechanism and factors associated with frailty.

Many factors influence the development of frailty, including sarcopenia and cognitive dysfunction.[7] Sarcopenia, which is both common and associated with poor outcomes in chronic liver disease, has previously been studied in retrospective cohorts, yet findings are limited by selection bias given the need for imaging.[8,9] We have found that cognitive function is a crucial determinant of physical function.[10] We have also shown that the prognostic value of frailty is confounded by the presence of hepatic encephalopathy.[11] However, hepatic encephalopathy defines late-stage cirrhosis, and as such, its impact on frailty measures may reflect many factors. For example, cirrhosis is an intensely pro-inflammatory state owing to the translocation of gut bacteria. Inflammation, in turn, plays a key role in mediating the development of both sarcopenia and cognitive dysfunction in persons with and without chronic liver disease.[12–15] It is challenging, however, to study the associations between these factors and frailty in persons on the transplant waitlist with decompensated cirrhosis given that they are nearly universal at this stage. Data from persons with earlier stages of liver disease or without liver disease are needed to elucidate the independent mechanisms and capacities that govern the risk of frailty. The Liver Frailty Index and its cutoffs are reproducible in healthy controls as well as those with early liver disease.[16] To date, however, data regarding Liver Frailty Index in an unselected community-based cohort, including its determinants, are lacking. Herein we study Framingham Heart Study to evaluate factors associated with the Liver Frailty Index in a prospective cohort of community-dwelling participants without advanced cirrhosis with a focus on markers of cognitive function, inflammation, and sarcopenia.

METHODS

Design

This is a cross-sectional study using data prospectively collected for participants in the Framingham Heart Study (FHS). FHS is a long-term, ongoing prospective cohort study of cardiovascular disease and its determinants. This study was approved by the University

of Michigan IRB (HUM00181496), and the FHS was approved by the Boston University School of Medicine institutional review board.

Population

This analysis included participants from the FHS Generation-2 cohort (Offspring Cohort) and a multiethnic cohort (Omni 1) who presented for a core examination visit between 2011 and 2014 (total number = 2586). These cohorts were chosen because they included the measures required for our analysis. From these cohorts, we included participants who had available laboratory data (aspartate aminotransferase [ALT], alanine aminotransferase [AST], and platelet count), cognitive testing data, and complete Liver Frailty Index data. Our final analysis sample consisted of 1208 participants with and without liver disease, defined as abnormal liver enzymes (an elevated ALT or AST, >19 U/L for women or >30 U/L for men) or evidence of hepatic steatosis on imaging. Specifically, hepatic steatosis was derived from the liver attenuation (Hounsfield Units [HU]) of 3 areas in the liver on computed tomography (CT) imaging in relation to a calcium-based reference material (called a "phantom") using the data obtained from multidetector CT with 64-slice multidetector CT technology (LightSpeed Ultra, General Electric). As described elsewhere and consistent with prior FHS publications, hepatic steatosis was defined by a liver/phantom ratio ≤0.33.[17] Figure 1 summarizes inclusions/exclusions.

Exposures

We evaluated the associations of 3 exposure variables with frailty: cognitive function, sarcopenia, and inflammation. Cognitive function was measured using 5 cognitive tests: Trail A, Trail B, Animal Naming Test, Digit Span Forward, and Digit Span Backward. For the Trail tests, the participant was given a paper with 25 circles containing the numbers 1-25 (Trail A) or 1-13 and A-L (Trail B). The participant's score was the time taken to draw a trail connecting the circles in ascending order (1-2-3 …) for Trail A and alternating numbers and letters (1-A-2-B …) for Trail B. If a mistake was made, the tester immediately pointed it out and participants were allowed to correct their mistake; mistakes only affected the score through the time taken to make the correction. A lower score indicated greater cognitive ability. Trail A tests visual attention and processing speed, and Trail B tests executive abilities including set shifting and mental flexibility. In the Digit Span tests, testers read out a series of increasingly longer digit sequences in a steady, monotonous tone. The participant was asked to repeat the sequences back, either in forward or reverse order. Each digit span/length had 2 sequences to be tested for each length. The participant's score was the longest digit sequence reached before making an error, with higher scores reflecting better cognitive function. For the Animal Naming Test, the participant was asked to name as many animals as possible in 60 seconds. This test measured expressive language ability, executive ability, processing speed, and memory with higher scores indicating greater cognitive function. Each test was then converted into a z-score yielding performance relative to the whole population sample. We derived the summary z-scores for the following: combined Trails A and B, Animal Naming Test, and the combined Digit Span Test Forward/Backward.

