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Low Relative Handgrip Strength Is Associated with a High Risk of Non-Alcoholic Fatty Liver Disease in Italian Adults: A Retrospective Cohort Study

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Abstract: Background: Non-alcoholic fatty liver disease (NAFLD) and the presence of low muscle mass (sarcopenia) represent noteworthy health issues. Handgrip strength, a muscle function indicator, is vital for sarcopenia diagnosis. We investigated the link between handgrip strength and hepatic steatosis in Italian adults. Methods: We retrospectively assessed 388 adults (≥50 years), measuring muscle function and hepatic steatosis using a dynamometer and transient elastography. We divided participants into handgrip strength tertiles. Results: 207 had NAFLD. The lowest handgrip strength tertile had a higher NAFLD prevalence (64% vs. 46%, $p = 0.02$). Tertiles I and II exhibited increased odds of NAFLD in comparison to tertile III, with an odds ratio of 5.30 (95% confidence interval: 2.24–12.57, $p < 0.001$) and 2.56 (95% confidence interval: 1.17–5.59, $p = 0.01$), respectively. rHGS predicted NAFLD with an AUC of 0.41 (SE = 0.029, $p = 0.003$). An rHGS of 1.22 achieved 18% sensitivity and 80% specificity for hepatic steatosis prediction. Conclusion: Low handgrip strength is linked to an increased susceptibility to NAFLD among the Italian population, implying its potential utility in the identification of risk for hepatic steatosis.

Keywords: handgrip strength; sarcopenia; hepatic steatosis; liver transient elastography; CAP score; nutrition-related diseases

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1. Introduction

Handgrip strength (HGS) is an indicator of muscle function [1], and current guidelines have emphasized the significance of HGS as the principal metric for sarcopenia diagnosis [2]. Among adult individuals, HGS is a recognized marker of frailty as well as a reflection of their present nutritional status [3–7]. Furthermore, the loss of muscle function predisposes older adults to an increased risk of several clinical conditions [8] and mortality [5,9–11]. It is established that muscle strength surpasses skeletal muscle mass in its predictive capacity for adverse outcomes [9,12]. For these reasons, evaluating muscle strength is gaining greater significance in both research and clinical environments, with the aim of enhancing the well-being of aging populations. Non-alcoholic fatty liver disease (NAFLD) represents the most common chronic liver disorder [13,14]. NAFLD presents a significant public health challenge due to its global surge, attributable to the obesity epidemic [13,15], and its growing role as a primary contributor to hepatocellular carcinoma (HCC) [16]. NAFLD is also a predictor of cardiovascular diseases and a greater mortality rate [17–19]. Interestingly, hepatic steatosis and sarcopenia, both linked to the subject's

dietary habits, may share common pathogenic mechanisms such as insulin resistance (IR), chronic low-grade inflammation, and decreased physical activity [20–22]. Additionally, molecules such as myostatin, insulin-like growth factor-1 (IGF-1), and sirtuin 1 (SIRT 1) are implicated in this relationship. Myostatin, a myokine expressed in skeletal muscle that is a negative regulator of skeletal muscle growth in animals and human is significantly higher in adults with sarcopenia than in those without sarcopenia [23]. Preclinical studies have demonstrated that inhibition of myostatin increases muscle mass, improves insulin sensitivity, and protects against liver steatosis [24,25].

A low level of IGF-1, a regulator of both hepatic glucose production and skeletal muscle cells, has been demonstrated in individuals with NAFLD [26] as well as sarcopenia [27].

SIRT1 is also linked to the spectrum of liver damage and muscle atrophy [28,29]. SIRT1 plays important roles in regulating lipid metabolism, inflammation, and oxidative stress in the liver through deacetylating some transcriptional regulators against the progression of fatty liver diseases [28]. Hepatic oxidative stress aggravates liver damage and muscle wasting progression. Indeed, in subjects with NAFLD, muscular oxidative stress promotes protein degradation, cell apoptosis, and the development of muscle atrophy [30]. Activation of SIRT-1 attenuates hepatic steatosis and improves muscle atrophy in an animal model of non-alcoholic steatohepatitis [30].

Furthermore, recent findings have shown that sarcopenia and reduced appendicular muscle mass serve as indicators for the development of impaired fasting glucose and type 2 diabetes in older women [31], and that IR and inflammation may modulate the connection between HGS and the risk of NAFLD [32]. To date, some studies have evaluated the relationship between muscle function and NAFLD, but especially in Asian populations [32–39]. However, only two Asian studies have investigated this relationship exclusively in adults aged ≥50 years [35,37], who represent the most vulnerable population to sarcopenia and its consequences. Hence, extrapolating these results to non-Asian groups may be problematic due to differences in muscle strength among ethnicities [9]. To date, this relationship has only been evaluated in two studies involving Caucasians [40,41]. In particular, the first study supports the relationship between sarcopenia (as defined in the skeletal muscle index) and NAFLD, assessed with ultrasound, in American Caucasians [40]. The second study, utilizing information from the UK Biobank, revealed that reduced handgrip strength was linked to an elevated risk of developing severe NAFLD (defined as hospitalization or mortality) following an approximately 10-year follow-up period in adults aged between 37 and 73 years [41]. In addition, in most of these Asian studies [32,34,35,37], NAFLD has been identified using steatosis scores calculated with anthropometric and biochemical parameters and not with specific techniques for assessing liver steatosis and fibrosis [42]. Transient elastography (TE) was created to identify and measure liver steatosis through a non-invasive parameter, specifically the CAP (Controlled Attenuation Parameter), which demonstrates a correlation with the histopathological assessment of hepatic steatosis [43,44]. This method is widely employed in population-based investigations owing to its non-invasive nature and ready availability [44]. Consequently, the primary objective of this study was to assess the association between HGS and NAFLD in the Italian adult population. In particular, the primary outcome was to verify whether there is a significant difference in the prevalence of hepatic steatosis, quantified using the CAP score, among HGS tertiles.

