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Sarcopenia is associated with the risk of significant liver fibrosis in metabolically unhealthy subjects with chronic hepatitis B

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Summary

Background: Sarcopenia is significantly associated with the degree of liver fibrosis. This study investigated the influence of sarcopenia on liver fibrosis in individuals with chronic hepatitis B.

Methods: Data from the Korean National Health and Nutrition Examination Surveys 2008-2011 were analysed. The sarcopenia index (total appendicular skeletal muscle mass [kg]/body mass index [kg/m^2]) was calculated using dual-energy X-ray absorptiometry. Sarcopenia was defined as the lowest quintile sarcopenia index value (cut-offs: 0.89 for men and 0.58 for women). The fibrotic burden was assessed using the nonalcoholic fatty liver disease fibrosis score and fibrosis-4 index. Significant fibrosis was defined as the highest nonalcoholic fatty liver disease fibrosis score quartile and a fibrosis-4 index ≥2.67.

Results: Among the 506 respondents with chronic hepatitis B (258 men and 248 women), the nonalcoholic fatty liver disease fibrosis score and fibrosis-4 index identified sarcopenia and significant fibrosis in 126 (24.9%) and 217 (42.9%), respectively. Sarcopenia was significantly associated with significant fibrosis, regardless of the fibrosis prediction model used (all $P < 0.05$). When the study population was stratified according to metabolic factors, sarcopenia was specifically associated with an increased risk of significant fibrosis among subgroups with obesity, insulin resistance, metabolic syndrome and liver steatosis (odds ratio 2.37-3.57; all $P < 0.05$). An independent association between sarcopenia and significant fibrosis was identified after adjusting for other confounders (odds ratio 2.67-3.62 by the nonalcoholic fatty liver disease fibrosis score and 2.04-2.62 by the fibrosis-4 index; all $P < 0.05$).

Conclusions: Sarcopenia is associated with significant fibrosis in subjects with chronic hepatitis B, specifically those with obesity, insulin resistance, metabolic syndrome and liver steatosis.

Eugene Han and Yong-ho Lee equally contributed to this work.

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1 | INTRODUCTION

Despite an effective vaccine and anti-viral therapy (AVT), chronic hepatitis B (CHB) is still a major public health problem worldwide, especially in Asian countries, where hepatitis B virus (HBV) infections are endemic.[1] More than 350 million people have HBV infections worldwide, and nearly 1 million deaths occur each year because of HBV-related complications, such as liver cirrhosis and hepatocellular carcinoma.[2]

Liver fibrosis is the final outcome of a wound healing response; it is driven by necroinflammation in response to parenchymal acute or chronic injury.[3] There are many well established risk factors for the progression of fibrosis from mild to advanced liver fibrosis or cirrhosis in CHB patients.[4] These include demographic factors (older age, male gender, significant alcohol consumption), metabolic factors (liver steatosis, obesity, diabetes) and virus-related factors (co-infection with hepatitis C virus, hepatitis D virus, or human immunodeficiency virus, the presence of hepatitis B e antigen, uncontrolled HBV replication). Nevertheless, the degree of liver fibrosis is regarded as the single most important predictor of the long-term prognosis of CHB patients.[5]

Effective AVT can suppress the virus-related factors related to fibrosis progression and subsequently induce the regression of liver fibrosis and even the reversal of liver cirrhosis in CHB patients.[6,7] However, other demographic or metabolic factors cannot be controlled by AVT alone, and CHB patients are still susceptible to fibrosis progression. Therefore, it remains of paramount importance to identify risk factors for fibrosis progression other than virus-related factors and assess the fibrotic burden under AVT in the service of identifying high-risk subjects and determining the optimal time point for initiating medical interventions, especially in this era of active and potent AVT.

A recent study reported that sarcopenia is independently associated with liver cirrhosis.[8] Loss of skeletal muscle mass or sarcopenia is the most common complication of cirrhosis. It adversely affects survival, quality of life, outcome after liver transplantation and response to stress, including infection and surgery.[9] Indeed, sarcopenia is recognised as a major complication of a number of chronic diseases, including cancer, chronic obstructive pulmonary disease, chronic heart failure and chronic renal failure.[9-11] Additionally, several recent Korean cross-sectional epidemiologic studies found that sarcopenia was independently associated with nonalcoholic fatty liver disease (NAFLD)-related advanced fibrosis,[12] independent of insulin resistance and obesity.[13,14] However, no association between sarcopenia and degree of liver fibrosis has been reported in CHB patients.

Thus, we investigated whether, independent of several metabolic factors (eg obesity, insulin resistance, metabolic syndrome and liver steatosis), sarcopenia is significantly associated with the degree of liver fibrosis in CHB subjects. This study analysed data from the Korea National Health and Nutrition Examination Survey (KNHANES), a nationwide cross-sectional cohort study conducted annually with a nationally representative sample of the Korean population by the Korea Center for Disease Control and Prevention to regularly assess the health and nutritional status of the general civilian population.

2 | SUBJECTS AND METHODS

2.1 | Study subjects

The KNHANES is a nationwide, population-based, cross-sectional health examination and survey that is regularly conducted by the Division of Chronic Disease Surveillance of the Korea Centers for Disease Control and Prevention in the Ministry of Health and Welfare to monitor the general health and nutrition status of South Koreans.[15] Each KNHANES is composed of independent data sets of subjects from the general population of South Korea. Subjects are randomly selected from 600 randomly selected districts of cities and provinces in South Korea. As depicted in Figure 1, of the 37 753 subjects from the KNHANES 2008-2011, we initially selected 28 071 subjects aged ≥20 years (12 160 men and 15 911 women). Then, 27 565 subjects who met the following criteria were excluded: (1) insufficient clinical and laboratory information to calculate muscle mass and body mass index or calculate the degree of liver fibrosis or steatosis, (2) negative serologic markers for HBV or hepatocellular carcinoma at enrolment or past history of it, or (3) co-infection with hepatitis C virus.

Written informed consent was secured from all subjects before the study began, and the KNHANES was conducted following ethical approval by the Institutional Review Board of the Korea Center for Disease Control and Prevention (No: 2008-04EXP-01-C, 2009-01CON-03-2C, 2010-02CON-21-C, and 2011-02CON-06C).

2.2 | Appendicular skeletal muscle mass and the definition of sarcopenia

As described previously,[13] appendicular skeletal muscle mass was measured using dual-energy X-ray absorptiometry (QDR 4500A; Hologic Inc., Bedford, MA, USA). The sarcopenia index was calculated as follows: sarcopenia index = total appendicular skeletal muscle mass (kg)/body mass index (kg/m^2); this was officially designated as a definition by a recent consensus meeting known as the "Foundation for the National Institutes of Health Sarcopenia Project".[16] Sarcopenia was defined as the lowest quintile for sex-specific sarcopenia index cut-off values (<0.89 for men and <0.58 for women) modified from the Foundation for the National Institutes of Health recommendation.

