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Evaluation of Sarcopenic Obesity in Patients with MASLD

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Abstract

Sarcopenic obesity (SO) has gained growing attention in metabolic dysfunction-associated steatotic liver disease (MASLD), yet data in Caucasian populations remain limited. The aim of the study was to assess the prevalence of SO using different definitions and to explore its relationship with steroid androgens, physical performance and frailty in MASLD individuals. Two hundred Caucasian patients with MASLD and available dual-energy X-ray absorptiometry (DEXA) data were evaluated. Clinical, biochemical, hormonal and elastography data were recorded, while physical performance was assessed using the Short Physical Performance Battery (SPPB) and Liver Frailty Index (LFI). SO prevalence ranged from 34.5% to 76.5% based on different SO definitions. SO individuals showed greater hepatic steatosis, more metabolic comorbidities and demonstrated poorer physical performance. Lower dehydroepiandrosterone sulfate (DHEAS) levels were independently associated with SO when definition is based on total body fat percentage, and waist circumference (WC) was consistently linked to SO across all definitions. Separate analysis based on gender, confirmed DHEAS being independently associated with SO in men, while WC represented an independent SO predictor in both genders. In conclusion, SO is common among Caucasian MASLD patients and is accompanied by metabolic, hepatic, hormonal, and functional alterations, highlighting the need for better identification in clinical practice.

Keywords: MASLD; sarcopenic obesity; dual-energy X-ray absorptiometry (DEXA); dehydroepiandrosterone sulfate (DHEAS); frailty; physical performance; short physical performance battery (SPPB); liver frailty index (LFI)

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1. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the updated term of what was formerly referred to as non-alcoholic fatty liver disease (NAFLD), with the redefinition highlighting its strong association with metabolic disorders [1]. MASLD encompasses a broad spectrum of severity ranging from simple hepatic steatosis (metabolic dysfunction-associated steatotic liver, MASL) to metabolic dysfunction-associated steatohepatitis (MASH), fibrosis and cirrhosis [2]. Nowadays, MASLD has emerged as the primary cause of hepatic disease, with a prevalence higher than 30% in adult population and projected to reach up to 55% by 2040 [3]. Meanwhile, among individuals with obesity, prevalence of MASLD may exceed 75%, with approximately 7% already having advanced fibrosis [4]. The impact of MASLD extends beyond the liver and is often associated with systemic complications, including cardiovascular and renal disease, sleep-apnea, extra-hepatic cancers, and sarcopenia. The latter is described as a reduction in muscle mass and muscle strength, which may be accompanied by limitations in physical performance [5]. Sarcopenia affects almost 10-16% of older adults, and it is linked to increased frailty and reduced quality of life [6]. Its prevalence in MASLD may reach up to 24% representing an independent risk factor for fibrosis and being associated with a greater risk of frailty and mortality [7,8].

The coexistence of sarcopenia and obesity is defined as sarcopenic obesity (SO), with an estimated global prevalence at around 11% among older adults [9]. Instead of a neutral simultaneous presence of these two conditions, their coexistence might be associated with higher complications and mortality rates than with sarcopenia or obesity alone [10,11]. In fact, SO presence in adults has been linked to a 24% higher all-cause mortality rate and to worse cardiovascular outcomes, compared to individuals with either condition alone or neither condition [12,13]. Although the mechanisms underlying SO have not been fully clarified, shared pathways between sarcopenia and obesity are thought to contribute to SO development, such as insulin resistance, low-grade inflammation, adipose tissue dysfunction, and hormonal disturbances [14]. Regarding the latter, disruption of the hormonal milieu, reflected by lower testosterone and dehydroepiandrosterone sulfate (DHEAS) levels has been reported with aging in both men and women, contributing to the pathogenesis of SO [15,16].

In patients with MASLD, the prevalence of SO may rise to 47% [10] but this may differ depending on the definition criteria used. Nevertheless, epidemiological data on SO remains limited in MASLD, particularly in Caucasian population [17]. In addition, although evidence suggests that SO may be associated with more advanced stages of liver steatosis and fibrosis [18,19], these studies have several limitations including the absence of more accurate evaluation of liver steatosis, such as controlled attenuation parameter (CAP), and/or precise assessment of body fat and muscle mass with methods such as dual-energy X-ray absorptiometry (DEXA) [20]. Moreover, the impact of SO on physical performance and frailty in MASLD and the possible implication of steroid androgens remains poorly explored in MASLD population [21].

