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Impact of sociodemographic disparities on sarcopenia, telomere length, and mortality in patients with liver disease in the US population

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Abstract

Background & aims Sarcopenia is common in patients with liver disease and both sarcopenia and short telomeres are associated with mortality, however their relationship in patients with liver disease remains unknown.

Methods A cohort of 16,072 adults from the National Health and Nutrition Examination Survey from 1999 to 2006 was analyzed. Liver disease was defined by aminotransferases and classified into etiology-based categories. Sarcopenia was defined by dual-energy x-ray absorptiometry. All analyses were conducted separately on each multiple imputation data set and combined via Rubin's rules. *P*-values for group comparisons were calculated by testing logistic regression parameter estimates. Cox proportional hazards regression was used for mortality analysis with mortality data available until 2015.

Results Sarcopenia was present in 9.5% of patients with liver disease. Age, race, income, education, physical inactivity, and certain medical comorbidities were associated with sarcopenia. Patients with liver disease and sarcopenia had significantly shorter telomeres than patients with liver disease without sarcopenia when unadjusted for age. The interaction between telomere length and sarcopenia was significantly associated with all-cause mortality.

Conclusions The implications of telomere length on all-cause mortality in patients with liver disease varied by age and sarcopenia status. Shorter telomeres appear to be more highly associated with increased mortality in older patients without sarcopenia.

Keywords Sarcopenia, Chronic liver disease, Telomeres, Mortality, NHANES

Introduction

Sarcopenia is a condition of malnutrition with declining muscle mass and function that is associated with aging as well as certain systemic diseases, including chronic liver disease (CLD) [1, 2]. In patients with CLD, there is dysregulated muscle protein turnover through a variety of mechanisms resulting in the development of sarcopenia [3]. Furthermore, sarcopenia is common in patients with cirrhosis, affecting 30–70% of patients [4] and is associated with worse outcomes in this patient population including increased mortality and complications of liver

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disease and decreased quality of life [4]. The treatment of sarcopenia in patients with cirrhosis requires a multidisciplinary approach including nutrition, exercise, and psychological and pharmacological interventions [3, 5].

There are currently no standardized definitions for the diagnosis of sarcopenia in cirrhosis [3], and there are a variety of methods of defining sarcopenia with significant heterogeneity in the literature. The diagnosis of skeletal muscle mass loss necessitates analysis of body composition with options including anthropometry, dual-energy x-ray absorptiometry (DEXA), bioelectrical impedance analysis, impedance plethysmography, ultrasonography, CT, and MRI [4]. Muscle function can be assessed through measurements such as hand grip strength [4]. Regardless of the methodology used for defining sarcopenia, sex and age specific cut-offs are necessary.

In cirrhosis, inflammation and subsequent exposure to reactive oxygen species results in cell death and as a result maturation of hepatocytes with telomere shortening [6]. Telomeres are repeat DNA sequences at the end of chromosomes which protect against DNA damage and play an important role in regeneration. Sarcopenia and shortened telomere length are affected by oxidative stress and are associated with increased mortality, however the relationship between sarcopenia, telomere length, and mortality in patients with liver disease remains unknown [7].

In this study, we evaluated cross-sectional data from The National Health and Nutrition Examination Survey (NHANES) to determine the relationship between sarcopenia and telomere length in individuals with liver disease, and their impact on mortality at the population level.

Patients and methods

NHANES

NHANES is a continuous annual survey conducted by the National Center of Health Statistic's Division and Health and Nutrition Examination Surveys in the Centers for Disease Control and Prevention [8]. It is a survey of the noninstitutionalized civilian resident population of the United States [8]. The goal of this survey is to provide national estimates on health-related topics [8]. This iteration of NHANES began in 1999 with 2-year data-release cycles [8, 9]. Demographic data was obtained from the cohort including sex, age, race, educational level, income level, as well as medical comorbidities. Mortality follow up was available through 2015.

Sarcopenia assessment

Our study cohort consisted of all NHANES participants from 1999–2006 who were at least 18 years or older. All NHANES participants ages 8–69 were eligible for DEXA scan. Our sarcopenia analysis consisted of NHANES data from 1999–2006 (Fig. 1) as assessed by DEXA scan. NHANES exclusion criteria for DEXA evaluation included the following: pregnancy, history of contrast material exposure in the past 7 days, weight over 300 pounds, and height greater than 6'5". Of the 16,072 subjects meeting inclusion criteria, 15,414 had DEXA data available. Due to missing and invalid DEXA data, NHANES employed multiple-imputation methodology to provide complete and representative data. Sarcopenia was defined according to the Foundation for the National Institutes of Health Sarcopenia (FNIH) Project definition using appendicular lean mass (ALM) obtained by DEXA adjusted for BMI (weight divided by height^2 (kg/m^2), calculated as ALM divided by BMI. The sex specific cut points for sarcopenia were <0.789 for men and <0.512 for women [10].

Physical activity and food security

Physical activity was assessed using the NHANES physical activity questionnaire from years 1999–2006. This survey includes a series of questions pertaining to daily activities, leisure-time activities, and sedentary activities at home. The survey included questions regarding physical activity as these pertain to transportation and household activities. Based on their responses, participants' total physical activity levels were calculated as follows:

$$\text{Total Physical Activity} = (\text{moderate leisure} - \text{time physical activity} + 2 \times \text{vigorous leisure} - \text{time physical activity} + \text{transportation} + \text{work}).$$

Participants were labeled as inactive if they had less than 150 min of activity per week, moderately active if achieving 150–299 min of activity per week, and ideally active if achieving at least 300 min of activity per week.