2.3 | Clinical parameters and biochemical analysis

As described previously,[13] KNHANES examined subject demographics and personal and family medical history, including data on anthropometrics, smoking history and physical activity, using standardised

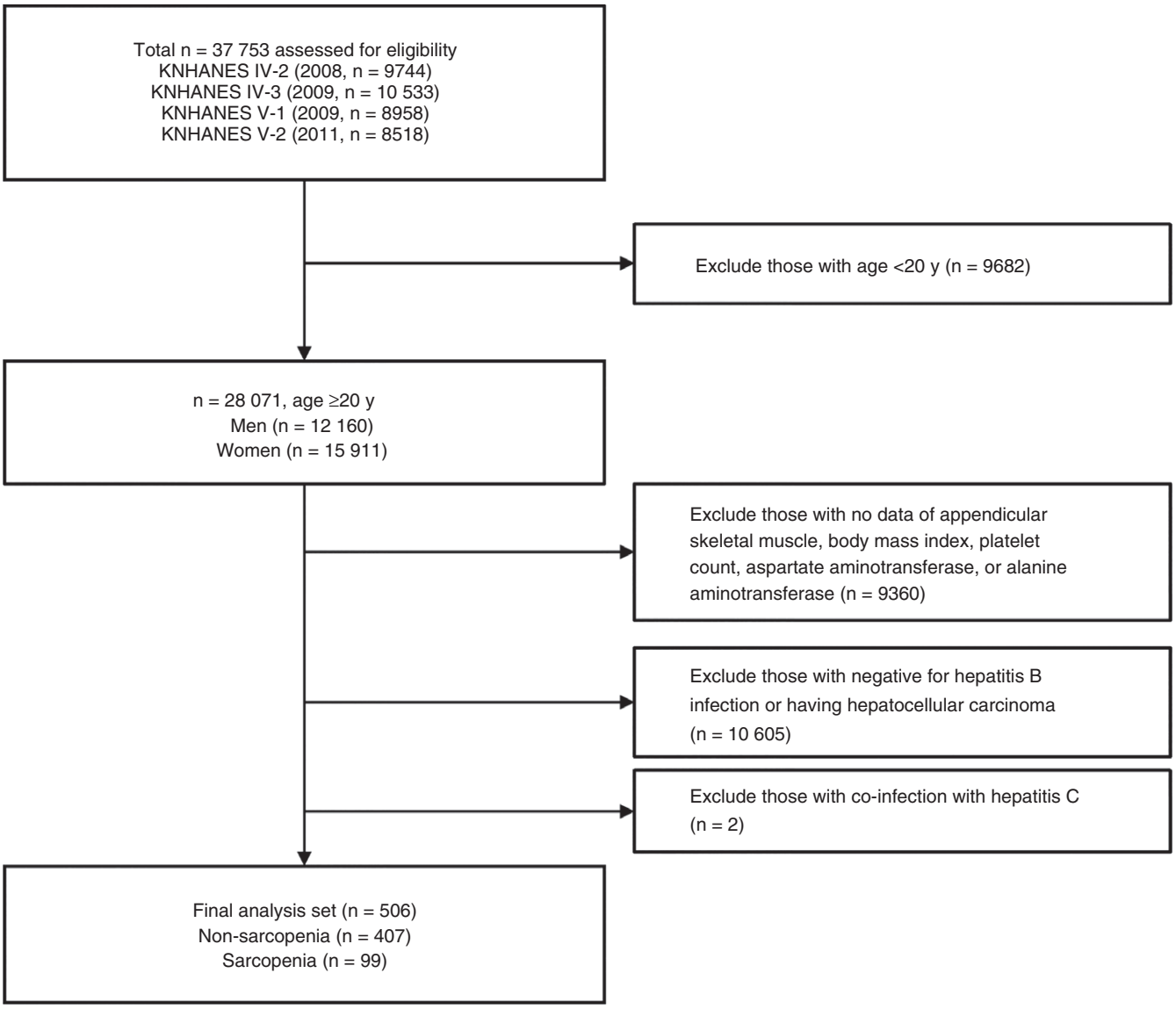

FIGURE 1 Flow diagram of subject inclusion and exclusion in the Korea National Health and Nutrition Examination Surveys (KNHANES IV and V). Of all the study subjects (n = 37 753), 506 with chronic hepatitis B were finally included (407 with nonsarcopenia and 99 with sarcopenia).

health questionnaires. Respondents' smoking status was categorised by self-report as non- or current smoker. Regular exercise was defined as engaging in moderate or vigorous exercise on a regular basis (≥20 min at a time at least 3 times per week).[17] Diabetes mellitus was defined based on (1) use of insulin or oral hypoglycaemic agents or (2) fasting plasma glucose ≥126 mg/dL. Subjects were diagnosed as hypertensive when the systolic pressure was ≥140 mm Hg and the diastolic pressure was ≥90 mm Hg, or if antihypertensive medications were currently used.

After overnight fasting for at least 8 h, blood specimens collected from each subject were processed and transported in cold storage to the Central Testing Institute (Neodin Medical Institute, Seoul, Korea). All blood samples were analysed within 24 h of transportation, as previously described.[17] The estimated glomerular filtration rate was derived from the Chronic Kidney Disease Epidemiology Collaboration equation.[18]

2.4 | Liver fibrosis and steatosis

The degree of liver fibrosis was assessed using previous validated liver fibrosis prediction models: (1) the NAFLD fibrosis score,[19] (2) the fibrosis-4 index,[20] and (3) Forns index.[21] Liver steatosis was defined using previous validated fatty liver prediction models: (1) the fatty liver index[22,23] and (2) the comprehensive NAFLD score.[24] The equations are described in Table S1. Serum albumin was not measured in the KNHANES; therefore, significant fibrosis was defined as either the highest quartile of the NAFLD fibrosis score, the highest quintile of Forns index,[13] or fibrosis-4 index ≥2.67,[25] whereas a fatty

liver index ≥30 or a comprehensive NAFLD score ≥40 was considered indicative of a fatty liver.[22,24]

2.5 | Definitions of obesity, insulin resistance and metabolic syndrome

Based on the criteria for the Asian-Pacific region, subjects were considered to be obese when their body mass index was ≥25 kg/m^2.[26] Insulin resistance was assessed based on the homoeostasis model assessment of insulin resistance (HOMA-IR).[27] Metabolic syndrome was defined according to the revised the National Cholesterol Education Program criteria,[28] and cut-off points of waist circumference (≥90 cm for men and ≥85 cm for women) were applied based on criteria from the Korean Society for the Study of Obesity.[26] Heavy alcohol consumption was defined as alcohol consumption >210 g/wk for men and 140 g/wk for women.[13]

2.6 | Statistical analysis

The characteristics of the study subjects were analysed according to sarcopenia status using Student's *t* tests for continuous variables and χ^2 tests for categorical variables. The association between the sarcopenia index and the liver fibrosis prediction scores (NAFLD fibrosis score, Forns index and fibrosis-4 index) was evaluated using a χ^2 test after transformation of these variables into quartiles. For binary stratification to control for the effects of obesity or insulin resistance, the study population was divided into 2 groups according to the presence of either central obesity (defined as a waist circumference <90 cm vs ≥90 cm for men and <85 cm vs ≥85 cm for women), obesity (body mass index <25 kg/m^2 vs ≥25 kg/m^2) or insulin resistance (HOMA-IR <2.5 vs ≥2.5).

Because there were significant correlations between age and sarcopenia index, an interaction term between age and sarcopenia index (age × sarcopenia index) was included in regression models.[13] Multivariate logistic regression analysis was applied to determine the independent association between sarcopenia and significant liver fibrosis after adjusting for age, age × sarcopenia index and gender in Model 1. Variables in Model 1, smoking, alcohol consumption, exercise, central obesity, hypertension, diabetes, history of cardiovascular disease and obesity (body mass index cut-off 25 kg/m^2) were adjusted in Model 2. Variables in Model 2, the HOMA-IR, and the systolic blood pressure as well as the triglycerides, fasting blood sugar, aspartate aminotransferase and alanine aminotransferase levels were adjusted in Model 3. Variables in Model 1, smoking, alcohol consumption, exercise, history of cardiovascular disease, metabolic syndrome and fatty liver by the comprehensive NAFLD score were adjusted in Model 4.