Sarcopenia was defined using an estimate of muscle mass using a novel method involving the ratio of serum creatinine and cystatin C levels.[18] Lower creatinine and cystatin C

ratios are associated with lower muscle mass and the higher presence of sarcopenia.[19] The creatinine-to-cystatin C ratio is tightly correlated with sarcopenia defined by height-indexed skeletal muscle on CT.[20,21] It is also strongly correlated with handgrip strength, gait speed, and 6-minute walk distances and is predictive of short- and long-term survival.[21–24] Inflammation was measured using both interleukin-6 and soluble tumor necrosis factor receptor II blood laboratory values. To improve the interpretation of the association between the inflammatory markers and our outcomes, we used log-transformation.

Outcomes

The primary outcome was the Liver Frailty Index.[1] The Liver Frailty Index was designed and validated to measure an individual's physical ability based on a transformed sum of timed chair-stands, balance tests, and gender-adjusted handgrip strength. The score ranges from 1.0 to 7.0 with 3.8 representing the median score in a sample of patients who were transplant-waitlisted, and scores ≥4.5 considered to reflect frailty. The primary outcome was the absolute Liver Frailty Index score. The secondary outcome was dichotomous, with a Liver Frailty Index ≥4.5 representing frailty.[1]

Covariates

We tabulated several covariates to characterize our study population (Table 1). We defined alcohol misuse as a reported episode of binge drinking (>5 drinks per day for men or >4 drinks per day for women) in the last 30 days or an average weekly consumption of alcohol of >14 drinks per week for men or 7 drinks per week for women. Current smoking was defined relative to the laboratory visit. We calculated Fibrosis-4 (FIB-4) Index as a noninvasive proxy for advanced fibrosis. Using conventional cutoffs, a FIB-4 was considered high if >2.67.[25] FIB-4 was used in modeling to adjust for the possibility of occult advanced fibrosis. All blood and serum measures were obtained from fasting or morning samples.

Analysis

Our analytic approach consisted of 2 main methods. First, we used univariable and multivariable linear regression to evaluate associations of cognitive function, sarcopenia, and inflammation with Liver Frailty Index. Multivariable models included all variables assumed a priori to influence the outcome or interpretation of the covariate effect. These variables included age, sex, education, body mass index (BMI), alcohol use, and FIB-4. For example, we assume that occult advanced fibrosis would confound some associations (for which FIB-4 is the best available measure), and we have found using nationally representative data that age, education, any alcohol used, and BMI are associated with cognitive function.[26] We then constructed a combined multivariable model with the cognitive test with the strongest association, sarcopenia, and an inflammation marker (interleukin-6 and tumor necrosis factor receptor II). We repeated this analysis based on the presence or absence of liver disease to determine if liver disease modified the association between the exposures with the Liver Frailty Index. Second, we used Firth logistic regression to evaluate associations between the exposures and frailty (Liver Frailty Index ≥4.5). Firth logistic regression was used to counteract potential overfitting. Associations were considered significant at a 2-sided P value <.05. All analyses were performed using RStudio.

RESULTS

Characteristics for the study cohort are presented in Table 1. In general, participants were a median of 70 years old (interquartile range [IQR] 65-76), 56% women, 50% college educated, and with a median BMI of 27.6 kg/m^2. Overall, 48.5% were classified as having liver disease (elevated liver enzymes or radiographic hepatic steatosis). Participants with liver disease were more likely to be women, younger, and had higher prevalence of sarcopenia (creatinine/cystatin C). Among these participants with liver disease, 10.8% had alcohol misuse. Overall, the median Liver Frailty Index was 3.55 (interquartile range 3.25-3.85), and 2% were frail with a LFI ≥4.5. No difference was found between median Liver Frailty Index based on the presence of liver disease ($P = .28$). There was a small, but statistically significant, decrease in Trail A (0.47 vs 0.48) and Trail B (1.20 vs 1.27) scores in participants classified as having liver disease.