Food security was assessed using the NHANES Food Security questionnaire where participants were asked questions about household food security. The number of questions varied based on presence of children under 18 years of age in the home.

Telomere length assessment

The telomere length analysis consisted of NHANES data from 1999 to 2002. Adults 20 years and older were eligible for participation. Telomere length was assessed on serology in the laboratory of Dr. Elizabeth Blackburn at the University of California, San Francisco, using quantitative polymerase chain reaction method to measure telomere length relative to standard reference DNA (T/S ratio) [11, 12].

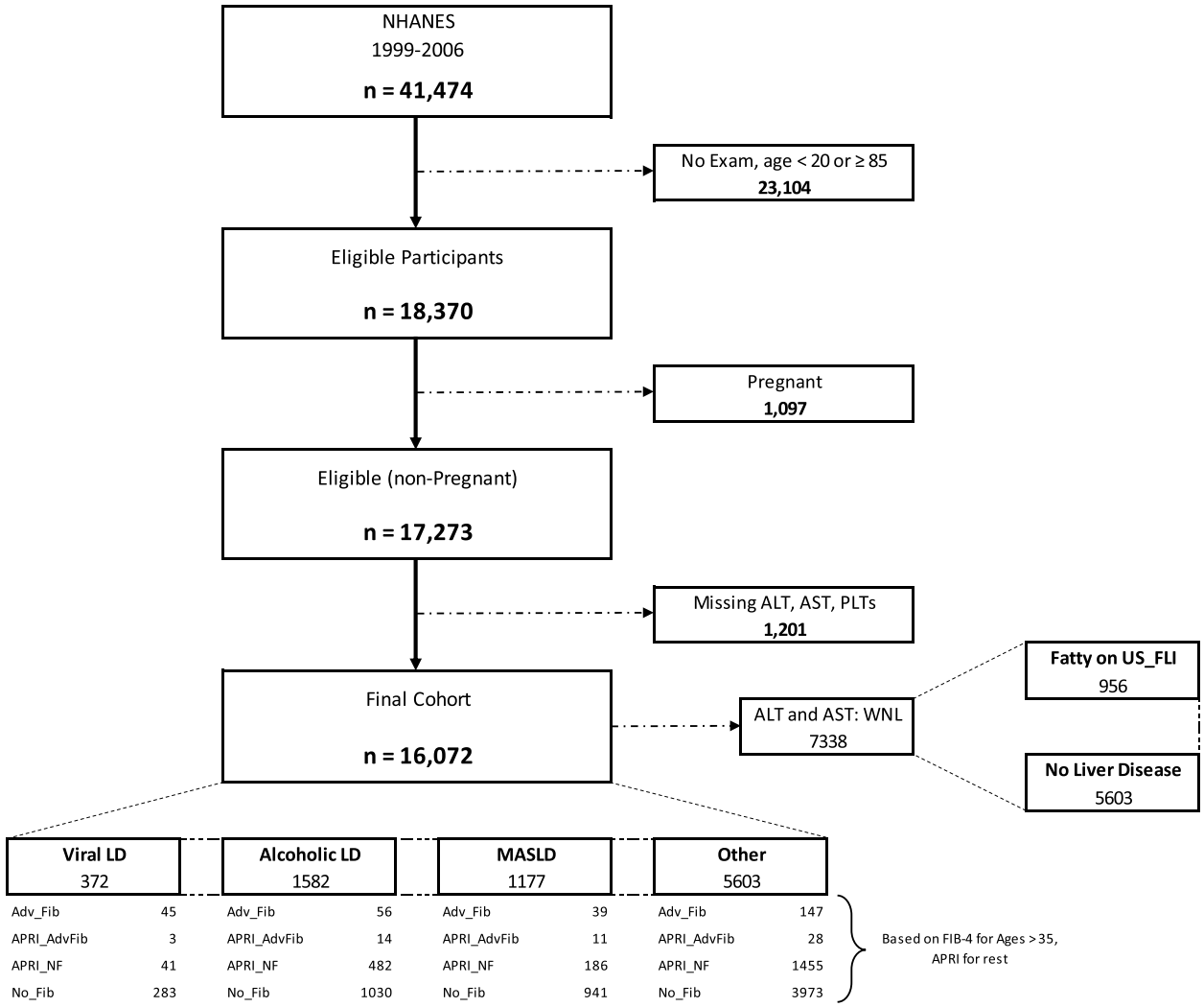

Fig. 1 Flowchart of Cohort Selection for Sarcopenia Analysis for NHANES 1999–2006

Definition of liver disease

The presence of liver disease was defined and stratified sequentially by etiology and presence of advanced fibrosis. As such, patients without available serum aminotransferase levels or platelet counts were excluded. Participants with normal alanine transaminase (ALT) and aspartate transaminase (AST) levels were classified as having metabolic associated steatotic liver disease (MASLD) ($n = 956$) if they met the Improved Fatty Liver Index for the multi-ethnic US population (US FLI) criteria. The US FLI is a biochemical model that predicts the presence of fatty liver based on age, race/ethnicity, waist circumference, gamma glutamyltransferase (GGT) activity, fasting insulin, and fasting glucose [13]. Participants were also considered as having MASLD ($n = 1177$) if they had abnormal ALT or AST (> 19 IU for females and > 29 IU for males) [14] and also met criteria for metabolic syndrome. Metabolic syndrome was defined as having three of more of the following conditions: (1) impaired glycemic control (hemoglobin $A_{1c} \geq 5.7\%$, or fasting serum glucose ≥ 100 mg/dL, or use of diabetes medications), (2) either increased waist circumference (≥ 88 cm for females, ≥ 101 cm for males) or elevated BMI (≥ 30 Kg/m^2), (3) low high-density lipoprotein cholesterol (< 50 mg/dL in females, < 40 mg/dL in males), (4) high triglyceride levels (≥ 150 mg/dL), or (5) hypertension (systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg) [9]. Participants with evidence of active infection with either Hepatitis B virus (HBV) (positive for HBsAg), or Hepatitis C virus (HCV) (positive for HCV RNA or positive for antibodies to HCV with non-negative HCV