The sarcopenia index values were standardised (z-standardisation) before entry into the logistic models. Continuous and categorical variables were expressed as means ± SDs and numbers (%), respectively. A *P* value <0.05 was considered to be statistically significant. Statistical analyses were performed using SPSS version 23.0 for Windows (IBM Corp., Armonk, NY, USA).

3 | RESULTS

3.1 | Baseline characteristics of study population

After excluding subjects who met the exclusion criteria, 506 subjects (258 men and 248 women) were included in the final statistical analysis (Figure 1). The clinical characteristics of the study population are described in Table 1. The mean age of the study population was 50.7 years. The mean appendicular skeletal muscle mass and sarcopenia index were 19.5 kg and 0.8 respectively. Metabolic syndrome, diabetes, central obesity and obesity were identified in 130 (25.7%), 52 (10.3%), 198 (39.4%) and 169 (33.4%) subjects respectively. The proportion of the medical treatment was statistically similar between sarcopenic and the nonsarcopenic groups (19.3% vs 24.1%, $P = 0.523$). The mean NAFLD fibrosis score, Forns index and fibrosis-4 index were 1.1, 4.4 and 1.5, respectively, and significant liver fibrosis was identified in 126 (24.9%), 73 (19.8%) and 217 (42.9%) subjects by the NAFLD fibrosis score, Forns index and fibrosis-4 index respectively. Fatty liver was identified in 168 (39.4%) and 154 (36.1%) subjects using the fatty liver index and comprehensive NAFLD score respectively.

3.2 | Comparison between nonsarcopenic and sarcopenic subjects

Ninety-nine (19.6%) of the study subjects had sarcopenia. As shown in Table 1, sarcopenic subjects were significantly older than nonsarcopenic subjects (mean 59.8 vs 48.5 y; $P < 0.05$). Additionally, sarcopenic subjects had a significantly lower appendicular skeletal muscle mass (mean 17.6 vs 20.0 kg), higher waist circumference (mean 88.9 vs 81.1 cm), higher body mass index (mean 26.1 vs 23.4 kg/m^2) and lower sarcopenia index (mean 0.7 vs 0.9) values than nonsarcopenic subjects (all $P < 0.05$). The proportions of participants with hypertension (55.6% vs 21.9%), metabolic syndrome (51.5% vs 19.4%), diabetes (17.2% vs 8.6%), cardiovascular disease (7.1% vs 2.0%), central obesity (69.4% vs 32.4%) and obesity (64.6% vs 25.8%) were significantly higher in sarcopenic subjects (all $P < 0.05$), whereas the proportion of subjects with heavy alcohol consumption (8.1% vs 17.7%) was significantly lower in sarcopenic subjects ($P < 0.05$).

According to the laboratory tests, the insulin (mean 13.2 vs 10.4 μIU/mL), HOMA-IR (mean 3.3 vs 2.5), triglycerides (mean 139.5 vs 112.2 mg/dL) and gamma glutamyl-transpeptidase (mean 42.5 vs 34.8 IU/L) levels were significantly higher in sarcopenic subjects than nonsarcopenic subjects (all $P < 0.05$), whereas the high-density lipoprotein cholesterol levels (mean 43.8 vs 48.8 mg/dL) and kidney function were significantly lower (mean estimated glomerular filtration rate 88.8 vs 93.2 mL/min/1.73 m^2) in sarcopenic subjects (all $P < 0.05$).

In terms of the fibrosis assessment, sarcopenic subjects had more fibrotic livers than nonsarcopenic subjects, and this was reflected by significantly higher NAFLD fibrosis score (mean 1.9 vs 0.9), Forns index (mean 4.2 vs 5.2) and fibrosis-4 index (mean 1.9 vs 1.3) values (all $P < 0.001$). Additionally, the prevalence of significant liver fibrosis

TABLE 1 Baseline characteristics

Variables	Subjects without sarcopenia (n = 407, 80.4%)	Subjects with sarcopenia (n = 99, 19.6%)	*P* value
Demographic variables			
Age, y	48.5 ± 12.9	59.8 ± 13.2	<0.001
Male gender	206 (50.6)	52 (52.5)	0.733
Appendicular skeletal muscle, kg	20.0 ± 5.0	17.6 ± 4.5	<0.001
Waist circumference, cm	81.1 ± 8.8	88.9 ± 10.0	<0.001
Body mass index, kg/m^2	23.4 ± 2.9	26.1 ± 3.3	<0.001
Sarcopenic index	0.9 ± 0.2	0.7 ± 0.1	<0.001
Hypertension	89 (21.9)	55 (55.6)	<0.001
Metabolic syndrome	79 (19.4)	51 (51.5)	<0.001
Diabetes	35 (8.6)	17 (17.2)	0.012
Cardiovascular disease	8 (2.0)	7 (7.1)	0.007
Heavy alcohol consumption	72 (17.7)	8 (8.1)	0.019
Current smoker	100 (24.6)	19 (19.2)	0.258
Central obesity[a]	130 (32.4)	68 (69.4)	<0.001
Obesity[b]	105 (25.8)	64 (64.6)	<0.001
Anti-viral therapy	78 (19.3)	24 (24.1)	0.523
Laboratory variables			
Fasting blood glucose, mg/dL	96.9 ± 20.4	100.7 ± 15.6	0.085
Insulin, μIU/mL[c]	10.4 ± 4.3	13.2 ± 7.7	<0.001
Homoeostatic model assessment of insulin resistance[c]	2.5 ± 1.3	3.3 ± 2.2	<0.001
Total cholesterol, mg/dL	182.1 ± 32.1	188.1 ± 33.9	0.102
Triglyceride, mg/dL[c]	112.2 ± 74.7	139.5 ± 65.2	<0.001
High density lipoprotein cholesterol, mg/dL[c]	48.8 ± 11.8	43.8 ± 9.9	<0.001
Low density lipoprotein cholesterol, mg/dL[c]	110.7 ± 29.6	115.5 ± 29.4	0.185
Serum creatinine, mg/dL	0.9 ± 0.2	0.8 ± 0.2	0.285
Estimated glomerular filtration rate, mL/min/1.73 m^2	93.2 ± 15.4	88.8 ± 15.7	0.011
Aspartate aminotransferase, IU/L[c]	27.6 ± 20.1	29.1 ± 20.5	0.492
Alanine aminotransferase, IU/L[c]	26.7 ± 20.4	27.1 ± 26.1	0.988
Platelet count, 10^9/L[c]	222.6 ± 61.5	223.2 ± 72.6	0.790
Gamma glutamyl-transpeptidase, IU/L[c]	34.8 ± 42.9	42.5 ± 43.7	0.006
Liver fibrosis			
NAFLD fibrosis score	0.9 ± 1.3	1.9 ± 1.6	<0.001
Significant fibrosis by NAFLD fibrosis score	81 (19.9)	45 (45.5)	<0.001
Forns index[d]	4.2 ± 1.7	5.2 ± 1.5	<0.001
Significant fibrosis by Forns index	47 (16.3)	25 (33.8)	0.001
Fibrosis-4 index	1.3 ± 0.1	1.9 ± 0.2	0.029
Significant fibrosis by fibrosis-4 index	160 (39.3)	57 (57.6)	0.001
Liver steatosis			
Fatty liver index	25.7 ± 21.9	44.5 ± 25.9	<0.001
Fatty liver by fatty liver index[e]	136 (33.6)	62 (63.3)	<0.001
Comprehensive NAFLD score	29.3 ± 27.9	50.7 ± 32.1	<0.001
Fatty liver by comprehensive NAFLD score[e]	103 (29.9)	51 (61.4)	<0.001

