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Frailty and Sarcopenia Modify the Prognostic Impact of Liver Disease in Community-Dwelling Older Adults: A Prospective Cohort Study

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Article

Keywords: Frailty, sarcopenia, older adults, liver disease, mortality

Posted Date: August 25th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9537528/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

Although frailty and sarcopenia are clinically important in advanced liver disease, their impact on community-dwelling older adults remains unclear. We aimed to assess their prevalence according to liver disease status and evaluate their association with mortality and long-term hospitalization.

Methods

We conducted a prospective population-based study of adults aged ≥ 65 years in Korea (2014–2020). The prevalence of frailty and sarcopenia was compared by liver disease status. Among participants with liver disease, multivariable Cox proportional hazards models were used to assess associations with all-cause mortality and long-term hospitalization, adjusting for potential confounders.

Results

Of 1,886 participants, 513 (27.2%) had liver disease, mostly non-cirrhotic. Liver disease alone was not associated with the prevalence of frailty or sarcopenia, nor with mortality or long-term hospitalization after adjustment. However, among those with liver disease, frailty and sarcopenia were independently associated with increased risk of the composite outcome (frailty: adjusted hazard ratio [aHR], 3.62; 95% confidence interval [CI], 2.04–6.43; sarcopenia: aHR, 2.41; 95% CI, 1.49–3.91).

Conclusions

In community-dwelling older adults, liver disease alone may not significantly influence outcomes. However, coexisting frailty or sarcopenia markedly increased the risks of mortality and long-term hospitalization highlighting the importance of geriatric assessment and targeted interventions.

INTRODUCTION

Liver disease is recognized as a major public health issue, contributing substantially to morbidity, mortality, and healthcare costs[1]. While advanced stages, such as cirrhosis and hepatocellular carcinoma (HCC), have long been a primary focus, there is increasing attention toward the potential impact of chronic, non-cirrhotic liver conditions—including metabolic-associated steatotic liver disease, alcohol-associated liver disease, and viral hepatitis—within the general population[1–3]. The clinical manifestations of these conditions can be heterogeneous. Depending on the underlying etiology and the individual's response to pharmacological treatments or lifestyle modifications, clinical trajectories may vary widely, ranging from the recovery of liver function to, in some cases, progression toward advanced disease[1–3].

Given the current increase in average life expectancy and the rapid aging of the population globally,[4] the effective treatment of liver disease must consider not only the severity of the disease itself but also the individual's functional status. Among geriatric syndrome, frailty and sarcopenia stand out as key prognostic indicators[5–7].

Frailty is a clinical state of increased vulnerability to stressors, characterized by reduced strength and physiological malfunctioning, which results in decreased homeostatic reserve[5, 6]. Sarcopenia involves the progressive loss of skeletal muscle mass and physical function[7]. Both are highly prevalent in older adults and have been established as powerful independent risk factors for mortality and hospitalization[5–7].

Geriatric syndrome, frailty and sarcopenia, also showed its importance on clinical outcomes for the patients with advanced liver disease[8–11]. However, a critical gap exists in understanding these relationships outside of tertiary referral centers. There is a scarcity of prospective data examining the influence of liver disease—encompassing early or non-cirrhotic stages—on frailty, sarcopenia and subsequent mortality in community-dwelling older adults. Consequently, it remains unclear whether the presence of liver disease per se independently dictates poor outcomes in a regional cohort, or if the risk is predominantly driven by a synergistic interaction between liver disease and functional decline – frailty, and sarcopenia.

To address this crucial knowledge gap, we conducted a prospective study using the Pyeongchang-gun community-based cohort to investigate the interplay between liver disease, geriatric syndrome (frailty and sarcopenia), and mortality. Our primary objectives were to: 1) compare the prevalence of frailty and sarcopenia according to the presence of liver disease; and 2) examine the prognostic impact of frailty and sarcopenia on all-cause mortality and long-term hospitalization in individuals with liver disease.

PATIENTS AND METHODS

Study design and population

We analyzed the records of the Aging Study of Pyeongchang Rural Area (ASPRA), a prospective, population-based cohort of older adults in Pyeongchang, Gangwon, South Korea, established in 2014. This cohort is designed to focus on frailty and geriatric syndromes in community-dwelling older adults. The detailed design and protocols of the ASPRA have been previously described[12]. The eligibility criteria for participating in ASPRA were: (1) age 65 years or older, (2) registration in the National Healthcare Insurance Service (NHIS), (3) ability to walk independently or with an assistive device, (4) residing at home, and (5) capacity to provide informed consent either personally or through a representative. Individuals who were on long-term institutionalized, hospitalized, or bed-ridden and receiving nursing home-level care at the time of recruitment were excluded. The ASPRA cohort includes approximately 90% of the eligible residents of Pyeongchang. Although it is a localized community cohort, its demographic and health profiles demonstrate comparability with the general population residing in South Korea's rural areas[12]. For the current study, a total of 2,075 participants were screened between 2014 and 2020.

To longitudinally evaluate healthcare utilization, mortality, and long-term care outcomes in this study, ASPRA participants were linked to the Korea NHIS database using personal identifiers such as name, age, and date of birth. The NHIS operates a universal health coverage system for almost all citizens of South Korea[13]. The NHIS database is a nationwide cohort that includes not only demographic information but also comprehensive healthcare utilization data, such as diagnoses based on the International Classification of Diseases, 10th Revision (ICD-10) codes, drug prescriptions, medical procedures, and results from national health examinations (2). This combined research design allowed for the long-term follow-up of major outcomes including mortality and hospitalization.