RNA) were considered as having viral liver disease (VLD) ($n=372$). Next, alcohol-associated liver disease (ALD) ($n=1582$) was defined by elevated ALT or AST (>19 IU for females and >29 IU for males) [14] and self-reported evidence of either (1) current heavy alcohol use (≥3 drinks per day for females, ≥4 drinks per day for males, or binge drinking [≥4 drinks on same occasion for females, ≥5 drinks on same occasion for males] on 5 or more days per month), (2) current moderate alcohol use (≥2 drinks per day for females, ≥3 drinks per day for males, or binge drinking ≥2 days per month), or (3) a history of daily binge drinking. Patients were categorized as having other liver disease (OLD) ($n=5603$) if they had abnormal ALT or AST (>19 IU for females and >29 IU for males) but did not meet criteria for MASLD, VLD, ALD. Lastly, patients who did not meet any of the above criteria were considered as having no liver disease (NLD) ($n=5603$). By employing aminotransferase elevation as the initial branch point for the presence or absence of liver disease, the studied patient population captures the broad spectrum of liver disease, not being limited to just those with chronic liver disease and/or advanced fibrosis. The following statistical analysis focuses on patients with liver disease as the cohort of interest within the representative population.

Advanced fibrosis was defined by Fibrosis-4 Index (FIB-4) for patients older than 35 years old with FIB-4>2.67 indicating advanced fibrosis [15]. For patients younger than 35 years old, AST to Platelet Ratio Index (APRI) was used to define advanced fibrosis with a cut off of ≥0.7 indicating advanced fibrosis [16].

Statistical analysis

All analyses were conducted separately on each multiple imputation data set and combined via Rubin's rules. Sampling weights were calculated using Table E from the NHANES 99−10 Analytic Guidelines. Since DEXA results were used to calculate sarcopenia, examination weights were used. Waves 99−00 and 01–02 were normalized using 4-years weights; other waves used the 2-year weights. All numbers in the results are based on weighted summaries, unless otherwise noted. Descriptive tables were compiled using median and IQR for numeric variables (unless otherwise noted) and frequencies and percentages for categorical variables. Summary statistics are reported based on weighted data normalized to give appropriate group totals and p-values. Formal testing for probability of sarcopenia was done using logistic regression adjusting for multiple imputation. Cox proportional hazards regression was used for mortality analysis. Odds ratios and hazard ratios were reported accordingly with a 95% confidence interval and were adjusted based on key clinical characteristics. All analyses were conducted in R 4.2.2 (R Foundation, Vienna, Austria).

Results

Prevalence of sarcopenia in liver disease

Of 16,072 patients in the cohort, 8,891 patients had liver disease. Sarcopenia classification was available in 8,480 and determined to be present in 807 (9.5%). Demographic data for the cohort of patients with liver disease by sarcopenia status is shown in Table 1. Sarcopenia adjusted for BMI (ALM/BMI) was more prevalent in patients with MASLD (18.4%) compared to other etiologies of liver disease, including ALD (8.7%), OLD (8.3%),

Table 1 Demographics by sarcopenia status in patients with liver disease

	Sarc(-) ($N=7673$)	Sarc(+) ($N=807$)
Age, y		
Median (Q1, Q3)	44.0 (33.0, 54.0)	56.0 (45.0, 67.0)
Sex		
Male	2896 (37.7%)	312 (38.6%)
Female	4776 (62.3%)	495 (61.4%)
Body Mass Index		
Median (Q1, Q3)	27.4 (23.9, 31.7)	32.1 (28.3, 37.0)
Obesity class		
BMI ≤ 30	5142 (67.0%)	289 (35.8%)
BMI > 30	2530 (33.0%)	518 (64.2%)
Education Level		
<9th grade	400 (5.2%)	141 (17.5%)
9-11th grade	926 (12.1%)	142 (17.6%)
HS Grad[a]/GED[a]	1980 (25.8%)	211 (26.2%)
Some college/AA[a]	2353 (30.7%)	217 (27.0%)
College Graduate	2007 (26.2%)	95 (11.8%)
Household Income		
<$20K	1137 (15.8%)	197 (26.1%)
>20 K	92 (1.3%)	17 (2.3%)
$20K-$45K	1964 (27.3%)	251 (33.3%)
$45K-$75K	1837 (25.6%)	169 (22.4%)
>$75K	2155 (30.0%)	120 (15.9%)
Physical Activity Level		
Ideal	3118 (60.7%)	174 (47.3%)
Moderate	1008 (19.6%)	80 (21.8%)
Inactive	1009 (19.7%)	114 (31.0%)
Household Food Security		
HH[a] fully food secure	3035 (85.7%)	286 (79.5%)
HH[a] marginally food secure	192 (5.4%)	22 (6.2%)
HH[a] food insecure w/o hunger	191 (5.4%)	36 (9.9%)
HH[a] food insecure w/hunger	123 (3.5%)	16 (4.4%)