Variables are expressed as mean ± SD or number (%).
NAFLD, nonalcoholic fatty liver disease.
[a]Central obesity was defined waist circumference ≥90 cm in men, ≥85 cm in women.
[b]Obesity was defined body mass index ≥25 kg/m^2.
[c]Log transformed.
[d]A total of 363 subjects were analysed due to missing gamma glutamyl-transpeptidase.
[e]A total of 503 subjects were analysed due to missing waist circumference values.

was significantly higher in sarcopenic subjects than nonsarcopenic subjects (45.5% vs 19.9% by the NAFLD fibrosis score, 16.3% vs 33.8% by Forns index and 57.6% vs 39.3% by the fibrosis-4 index; all $P < 0.001$). The degree of liver steatosis was also significantly higher in the sarcopenic group regardless of the fatty liver indices (mean 44.5 vs 25.7 by the fatty liver index and 50.7 vs 29.3 by the comprehensive NAFLD score). More subjects with than without sarcopenia had fatty livers (63.3% vs 33.6% by the fatty liver index and 61.4% vs 29.9% by the comprehensive NAFLD score; both $P < 0.001$).

3.3 | Association between sex-specific SI and fibrotic burden by quartile stratification

When the sex-specific sarcopenia index and fibrotic burden were stratified by quartiles, the sarcopenia index exhibited a strong negative relationship with the fibrotic burden, regardless of the fibrosis indices (NAFLD fibrosis score and fibrosis-4 index, both $P < 0.001$) (Figure 2). The fibrosis index values tended to decrease from the lowest to the highest sarcopenia index quartiles (mean 1.7 vs 1.2 vs 0.9 vs 0.5 by NAFLD fibrosis score, $P < 0.001$; mean 1.7 vs 1.6 vs 1.5 vs 1.1 by fibrosis-4 index, $P = 0.009$).

3.4 | Relative risk of significant liver fibrosis according to metabolic confounders

To investigate the relative risk of significant liver fibrosis according to sarcopenic status using the NAFLD fibrosis score and fibrosis-4 index without confounding influences, the study population was stratified into 2 groups according to several metabolic factors, such as waist circumference, body mass index, HOMA-IR, presence of metabolic syndrome and presence of fatty liver by the fatty liver index and comprehensive NAFLD score. The cut-off values for waist circumference were 90 cm for men and 85 cm for women (n = 305 [60.2%] without central obesity and n = 198 [39.1%] with central obesity), those for body mass index were 25 kg/m^2 (n = 337 [66.6%] with body mass index <25 kg/m^2 and n = 169 [33.4%] with body mass index ≥25 kg/m^2) and those for HOMA-IR were 2.5 (n = 291 [57.5%] with HOMA-IR ≤2.5 and n = 214 [42.3%] with HOMA-IR >2.5). Additionally, the study population was stratified according to the absence or presence of metabolic syndrome (n = 376 [74.3%] without metabolic syndrome and n = 130 [25.7%] with metabolic syndrome) and fatty liver by the fatty liver index and comprehensive NAFLD score (n = 305 [60.3%] without fatty liver by the fatty liver index and n = 198 [39.1%] with fatty liver by the fatty liver index; n = 273 [54.0%] without fatty liver by the comprehensive NAFLD score and n = 154 [30.4%] with fatty liver by the comprehensive NAFLD score).

According to the assessment of the degree of liver fibrosis by the NAFLD fibrosis score, the proportion of significant liver fibrosis was significantly higher in sarcopenic subjects (n = 68) than nonsarcopenic subjects (n = 130) in the subgroup with central obesity (54.4% vs 26.2%, odds ratio [OR] = 3.37, 95% CI = 1.82-6.25, $P < 0.001$), whereas it did not differ significantly in the subgroup without central obesity ($P = 0.195$) (Figure 3A). Our analysis of obesity by body mass index cut-off values showed that the proportion of individuals with significant liver fibrosis was higher in sarcopenic subjects with a body mass index ≥25 kg/m^2 (53.1% vs 28.6%, OR = 2.83, 95% CI = 1.48-5.42, $P = 0.001$) or a body mass index <25 kg/m^2 (31.4% vs 16.9%, OR = 2.26, 95% CI = 1.04-4.89, $P = 0.040$) (Figure 3B). Similar findings were observed when the

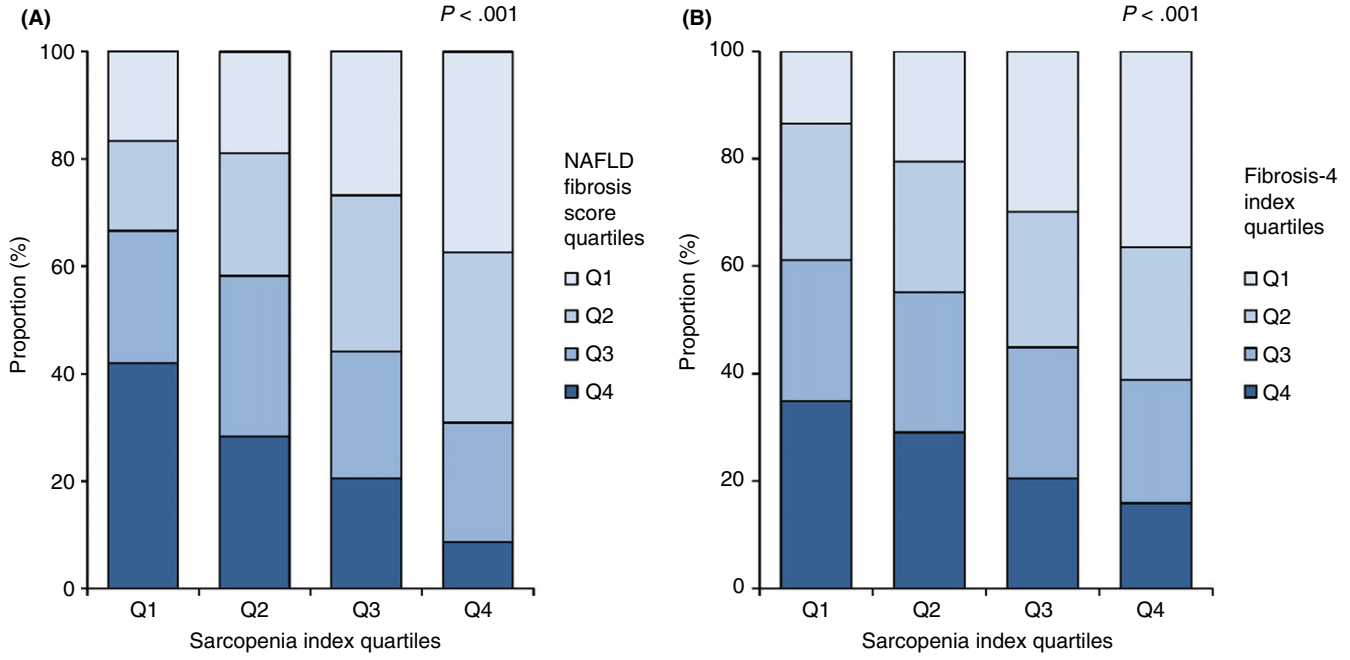

FIGURE 2 Association between sex-specific sarocpenia index and fibrotic burden by quartile stratification. The sarcopenia index showed a strong negative relationship with the fibrotic burden by the NAFLD fibrosis score (A) and fibrosis-4 index (B) (both $P < 0.001$)