Out of the initial 2,075 screened ASPRA participants, individuals who met one of the following criteria were excluded from the final analysis: (1) those whose records could not be successfully linked to the NHIS database (n = 157); (2) those with a history of hepatocellular carcinoma (HCC) within five years prior to the index date (n = 7); and (3) those with a history of extrahepatic malignancies within five years prior to the index date (n = 25). There were no participants who had undergone a solid organ transplantation, including liver transplantation, prior to the index date. A total of 1,886 participants were included in the final analysis.

From this final cohort, participants with liver disease were defined as those who had at least two claims for liver disease (identified by relevant ICD-10 codes) to the NHIS database during the two years preceding the index date.[14–16] This yielded a liver disease group of 513 participants. The complete working definition of the diseases and outcomes used in this study is summarized in Supplementary Table 1. All methods were performed in accordance with the relevant guidelines and regulations. This study was conducted in accordance with the ethical standards of the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of Asan Medical Center (IRB No. 2015 – 0673). Informed consent was obtained from all participants and/or their legal guardians prior to their inclusion in the study.

Geriatric assessment

Frailty status was evaluated using three established tools: the Cardiovascular Health Study (CHS) frailty phenotype, the Frailty Index (FI), and the FRAIL questionnaire. Both the CHS phenotype, comprising exhaustion, low activity, slowness, weakness, and weight loss and the FRAIL questionnaire, assessing fatigue, resistance, ambulation, illness, and weight loss, utilize a 0–5 point scale to categorize participants as robust (0), prefrail (1–2), or frail (3–5)[17, 18]. Frailty index represents the cumulative deficit of the impaired items as a proportion of the total 34 assessment items[19]. Sarcopenia was evaluated based on the three core components: muscle mass, physical performance, and muscle strength following the criteria of both the Asian Working Group for Sarcopenia (AWGS 2019) and the European Working Group on Sarcopenia in Older People (EWGSOP2)[20, 21]. Detailed definition of frailty, sarcopenia, and other geriatric assessment is summarized in Supplementary Table 2.

Data collection from NHIS

Data regarding socioeconomic status and comorbidities documented during the two years prior to enrollment were collected. Socioeconomic status was determined based on household income as recorded in the income-based insurance contribution system. The Charlson Comorbidity Index (CCI) was calculated, excluding liver disease to facilitate comparisons between participants with and without liver disease[22]. Decompensated liver cirrhosis, representing advanced liver disease with major complications, was defined by the presence of an ICD-10 code for liver cirrhosis (K74) in conjunction with a documented clinical history of at least one of the following conditions: paracentesis or diuretic use for ascites control, treatment for variceal bleeding, or the administration of lactulose or rifaximin for hepatic encephalopathy. These conditions reflect clinically significant complications of portal hypertension or liver failure and therefore indicate severe comorbidity. Additionally, information on healthcare utilization (including outpatient visits and hospital admissions), mortality obtained through linkage with the national death registry, and long-term hospitalization was retrieved from the NHIS claims database.

Study outcomes

The primary outcome of this study was to compare the prevalence of frailty and sarcopenia according to the presence of liver disease and to investigate the association between liver disease and these geriatric syndromes within the general elderly population.

The secondary outcome focused specifically on the subgroup of participants with liver disease to analyze the impact of frailty and sarcopenia on adverse clinical outcomes. Specifically, we performed a risk analysis to determine the association of frailty and sarcopenia with mortality and long-term hospitalization among individuals with liver disease.

Statistical analysis

Participants from the ASPRA cohort were divided into two groups based on the presence or absence of liver disease. Categorical and continuous variables were compared between the groups using the chi-square test (or Fisher's exact test, if applicable) and the two sample T-test, respectively. To investigate the association between liver disease and the prevalence of geriatric syndromes (frailty and sarcopenia), logistic regression analysis was performed to estimate odds ratios (ORs) and their corresponding 95% confidence intervals (CIs), adjusting for potential confounders. The incidence rates (IRs) for mortality and long-term hospitalization were expressed as the number of events per 1,000 person-years, with confidence limits calculated based on the exact Poisson distribution. To compare these rates between the groups, incidence rate ratios (IRRs) were estimated. To assess the relative risk of mortality or long-term hospitalization, Cox proportional hazards models with robust standard errors were employed to estimate adjusted hazard ratios (aHRs). The cumulative incidence of death or hospitalization was illustrated using Kaplan–Meier curves and compared using the log-rank test. Statistical significance was defined as a P-value < 0.05. All statistical analyses were performed using SAS Enterprise Guide version 7.1 (SAS Institute, Inc., Cary, NC, USA) and R version 4.0.3 (R foundation for Statistical Computing, Vienna, Austria).

RESULT

Baseline characteristics of the study population

A total of 1,886 participants were enrolled, consisting of 513 individuals who had liver disease and 1,373 did not. (Table 1). Among participants with liver disease, nine were identified as having concomitant decompensated cirrhosis. The study population was characterized by a high proportion of individuals aged 70 years (49.7%), a female majority (58.3%), while 25.2% lived alone and 79.8% had an education level of elementary school or lower. The group with liver disease exhibited a significantly higher burden of comorbidities compared to those without liver disease, as reflected by higher CCI scores (3.11 ± 1.64 vs. 1.45 ± 1.36, P < .001). Specifically, the prevalence of hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, heart failure, and chronic lung disease was notably higher in the liver disease group than the counterpart.