[a] High school graduate (HS Grad), High school equivalency (GED), Associate of Arts degree (AA), Household (HH)

VLD (6.4%) or no liver disease (8.7%) ($P<0.001$) (Supplementary Table 1). When defining sarcopenia with ALM alone (unadjusted for BMI) with sex-specific cut offs of < 19.75 kg for men and < 15.02 kg for women [10], sarcopenia continued to be significantly associated with etiology of liver disease ($P<0.001$) and sarcopenia was more prevalent overall with this definition. Applying the unadjusted ALM definition, sarcopenia was present in 10.2% of patients with ALD, 20.5% of patients with VLD, 13.1% of patients with NLD, 7.7% of patients with MASLD, and 12.8% of patients with OLD.

Impact of Sociodemographics on Sarcopenia

In a multivariable analysis of patients with liver disease, the following were associated with sarcopenia: age, all levels of education less than a college degree, all levels of physical activity less than ideal, race, income levels < 20 K and 20 K-45 K, hypertension, diabetes mellitus, chronic kidney disease, and lung disease (Supplementary Table 2). Compared to White race, other races/ethnicities had increased risk of sarcopenia, except non-Hispanic Black race which was associated with decreased sarcopenia, (OR 0.21 [0.13, 0.34] $P<0.001$). Advanced fibrosis was not significantly associated with sarcopenia (OR 0.85 [0.45, 1.62] $P=0.63$). In patients with liver disease, the prevalence of sarcopenia decreased as income level and education level increased (Figs. 2 and 3).

Survival analysis

In a Cox model for survival, male sex, age, advanced fibrosis, level of education between 9th and 11th grade, level of education attending some college, income between 20 and 45 K, current smoking, hypertension, chronic kidney disease, and lung disease were significantly associated with mortality in patients with liver disease (Supplementary Table 3). Sarcopenia was not significantly associated with mortality (HR 1.14 [0.79, 1.65] $P=0.49$). In a separate model, the interaction between sarcopenia and advanced fibrosis was not significantly associated with mortality either (HR 1.18 [0.68, 2.03] $P=0.56$).

Telomere length

Telomere measurements were available in 3,713 patients with liver disease from 1999 to 2002. Patients with liver disease and sarcopenia had significantly shorter telomeres than patients with liver disease without sarcopenia ($P<0.001$), however this relationship did not remain significant when adjusted for age ($P=0.13$), (Figs. 4 and 5). In patients with liver disease, the interaction also known as effect-modification between telomere length and sarcopenia was significantly associated with mortality (HR 2.83 [1.06, 7.57] $P=0.039$) (Table 2). Table 3 demonstrates from this model how the effects of sarcopenia and telomere length interact with one another, as well as with age. Sarcopenia had a greater impact on mortality at younger ages, with shorter telomeres attenuating that effect. Longer telomeres were generally associated with increased mortality at younger ages, especially in those with sarcopenia. However, at older ages, longer telomeres were