We first assessed the relationship among cognitive function, sarcopenia, and inflammation on the Liver Frailty Index (Table 2). On univariable analysis, the Liver Frailty Index increased with worsened performance for each cognitive test, decreased muscle mass, and higher inflammatory marker values (both interleukin-6 and tumor necrosis factor receptor II). We then formed a multivariable model, adjusting for age, sex, alcohol use, education, BMI, and FIB-4 index, that included creatinine/cystatin C, an inflammatory marker (interleukin-6 and tumor necrosis factor receptor II), and the best performing cognitive test on univariable analysis (Trails A/B). Trails A/B (β 0.05, $P < .001$), creatinine/cystatin C (β −0.17, $P = .006$), and the inflammatory markers, both interleukin-6 levels (β 0.16, $P = .002$) and tumor necrosis factor receptor II (β 0.21, $P = .04$), remained associated with the Liver Frailty Index.

We next examined if the presence of liver disease modified the relationship between the exposures (cognitive tests, creatinine/cystatin C, and an inflammatory marker) and the Liver Frailty Index. In those with liver disease or without liver disease, the combined Trails A/B (adjusted β 0.04, $P = .02$ and adjusted β 0.05, $P < .001$, respectively) was associated with the Liver Frailty Index. Interleukin-6 was significantly associated with the Liver Frailty Index in the presence of but not in the absence of liver disease. Tumor necrosis factor receptor II was not significantly associated with the Liver Frailty Index in the presence of or in the absence of liver disease. In contrast, sarcopenia was significantly associated with the Liver Frailty Index in those without liver disease and not in those with liver disease when adjusted for inflammation and cognitive performance.

Using a Liver Frailty Index cutoff of ≥4.5 to define frailty, 25 were classified as frail and 1183 as nonfrail. On univariable analysis, frailty was significantly associated with Trails A/B (odds ratio [OR] 1.28, 95% confidence interval [CI] 1.15-1.42), Animal Naming Test (OR 0.48, 95% CI 0.32-0.71), sarcopenia (OR 0.08, 95% CI 0.01-0.65), interleukin-6 (OR 6.90, 95% CI 2.09-22.79), and tumor necrosis factor receptor II (OR 1.0004, 95% CI 1.0002-1.0007) (Table 3). In the adjusted model, the Liver Frailty Index was significantly associated with Trails A/B (OR 1.21, 95% CI 1.07-1.37), Animal Naming Test (OR 0.64, 95% CI 0.42-0.97), sarcopenia (OR 0.10, 95% CI 0.01-0.73), and interleukin-6 (OR per

log 4.99, 95% CI 1.03-15.53) or tumor necrosis factor receptor II (OR 1.0003, 95% CI 1.0000-1.0006).

DISCUSSION

In clinical hepatology, attention to frailty and its impact on morbidity and mortality is often delayed to the late stages of cirrhosis.[6] Nonetheless, frailty is prevalent in both the compensated and decompensated stages of cirrhosis,[4,27] developing far in advance of transplant evaluation and even prior to the diagnosis of cirrhosis itself. Understanding the physiological contributors to the frail state at the earliest stage of liver disease is therefore crucial for the design and implementation of interventions to modify outcomes. To date, prior studies assessed the association of cognitive function and sarcopenia on frailty individually[4,7,10,28] but rarely in the same analysis and not while combined, or adjusted for, inflammatory markers. In the current study of community-dwelling persons without clinically apparent or decompensated cirrhosis, our findings highlight the early contributors of cognitive performance, inflammation, and muscle mass on physical frailty as measured by the Liver Frailty Index (Figure 2). We found that even after adjusting for each exposure and potential confounders, cognitive function, sarcopenia, and inflammation remained significantly associated with frailty.