Table 1
Baseline characteristics of study population according to the presence of liver disease

	Total	With liver disease	Without liver related disease	P-value
	(n = 1,886)	(n = 513)	(n = 1,373)	
Follow-up duration, mean (SD), y	4.83 (1.98)	4.25 (2.04)	5.04 (1.91)	< 0.001
Age groups, n (%)				0.339
65–69 years	519 (27.5)	135 (26.3)	384 (28.0)	
70–74 years	471 (25.0)	140 (27.3)	331 (24.1)	
75–79 years	466 (24.7)	134 (26.1)	332 (24.2)	
80–84 years	267 (14.2)	66 (12.9)	201 (14.6)	
85- years	163 (8.6)	38 (7.4)	125 (9.1)	
Female sex, n (%)	1,099 (58.3)	304 (59.3)	795 (57.9)	0.632
Socioeconomic status, n (%)				0.436
National health insurance	1,748 (92.7)	469 (91.4)	1279 (93.2)	
Household income < 30%	347 (18.4)	91 (17.7)	256 (18.6)	
Household income 30–70%	561 (29.7)	141 (27.5)	420 (30.6)	
Household income ≥ 70%	840 (44.5)	237 (46.2)	603 (43.9)	
Medical aid	102 (5.4)	31 (6.0)	71 (5.2)	
Unknown	36 (1.9)	13 (2.5)	23 (1.7)	
Living alone, n (%)	475 (25.2)	122 (23.8)	353 (25.7)	0.424
Education level				0.034
University, college or higher	82 (4.3)	17 (3.3)	65 (4.7)	
High school	141 (7.5)	43 (8.4)	98 (7.1)	
Middle school	158 (8.4)	40 (7.8)	118 (8.6)	
Elementary school	491 (26.0)	157 (30.6)	334 (24.3)	
Incomplete elementary school	1,014 (53.8)	256 (49.9)	758 (55.2)	
CCI score*, mean (SD)	1.90 (1.62)	3.11 (1.64)	1.45 (1.36)	< 0.001
Comorbidities, n (%)				
Hypertension	1,311 (69.5)	403 (78.6)	908 (66.1)	< 0.001
Diabetes mellitus	782 (41.5)	296 (57.7)	486 (35.4)	< 0.001
Dyslipidemia	1,173 (62.2)	446 (86.9)	727 (52.9)	< 0.001
Chronic kidney disease	46 (2.4)	19 (3.7)	27 (2.0)	0.045

	Total	With liver disease	Without liver related disease	P-value
	(n = 1,886)	(n = 513)	(n = 1,373)	
Heart failure	221 (11.7)	85 (16.6)	136 (9.9)	< 0.001
Myocardial infarction	51 (2.7)	17 (3.3)	34 (2.5)	0.402
Chronic lung disease	759 (40.2)	241 (47.0)	518 (37.7)	< 0.001
Decompensated cirrhosis	9 (0.5)	9 (1.8)	0 (0)	< 0.001
Multimorbidity[†]	753 (39.9)	251 (48.9)	502 (36.6)	< 0.001
Cognitive dysfunction by MMSE-DS	489 (26.1)	128 (25.0)	361 (26.5)	0.568
Depression by CES-D	155 (8.3)	47 (9.2)	108 (7.9)	0.413
Malnutrition by MNA-SF[‡]				0.144
Normal	1,173 (62.2)	302 (58.9)	871 (63.4)	
At risk of malnutrition	641 (34.0)	187 (36.5)	454 (33.1)	
Malnourished	72 (3.8)	24 (4.7)	48 (3.5)	
ADL, n (%)	326 (17.3)	112 (21.8)	214 (15.6)	0.002
IADL, n (%)	508 (26.9)	131 (25.5)	377 (27.5)	0.436
SPPB[§]	7.8 (3.6)	8.2 (3.5)	7.7 (3.6)	0.003
Body mass index, mean (SD), kg/m^2	24.7 (3.2)	24.9 (3.3)	24.6 (3.2)	0.019
ASM/height$^{2\|\|}$, kg/m^2, mean (SD)	6.46 (1.18)	6.51 (1.23)	6.45 (1.16)	0.258
Grip strength, kg, mean (SD)	22.58 (9.50)	22.41 (9.51)	22.64 (9.50)	0.633
Gait speed, m/s, mean (SD)	0.80 (0.32)	0.79 (0.32)	0.81 (0.32)	0.216
Smoking, n (%)	157 (8.3)	35 (6.8)	122 (8.9)	0.177
Alcohol consumption[¶], n (%)				0.751
Non or mild drinker	1,827 (96.9)	498 (97.1)	1,329 (96.8)	
Moderate drinker	47 (2.5)	11 (2.1)	36 (2.6)	
Severe drinker	12 (0.6)	4 (0.8)	8 (0.6)	

	Total	With liver disease	Without liver related disease	P-value
	(n = 1,886)	(n = 513)	(n = 1,373)	
* CCI was calculated by excluding liver disease to avoid overlapping with the main exposure				
†Multimorbidity was defined as the presence of two or more following chronic conditions: angina, arthritis, asthma, cancer excluding minor skin cancer, chronic lung disease, congestive heart failure, diabetes, heart attack, hypertension, kidney disease, and stroke				
‡Mini-Nutritional Assessment Short-Form (MNA-SF) score < 8 points; At risk for malnutrition as 8–11 points; and Normal nutrition as 12–14 points.				
§ The Short Physical Performance Battery consists of three objective physical function tests: standing balance, gait speed, and the chair stand test. Scores range from 0 (worst) to 12 (best).				
‖ Calculated as the sum of lean muscle mass in the four limbs divided by the square of the height.				
¶ Alcohol consumption as non or mild (M: 0–30 g/day, F: 0–20 g/day), moderate (M: 30–60 g/day, F: 20–50 g/day), and severe (M: >60 g/day, F: >50 g/day).				