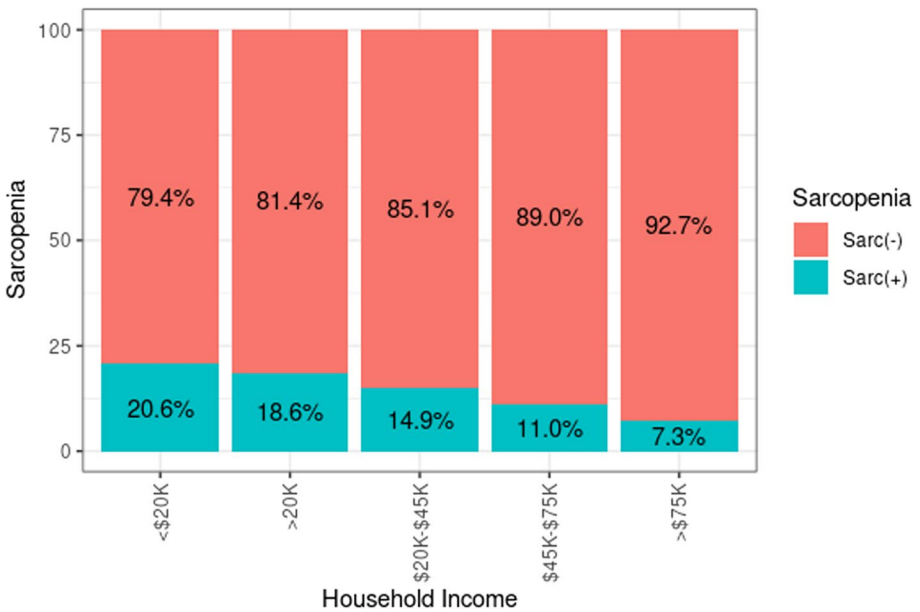

Fig. 2 Sarcopenia by household income in patients with liver disease

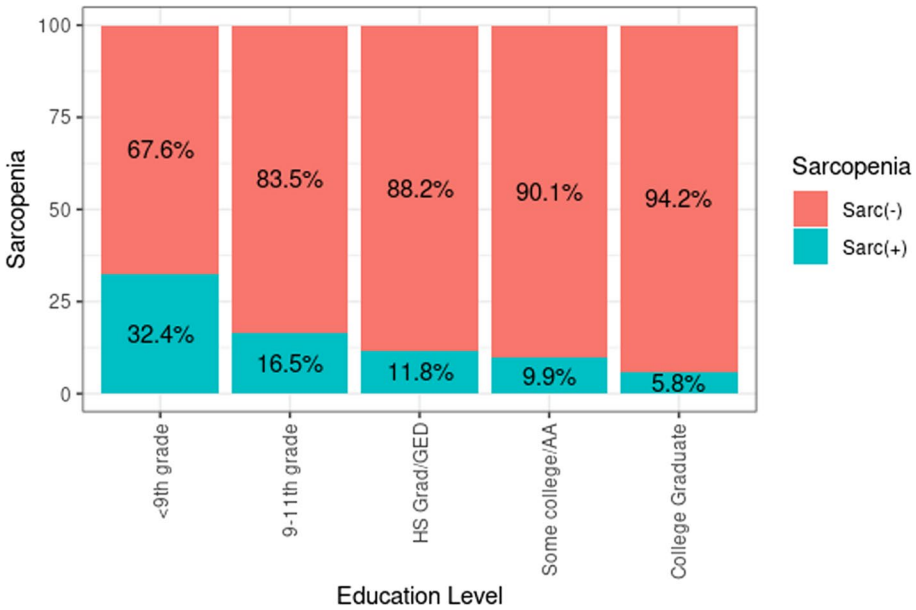

Fig. 3 Sarcopenia by education level in patients with liver disease

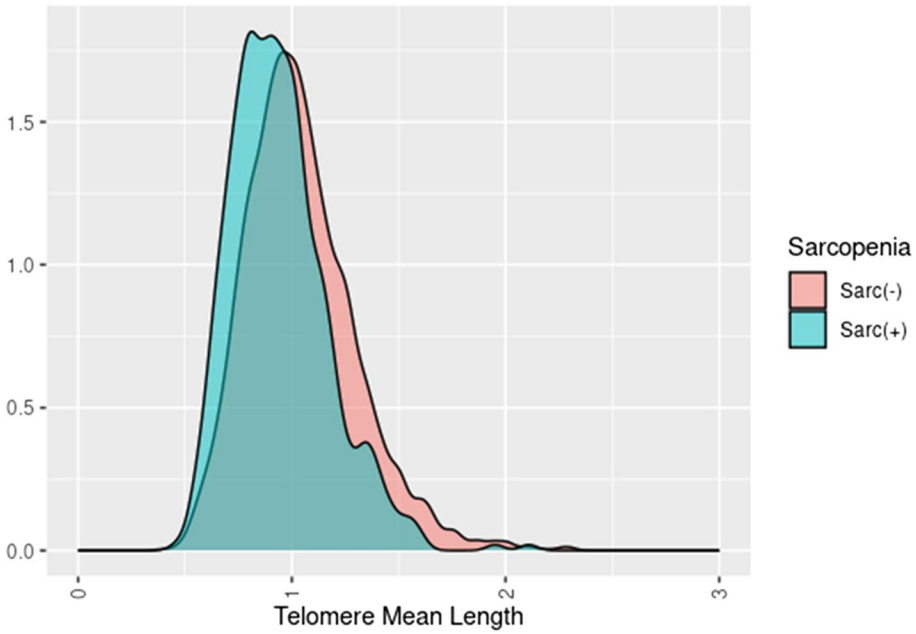

Fig. 4 Telomere length in patients with chronic liver disease with and without sarcopenia unadjusted

associated with decreased mortality in those without sarcopenia.

Discussion

Here we demonstrate the prevalence of sarcopenia in patients with liver disease overall, particularly in those with MASLD. In patients with MASLD, there are alterations of the metabolic pathways related to insulin resistance, lipogenesis, chronic inflammation, physical inactivity, and vitamin D deficiency that contribute to the development of sarcopenia [17]. In a cohort study of over 50,000 patients, MASLD (NAFLD) was associated with an increased risk of sarcopenia as measured by faster loss of skeletal muscle mass [18]. While numerous studies have demonstrated an association between sarcopenia, MASLD, and worse outcomes, the optimal diagnostic

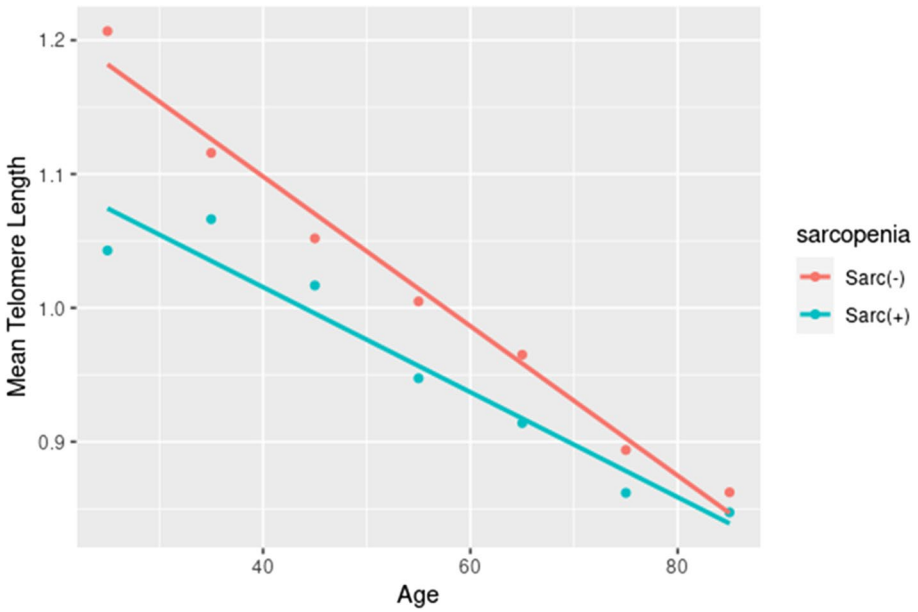

Fig. 5 Association of telomere length with sarcopenia, adjusted for age in patients with chronic liver disease. Each point is a within group mean telomere length for patients within 10-year period. For example, point at age 25 is average of telomere length of patients between ages 20–30