2. Materials and Methods

2.1. Study Design

This retrospective cohort study involved the inclusion of 5708 assessments of consecutive outpatient individuals who underwent screening examinations for potential fatty liver disease using transient elastography (TE). The examinations took place at the Nutrition Clinic of the "Mater Domini" University Hospital in Catanzaro, Italy, spanning the period from April 2014 to March 2021. For this study, data available in existing databases was used. We included adults of both genders, those ≥50 years old, with a wide range of

body mass index (BMI), whose HGS data were available. We excluded individuals from the study who displayed laboratory and clinical indications of chronic hepatitis B and/or C virus infections. Additionally, we excluded those with a history of or current alcohol misuse, defined as consuming more than 20 g of alcohol per day, where hard liquor equals 45 mL (1.5 oz), wine equals 120 mL (4 oz), and beer equals 350 mL (12 oz), each containing 10 g of alcohol, as confirmed by their medical records. Furthermore, we excluded individuals with ascites and liver cirrhosis, autoimmune liver disease, cholestatic liver disease, chronic kidney disease, nephrotic syndrome, pregnancy, and those taking methotrexate, corticosteroids, antiretroviral agents, valproate, and amiodarone. For the purpose of this analysis, we also removed all patients with a liver stiffness value of $\geq$7 kPa [45] and those for whom it was technically infeasible to evaluate the CAP score. To detect a difference in the prevalence of hepatic steatosis of at least 18% between HGS tertiles, with a power of 80% and a two-sided significance level of 0.05, approximately 243 participants are needed. Among the adults initially selected, 388 patients meet all eligibility criteria (Figure 1). The protocol was approved by the "Mater Domini" Azienda University Hospital's local ethical committee (protocol n.121 on 21 April 2023). All participants provided written informed consent, and this study adhered to the ethical guidelines specified in the Declaration of Helsinki. All participants underwent a medical interview, during which anthropometric measurements, HGS assessments, and TE evaluations were conducted. The baseline clinical characteristics of the population, as well as their biochemical parameters, were retrieved from their medical records. Various cardiovascular risk factors were defined according to the following criteria: Hypertension: systolic blood pressure (SBP) $\geq$ 140 mmHg and/or diastolic blood pressure (DBP) $\geq$ 90 mmHg or the use of antihypertensive medications.

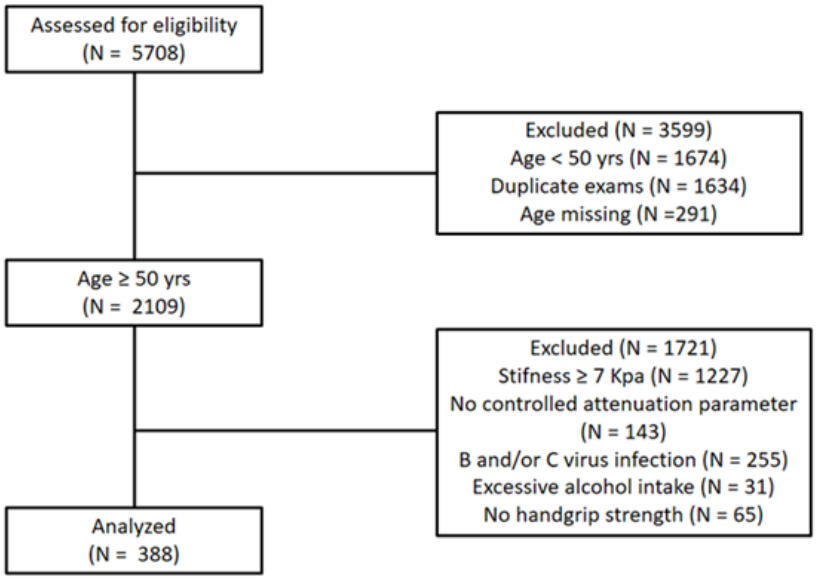

Figure 1. Flow diag.am of participants for the study.

Dyslipidemia: total cholesterol levels > 200 mg/dL and/or triglycerides > 200 mg/dL or the use of lipid-lowering drugs.

Type 2 diabetes: fasting blood glucose levels $\geq$ 126 mg/dL or the use of antidiabetic treatments.

General obesity: a body mass index (BMI) of $\geq$30 kg/m^2.

Smoking: individuals who were current or past smokers (at least in the preceding four months).