Abbreviations: ADL, activities of daily living; ASM, appendicular skeletal muscle mass; BMI, body mass index; CCI, Charlson comorbidity index; CES-D, Center for Epidemiological Studies Depression scale; IADL, instrumental activities of daily living; MMSE-DS, Mini-Mental State Examination for Dementia Screening; MNA-SF, Mini Nutritional Assessment-Short Form; SD, standard deviation; SPPB, Short Physical Performance Battery

Association between liver disease, frailty, and sarcopenia

The baseline prevalence of frailty did not differ significantly between individuals with and without liver disease, regardless of the assessment tool used: frailty phenotype (21.8% vs. 21.0%; P = 0.778), frailty index (32.0% vs. 30.1%; P = 0.570), or FRAIL criteria (16.4% vs. 18.4%; P = 0.279). Similarly, the prevalence of sarcopenia was comparable between the two groups when defined by both AWGS (21.1% vs. 24.2%; P = 0.284) and EWGSOP2 criteria (24.2% vs. 27.5%; P = 0.329).

After adjusting for age, sex, socioeconomic status, living alone, and education level, liver disease was not significantly associated with frailty or sarcopenia across all models (Table 2). Regarding frailty, the frailty phenotype, frailty index, and FRAIL criteria showed no statistically significant associations with liver disease. Similarly, liver disease was not significantly associated with sarcopenia defined by EWGSOP or AWGS criteria. Overall, no statistically significant associations were found between liver disease and either frailty or sarcopenia in this population.

Table 2
Association between liver disease and the risk of frailty and sarcopenia (n = 1,886)

	Model 1		**Model 2**		**Model 3**		**Model 4**		**Model 5**	
	Frailty by frailty phenotype		**Frailty by frailty index**		**Frailty by FRAIL criteria**		**Sarcopenia by AWGS**		**Sarcopenia by EWGSOP**	
	OR (95% CI)*	P-value	OR (95% CI)*	P-value	OR (95% CI)*	P-value	OR (95% CI)*	P-value	OR (95% CI)*	P-value
Main exposure										
No	ref		ref		ref		ref		ref	
Yes	1.10 (0.84–1.43)	0.489	1.16 (0.90–1.50)	0.247	0.88 (0.66–1.18)	0.401	0.88 (0.69–1.11)	0.264	0.85 (0.67–1.07)	0.170
Age group										
65–69 years	ref		ref		ref		ref		ref	
70–74 years	2.15 (1.42–3.25)	< 0.001	2.50 (1.71–3.66)	< 0.001	2.53 (1.60–3.99)	< 0.001	1.91 (1.38–2.64)	< 0.001	1.74 (1.32–2.30)	< 0.001
75–79 years	3.23 (2.17–4.81)	< 0.001	5.00 (3.46–7.22)	< 0.001	3.39 (2.18–5.28)	< 0.001	3.21 (2.34–4.39)	< 0.001	4.04 (3.02–5.40)	< 0.001
80–84 years	4.73 (3.09–7.25)	< 0.001	7.93 (5.28–11.89)	< 0.001	4.71 (2.95–7.52)	< 0.001	5.43 (3.82–7.72)	< 0.001	6.05 (4.17–8.78)	< 0.001
≥ 85 years	7.40 (4.65–11.75)	< 0.001	11.38 (7.16–18.10)	< 0.001	5.11 (3.07–8.49)	< 0.001	10.00 (6.58–15.20)	< 0.001	9.46 (5.68–15.76)	< 0.001
Sex										
Female	ref		ref		ref		ref		ref	
Male	0.63 (0.48–0.83)	0.001	0.32 (0.25–0.42)	< 0.001	0.57 (0.42–0.77)	< 0.001	1.25 (0.99–1.57)	0.055	0.65 (0.52–0.81)	< 0.001
Socioeconomic status										
Household income < 30%	ref		ref		ref		ref		ref	

*All models were adjusted for age, sex, socioeconomic status, living alone, and education level.

Abbreviations: AWGS, Asian Working Group for Sarcopenia; CHS, Cardiovascular Health Study; CI, confidence interval; EWGSOP, European Working Group on Sarcopenia in Older People; FRAIL, fatigue, resistance, ambulation, illness, and loss of weight; OR, odds ratio

	Model 1		Model 2		Model 3		Model 4		Model 5	
	Frailty by frailty phenotype		Frailty by frailty index		Frailty by FRAIL criteria		Sarcopenia by AWGS		Sarcopenia by EWGSOP	
Household income 30–70%	0.80 (0.56–1.14)	0.210	0.76 (0.54–1.07)	0.110	0.78 (0.54–1.13)	0.190	0.95 (0.70–1.28)	0.886	1.01 (0.74–1.39)	0.088
Household income ≥ 70%	0.90 (0.65–1.24)	0.520	0.78 (0.57–1.07)	0.130	0.83 (0.59–1.17)	0.300	0.71 (0.53–0.94)	0.018	1.20 (0.89–1.61)	0.240
Medical aid	1.46 (0.88–2.43)	0.162	1.41 (0.84–2.36)	0.078	1.50 (0.89–2.54)	0.172	0.93 (0.57–1.50)	0.972	2.25 (1.27–4.01)	0.010
Unknown	1.56 (0.67–3.62)	0.294	1.12 (0.47–2.64)	0.718	1.93 (0.82–4.54)	0.112	1.13 (0.52–2.45)	0.523	1.13 (0.51–2.50)	0.741
Living alone	0.97 (0.74–1.27)	0.796	0.94 (0.72–1.22)	0.637	1.04 (0.79–1.38)	0.774	1.17 (0.92–1.50)	0.200	1.17 (0.90–1.52)	0.253
Education level										
Elementary education or less	ref		ref		ref		ref		ref	
Middle school or higher	0.58 (0.49–0.68)	< 0.001	0.50 (0.43–0.59)	< 0.001	0.49 (0.40–0.60)	< 0.001	0.70 (0.62–0.79)	< 0.001	0.56 (0.50–0.62)	< 0.001

*All models were adjusted for age, sex, socioeconomic status, living alone, and education level.