Table 2 Association of age, telomere length, and sarcopenia with mortality in patients with liver disease

Variable	Hazard Ratio (95% CI)	*P*-value
Age	1.10 (1.09, 1.12)	**< 0.001**
Telomere Length	2.51 (1.30, 4.86)	**0.006**
Sarcopenia	2.04 (0.37, 11.22)	0.41
Age*Telomere	0.98 (0.96, 0.99)	**0.008**
Age*Sarcopenia	0.98 (0.96, 1.00)	**0.029**
Telomere*Sarcopenia	2.83 (1.06, 7.57)	**0.039**

*Indicates interaction between variables

Table 3 Impact of sarcopenia and telomere length on mortality in patients with liver disease

Variable	Hazard Ratio (95% CI)
Sarcopenia(+) Effect	
Age 35, Telomere Length 0.75	2.27 (1.15, 4.48)
Age 35, Telomere Length 1.25	3.81 (2.10, 6.91)
Age 75, Telomere Length 0.75	1.06 (0.80, 1.40)
Age 75, Telomere Length 1.25	1.78 (1.16, 2.72)
Telomere Effect (per 0.25 increase)	
Age 35, Sarcopenia(-)	1.05 (0.97, 1.13)
Age 35, Sarcopenia(+)	1.36 (1.07, 1.73)
Age 75, Sarcopenia(-)	0.85 (0.72, 1.00)
Age 75, Sarcopenia(+)	1.10 (0.89, 1.35)

criteria for sarcopenia in patients with MASLD remains controversial. A study of 156 patients with biopsy-proven MASLD (NAFLD) found significant heterogeneity in the prevalence of sarcopenia when comparing the Foundation for the National Institutes of Health (FNIH) definition of sarcopenia to other definitions including the skeletal muscle index and the ratio of skeletal muscle mass to body fat mass, concordance 0.058 [19]. In our study, sarcopenia was defined by ALM adjusted for BMI based on the recommendation of the FNIH consortium [10]; therefore as patients have increasing BMI, which is a risk factor for MASLD, they are more likely to be sarcopenic by definition. We demonstrated this concept by assessing the prevalence of sarcopenia by ALM alone unadjusted for BMI in which case sarcopenia was least prevalent in MASLD compared to when sarcopenia was defined by ALM adjusted for BMI, where sarcopenia was most prevalent in MASLD. This discordance highlights the challenges to accurately identifying sarcopenia in patients with MASLD, and future research needs to be done to optimize the definition in this patient population.

Our study demonstrates several sociodemographic disparities in the development of sarcopenia in patients with liver disease. Specifically, we identified racial and ethnic disparities in the development of sarcopenia, particularly in all minorities other than non-Hispanic White and Black races. Black race was significantly associated with decreased prevalence of sarcopenia. In an NHANES

study comparing ALM/BMI to grip strength and gait speed, Bigman and Ryan found that Black patients were less likely to have sarcopenia based on muscle mass index, however more likely to have sarcopenia by gait speed and no difference in risk was found by grip strength [20]. Therefore, the diagnosis of sarcopenia in various races must be interpreted with caution, and further research needs to be done looking at race specific definitions of sarcopenia, particularly in patients with liver disease. This study is limited to the U.S. civilian population, therefore the applicability of these findings to patients in other countries with different risk factors and etiologies of liver disease must be further investigated. Similar to previous literature, we also found that lower levels of income and education were associated with a higher prevalence of sarcopenia [21, 22]. These disparities highlight additional challenges some patients may face related to their propensity to develop sarcopenia and means to intervene and treat the disease thereafter.

Physical activity level has previously been shown to be an independent predictor of sarcopenia in chronic liver disease [23]. While physical activity is beneficial in patients with cirrhosis, there are multiple reasons why patients with cirrhosis may get less exercise. In addition, patients with cirrhosis have diminished cardiac response to exercise [24, 25]. They require frequent healthcare appointments and are at risk of falls for reasons related and unrelated to sarcopenia, including hepatic encephalopathy. Furthermore, the severity of liver disease, sarcopenia, and exercise capacity are related [25], meaning patients at greatest need of physical activity may be those least likely to be able to do so. Importantly, exercise can attenuate or even reverse sarcopenia [25, 26]. While it may not be feasible or safe for all patients with cirrhosis to achieve our study's definition of ideal physical activity, the odds ratio for developing sarcopenia in inactive patients was 1.73 as compared to 1.39 in those achieving moderate activity, indicating some activity is likely better than no activity.