2.2. Anthropometric Measurements

Body weight was determined with subjects lightly clothed after a night of fasting before breakfast, and the weight of clothing was subtracted. Height and body weight mea-

surements were taken with a wall-mounted stadiometer and a calibrated scale, respectively, with an accuracy of 1 cm and 0.1 kg. Waist and hip circumferences (WC and HC), along with the waist-to-hip ratio (WHR), were assessed according to established methods [46]. Android obesity was defined as a WHR exceeding 0.90 for males and 0.85 for females [47].

2.3. HGS Measurement

HGS was determined by a digital hand dynamometer (DynX®™ Akern srl, Florence, Italy) with less than 10% variation in results for varied grip postures by an experienced dietitian. At the time of the measurement, the participants were seated with their elbows supported and flexed at 90° [48]. Three measurements of maximal strength from the dominant hand were performed, and the mean value of the three values was recorded [36,37]. In alignment with prior research, the relative HG (rHGS) was computed by adjusting the mean HG of the dominant arm based on BMI using the formula HGS/BMI [33,34,36,38]. This adjustment takes into account the robust correlation between muscle strength and BMI [49].

2.4. Liver Transient Elastography (TE)

TE offers a non-invasive means of quantifying hepatic steatosis through the assessment of the Controlled Attenuation Parameter (CAP) and measuring liver stiffness using Fibroscan® 502 by Echosense SASU, Paris, France [44,45]. The CAP and stiffness scores were obtained from the same volume of liver parenchyma simultaneously. All individuals underwent examination with the standard 3.5 MHz M probe applied to the right lobe of the liver, accessing intercostal spaces while the subjects were in a supine position. The right arm was placed behind the head to facilitate access to the upper right quadrant of the abdomen. The probe transducer's tip was positioned on the skin between the ribs, at the level of the liver's right lobe. The same investigator conducted all of the scans. The hepatic stiffness was determined by using the median value (in kPa) derived from 10 measurements taken within a depth range of 25 to 65 mm. Only data with ten valid images and a liver stiffness ratio represented by a 30% interquartile range (IQR) over the median were considered for inclusion. Given the device's unique CAP algorithm, we exclusively employed the M probe to calculate the CAP score. Each patient underwent 10 successful measurements, and only individuals with all 10 measurements deemed successful were included in this study. The success rate was determined by dividing the total count of successful measurements by the overall number of measurements. We calculated the IQR-to-median ratio of liver stiffness (IQR/MLSM) as an indicator of variability. The ultimate CAP score, within a range of 100 to 400 decibels per meter (dBm–), was computed as the median of individual measurements. A CAP score equal to or greater than 248 dB/m was utilized to diagnose NAFLD. Distinct cutoff values were applied to determine the grade of steatosis: a CAP score of 248 dB/m or higher for the diagnosis of S1 grade, a CAP score of 269 dB/m or higher for the diagnosis of S2 grade, and a CAP score of 281 dB/m or higher for the diagnosis of S3 grade, indicating severe steatosis [50].

2.5. Biochemical Evaluation

Following an overnight fasting period, venous blood samples were collected into vacutainer tubes (Becton & Dickinson, Plymouth, UK) and then promptly centrifuged within 4 h. Serum levels of glucose, creatinine, high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), triglycerides (TG), ALT, AST, and gamma-glutamyl transferase (GT) were determined using a chemiluminescent immunoassay, following the manufacturer's instructions, and conducted on a COBAS 8000 analyzer (Roche, Switzerland). The Friedewald formula was applied to compute low-density lipoprotein cholesterol (LDL-C).

2.6. Statistical Analysis

Data are reported as mean ± SD. The prevalence of NAFLD in adults was 21.8% [29].

Participants were divided into tertiles based on rHGS, and an ANOVA test was conducted to compare the means among the tertiles. A χ^2 test was employed to analyze the

prevalence across rHGS tertiles. A general linear model (GLM) was used to adjust the CAP score values, the prevalence of NAFLD, and its severity (S3 grade) for confounding factors (as age, gender, smoking habit, physical activity, hyperlipidemia, general and android obesity, HDL-C, TG, creatinine, and AST) in analyzing rHGS groups. We also repeated the same tests on the subgroup of women because the population of this study is mainly made up of women (n = 271). In the population divided into rHGS tertiles, we also examined the prevalence of NAFLD in two groups: those with a normal weight (BMI $\leq$ 25 kg/m^2) and those who are overweight/obese (BMI > 25 kg/m^2). We finally assessed muscle strength (rHGS) in subjects both with and without NAFLD. To assess the risk of hepatic steatosis among individuals with varying rHGS, we conducted a multinomial logistic regression analysis to estimate the adjusted odds ratios (ORs). The ORs were adjusted for confounding variables, i.e., those that were statistically different in the ANOVA and χ^2 test. In particular, in Model 1, the ORs of NAFLD were adjusted only for age and gender; and in Model 2, the ORs were adjusted, in addition to age and gender, for smoking habit, physical activity, hyperlipidemia, general obesity, HDL-cholesterol, triglycerides, creatinine, and AST. In Model 3, the ORs were adjusted for the same variables as in Model 2, but the variable "general obesity" was replaced by "android obesity" in the analysis. Subsequently, we conducted a ROC curve analysis to determine the optimal rHGS cutoff point for detecting NAFLD in adult individuals. Statistical significance was considered at $p < 0.05$ (two-tailed). All statistical comparisons were carried out using SPSS 25.0 for Windows, provided by IBM Corporation, New York, NY, USA.