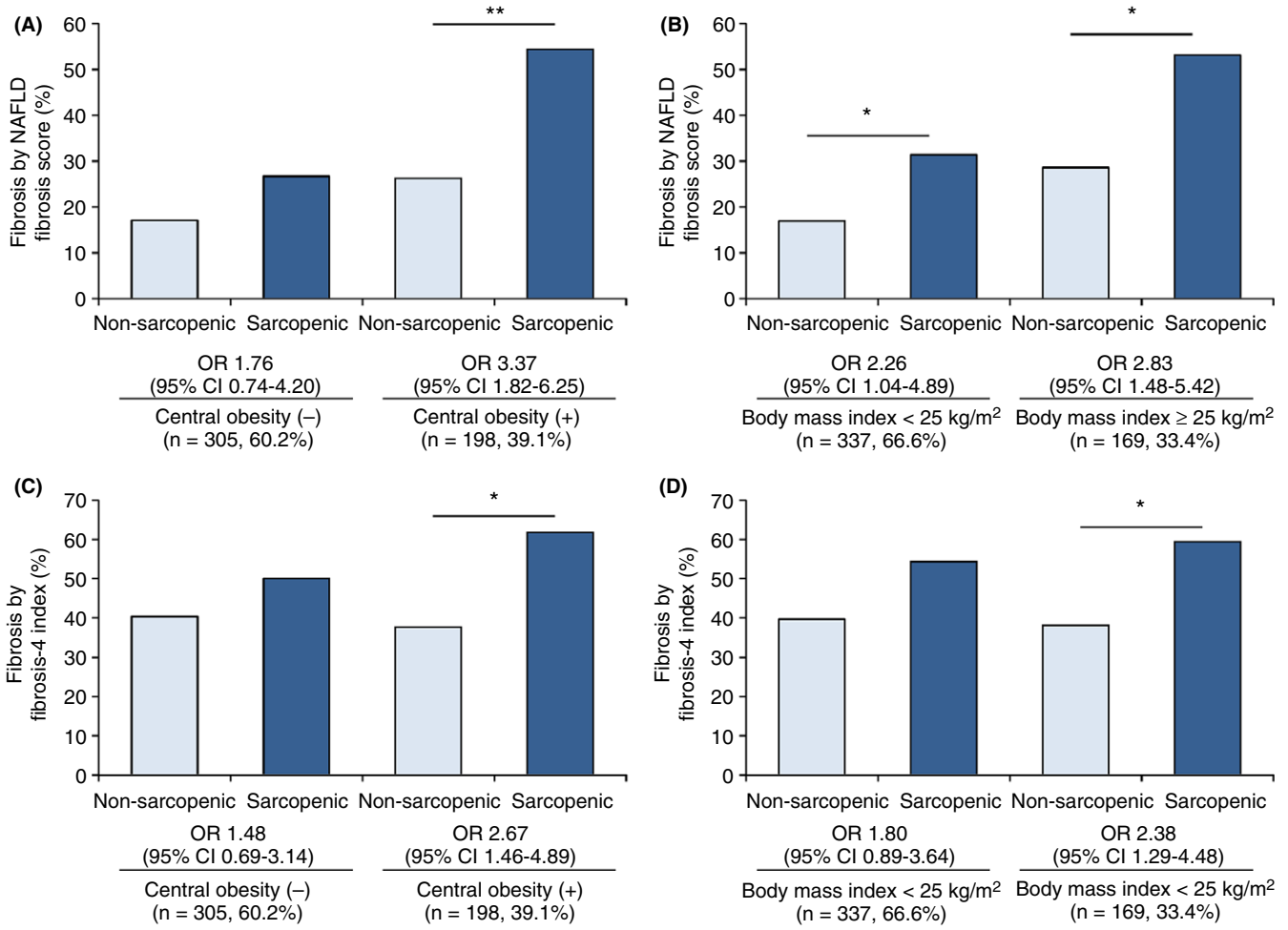

FIGURE 3 Prevalence of significant liver fibrosis assessed using the NAFLD fibrosis score (A and B) and fibrosis-4 index (C and D) according to sarcopenic status after stratification according to central obesity† (A and C) and body mass index (B and D). According to the NAFLD fibrosis score and fibrosis-4 index, the prevalence of significant liver fibrosis was significantly higher in sarcopenic subjects than nonsarcopenic subjects in subgroups with central obesity and a body mass index ≥25 kg/m^2 (all $P < 0.05$). OR, odds ratio; CI, confidence interval. *$P < 0.05$, **$P < 0.001$. †Data from 503 subjects were analysed due to missing waist circumference values (A and C)

fibrosis-4 index was used to assess the degree of liver fibrosis (Figures 3C and D). Similarly, the proportion of individuals with significant liver fibrosis by the NAFLD fibrosis score was significantly higher in sarcopenic subjects (n = 51) than nonsarcopenic subjects (n = 79) in the subgroup with metabolic syndrome (68.6% vs 38.0%, OR = 3.57, 95% CI = 1.70-7.53, $P = 0.001$) and a HOMA-IR >2.5 (48.3% vs 26.9%, OR = 2.53, 95% CI = 1.36-4.73, $P = 0.004$) (Figures 4A and B). Similar findings were observed in the subgroup with a HOMA-IR ≤2.5 (41.5% vs 15.6%, OR = 3.83, 95% CI = 1.89-7.79, $P < 0.001$). When the fibrosis-4 index was used to assess liver fibrosis, the proportion of individuals with significant liver fibrosis was significantly higher in sarcopenic subjects (n = 51) than nonsarcopenic subjects (n = 79) in the subgroups with metabolic syndrome (70.6% vs 41.8%, OR = 3.35, 95% CI = 1.58-7.08, $P = 0.002$) and a HOMA-IR >2.5 (58.6% vs 36.5%, OR = 2.46, 95% CI = 1.33-4.56, $P = 0.004$), but it did not differ significantly in the subgroup without metabolic syndrome and with a HOMA-IR ≤2.5 (both $P > 0.05$) (Figures 4C and D). Similar results were found when Forns index was used to identify significant liver fibrosis (Figure S1).

When liver steatosis was assessed using the fatty liver index to investigate the relative risk of significant liver fibrosis according to fatty liver, the proportion of individuals with significant liver fibrosis was significantly higher in sarcopenic subjects (n = 62) than nonsarcopenic subjects (n = 136) in the subgroup with fatty livers, regardless of the fibrosis index (58.1% vs 27.9%, OR = 3.57, 95% CI = 1.91-6.69, $P < 0.001$ by the NAFLD fibrosis score and 64.5% vs 43.4%, OR = 2.37, 95% CI = 1.28-4.42, $P = 0.006$ by the fibrosis-4 index). It did not differ significantly in the subgroup without fatty livers (all $P > 0.05$) (Figures 5A,B). When the comprehensive NAFLD score was used to assess the degree of liver steatosis, similar findings were observed (Figure S2).