Abbreviations: AWGS, Asian Working Group for Sarcopenia; CHS, Cardiovascular Health Study; CI, confidence interval; EWGSOP, European Working Group on Sarcopenia in Older People; FRAIL, fatigue, resistance, ambulation, illness, and loss of weight; OR, odds ratio

Association between liver disease and mortality or long-term hospitalization

There were no significant differences in the risk of mortality or long-term hospitalization between groups with and without liver disease. Over a mean follow-up of 4.83 ± 1.98 years, the liver disease group experienced 46 deaths and 65 long-term hospitalizations, yielding an IR of 45.58 per 1,000 person-years (95% CI, 36.31–54.85). In comparison, the group without liver disease had 170 deaths and 233 long-term hospitalizations (IR 50.56; 95% CI, 45.05–56.07), with an IRR of 0.90 (95% CI, 0.72–1.14; P = 0.379). After adjusting for age, sex, socioeconomic status, frailty, and sarcopenia, the adjusted hazard ratio for the composite outcome was 1.14 (95% CI, 0.90–1.44; P = 0.267), indicating no significant independent association with liver disease status (Supplementary Table 3, Supplementary Fig. 1).

Prognostic impact of frailty in participants with liver disease

Among the 513 participants with liver disease, 112 (21.8%) were classified as frail and 401 (78.2%) as non-frail based on the frailty phenotype (Supplementary Table 4). The frail group was significantly older than the non-frail group and was predominantly female. Lower educational attainment was more prevalent in the frail group, with 72.3% not having completed elementary school. Additionally, frailty was associated with a higher burden of cognitive dysfunction and poorer nutritional status compared to the non-frail group.

During a mean follow-up of 4.25 ± 2.04 years, the frailty group (defined by frailty phenotype) experienced 48 events (IR, 29.36 per 1,000 person-years), while the non-frailty group had 45 events (IR, 6.60 per 1,000 person-years). The IRR was 4.44 (95% CI, 2.96–6.67; P < .001), indicating a significantly higher event rate in the frail group. Likewise, the IRRs for the frailty index and FRAIL criteria were also significantly elevated at 5.81 (95% CI, 3.73–9.05) and 2.74 (95% CI, 1.82–4.12), respectively (Table 3). After adjustment, frailty remained an independent predictor of adverse outcomes including mortality and long-term hospitalization, with the strongest association observed for the frailty index (aHR 3.62; 95% CI, 2.04–6.43; P < .001), followed by the frailty phenotype (aHR 2.59; 95% CI, 1.53–4.38; P < .001), whereas the FRAIL criteria did not reach statistical significance (aHR 1.48; 95% CI, 0.89–2.46; P = 0.130) (Supplementary Table 5, Fig. 1A–C).

Table 3
Incidence rates and incidence rate ratios of mortality and long-term hospitalization by frailty and sarcopenia status in patients with liver disease (n = 513)

Outcome	Group	Events, n (%)	Sum of person-years	Incidence rate (95% CI)	Incidence rate ratio (95% CI)	P-value
Frailty phenotype	No	45 (6.6)	6814.55	6.60 (4.68–8.53)	ref	< 0.001
	Yes	48 (29.4)	1635.06	29.36 (21.05–37.66)	4.44 (2.96–6.67)	
Frailty index	No	28 (4.6)	6094.43	4.59 (2.89–6.29)	ref	< 0.001
	Yes	65 (27.6)	2355.18	27.60 (20.90–34.30)	5.81 (3.73–9.05)	
FRAIL criteria	No	59 (8.5)	6974.78	8.46 (6.31–10.61)	ref	< 0.001
	Yes	34 (23.2)	1465.75	23.20 (15.42–30.98)	2.74 (1.82–4.12)	
Sarcopenia by AWGS	No	37 (6.4)	5778.03	6.40 (4.34–8.46)	ref	< 0.001
	Yes	56 (21.0)	2671.58	20.96 (15.48–26.44)	3.69 (2.44–5.59)	
Sarcopenia by EWGSOP	No	31 (5.2)	5941.95	5.22 (3.38–7.05)	ref	< 0.001
	Yes	62 (24.7)	2507.67	24.72 (18.57–30.87)	4.57 (2.97–7.04)	

* Incidence rate: Calculated as the number of events per 1,000 person-years.