Inflammation Is Associated with Frailty

Both interleukin-6 and tumor necrosis factor receptor II, markers of inflammation, were strongly associated with frailty. The aging literature has identified this pro-inflammatory marker as being associated with functional decline.[29] In another study of community-dwelling elderly subjects, higher levels of both interleukin-6 and tumor necrosis factor II were found in those classified as frail based on the Fried Frailty Index.[30,31] Our findings highlight inflammation as a likely physiological source of frailty and a possible biomarker for the identification of at-risk patients. In patients with cirrhosis, inflammation is central to the pathophysiology of many complications.[32] As shown by Shawcross,[15] inflammatory burden (including interleukin-6 levels) is a crucial determinant of ammonia-associated minimal hepatic encephalopathy. Our data, among patients without cirrhosis, show that inflammation is associated with frailty outside the context of portal hypertensive physiology. Our data highlight an effect of inflammation on the frailty phenotype as measured by the Liver Frailty Index independent of other cirrhotic processes such as hyperammonemia and indicate a role for expanding the scope of research on inflammation to earlier stages of liver disease.

Cognitive Function Impacts Physical Function

In the current study, a significant relationship between the Liver Frailty Index and cognitive performance was seen across multiple cognitive tests. Importantly, the association was significant after controlling for potential confounders of disease severity, including inflammation, sarcopenia, and advanced fibrosis. Although we previously illustrated the impact of hepatic encephalopathy on frailty, it was unclear whether its impact was a product of advanced disease or whether it identified an independent role of cognitive dysfunction on frailty.[11] We evaluated tests that are part of the gold-standard psychometric

hepatic encephalopathy score (PHES) as well as the recently validated-for-cirrhosis Animal Naming Test.[33] These findings further add to the literature suggesting a potential role of cognitive dysfunction in the development of the frailty phenotype,[34] thereby identifying another target for reducing frailty. Patients with cognitive dimensions to their frailty phenotype may benefit from medical or supportive therapy aimed at the source of their cognitive dysfunction. Future studies of cirrhosis with cognition-associated frailty could evaluate hepatic encephalopathy-directed therapy. There may be also value in adjunctive therapies. Intensive cognitive exercises over several weeks were associated with a significant improvement in the Fried Frailty Index.[35]

Sarcopenia Is Associated with Frailty

We found that the creatinine-to-cystatin C ratio, a validated measure of sarcopenia,[20–24] was associated with frailty. Although sarcopenia is often defined by cross-sectional imaging measurements,[9] CT scans are obtained by a minority of persons at risk for frailty.[7] As such, relying on CT scans to assess for frailty results in a selection bias. The creatinine-to-cystatin C ratio is tightly correlated with sarcopenia defined by height-indexed skeletal muscle on CT and provides a more accessible means of identifying sarcopenia using simple serologic tests.[20,21] The creatinine-to-cystatin C ratio is also strongly correlated with handgrip strength, walk distance, and gait speed and predictive of short- and long-term survival in multiple cohorts.[21–24] It is a clear limitation of this population-based study that we did not have access to direct measurements of muscle. However, the creatinine-to-cystatin C ratio is a validated metric that enriches our understanding of muscle's contribution to frailty, extending the relationship between it and frailty to the Liver Frailty Index while also adjusting for novel factors such as inflammation and cognitive function.

Contextual Factors

These findings must be interpreted in the context of our study design. First, this is a cross-sectional study, and we are therefore unable to establish causal interactions between the study variables. Second, although there are multiple measures of cognitive performance that may be important in frailty, our analysis was limited to the cognitive measures available in the Framingham Heart Study cohort. Reassuringly, each score is an established measure of cognitive performance, and our results are consistent with the literature on cognition and frailty. Further, we evaluated cognitive function as a function of population norms and adjusted for age and education, strengthening the association. However, as cognitive testing was completed among older patients, these may not generalize to younger persons with liver disease. Third, we did not evaluate these associations in a large cohort of persons with cirrhosis. Although many patients in our cohort had evidence of possible liver disease, hepatosteaosis or elevated liver enzymes, it is unlikely that many patients had advanced liver disease. The objective of this study was to evaluate the physiological underpinnings of frailty prior to the onset of the confounding factors in decompensated cirrhosis in which sarcopenia, inflammation, and cognitive dysfunction are highly prevalent and severe. As such, these data demonstrating associations between frailty and sarcopenia, inflammation, and cognitive dysfunction among persons with earlier stage disease are likely to generalize to persons with more advanced liver disease in which each factor is exaggerated but still need to be confirmed in that setting.