3. Results

The mean age of the study population was 60.8 $\pm$ 7 years, with 70% of the sample being female. The prevalence of NAFLD was 53%, and general and android obesity were 34% and 73%, respectively. The mean HGS was 17.9 $\pm$ 3 kg, 22.4 $\pm$ 4 kg, and 36.1 $\pm$ 7 kg, and the rHGS was 0.59 $\pm$ 0.09, 0.80 $\pm$ 0.08, and 1.33 $\pm$ 0.25 in tertile I, tertile II, and tertile III, respectively (Table 1). An increase in muscle strength was associated with a decrease in the mean age and BMI ($p < 0.001$ for both factors; Table 1). In the rHGS tertiles, there was also a statistically significant difference in TG, HDL-C, AST, creatinine level, and the prevalence of gender, smoking habit, physical activity, hyperlipidemia, and general and android obesity (Table 1). Furthermore, the CAP score was significantly higher in the individuals in the first tertile of rHGS than those in the second and third tertiles (266 $\pm$ 48 dB/m, 252 $\pm$ 49 dB/m, and 249 $\pm$ 47 dB/m, $p = 0.012$, respectively) (Table 1).

GLM shows that the CAP score was significantly different among tertiles even after adjustment for confounding variables ($p = 0.001$; Table 1). The prevalence of hepatic steatosis was 64%, 51%, and 46% in the tertile I, tertile II, and tertile III of rHGS, respectively ($p = 0.004$) (Figure 2a). The prevalence of the diagnosis S3 grade of steatosis was 37% in the first tertile, 31% in the second tertile, and 28% in the third tertile of rHGS ($p = 0.024$) (Figure 2b). After adjustment for confounding variables, the statistically significant differences in the prevalence of NAFLD and of steatosis of S3 grade persisted among rHGS tertiles ($p = 0.023$ and $p = 0.005$, respectively) (Figure 2a,b).

Demographic, clinical, and instrumental characteristics of the women divided into rHGS tertiles are shown in Table S1. In the female population, we found that the CAP score, prevalence of NAFLD, and hepatic steatosis S3 grade were significantly higher in the first and second tertiles of rHGS than those in the third tertile (Table S1). In women, these results remained significantly different among rHGS tertiles even after adjustment for confounding variables (Supplementary Table S1). We also investigated the prevalence of NAFLD in the population stratified by BMI. Within the normal-weight population divided into rHGS tertiles, we observed a higher prevalence of NAFLD in the first and second tertiles compared to the third (39%, 23%, and 10%, $p = 0.035$, respectively) (Supplementary Figure S1A). The same result is also confirmed in the overweight/obese population categorized by rHGS tertiles (77%, 63%, and 48%, $p = 0.013$, respectively) (Supplementary Figure S1B). Additionally, our analysis of participants with or without NAFLD revealed that those with

hepatic steatosis exhibited significantly lower rHGS compared to those without NAFLD (0.86 ± 0.3 vs. 0.96 ± 0.4, $p = 0.008$, respectively). Notably, this result retained statistical significance even after adjusting for confounding variables such as age, gender, smoking habits, physical activity, hyperlipidemia, and general and android obesity ($p = 0.004$).

Table 1. Demographic, clinical, and instrumental characteristics of the population according to relative handgrip strength tertiles.

Variables	Total (n = 388)	T1 (n = 129)	T2 (n = 130)	T3 (n = 129)	*p* for Trend	*p* for Post Hoc Analysis
rHGS (Range)	0.26–1.97	0.26–0.69	0.70–0.98	0.99–1.97		
Age (years)	60.8 ± 7.1	62.4 ± 7	61.8 ± 7	58.1 ± 6	<0.001	T1 vs. T3 < 0.001 T2 vs. T3 < 0.001
BMI (kg/m^2)	28.7 ± 4.4	30.8 ± 5	27.9 ± 4	27.3 ± 4	<0.001	T1 vs. T2 < 0.001 T1 vs. T3 < 0.001
HGS (kg)	25.5 ± 9.3	17.9 ± 3	22.4 ± 4	36.1 ± 7	<0.001	T1 vs. T2 < 0.001 T1 vs. T3 < 0.001 T2 vs. T3 < 0.001
WHR	0.91 ± 0.08	0.89 ± 0.07	0.89 ± 0.09	0.94 ± 0.09	<0.001	T1 vs. T3 < 0.001 T2 vs. T3 < 0.001
SBP (mmHg)	125 ± 16	125 ± 16	126 ± 18	125 ± 13	0.85	/
DBP (mmHg)	76 ± 10	76 ± 11	76 ± 9	77 ± 9	0.56	/
Glucose (mg/dL)	99 ± 21	99 ± 16	98 ± 24	99 ± 22	0.92	/
TC (mg/dL)	208 ± 42	210 ± 39	208 ± 42	206 ± 46	0.68	/
HDL-C (mg/dL)	57 ± 16	61 ± 17	59 ± 16	52 ± 14	<0.001	T1 vs. T3 < 0.001 T2 vs. T3 0.001
TG (mg/dL)	129 ± 70	123 ± 62	119 ± 62	144 ± 81	0.010	T2 vs. T3 0.019
LDL-C (mg/dL)	125 ± 38	125 ± 36	124 ± 37	125 ± 40	0.99	/
Creatinine (mg/dL)	0.81 ± 0.17	0.77 ± 0.2	0.75 ± 0.1	0.91 ± 0.2	<0.001	T1 vs. T3 < 0.001 T2 vs. T3 < 0.001
AST (IU/L)	22 ± 7	21 ± 7	21 ± 7	23 ± 8	0.018	T1 vs. T3 0.039
ALT (IU/L)	23 ± 14	21 ± 12	23 ± 17	25 ± 13	0.09	/
γGT (IU/L)	29 ± 26	36 ± 41	23 ± 15	29 ± 24	0.15	/
CAP (Db/m)	256 ± 48	266 ± 48	252 ± 49	249 ± 47	0.012	T1 vs. T3 0.021
IQR (%)	20 ± 6	20 ± 6	21 ± 6	20 ± 6	0.90	
aCAP [§] (Db/m)	/	269 ± 5	253 ± 4	237 ± 6	0.001	T1 vs. T2 0.023 T1 vs. T3 0.001
Stiffness (KPa)	4.8 ± 1	4.9 ± 1	4.7 ± 1	4.7 ± 1	0.49	/
			Prevalence (%)			
Gender, female	70	98	85	26	<0.001	/
Smokers	27	19	25	38	0.001	/
Physical activity	35	18	37	50	<0.001	/
T2DM	9	12	9	7	0.22	/
Dyslipidaemia	69	65	62	81	0.007	/
Hypertension	47	54	45	42	0.06	/
General Obesity	34	50	32	20	<0.001	/
Android Obesity	73	72	66	80	0.034	/