3.5 | Vigorous exercise reduces the risk of significant liver fibrosis

Because vigorous exercise has been shown to reduce the risk of sarcopenia,[29] we next investigated whether vigorous exercise could also reduce the risk of significant liver fibrosis. The proportion of

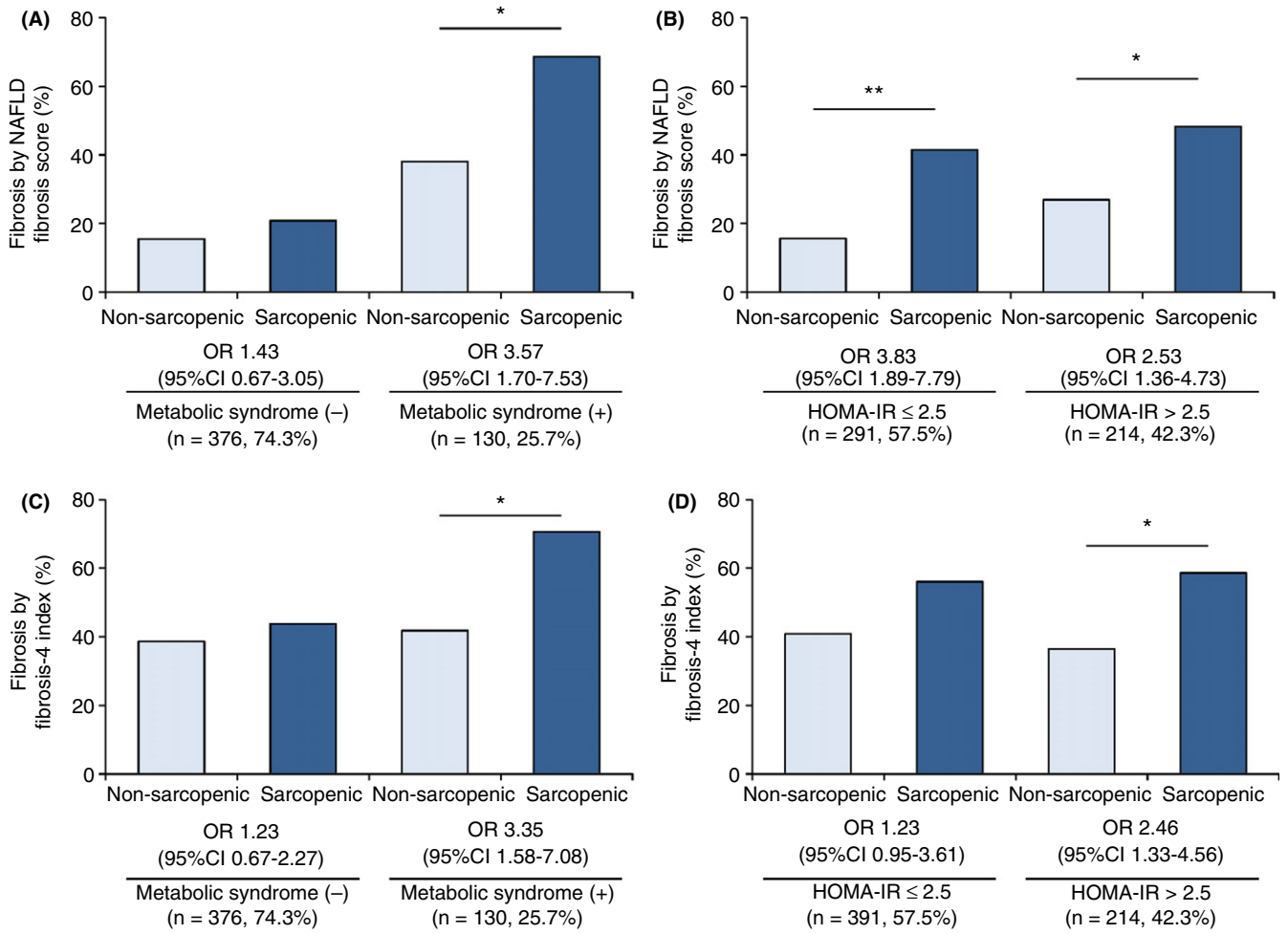

FIGURE 4 Prevalence of significant liver fibrosis assessed using the NAFLD fibrosis score (A and B) and fibrosis-4 index (C and D) according to sarcopenic status after stratification according to metabolic syndrome (A and C) and HOMA-IR† (B and D). According to the NAFLD fibrosis score and fibrosis-4 index, the prevalence of significant liver fibrosis was significantly higher in sarcopenic subjects than nonsarcopenic subjects in subgroups with metabolic syndrome and a HOMA-IR >2.5 (all $P < 0.05$). OR, odds ratio; CI, confidence interval; HOMA-IR, homoeostasis model of insulin resistance. *$P < 0.05$, **$P < 0.001$. †Data from 505 subjects were analysed due to missing information about insulin concentrations (B and D)

individuals with significant liver fibrosis was significantly higher in sarcopenic subjects (n = 86) than nonsarcopenic subjects (n = 333) in the subgroup that did not engage in vigorous exercise, regardless of the fibrosis index (47.7% vs 20.7%, OR = 3.49, 95% CI = 2.12-5.74, $P < 0.001$ by the NAFLD fibrosis score and 59.3% vs 38.4%, OR = 2.33, 95% CI = 1.44-3.79, $P = 0.001$ by the fibrosis-4 index). In contrast, the risk of significant liver fibrosis was attenuated in the subgroups that did engage in vigorous exercise (30.8% vs 16.2%, $P = 0.221$ by the NAFLD fibrosis score and 43.3% vs 46.2%, $P = 0.845$ by the fibrosis-4 index) (Figures 6A,B).

3.6 | Independent association between sarcopenia and significant liver fibrosis

To adjust for confounding covariates that potentially affect liver fibrosis, 4 multivariate logistic regression models were used (Table 2). After significant liver fibrosis was assessed using the NAFLD fibrosis score, subjects with higher sex-specific sarcopenia index values showed a reduced risk of significant liver fibrosis in a crude model (OR = 0.30, 95% CI 0.19-0.47, $P < 0.001$). Using a minimally adjusted model (Model 1) that included age, age × sarcopenia index and gender, individuals with lower sarcopenia index values showed a higher risk of significant liver fibrosis (adjusted OR = 3.62, 95% CI 2.03-6.44, $P < 0.001$). When the model was further adjusted for other variables, the independent association between sarcopenia and significant liver fibrosis was maintained (OR = 2.94, 95% CI 1.41-6.16, $P = 0.004$ for Model 2; OR = 2.67, 95% CI 1.16-6.12, $P = 0.021$ for Model 3; and OR = 3.01, 95% CI 1.44-6.29, $P = 0.003$ for Model 4) (Table 2). Similar results were obtained when the fibrosis-4 index was used to assess the degree of liver fibrosis.