CONCLUSION

Although frailty is measured through tests of physical performance, these data reinforce that it is an epiphenomenon of physical, cognitive, and other physiological and psychosocial factors. To reverse frailty, interventions must be addressed toward its causative factors. This study examined a population-based cohort, many of whom had early liver disease and determined that the leading metric of physical frailty, the Liver Frailty Index, is associated with neurocognitive capacities, inflammation, and sarcopenia. Each of these factors are considerably more severe in persons with cirrhosis. Accordingly, research that aims to address and reverse the frailty phenotype in cirrhosis ought to first classify the dominant risk factors—be it cognitive dysfunction, sarcopenia, or inflammation—and develop interventions aimed at modifying possible contributors to frailty.

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Conflicts of Interest:

MTL's institution receives grants from Echosens Corporation and Gilead Sciences and reports serving on the advisory board for Ionis Pharmaceuticals and consulting for Iterative Scopes. EBT reports grant funding from Gilead and Bausch, consulting for Kaleido, Axcella, Novo Nordisk, Novartis, and Allergan, and serving on advisory boards for Bausch and Mallinckrodt. MM, JL, NSP report none.

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CLINICAL SIGNIFICANCE

- The Liver Frailty Index (LFI) is associated with inflammation measured using interleukin-6 (IL-6) and tumor necrosis factor (TNF)-receptor II levels, cognitive function measured using Trails A and B as well as the Animal Naming Test, and sarcopenia measured using the creatinine-to-cystatin C ratio.
- Each of these factors is associated among unselected subjects from the Framingham Heart Study with, at most, early liver disease.