[§] aCAP score adjusted for gender, age, smoking habit, physical activity, hyperlipidemia, general and android obesity, HDL-C, TG, creatinine, and AST. rHGS = relative handgrip strength; BMI = body mass index; WHR = waist to hip ratio; SBP = systolic blood pressure; DBP = diastolic blood pressure; CAP = controlled attenuation parameter; IQR = interquartile range; TC = total cholesterol; TG = triglycerides; LDL-C = low density lipoprotein cholesterol; AST = aspartate aminotransferase; ALT = alanine aminotransferase; γGT = gamma glutamyl transferase; T2DM = Type 2 diabetes mellitus; general obesity = obesity classified on BMI; and android obesity = obesity classified on WHR.

After adjusted for age and gender (Model 1), the multinomial logistic regression analysis showed that adults in tertile I and tertile II have significantly higher ORs of having NAFLD (Tertile I: OR = 4.85, 95% CI = 2.30–10.20, $p < 0.001$; Tertile II: OR = 2.48, 95% CI = 1.26–4.87, $p = 0.008$, respectively) compared to those in rHGS tertile III (Table 2). In Model 2, only the subjects in the first tertile exhibited a significantly higher odds ratio (OR)

compared to those in the second and third tertiles of rHGS (OR = 3.63, 95% CI = 1.49–8.82, $p = 0.004$; Table 2).