Thus, the aim of our study was to evaluate the prevalence of SO in Caucasian patients with MASLD, to investigate its potential correlation with severity of liver disease and frailty and to examine the association of steroid androgens with SO and frailty in MASLD patients concurrently for the first time.

2. Materials and Methods

2.1. Study Design and Population

This cross-sectional study included 200 individuals with a diagnosis of MASLD, followed up at the liver steatosis outpatient clinic of "Laiko" General Hospital in Athens, Greece. The inclusion criteria were age ≥18 years old with MASLD and availability of body composition data measured by DEXA. Exclusion criteria included decompensated liver cirrhosis, acute infection confirmed clinically and by laboratory tests, hemodynamic instability, pregnancy or lactation, acquired

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immunodeficiency syndrome and the administration of any medication containing steroids (e.g. tablets, inhalers, or ointments etc.) or hormone replacement therapy.

In our study population, to diagnose MASLD the presence of hepatic steatosis along with at least one cardiometabolic risk factor was required (22). Hepatic steatosis was identified by liver ultrasound. Cardiometabolic risk factors for MASLD definition adapted to the Greek (European) population were: i) overweight or obesity: BMI ≥ 25 kg/m^2 or WC ≥94 cm in men and ≥80 cm in women, ii) prediabetes or type 2 diabetes (T2D): hemoglobin A1c (HbA_{1c}, %) 5.7 - 6.4%, fasting plasma glucose 100 - 125 mg/dl or 2-hour plasma glucose during oral glucose tolerance test (OGTT) 140 - 199 mg/dl (prediabetes) or HbA_{1c} ≥6.5%, fasting plasma glucose ≥126 mg/dl or 2-hour plasma glucose during OGTT ≥200 mg/dl (T2D) or assumption of antidiabetic medication, iii) hypertrygliceridemia: triglycerides ≥150 mg/dl or lipid-lowering treatment iv) low high-density lipoprotein cholesterol (HDL cholesterol): HDL cholesterol ≤39 mg/dl in men and ≤50 mg/dl in women or lipid-lowering treatment, v) high blood pressure: blood pressure ≥130/85 mmHg or antihypertensive treatment [2]. Moreover, to confirm the diagnosis other major etiologies for hepatic steatosis, including viruses and pharmaceutical agents, were excluded, while alcohol intake was required to be limited to less than 20 gr per day for women and less than 30 gr per day for men [2].

2.2. Clinical Data and Laboratory Findings

Medical history regarding demographic characteristics and comorbidities was recorded. Anthropometric measurements included body weight (kg) in light clothing, and waist circumference (WC, cm), while body mass index (BMI) was calculated using the formula: BMI = weight (kg)/[height(m)]^2.

The main laboratory exams recorded included HbA1c, blood glucose (Glu, mg/dl), insulin (μU/ml), homeostatic model assessment of insulin resistance (HOMA-IR) index estimated using the following formula: HOMA-IR = Fasting Insulin (μU/mL) x Fasting Glucose (mg/dL)/ 405 [23], total cholesterol (mg/dL), HDL cholesterol (mg/dL), low-density lipoprotein cholesterol (LDL cholesterol, mg/dL), triglycerides (mg/dL), aspartate aminotransferase (AST, U/L), alanine aminotransferase (ALT, U/L), gamma-glutamyl transferase (γ-GT, U/L), 25-hydroxy-vitamin D [25(OH)VitD, ng/ml] and ferritin (ng/ml).

Regarding the hormonal profile, follicle-stimulating hormone (FSH, mIU/ml), luteinizing hormone (LH, mIU/ml) was measured with chemiluminescent assay (Liaison, DiaSorin, Saluggia, Italy), dehydroepiandrosterone sulfate (DHEAS, μg/dl), sex hormone-binding globulin (SHBG, nmol/L), and total serum testosterone (Testo, ng/ml) were measured with electrochemiluminescence (Combass e801 Roche, Mannheim, Germany), while free testosterone (free Testo, ng/ml) was calculated indirectly using the Vermeulen formula [24]. Finally, Δ4 androstenedione (Δ4, ng/ml), measured by radioimmunoassay (Demeditec Diagnostics GmbH, Kiel, Germany), was recorded. Both biochemical and hormonal tests have been performed in the morning, (8:00-8:30 a.m.) after overnight fasting.