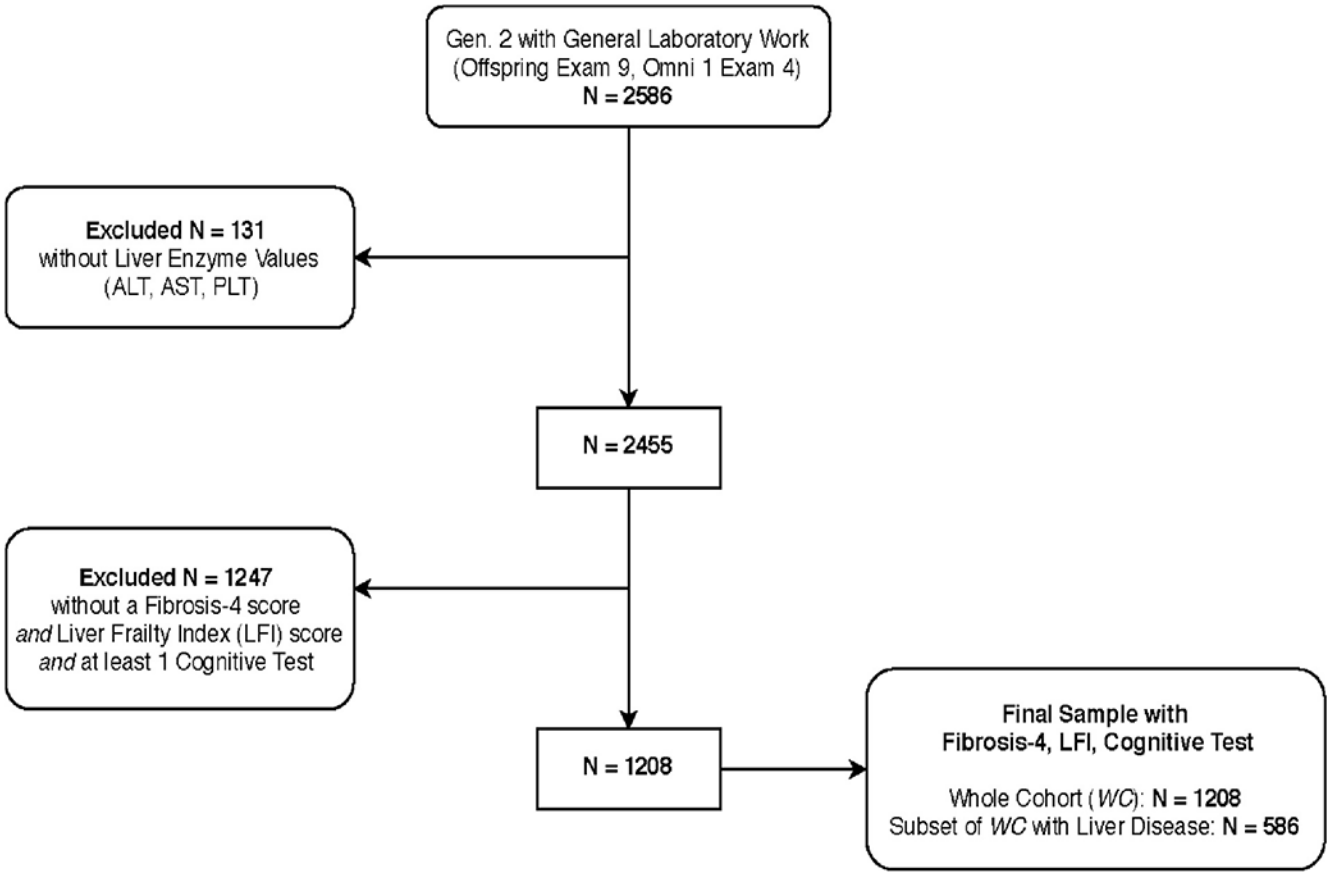

Figure 1.

Cohort construction: The cohort was derived from the Framingham Heart Study participants with laboratory data, including those who participated in the ninth examination of the Offspring cohort and the fourth examination of the Omni cohort. We excluded participants without liver enzymes or platelet counts, without frailty testing sufficient for calculation of the liver frailty index, and without cognitive testing.