Telomere length shortens with age and shorter telomeres have been associated with increased mortality [27]. In this study, the interaction between telomere length and sarcopenia was significantly associated with mortality in patients with liver disease. In an NHANES study encompassing the years 1999–2002, in patients with sarcopenia (not limited by those with liver disease), there was not a significant association between telomere length and mortality [7]. Shortened telomere length has been associated with a higher risk of all-cause mortality in patients with liver disease [9]. Our results demonstrate that sarcopenia is associated with higher mortality at younger ages, and that shorter telomeres attenuate this effect. Telomerase, the enzyme responsible for telomere length regulation, is necessary for cell immortalization and oncogenesis [28]. The shortening of telomeres has two oppositional effects on cancer development, one being a tumor-suppressive effect through arrest of cellular proliferation and the other being telomere crisis where there is significant genome instability that can result in cancer development [29]. There is significant heterogeneity within the literature as to the impact of telomere length on cancer development, however longer telomeres have been shown to increase the risk for several cancers and reduce the risk for some other diseases, including cardiovascular disease [30]. An NHANES study from years 1999–2002 evaluating the association of telomere length with all-cause, cardiovascular, and cancer specific mortality risk among US adults when adjusted for sociodemographic and health-related characteristics including age found that increasing telomere length was associated with lower all-cause and cardiovascular mortality rates, but not cancer-relate mortality [31]. Therefore, the conflicting data in the literature regarding the association between telomere length and mortality is likely intertwined with cause of death. While our cross-sectional study assessed all-cause mortality, it is possible that the negative impact of longer telomeres on overall survival in younger patients with sarcopenia seen here is actually reflective of associations between telomere length and cause of death.

Strengths of our study include the large database of patients evaluated and that the NHANES survey is designed to be representative of the US population at large. Limitations of this study include the cross-sectional survey design of NHANES which is limited by the data that is publicly available and much of the survey data is self-reported by participants. DEXA scan is widely available and validated in the literature for the assessment of sarcopenia but does have limitations in its lack of functional assessment of muscle strength, limiting its accuracy in capturing the entirety of frailty syndrome. The Asian Working Group for Sarcopenia (AWGS) as well as the European Working Group on Sarcopenia in Older People (EWGSOP) include both muscle mass and strength in their definitions of sarcopenia [32, 33]. Our study is limited in the lack of assessment of muscle strength however DEXA scan is a readily available tool that makes the assessment of sarcopenia scalable to a large patient population at risk for this syndrome. DEXA can be used to measure three body components: fat, bone minerals, and lean tissue [34]. Appendicular lean mass (ALM) is the sum of lean mass from both arms and legs and when adjusted for BMI has been recommended by The FNIH Biomarkers Consortium Sarcopenia Project for the diagnosis

of sarcopenia [10]. Advantages of the use of DEXA for defining sarcopenia include its availability, efficiency, and reproducibility [5]. Disadvantages include that the equipment is not portable, and it is an indirect measurement of lean and fat mass meaning results can be affected by hydration status, body fluid changes, and ascites [5, 35].

An additional limitation of this study is that the available data is limited to that of the NHANES database. Specifically, DEXA scan was only obtained from years 1999–2006 and mortality data until 2015, therefore more recent DEXA and mortality data is not available. The overall prevalence and trends in prevalence of sarcopenia are difficult to discern given the heterogeneity of definitions used to define sarcopenia in the literature, therefore this large population-based study is indeed very relevant as we look to further understand and characterize sarcopenia at the population level. Additionally, other potential confounding variables such as genetics and nutritional habits were not able to be accounted for given the limitations of the NHANES database.

This study highlights the importance of assessing patients with liver disease for social determinants of health in order to identify risk factors that are associated with sarcopenia so appropriate resources can be provided. In addressing these health disparities, we may be able to prevent sarcopenia in some of our patients or at a minimum intervene more effectively. The implications of telomere length on mortality in patients with liver disease varies by age and sarcopenia status. Shorter telomeres appear to be more highly associated with increased mortality in older patients without sarcopenia. Future research on the complex interplay between sarcopenia, telomere length, and age is needed to fully elucidate their impact on outcomes including mortality in patients with liver disease.

Abbreviations

ALT	Alanine transaminase
ALD	Alcohol-associated Liver Disease
ALM	Appendicular Lean Mass
APRI	AST to Platelet Ratio Index
AST	Aspartate transaminase
BMI	Body Mass Index
CLD	Chronic Liver Disease
DEXA	Dual-energy x-ray absorptiometry
FIB-4	Fibrosis-4 Index
FNIH	Foundation for the National Institutes of Health
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
US FLI	Improved Fatty Liver Index for the multi-ethnic US population
MASLD	Metabolic-associated steatotic liver disease
NHANES	National Health and Nutrition Examination Survey
NLD	No Liver Disease
OLD	Other Liver Disease
VLD	Viral Liver Disease

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-024-03488-1.

Supplementary Material 1.

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Authors' contributions
All authors (CK, VK, BK, RL, PR, VS, PK, DS) contributed to study design and manuscript revision. CK wrote the background, methods, results, conclusion. BK and RL wrote the methodology. CK made all figures and tables except Figure 1 which was made by PR. BK, RL, PR performed the data analysis. VK provided revisions and reviewer response.

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Data availability
The datasets generated during and/or analyzed during the current study are available in the NHANES repository, NHANES - National Health and Nutrition Examination Survey Homepage (cdc.gov).