Abbreviations: AWGS, Asian Working Group for Sarcopenia; CI, confidence interval; EWGSOP, European Working Group on Sarcopenia in Older People; FRAIL, fatigue, resistance, ambulation, illness, and loss of weight; HR, hazard ratio; IRR, incidence rate ratio

Prognostic impact of sarcopenia in participants with liver disease

Among 513 participants with liver disease, 160 (31.2%) were classified as having sarcopenia and 353 (68.8%) as non-sarcopenic based on the AWGS criteria. The sarcopenia group was significantly older than the non-sarcopenia group. Lower educational attainment was more prevalent in the sarcopenia group than the counterpart, with 66.9% not having completed elementary school. The participants with sarcopenia had higher burden of cognitive dysfunction and poorer nutritional status compared to those without sarcopenia (Supplementary Table 6). During a mean follow-up of 4.25 ± 2.04 years among participants with liver disease, the sarcopenia group by AWGS criteria experienced 56 events of death or long-term hospitalization (IR = 20.96 per 1,000 person-years), while the non-sarcopenia group had 37 events (IR = 6.40 per 1,000 person-years). The IRR was 3.69 (95% CI 2.44–5.59; P < .001), indicating a significantly higher event rate in the sarcopenia group (Table 3). Consistent results were found using the EWGSOP criteria, which yielded an even higher IRR of 4.57 (95% CI, 2.97–7.04; P < .001) based on 62 events in

the sarcopenia group (IR, 24.72 per 1,000 person-years). Sarcopenia remained an independent predictor of poor prognosis in both models; the adjusted risk was significantly elevated under both EWGSOP (aHR 2.41; 95% CI, 1.49–3.91; P < .001) and AWGS criteria (aHR 2.12; 95% CI, 1.34–3.36; P = 0.001) (Supplementary Table 5, Fig. 2A, 2B).

DISCUSSION

This prospective, community-based cohort study provides insight into the prognostic relevance of geriatric syndromes in older adults with predominantly mild, non-cirrhotic liver disease. In this setting, liver disease *per se* was not independently associated with frailty, sarcopenia, or adverse clinical outcomes. However, among participants with liver disease, frailty and sarcopenia were associated with a substantially higher risk of the composite outcome of all-cause mortality or long-term hospitalization.

Importantly, our findings should not be interpreted as evidence that liver disease is clinically irrelevant in older adults. Rather, they suggest that in a community-dwelling population with largely compensated or early-stage liver disease, functional vulnerability may represent a more proximal determinant of prognosis than liver disease status alone. This contrasts with previous studies reporting strong associations between liver disease and geriatric syndromes; however, most prior evidence was derived from hospital-based populations with advanced liver disease[8–11, 23, 24]. In the hospital-based cohort, frailty and sarcopenia have consistently been associated with disease progression, unplanned hospitalizations, prolonged length of stay, complications, and mortality[8–10]. In contrast, our study was conducted in a community-dwelling population in which liver disease was predominantly mild and non-cirrhotic, with only 1.8% of participants meeting criteria for decompensated cirrhosis. Thus, the overall physiological burden attributable to hepatic dysfunction was likely modest in most individuals. It is therefore plausible that early-stage liver disease, in isolation, may not generate sufficient systemic stress to independently drive functional decline or adverse outcomes. Differences in age distribution may further explain the divergence from earlier reports. Whereas prior studies included broader adult populations with mean ages ranging from 47 to 69 years, our cohort consisted exclusively of adults aged 65 years or older[8–11, 23, 24]. In advanced age, frailty and sarcopenia become highly prevalent as a consequence of intrinsic aging processes and cumulative multimorbidity[5–7, 20, 21]. Under these circumstances, functional vulnerability reflects a complex interplay of nutritional status, social determinants, chronic inflammation, and multiple comorbid conditions. Accordingly, in a population where age-related vulnerability is already common, the incremental contribution of mild liver disease may be relatively small and insufficient to meaningfully differentiate survival or functional trajectories contrast to younger or more clinically severe populations where hepatic dysfunction itself may represent a dominant driver of risk.

In our study, participants with concomitant liver disease and frailty exhibited a significantly increased risk of mortality and long-term hospitalization, with a 1.48- to 3.62-fold higher risk, depending on the frailty definition, compared to their non-frail counterparts. It is increasingly recognized as a multidimensional syndrome associated with chronic inflammation, metabolic dysregulation, and impaired homeostatic capacity[5, 6, 25, 26]. Persistent inflammatory signaling may potentiate hepatic stellate cell activation and fibrogenesis, while metabolic dysregulation exacerbates lipotoxicity and oxidative stress within hepatocytes. Under these systemic alterations, even mild liver disease may heighten individual vulnerability, leading to adverse outcomes. Zhong et al. reported that among individuals with mild liver disease, the coexistence of frailty is associated with a markedly increased risk of progression to cirrhosis and hepatocellular carcinoma, with HRs ranging from 2.25 to 2.44 and 1.18 to 2.28,

respectively[27]. Previous studies have suggested that frailty may accelerate liver disease progression and amplify systemic consequences. This supports our finding that frailty acts as a critical risk factor for mortality and long-term hospitalization, rendering otherwise mild liver disease clinically consequential in older adults.

The coexistence of liver disease and sarcopenia in our cohort was associated with a 2.12- to 2.41-fold increased risk of mortality and long-term hospitalization. These findings align with prior evidence demonstrating that sarcopenia predicts adverse outcomes independently of the severity of hepatic dysfunction[28]. Rather than serving merely as a comorbid condition, sarcopenia appears to biologically interact with hepatic impairment, forming a self-reinforcing liver–muscle axis that amplifies systemic vulnerability. In aging individuals, skeletal muscle is characterized by anabolic resistance, mitochondrial dysfunction, and heightened inflammatory signaling. Superimposed liver disease exacerbates this milieu through chronic low-grade inflammation, altered nutrient sensing, and impaired endocrine signaling[29]. The chronic inflammation induced by both liver disease and the aging process produces pro-inflammatory cytokines which activate the ubiquitin–proteasome–dependent proteolysis and muscle atrophy[29, 30].