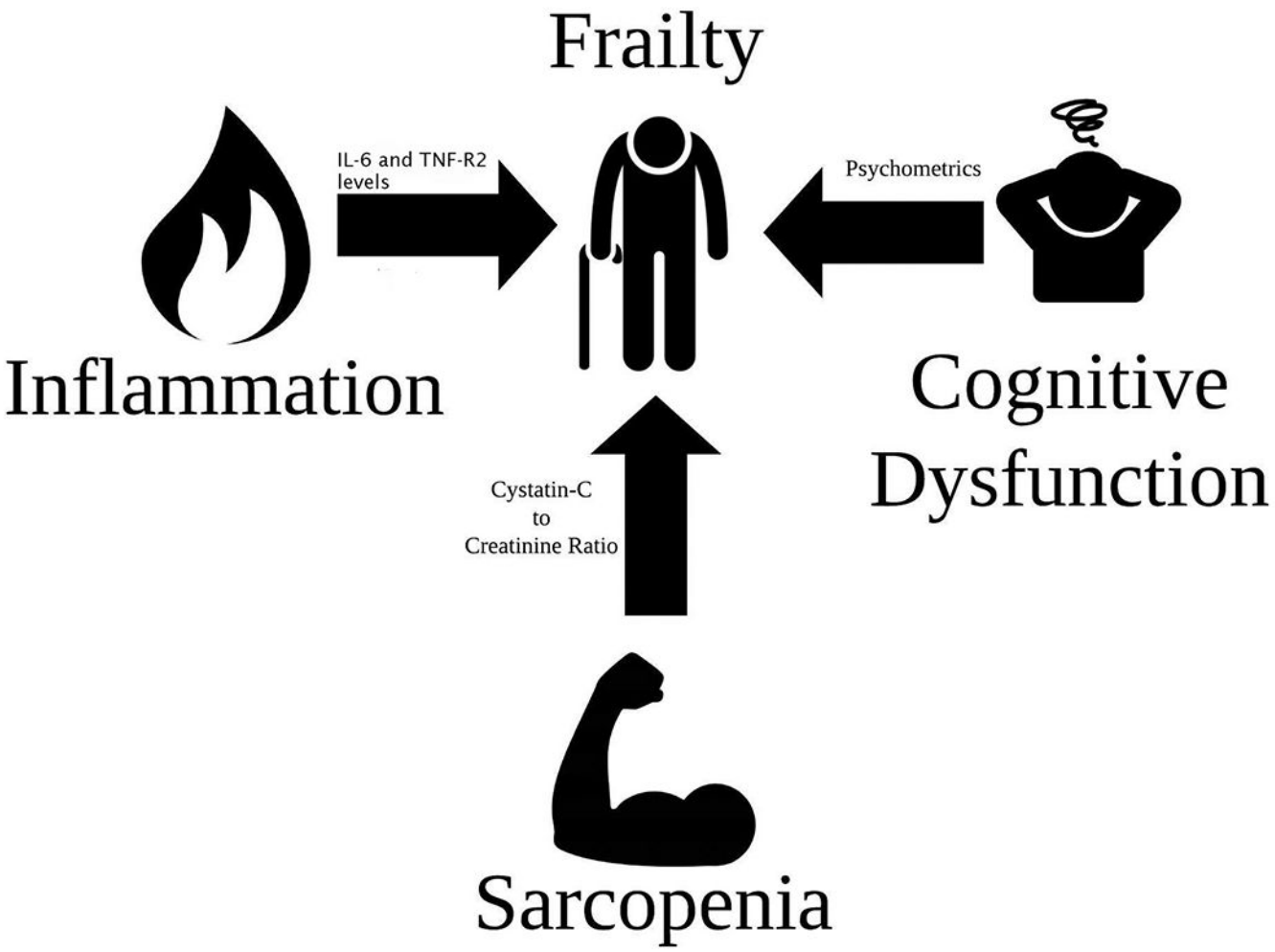

Figure 2.
The physiological underpinnings of physical frailty. In this study, we show that inflammation (measured using interleukin-6 and tumor necrosis factor receptor II levels), sarcopenia (estimated using the cystatin C-to-creatinine ratio), and cognitive function (quantified using standard psychometric tests) are associated with frailty measured using the Liver Frailty Index.

Table 1

Demographics and Clinical Characteristics of the Cohort According to the Presence of Liver Disease

	No Liver Disease	Liver Disease	*P* Value
N	622	586	
Age, median (IQR)	71.0 (66.0, 77.0)	68.0 (64.0, 74.0)	<.001
Women (%)	202 (32.5)	470 (80.2)	<.001
Education less than high school; high school; some college; college	3.9%; 21.9%; 21.9%; 52.4%	1.4%; 24.6%; 26.3%; 47.8%	.008
BMI, median (IQR)	27.9 (25.1, 30.6)	27.3 (23.9, 31.2)	.07
Systolic Blood Pressure, median (IQR)	125.0 (115.0, 136.0)	126.0 (114.0, 137.0)	.95
Current Smoker (yes) (%)	37 (6.0)	27 (4.6)	.36
Total Alcohol Drinks Weekly, median (IQR)	2.00 [0.00, 7.25]	2.00 [0.25, 7.00]	.92
Total Cholesterol, median (IQR)	176 [153, 202]	192 [165, 216]	<.001
Creatinine (mg/dL), median (IQR)	0.96 [0.83, 1.12]	0.82 [0.74, 0.95]	<.001
Cystatin C (mg/L), median (IQR)	0.92 [0.83, 1.01]	0.87 [0.79, 0.95]	<.001
Sarcopenia (creatinine/cystatin C), median (IQR)	1.05 [0.90, 1.19]	0.96 [0.86, 1.09]	<.001
Interleukin-6 (pg/mL), median (IQR)	1.65 [1.12, 2.58]	1.58 [1.09, 2.38]	.12
Fibrosis-4 index, median (IQR)	1.51 [1.17, 1.94]	1.50 [1.22, 1.94]	.46
Tumor Necrosis Factor Receptor II (pg/mL), median (IQR)	2345.61 [1911.49, 2882.13]	2249.80 [1894.73, 2823.73]	.25
Alanine Aminotransferase (U/L), median (IQR)	17 [14, 21]	23 [18, 30]	<.001
Aspartate Aminotransferase (U/L), median (IQR)	19 [17, 22]	24 [21, 28]	<.001
Platelet Count (1000 cells/uL), median (IQR)	218 (184, 261)	235 (201, 271)	<.001
Liver Frailty Index, median (IQR)	3.58 [3.25, 3.85]	3.54 [3.25, 3.83]	.28
Trail A (minutes), median (IQR)	0.48 [0.38, 0.62]	0.47 [0.37, 0.58]	.03
Trail B (minutes), median (IQR)	1.27 [0.97, 1.68]	1.20 [0.97, 1.58]	.03
Animals Naming Test, median (IQR)	18.00 [15.00, 22.00]	19.00 [16.00, 22.00]	.10
Digit Span Forward, median (IQR)	7.00 [6.00, 8.00]	7.00 [6.00, 8.00]	.54
Digit Span Backward, median (IQR)	5.00 [4.00, 6.00]	5.00 [4.00, 6.00]	.33

BMI = body mass index; IQR = interquartile range.