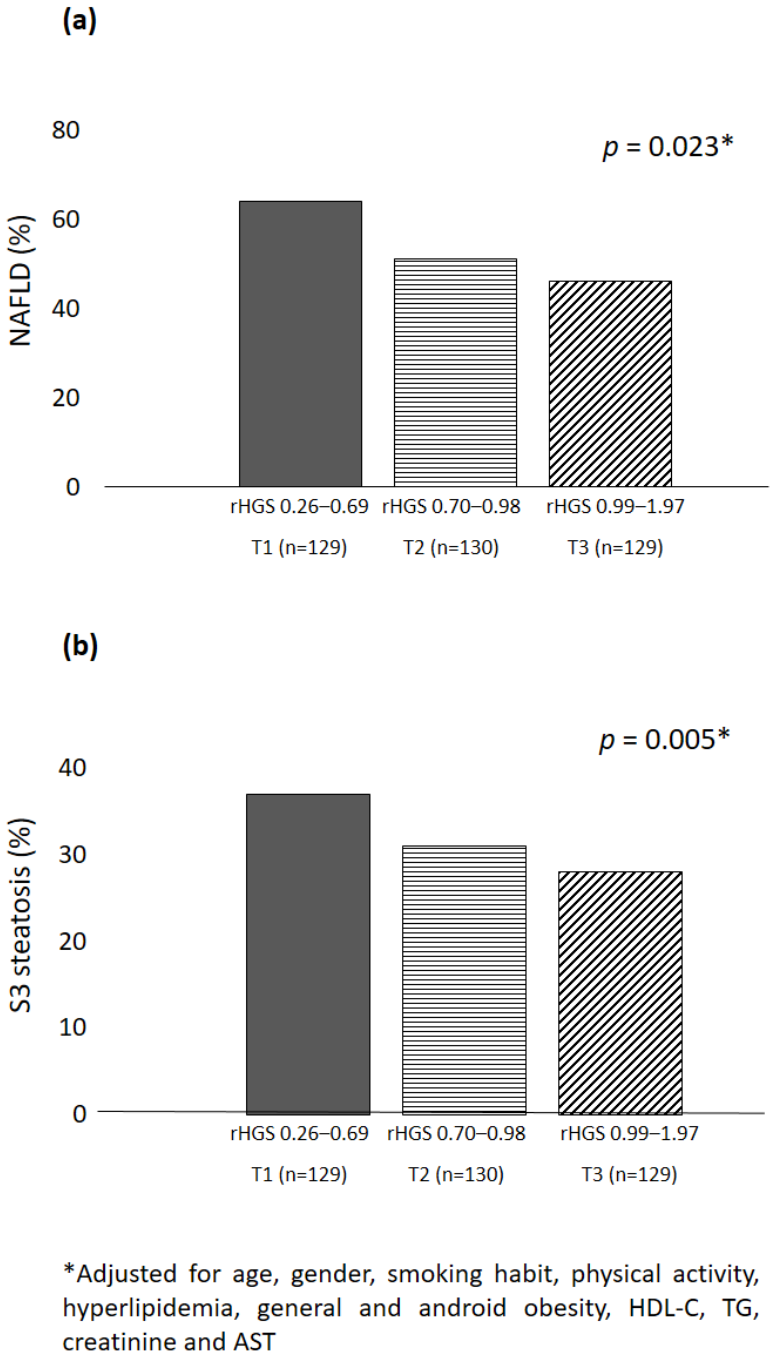

Figure 2. Prevalence (**a**) and severity (**b**) of NAFLD in the population according to relative handgrip strength tertiles. * Adjusted for age, gender, smoking habit, physical activity, hyperlipidemia, general and android obesity, HDL-C, TG, creatinine, and AST.

Finally, when the values were adjusted for android obesity rather than general obesity, the risk of NAFLD was 5.30 and 2.56 times higher for the elderly in the first and second tertiles of rHGS, respectively, than for those in the third tertile (Model 3; Table 2). Additionally, the area under the ROC curve for rHGS in detecting the presence of NAFLD was 0.412 (SE = 0.029, $p = 0.003$, with a lower limit of 0.35 and an upper limit of 0.46) (figure not displayed). An rHGS value of 1.22 exhibited low sensitivity (18%) but

high specificity (80%) in identifying hepatic steatosis. On the other hand, an rHGS value of 0.55 demonstrated excellent sensitivity (88%) but low specificity (5%) in predicting NAFLD among the elderly.

Table 2. Odds ratio for NAFLD risk by relative handgrip strength tertiles and other factors.

	OR (95% CI)	*p*
Model 1		
High rHGS	1 (ref)	
Mild rHGS	2.48 (1.26–4.87)	0.008
Low rHGS	4.85 (2.30–10.20)	<0.001
Gender	2.70 (1.40–5.21)	0.003
Model 2		
High rHGS	1 (ref)	
Mild rHGS	2.02 (0.91–4.48)	0.08
Low rHGS	3.63 (1.49–8.82)	0.004
General Obesity	2.44 (1.41–4.28)	0.002
Model 3		
High rHGS	1 (ref)	
Mild rHGS	2.56 (1.17–5.59)	0.018
Low rHGS	5.30 (2.24–12.57)	<0.001
Android Obesity	2.39 (1.36–4.18)	0.002

Model 1 was adjusted for age and gender. Model 2 was adjusted for age, gender, smoking habit, physical activity, hyperlipidemia, HDL-C, TG, creatinine, and AST. Model 3 was adjusted for age, gender, smoking habit, physical activity, hyperlipidemia, android obesity, HDL-C, TG, creatinine, and AST. NAFLD, non-alcoholic fatty liver disease; rHGS, relative handgrip strength; OR, odds ratio; CI, confidence interval.

4. Discussion

To our knowledge, this is the first report involving Italian adults that highlights a potential association between hepatic steatosis, as evaluated through TE, and a decline in muscle function, as indicated by reduced muscle strength.

The aging of societies and the increase in life expectancy in Italy are unfortunately also associated with a demographic and epidemiological transition towards a frail population. Although at an international level, this increase is seen as a public health success story, in approximately the same period of time, there has been an increase in several non-communicable diseases (NCDs), which include liver disease and sarcopenia [51]. In Italy, the estimated prevalence of NAFLD in the general population is approximately 25%, with higher prevalence rates in the southern regions compared to the northern regions (Campania region: 12.1% vs. Trentino Alto Adige region: 3.1%) [52]. In at-risk populations, such as obese and/or diabetic individuals, the prevalence increases to levels exceeding 50%. The prevalence of NAFLD found in our study is in line with that reported in other similar studies [53–55]. Approximately 30% of the Italian population will develop NAFLD by 2030 [56] with likely associated comorbidities, with an increase in the economic and healthcare burden associated with this disease. This treatable clinical condition has huge costs, precedes the appearance of diabetes, and predicts mortality. Therefore, our work suggests how to set up measures for the early identification of those individuals affected by NAFLD and how to treat them.