Furthermore, the aging liver even in the absence of advanced cirrhosis, characterized by a decline in regenerative capacity and increased mitochondrial oxidative stress, fails to clear systemic toxins, such as ammonia, effectively[30]. Hyperammonemia induces mitochondrial oxidative stress in skeletal muscle, upregulates myostatin expression, and suppresses mechanistic target of rapamycin (mTOR)–mediated protein synthesis, thereby further shifting muscle protein balance toward net degradation[31]. In parallel, diminished hepatic insulin-like growth factor-1 bioavailability, compounded by inflammation-associated growth hormone resistance, attenuates anabolic signaling and limits compensatory muscle regeneration[29, 31]. Importantly, skeletal muscle serves as a major site for insulin-mediated glucose disposal and functions as an auxiliary organ for ammonia detoxification through glutamine synthesis[31]. Progressive muscle loss therefore reduces metabolic buffering capacity and diminishes systemic resilience to metabolic stress. Within this liver–muscle axis, even mild hepatic dysfunction may become clinically consequential in sarcopenic individuals, culminating in the substantially increased risks of mortality and long-term hospitalization observed in our cohort.

This is a prospective, population-based study using a well-validated community-dwelling cohort linked with nationwide healthcare utilization data, which allowed for a robust longitudinal analysis of the synergistic impact of liver disease and geriatric syndromes on long-term clinical outcomes. However, there are several limitations. First, liver disease was identified using ICD-10 diagnostic codes from the NHIS database. While this approach is validated for large-scale epidemiological studies[13], it lacks laboratory results or imaging, which may lead to underdiagnosis. Further validation of liver disease and geriatric syndrome in community dwelling older adults are required. Second, the ASPRA cohort consisted of community-dwelling older adults in a specific rural region of South Korea. Although its demographic profile is comparable to other areas in Korea[12], the results may not be fully generalizable to different ethnic groups with different lifestyle and dietary habits. Future studies involving multi-ethnic and international cohorts are necessary to confirm the generalizability of the synergistic impact of liver disease and geriatric syndrome. Third, geriatric assessments were performed only at the time of enrollment. We could not account for potential longitudinal changes in frailty or sarcopenia status during the follow-up period.

In this community-dwelling older population, the presence of liver disease alone did not independently predict frailty, sarcopenia, or mortality. However, the coexistence of liver disease with frailty or sarcopenia was associated with a markedly increased risk of mortality or long-term hospitalization, even when liver disease was

predominantly mild and non-cirrhotic. Our results underscore the importance of incorporating geriatric assessment into the evaluation of older adults with liver disease and suggest that identifying and addressing frailty and sarcopenia may be critical for improving long-term outcomes.

Declarations

Ethics approval and consent to participate: This study was approved by the Institutional Review Board of Asan Medical Center (IRB No. 2015-0673). All participants provided written informed consent.

Preprint: This work has not been presented at any meeting and has not been posted as a preprint.

Consent for publication: Not applicable

Availability of data and materials: The data that support the findings of this study are available upon request from Il-Young Jang, upon reasonable request. The data are not publicly available as they contain information that could compromise the privacy of research participants.

Funding: This study supported by the grants from the Catholic Medical Center Research Foundation made in the program year of 2025 and by the Research fund of Hanyang University (HY-202500000001286).

Author contributions: All authors had full access to the data used in this study and take responsibility for its integrity and the accuracy of the analyses. All authors were responsible for the data acquisition and critical revision of the manuscript and approved the final version.

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Moonsuk Bae: Validation, Resources, Writing - Review & Editing

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Hwa Jung Kim: Conceptualization, Methodology, Formal analysis, Data Curation, Writing - Review & Editing, Supervision

Il-Young Jang: Conceptualization, Project administration, Supervision

Competing interests: None.