4 | DISCUSSION

This nationally representative, population-based study demonstrated that CHB subjects with sarcopenia had an approximately 3-fold

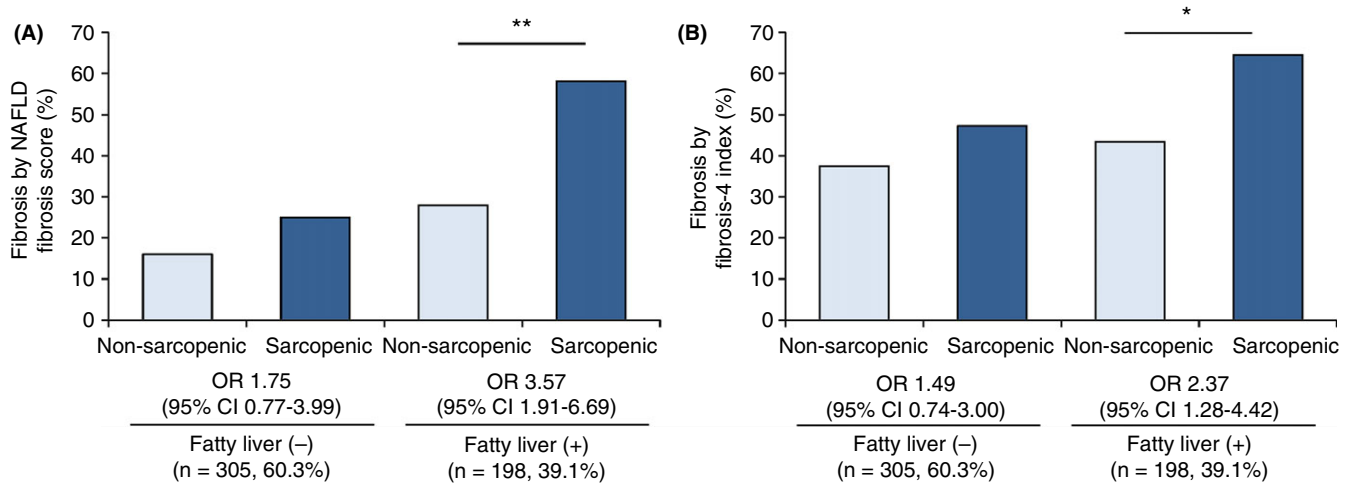

FIGURE 5 Prevalence of significant liver fibrosis assessed using the NAFLD fibrosis score (A) and fibrosis-4 index (B) according to the sarcopenic status after stratification according to fatty liver using by fatty liver index[†]. According to the NAFLD fibrosis score and fibrosis-4 index, the prevalence of significant liver fibrosis was significantly higher in sarcopenic subjects than nonsarcopenic subjects in the subgroup with fatty livers (all $P < 0.05$). OR, odds ratio; CI, confidence interval. *$P < 0.05$, **$P < 0.001$. [†]Data from 503 subjects were analysed due to missing waist circumference values

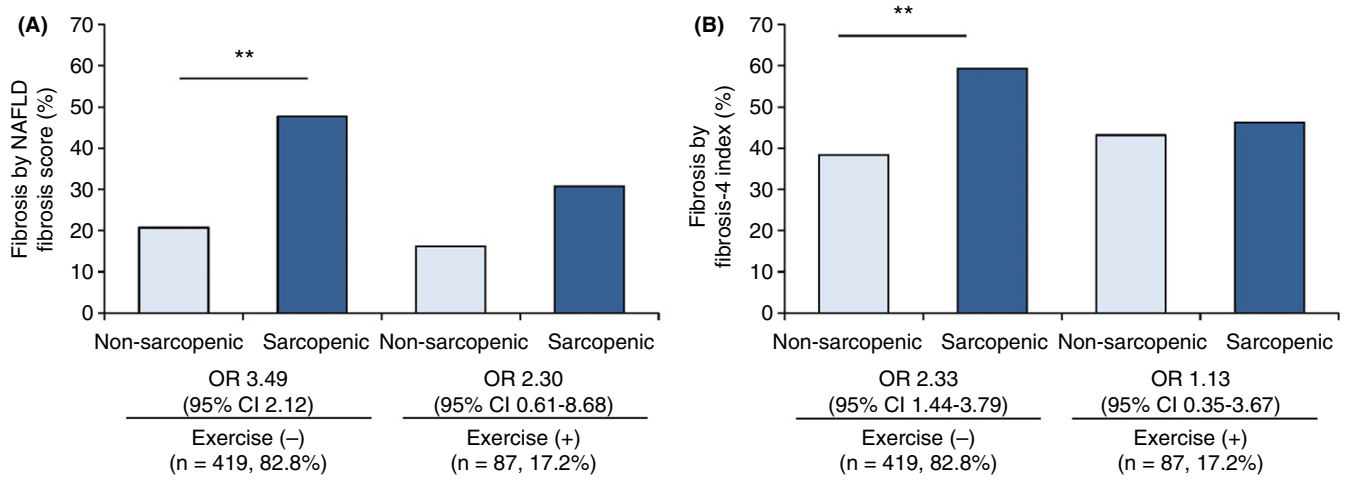

FIGURE 6 Influence of vigorous exercise on the risk of significant liver fibrosis by the NAFLD fibrosis score (A) and fibrosis-4 index (B). The proportion of significant liver fibrosis was significantly higher in sarcopenic subjects than nonsarcopenic subjects in the subgroup that did not engage in vigorous exercise, regardless of the fibrosis index used, the risk of significant liver fibrosis was attenuated in the subgroup that engaged in vigorous exercise. OR, odds ratio; CI, confidence interval. **$P < 0.001$

increased risk of significant liver fibrosis compared to those without this condition (OR 2.62-3.67) and showed that this relationship was independent of obesity, insulin resistance, metabolic syndrome and fatty liver. However, the mechanisms underpinning this independent association could not be assessed. Additionally, the fibrotic burden differed significantly according to sarcopenic status, especially among metabolically unhealthy subjects. Moreover, vigorous exercise is associated with the lower degree of significant liver fibrosis in sarcopenic subjects to the similar risk level of nonsarcopenic subjects.

This study has several strengths. First, the overall size of the cohort was sufficient (n > 500) to ensure statistical reliability and to investigate the independent risk of sarcopenia according to fibrotic burden by stratifying the study cohort according to metabolic parameters, especially given that the data were obtained from a nationwide sample according to well-established procedures. Furthermore, the proportion of sarcopenic subjects in the cohort (~19.6%) was similar to those in previous Asian studies.[30] This might support that the sarcopenic subjects in the current population-based cohort were selected appropriately and indicates that, although they should be validated in other ethnic populations, our results may be applicable to most Asian populations. After excluding CHB subjects without information regarding dual-energy X-ray absorptiometry or body mass index, we found the proportion of CHB subjects to be 4.1% (1152 of 28 071) among subjects aged >20 y, which is similar to the

TABLE 2 Crude and adjusted odds ratios of significant liver fibrosis according to the sarcopenia status

	Significant liver fibrosis					
	By nonalcoholic fatty liver disease fibrosis score (n = 126, 24.9%)			By fibrosis-4 index (n = 217, 42.9%)		
Variables	OR	95% CI	*P* value	OR	95% CI	*P* value
Crude	3.35	2.11-5.34	<0.001	2.10	1.34-3.27	0.014
Model 1	3.62	2.03-6.44	<0.001	2.04	1.15-3.60	0.007
Model 2	2.94	1.41-6.16	0.004	2.11	1.05-4.22	0.036
Model 3	2.67	1.16-6.12	0.021	2.62	1.11-6.18	0.029
Model 4	3.01	1.44-6.29	0.003	2.37	1.21-4.66	0.012

OR, odd ratio; CI, confidence interval.
Model 1 = age (categorical variable with a median cutoff value of 50), age × sarcopenia index, and gender.
Model 2 = Model 1 + smoking, alcohol consumption, exercise, central obesity, hypertension, diabetes, history of cardiovascular disease, and obesity (body mass index cutoff value of 25 kg/m^2).
Model 3 = Model 2 + homeostatic model assessment of insulin resistance, triglycerides (per 50 mg/dL), systolic blood pressure, fasting blood sugar, aspartate aminotransferase, and alanine aminotransferase.
Model 4 = Model 1 + smoking, alcohol consumption, exercise, metabolic syndrome, history of cardiovascular disease, homeostatic model assessment of insulin resistance, triglyceride (per 50 mg/dL) and fatty liver by fatty liver index.

reported prevalence of CHB in South Korea.[3] This also suggests that we selected the study population from the nationwide representative cohort in an appropriate manner. Additionally, liver fibrosis (calculated by easy-to-calculate fibrosis indices) was selected as the endpoint because it is the single most important factor and a clinically relevant issue that correlates with poor outcomes, such as progression to liver cirrhosis and the development of hepatocellular carcinoma in subjects with chronic liver diseases.[31,32] Taken together, these data can help physicians establish surveillance strategies for high-risk subjects and determine the optimal time for medical interventions.