In particular, our retrospective study reveals that adults, especially females in apparently good health belonging to the first rHGS tertile (lowest rHGS value), had a very high CAP score and a higher prevalence of NALFD than those in the third tertile of rHGS (Figure 2a and Tables 1 and S1), even after adjusting for confounding factors. Furthermore, individuals in tertile I also had a higher prevalence of severe hepatic steatosis than those in rHGS tertile III (Figure 2b). A key finding was that adults with lower rHGS had a greater risk of having NAFLD than those with higher rHGS values, and that this risk is independent of age (Table 2). These results are in line with those demonstrated for Asian adults

regarding the high risk of fatty liver disease in individuals with low muscle function [33–37]. Therefore, our findings suggest that differences in muscle strength values between different ethnicities do not affect this strong relationship [9]. This evidence is strengthened by the prospective study conducted on a European cohort [41]. Indeed, this study showed that individuals in the highest HGS tertile had a lower risk (95% CI 0.64–0.77) of severe NAFLD than those in the lowest HGS tertile [41]. In addition, in a recent meta-analysis, Han et al. also demonstrated that individuals with low HGS had a higher risk of NAFLD compared to those with normal HGS (OR = 3.32, 95% CI: 1.91–5.75). Furthermore, the authors reported that the risk among patients with low HGS affected by NAFLD was higher than that in normal people (OR = 3.31, 95% CI: 2.45–4.47) [57].

We observed, in our study, a higher prevalence of NAFLD among subjects of both genders and age $\geq$50 years than that found in a similar Asian population (53% vs. 22%, respectively) [35]. The observed dissimilarity may, in part, be attributed to the higher average BMI in our study population and the distinctive methodology employed for NAFLD diagnosis [35]. Notably, the CAP score might prove to be more precise in the detection of hepatic steatosis compared to the hepatic steatosis index [58].

We also found that low HGS had a greater and independent effect in the presence of obesity and, particularly, android obesity, which is already associated with a higher risk of developing NAFLD [59]. In light of the above, our results could have important implications because they confirm, in line with studies on adults in Asia and Caucasians in the USA and UK, that fatty liver disease could be directly associated with muscle strength during aging.

Studies focusing on muscle mass [60,61] have highlighted the link between muscle tissue and the liver; however, they may not be enough to fully explain this cross-talk. Studies have demonstrated that preserving or increasing muscle mass in isolation may not be sufficient to halt the decline in muscle function related to aging [62] and that muscle strength holds greater significance than muscle quantity when assessing mortality risk among the elderly [63].

Several studies have underscored the significance of evaluating muscle strength in individuals with liver disorders. These studies have revealed associations between handgrip strength (HGS) and health-related quality of life [64], as well as the occurrence of hepatic decompensation and HCC in adults with chronic liver conditions [65]. Furthermore, it has been established that a low HGS value serves as a negative prognostic factor for survival in individuals with liver cirrhosis [66] and HCC [67]. Notably, a study [67] involving HCC patients demonstrated that the low HGS group exhibited significantly shorter survival compared to the high HGS group, with low HGS emerging as an independent predictor for overall survival in multivariate analysis, while skeletal muscle depletion did not exhibit the same impact. Additionally, patients with low HGS tended to discontinue therapy more frequently than those with high HGS [67]. HGS is additionally linked to various unfavorable clinical consequences in cirrhosis, such as reduced physical activity and the development of hepatic encephalopathy [68]. Moreover, a study found that reduced handgrip strength (HGS) is linked to a twofold increase in the risk of all-cause and liver-related mortality [66]. Another investigation demonstrated that grip strength is associated with an elevated risk of mortality among patients on liver transplantation waiting lists [69]. Additionally, impaired preoperative HGS is correlated with increased postoperative complications, mortality, and extended hospitalization after surgery [70]. The HGS test stands out as an affordable, widespread screening tool with notable sensitivity and specificity for identifying morbidity and mortality across various healthcare settings. It can be easily administered by nurses, physicians, and other healthcare professionals. When considering the cost and expertise required by alternative tests and their influence on long-term survival, HGS assessment emerges as a superior option. HGS serves as a simple, non-invasive, cost-effective, and real-time predictor of long-term all-cause mortality [69]. Despite this accumulating evidence, the precise relationship between muscle health and metabolic disorders like NAFLD remains incompletely understood. Although our study

did not directly assess the mechanisms underlying this relationship, we can nevertheless make some hypotheses.

The role of IR, chronic inflammation, and decreased physical activity has already been demonstrated [20–22]. In fact, as IR and inflammation increase, the prevalence of NAFLD increases and muscle strength decreases [20,21,33,36]. Therefore, sarcopenia itself may aggravate IR in non-obese and obese individuals [71]. Furthermore, Lee et al. demonstrated that both non-obese and obese individuals exhibited a markedly higher prevalence of NAFLD in the presence of sarcopenia [34]. In particular, the prevalence of NAFLD was 9–30% in non-obese sarcopenic individuals and 4–14% in non-obese and non-sarcopenic patients, while the prevalence of NAFLD was 61–83% in obese sarcopenic and 50–72% in obese non-sarcopenic patients [34]. Hence, factors beyond insulin resistance and obesity may play a role in the connection between muscle tissue and the liver, including IGF-1, myostatin, and SIRT 1.

In particular, a systematic review and meta-analysis revealed that individuals with NAFLD exhibit lower levels of IGF-1 when compared to healthy control subjects [26]. Nevertheless, IGF-1 is also present in skeletal muscles, where it promotes muscle growth and strength, mitigates degeneration, hinders inflammatory processes, and stimulates the regenerative capacity of satellite cells [72]. In addition, a recent study demonstrated that elderly individuals with sarcopenia exhibit lower IGF-1 levels compared to those without sarcopenia (98.53 $\pm$ 28.45 vs. 136.41 $\pm$ 48.95 ng/mL, $p < 0.001$) [27].