Acknowledgements: None

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Figures

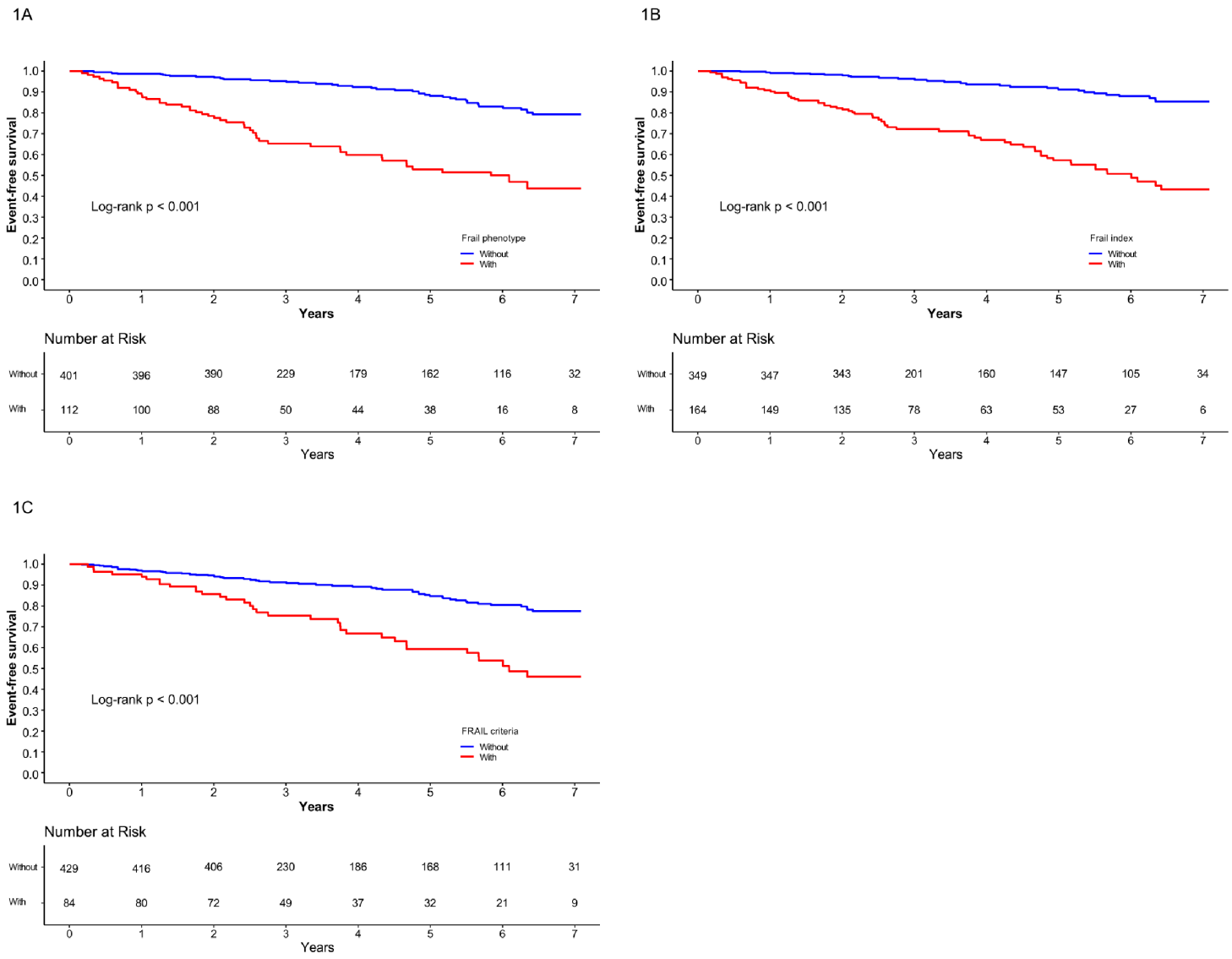


Figure 1

Kaplan-Meier curves for the risk of mortality and long-term hospitalization according to frailty status. Results are presented by (A) Frailty Phenotype, (B) Frailty Index, and (C) FRAIL criteria

P-value was determined by the log-rank test

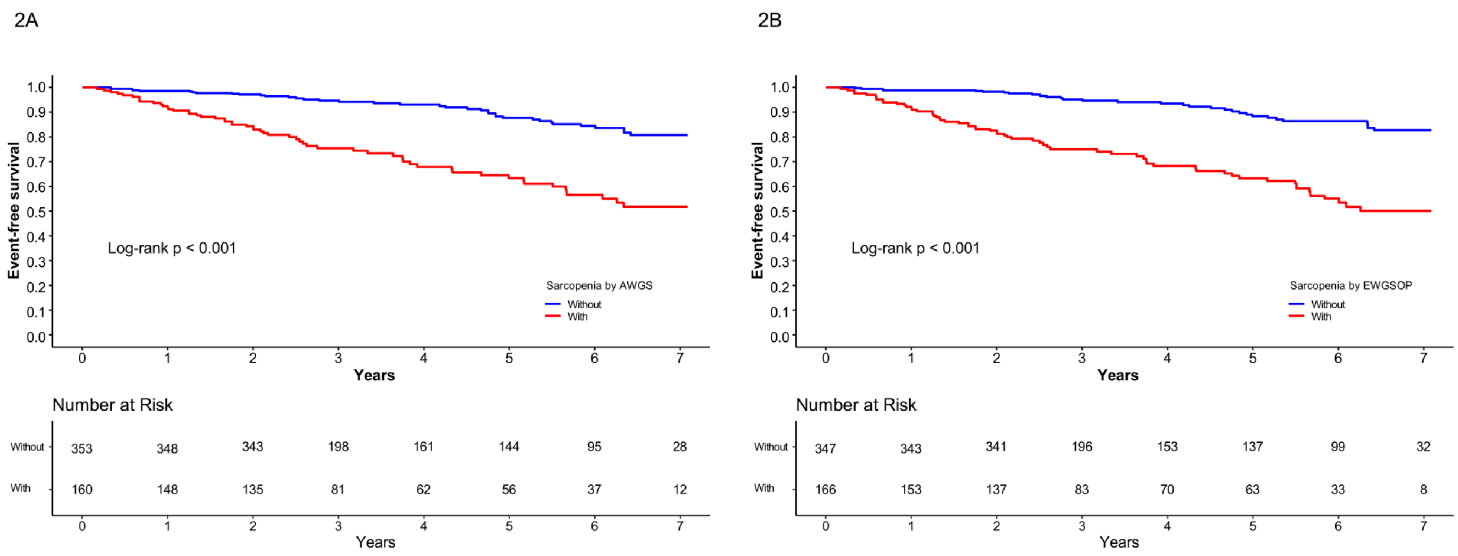


Figure 2

Kaplan-Meier curves for the risk of mortality and long-term hospitalization according to sarcopenia status. Results are presented by (A) sarcopenia by AWGS and (B) sarcopenia by EWGSOP.

P-value was determined by the log-rank test Abbreviations: AWGS, Asian Working Group for Sarcopenia; EWGSOP, European Working Group on Sarcopenia in Older People.

Supplementary Files

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- Supplementarymaterials.docx