Table 2

Associations Among Cognitive Function, Sarcopenia, and Inflammation and the LFI

Exposure	Beta ± Standard Error (*P* value) of relationship between exposure and LFI	
	Unadjusted	**Adjusted for confounders***
Trails A/B (per unit Z score)	0.08 ± 0.01	0.05 ± 0.01
Digit Span Forward/Backward (per unit Z score)	−0.03 ± 0.01	−0.02 ± 0.01
Animal Naming Test (per unit Z score)	−0.11 ± 0.01	−0.05 ± 0.02
Sarcopenia (Creatinine/Cystatin C) (per unit increase)	−0.17 ± 0.06	−0.21 ± 0.06
Interleukin-6 (per log increase)	0.31 ± 0.05	0.16 ± 0.05
Tumor Necrosis Factor Receptor II (per unit increase)	0.63 ± 0.10	0.27 ± 0.10
Combined multivariable model with the cognitive test with the strongest association, sarcopenia and an inflammation marker (either interleukin-6 or tumor necrosis factor receptor II)		
Trails A/B		0.05 ± 0.01 (*P* < .001)
Sarcopenia (Creatinine/Cystatin C)		−0.18 ± 0.07 (*P* = .006)
Interleukin-6		0.16 ± 0.05 (*P* = .002)
Trails A/B		0.05 ± 0.01 (*P* < .001)
Sarcopenia (Creatinine/Cystatin C)		−0.19 ± 0.06 (*P* = .003)
Tumor Necrosis Factor Receptor II		0.21 ± 0.10 (*P* = .04)

LFI = Liver Frailty Index.

*The confounders that adjust each estimate are age, sex, alcohol use, education, body mass index, and Fibrosis-4 index. Each cell represents the association between the variable and the outcome using linear regression expressed as a beta estimate, standard error, and *P* value. A beta estimate provides the difference in the outcome for each unit-change in the covariate. The Trails A/B Z-score is the combination of Z-scores for Trails A and B performance. The Digit Span Forward/Backward is the combined Z scores for the Digit Span Forward and Backward Tests.

Table 3

Associations with Frailty According to the Liver Frailty Index (≥4.5)

Exposure(s)	Odds ratio for frail LFI	
	Unadjusted OR (95% CI)	Adjusted for confounders* OR (95% CI)
Trails A/B (per unit Z score)	1.28 (1.15, 1.42)	1.21 (1.07, 1.37)
Digit Span Forward/Backward (per unit Z score)	0.84 (0.67, 1.07)	0.91 (0.73, 1.15)
Animal Naming Test (per unit Z score)	0.48 (0.32, 0.71)	0.64 (0.42, 0.97)
Sarcopenia (Creatinine/Cystatin C) (per unit increase)	0.08 (0.01, 0.65)	0.10 (0.01, 0.73)
Interleukin-6 (per log increase)	6.90 (2.09, 22.79)	4.99 (1.03, 15.53)
Tumor Necrosis Factor Receptor II (per unit increase)	1.0004 (1.0002, 1.0007)	1.0003 (1.0000, 1.0006)
Combined multivariable model with the cognitive test with the strongest association, sarcopenia, and an inflammation marker (either interleukin-6 or tumor necrosis factor receptor II)		
Trails A/B		1.14 (0.98, 1.34)
Sarcopenia (Creatinine/Cystatin C)		0.09 (0.01, 0.73)
Interleukin-6		4.01 (0.94, 17.14)
Trails A/B		1.16 (1.02, 1.33)
Sarcopenia (Creatinine/Cystatin C)		0.12 (0.02, 0.79)
Tumor Necrosis Factor Receptor II		1.0003 (1.0000, 1.0006)

CI = confidence interval; LFI = Liver Frailty Index; OR = odds ratio.

*The confounders that adjust each estimate are age, sex, alcohol use, education, body mass index, and Fibrosis-4 index. Each cell represents the association between the variable and the outcome using logistic regression expressed as an OR with CI. The Trails Z-score is the combination of Z scores for Trails A and B performance. The Digit Span Forward/Backward is the combined Z scores for the Digit Span Forward and Backward Tests.