Information on serum myostatin levels in individuals with sarcopenia is somewhat limited. However, a connection exists between IGF-1 and myostatin under usual circumstances. IGF-1 acts to obstruct the myostatin pathway; indeed, when IGF-1 is suppressed, myostatin becomes overexpressed [73]. SIRT1 is linked to liver damage and muscle atrophy, regulating lipid metabolism and countering oxidative stress in the liver. It plays a crucial role in fatty liver disease and muscle health [28,29].

All these mechanisms suggest a strong link between skeletal muscle and the liver and, consequently, between sarcopenia and NAFLD. However, it remains uncertain whether impaired muscle function and sarcopenia lead to NAFLD, if it's the other way around, or whether the relationship does not involve a causal link but rather simultaneous effects on both the liver and muscles.

In our study, we also found in tertile I a serum level of AST lower than tertile III (tertile I with a lower rHGS and higher CAP score than participants in tertile III). This is not surprising because it has already been shown that some patients with NAFLD may have laboratory abnormalities such as high ALT and AST, whereas others may have normal transaminase levels [74]. There is consensus on the fact that NAFLD is diagnosed in clinical settings using ultrasound imaging (as a liver biopsy is not practically feasible). Nice guidelines recommend not using routine liver blood tests to rule out NAFLD but rather offering a liver ultrasound to test people for NAFLD (National Guideline Centre (UK)) [75]. Risk groups recommended for NAFLD screening are the American Association for the Study of Liver Diseases (AASLD) and Asian Pacific Association for the Study of the Liver (APASL), diabetics, and patients who are overweight/obesity with a family history of cirrhosis, moderate-to-high alcohol consumption, or metabolic syndrome [76,77]. Despite having the disease, up to 50% of NAFLD patients can have normal ALT and AST levels [76,78,79]. Elastography can accurately diagnose liver steatosis, especially if the IQR is less than 30% of the median [80].

Our study does have certain limitations. It was conducted at a single center, which means the number of adult participants was restricted, and the study included both males and females, as well as obese and non-obese individuals. We did not find an association between HGS and NAFLD in males. It is essential to publish not only positive research results but also negative ones. Our population differs from that referenced in Kim et al. [35]. The study evaluated an Asiatic population. Additionally, the authors used the hepatic steatosis index as a surrogate marker for NAFLD, while we used TE assessment. There are no studies on the association between HGS and NAFLD in European males. Despite a small

sample size, we believe that our findings could be valuable in designing future research for both genders. Furthermore, we did not evaluate IR and inflammation status, serum levels of IGF-1, or myostatin. Due to the lack of muscle mass measurements, we were unable to verify the presence of sarcopenia. We did not perform any liver biopsies, mainly due to the apparently healthy study population, the high cost, and the associated risk. Due to the study design, we were unable to identify a causal relationship. Additional data from across EU countries is needed to confirm our findings. In addition, it is imperative to conduct prospective studies and intervention trials to ascertain a causal connection between impaired muscle function and fatty liver disease. The major strength of this study is that it was a cohort of adults, who are the subjects at greatest risk of metabolic disorders and sarcopenia, and that we used TE to detect NAFLD instead of steatosis scores [33]. Moreover, TE exhibits a high level of sensitivity and specificity in evaluating liver steatosis and fibrosis [34] and is commonly employed in population-based research due to its non-invasive nature and accessibility [35]. Finally, AUROC are 81–84% for ≥S1 (steatosis in at least 5–10% of hepatocytes), 85–88% for ≥S2 (33%), and 86–91% for S3 (66%) steatosis. The reported sensitivities for ≥S1, ≥S2, and ≥S3 are 60–75%, 69–84%, and 77–96%, respectively [81]. Some studies suggest that skin capsular distance (SCD) can affect the accuracy of the CAP score by overestimating this measurement, especially in those with a large SCD (≥25 mm) [82,83]. However, the FibroScan Model 502 and later models have an automated probe selection tool in their software that suggests the choice of the appropriate probe (M and XL) for each patient according to the real-time evaluation of the SCD [84]. Additionally, as in prior studies [32,33,35,36], we utilized HGS to assess muscle function, which bolsters the statistical robustness of our findings. Consequently, the primary outcome of this study highlights that diminished muscle function may represent a risk factor for NAFLD among aging adults who appear to be in good health.

5. Conclusions

We observed a greater risk of fatty liver disease in Italian adults with lower handgrip strength. Although decreased function mass has long been considered an inevitable consequence of aging, it is now regarded as a disease that should be diagnosed and treated to prevent sarcopenia and metabolic diseases such as NAFLD. Therefore, we suggest that a muscle strength assessment be performed for all subjects with NAFLD, and for adults with low appendicular muscle strength, the measurement of intrahepatic fat content should be performed. Although TE is a non-invasive test used for the diagnosis and staging of NAFLD in clinical practice, our data should be taken with caution. Further studies are needed to confirm our findings and identify interventions that increase muscle quality and reduce fatty liver content in order to improve the health of aging populations.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/app132212489/s1, Table S1: Demographic, clinical, and instrumental characteristics of the females' population according to relative handgrip strength tertiles. Figure S1: Prevalence of NAFLD in the population according to relative handgrip strength tertiles and stratified by BMI.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy.

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