Second, although several studies have proposed an association between sarcopenia and the presence of NAFLD or significant liver fibrosis in NAFLD subjects,[12,13] this is, as far as we know, the first study to investigate the influence of sarcopenia on degree of liver fibrosis in CHB subjects. Recent studies reported that effective AVT could suppress the virus-related factors related to fibrosis progression and subsequently induce the regression of liver fibrosis and even the reversal of liver cirrhosis in CHB patients.[6,7] Eventually, the risk of developing hepatocellular carcinoma could be also alleviated by effective long-term AVT.[33] However, despite the appropriate control of viral factors, other demographic or metabolic factors that cannot be controlled by AVT still expose CHB subjects to the risk of fibrosis or disease progression.[34,35] Cirrhotic patients with sarcopenia have reduced survival, increased rates of infection, have worse outcomes even following liver transplantation.[36] Thus, the identification of additional risk factors (other than those that are related to viruses) for fibrosis progression in CHB subjects might be important in this era of effective AVT. However, the pathophysiologic mechanisms related to the development of sarcopenia in CHB subjects and the interaction between sarcopenia and HBV infection are poorly understood. Thus, it is unclear whether the changes in muscle mass may play an additional role in fibrosis progression or regression in CHB subjects. Additionally, because some metabolic factors, such as insulin resistance and cytokine levels, can be shared by sarcopenia and fatty liver,[37-39] concurrent fatty liver might also be related to fibrosis progression in CHB subjects.[12,34] Indeed, fatty liver was found in around one-third of our study population,

Third, the current showed that sarcopenia might have an unfavourable association on the risk of significant fibrosis, especially among metabolically unhealthy subjects with obesity, metabolic syndrome, insulin resistance and fatty livers. Additionally, the risk of fibrosis was higher in individuals with central obesity determined by waist circumference than obesity determined by body mass index cut-off values, which may underscore the role of visceral adiposity. Paradoxically, this might indicate that another appropriate management strategy for liver fibrosis could involve maintaining a metabolically healthy status in spite of the presence of sarcopenia. Indeed, this hypothesis could be clinically relevant in older CHB subjects with an inherently higher chance of suffering from sarcopenia. These findings are also supported by the fact that vigorous exercise is associated with the lower degree of significant liver fibrosis in sarcopenic subjects to the similar risk level of nonsarcopenic subjects. Although some studies have reported that physical activity improves muscle mass,[40,41] others have concluded that physical activity is not always effective due to the underlying persistent molecular and metabolic abnormalities and the fact that exercise can lead to anabolic resistance to nutrients in individuals with chronic liver diseases.[42] Thus, further prospective randomised trials are warranted to confirm these findings.

Lastly, various variables related to demographic characteristics, laboratory findings and metabolic factors were sufficiently adjusted, which reinforced the independent correlation between sarcopenia and significant liver fibrosis in CHB subjects. Additionally, the study population was stratified into subgroups with different metabolic statuses to investigate the correlation between sarcopenia and significant fibrosis among subgroups. Similar to previous studies,[12,13] we found that sarcopenia was significantly correlated with significant fibrosis in CHB subjects, regardless of obesity and insulin resistance. The effect of sarcopenia on liver fibrosis was also independent of metabolic syndrome, which was recently identified as a risk factor for liver fibrosis[43] and an independent predictor of hepatocellular carcinoma development in CHB subjects.[35] In NAFLD patients, sarcopenia was associated with fibrosis and steatosis severity, and these associations were independently of hepatic and metabolic risk factors.[44] The proportion of subjects with fatty livers was 36.1%-39.4% according to the steatosis calculations in the current study, which is quite similar to the results of previous studies in Asian populations.[34,45] Finally, sarcopenia was also associated with significant liver fibrosis, and this association was independent from concurrent fatty liver in CHB subjects, which could increase the risk of HBV related hepatocellular

carcinoma development.[34] All these subgroup analyses suggest that sarcopenia is associated with significant liver fibrosis in CHB subjects.

We are also aware of several issues that remained unresolved in the current study. First, although we used well-validated liver fibrosis[20,22] and steatosis prediction models,[23,24] liver imaging and histological information was not available due to the high cost of ultrasonographic examination and the ethical concerns regarding screening a large national population-based cohort. KNHANES participants who gave informed consent had only tested for serum. Thus, the absence of biopsy-proven information would be a limitation for the current study. However, we believe that the solid evidence in this study could provide the rationale for future prospective studies focusing on the independent long-term influence of sarcopenia in CHB subjects. Second, due to the cross-sectional nature of the study design, we could not assess the longitudinal dynamic association between the progression or regression of liver fibrosis and changes in muscle mass during the course of CHB with and without AVT. We could not provide any prospective or longitudinal data supporting that sarcopenia is one of the causative factors for significant liver fibrosis. We were also unable to examine the effects of therapeutic interventions, such as lifestyle modification, exercise, weight loss, medications, nutritional support or protein supplements, on improving sarcopenia. Third, because the long-term use of AVT might have the most significant role in the regression of liver fibrosis, it should be investigated whether the improvement in sarcopenia has additional role in the process of fibrosis regression. Of note, it would be plausible that significant liver fibrosis leads to reduced appetite, decreased testosterone levels, exacerbates catabolic state, leading to sarcopenia.[46,47] Although the proportion of the medical treatment was statistically similar between sarcopenic and the nonsarcopenic groups (19.3% vs 24.1%, $P = 0.523$), detailed information regarding the phase of CHB, AVT (anti-viral agents or genotypic mutation) and the corresponding AVT was not available for our cohort. Thus, the potential influence of the CHB phase and long-term AVT on muscle mass should be investigated. Additionally, virus-related factors such as hepatitis B e antigen or HBV DNA were not available in this study. Only quantitative hepatitis B s antigen (qHBsAg) was available in our data set. The mean qHBsAg of the entire study population was 3125.6 ± 2783.2 IU/mL (3261.9 ± 2763.6 IU/mL for nonsarcopenic group and 2565.4 ± 2807.5 IU/mL for sarcopenic group; $P = 0.012$) and the adjustment of qHBsAg level did not influence the independent association between sarcopenia and significant liver fibrosis. KNHANES data set has been designed to examine the general health status of Korean population, not focusing on chronic hepatitis B patients. Due to the lack of detailed information for liver biopsy or other HBV-related markers including hepatitis B e antigen and HBV DNA, we could not assess the influence of liver histology and HBV related markers on the association between sarcopenia and liver fibrosis, therefore, detailed interaction between these virus-related factors and sarcopenia should be investigated in future studies.

In conclusion, this nationwide survey of a representative sample of Korean individuals demonstrated that sarcopenia is significantly associated with significant liver fibrosis in CHB subjects in a manner independent of obesity, insulin resistance, metabolic syndrome and fatty liver. Prospective, well-designed, longitudinal studies with sufficient laboratory and liver-imaging resources are needed to elucidate the complex relationship between sarcopenia and liver fibrosis progression in CHB patients.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section at the end of the article.

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