Declarations

Ethics approval and consent to participate
Approval for consent waived as NHANES data is publicly available.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Dhaliwal A, Armstrong MJ. Sarcopenia in cirrhosis: a practical overview. Clin Med (Lond). 2020;20(5):489–92.
2. Cho MR, Lee S, Song SK. A review of sarcopenia pathophysiology, diagnosis, treatment and future direction. J Korean Med Sci. 2022;37(18):e146.
3. Allen SL, et al. Sarcopenia in chronic liver disease: mechanisms and countermeasures. Am J Physiol Gastrointest Liver Physiol. 2021;320(3):G241-57.
4. Dasarathy S, Merli M. Sarcopenia from mechanism to diagnosis and treatment in liver disease. J Hepatol. 2016;65(6):1232–44.
5. Cruz-Jentoft AJ, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48(1):16–31.
6. Nault JC, et al. The role of telomeres and telomerase in cirrhosis and liver cancer. Nat Rev Gastroenterol Hepatol. 2019;16(9):544–58.
7. Rippberger PL, et al. The association of sarcopenia, telomere length, and mortality: data from the NHANES 1999–2002. Eur J Clin Nutr. 2018;72(2):255–63.
8. Zipf G, et al. National health and nutrition examination survey: plan and operations, 1999–2010. Vital Health Stat 1. 2013(56):1–37.
9. Rattan P, et al. Inverse association of telomere length with liver disease and mortality in the US population. Hepatol Commun. 2022;6(2):399–410.
10. Studenski SA, et al. The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. J Gerontol A Biol Sci Med Sci. 2014;69(5):547–58.
11. Needham BL, et al. Socioeconomic status, health behavior, and leukocyte telomere length in the National Health and Nutrition Examination Survey, 1999–2002. Soc Sci Medi. 2013;85:1–8.

12. Cawthon RM. Telomere measurement by quantitative PCR. Nucleic Acids Res. 2002;30(10):e47.
13. Ruhl CE, Everhart JE. Fatty liver indices in the multiethnic United States national health and nutrition examination survey. Aliment Pharmacol Ther. 2015;41(1):65–76.
14. Kwo PY, Cohen SM, Lim JK. ACG clinical guideline: evaluation of abnormal liver chemistries. Am J Gastroenterol. 2017;112(1):18–35.
15. McPherson S, et al. Age as a confounding factor for the accurate non-invasive diagnosis of advanced NAFLD fibrosis. Am J Gastroenterol. 2017;112(5):740–51.
16. Lin ZH, et al. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. Hepatology. 2011;53(3):726–36.
17. Singh A, et al. Implications of Protein and Sarcopenia in the Prognosis, Treatment, and Management of Metabolic DysfunctionAssociated Steatotic Liver Disease (MASLD). Nutrients. 2024;16(5):658.
18. Sinn DH, et al. Nonalcoholic fatty liver disease and accelerated loss of skeletal muscle mass: a longitudinal cohort study. Hepatology. 2022;76(6):1746–54.
19. Seko Y, et al. Clinical and pathological features of sarcopenia-related indices in patients with non-alcoholic fatty liver disease. Hepatol Res. 2019;49(6):627–36.
20. Bigman G, Ryan AS. Implications of race and ethnicity in Sarcopenia US National Prevalence of Sarcopenia by muscle mass, strength, and function indices. Gerontol Geriatr Res. 2021;4(1):126.
21. Dent E, et al. Toward the recognition and management of sarcopenia in routine clinical care. Nat Aging. 2021;1(11):982–90.
22. Tyrovolas S, et al. Factors associated with skeletal muscle mass, Sarcopenia, and sarcopenic obesity in older adults: a multi-continent study. J Cachexia Sarcopenia Muscle. 2016;7(3):312–21.
23. Ohashi K, et al. Relationship between sarcopenia and both physical activity and lifestyle in patients with chronic liver disease. J Clin Med Res. 2018;10(12):920–7.
24. Jones JC, Coombes JS, Macdonald GA. Exercise capacity and muscle strength in patients with cirrhosis. Liver Transpl. 2012;18(2):146–51.
25. Trovato FM, et al. The role of physical activity and nutrition in the sarcopenia of cirrhosis. J Funct Morphol Kinesiol. 2016;1(1):118–25.
26. Bowen TS, Schuler G, Adams V. Skeletal muscle wasting in cachexia and sarcopenia: molecular pathophysiology and impact of exercise training. J Cachexia Sarcopenia Muscle. 2015;6(3):197–207.
27. Shammas MA. Telomeres, lifestyle, cancer, and aging. Curr Opin Clin Nutr Metab Care. 2011;14(1):28–34.
28. Cong YS, Wright WE, Shay JW. Human telomerase and its regulation. Microbiol Mol Biol Rev 2002;66(3):407 – 25, table of contents.
29. Maciejowski J, de Lange T. Telomeres in cancer: tumour suppression and genome instability. Nat Rev Mol Cell Biol. 2017;18(3):175–86.
30. Haycock PC, et al. Association between telomere length and risk of cancer and non-neoplastic diseases: a mendelian randomization study. JAMA Oncol. 2017;3(5):636–51.
31. Kodali HP, Borrell LN. Telomere length and mortality risk among adults in the United States: the role of age and race and ethnicity. Ann Epidemiol. 2021;63:68–74.
32. Chen LK, et al. Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. J Am Med Dir Assoc. 2014;15(2):95–101.
33. Cruz-Jentoft AJ, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39(4):412–23.
34. Son SW, Song DS, Chang UI, Yang JM. Definition of Sarcopenia in Chronic Liver Disease. Life (Basel). 2021;11(4):349. https://doi.org/10.3390/life11040349.
35. Schweighofer N, et al. DXA-derived indices in the characterisation of sarcopenia. Nutrients. 2022;14(1):186.

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