2.3. Liver Steatosis and Fibrosis Assessment

Liver steatosis and fibrosis were assessed using ultrasound-based elastography data. Hepatic steatosis was quantified by controlled attenuation parameter (CAP, dB/m): <238 dB/m indicated absence of steatosis (S0), 238-259 dB/m mild steatosis (S1), 260-290 dB/m moderate steatosis (S2), and ≥291 dB/m severe steatosis (S3), while liver stiffness was evaluated by Fibroscan, with values of 6-7 kPa indicating mild fibrosis (stage F1), 7-9 kPa moderate fibrosis (stage F2), 9-12 kPa advanced fibrosis (stage F3), and >12 kPa cirrhosis (stage F4) [25,26]. Finally, fibrosis-4 index (FIB-4) was also calculated using this formula: FIB-4 = ((age [years]) x (AST [U/L])) / ((platelets [10^9/L]) x (√ALT [U/L])) [27].

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2.4. Body Composition

Body composition was assessed using DEXA (Hologic Horizon W, software version 13.6.0.4, Hologic Inc., Marlborough, MA, USA, with standard NHANES BCA calibration), which provided measurements of total and regional lean mass, fat mass and bone mineral content. Total body fat percentage (BF%) and appendicular lean mass (ALM) which reflects the muscle quantity of the limbs, were quantified. The appendicular lean mass-to-weight ratio (ALM/W, %) was further calculated by dividing ALM by body weight.

2.5. Evaluation of Physical Performance and Frailty

Physical performance was assessed using the Short Physical Performance Battery (SPPB) and the Liver Frailty Index (LFI). The SPPB (with score >10 showing good physical performance) included a balance test in three positions (side-by-side, semi-tandem, tandem), a 4-meter walk to assess gait speed and a chair stand test (time to rise from a chair 5 times without using arms) [28]. The LFI was calculated by measuring grip strength with a dynamometer, time to complete 5 chair stands and balance in three positions, with scores classified as robust (<3.2), prefrail (3.2 - 4.4) and frail (≥4.5) [29].

2.6. Definitions of SO

The diagnosis of SO was established by the concomitant presence of both obesity and sarcopenia. Obesity was defined either by body mass index [BMI (kg/m²)] ≥30 [30] or by total body fat percentage as assessed by DEXA [BF% >27 in men and >38 in women] [11]. Sarcopenia was defined using the ALM/W(%), calculated from DEXA, with cut-off values <23.47% in women and <28.27% in men [11]. SO was further defined using the AIM-SO score [SO diagnosed when score >0.420 in men and >0.515 in women], a sex-specific algorithm derived from fat mass (FM) and appendicular skeletal muscle mass (ASM) with the following formulas, as described by Azevedo et al. : AIM-SO score for men = ((5.243+ (0.124 x FM) + (0.449 x ASM)) / 15.95) + 0.60, AIM-SO score for women = ((6.013 + (0.133 x FM) + (-0.837 x bone mass) + (-0.914 x ASM)) / 24.28) + 0.62 [31].

2.7. Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics software (IBM Corp. IBM SPSS Statistics for Windows. Version 30.0. Armonk, NY, USA). First, the Shapiro-Wilk test was used to assess normality of distribution, with data considered normally distributed if p >0.05 and non-normally distributed if p ≤0.05. Comparisons were conducted using the independent t-test for normally distributed continuous variables and the Mann-Whitney U test for non-normally distributed continuous variables. Categorical variables were compared using the chi-squared test. Continuous variables are presented as mean ± standard deviation (SD), when normally distributed and as median with interquartile range (IQR: 25^{th} - 75^{th} percentile), when non-normally distributed. Categorical variables are expressed as absolute numbers and percentages (%). Multivariate analysis was performed using stepwise logistic regression, including all variables that were statistically significant (p <0.05) in the univariate analyses. Multivariate logistic regression analyses were also performed after adjusting for confounders. The discriminative ability of the independent variables that derived from multivariate analysis was assessed using the area under the receiver operating characteristic (ROC) curve (AUC) [32]. A p-value <0.05 was considered statistically significant.

3. Results

3.1. Main Characteristics of the Population

The main demographic, clinical and laboratory characteristics of the study population are summarized in **Table 1**. Among the 200 participants the mean age was 55.86 years, and the majority were women (54.5%). Regarding anthropometric parameters, the mean BMI was 31.7 kg/m², BF% 43.41%, and ALM/W 23.84%. SO diagnosis was made in 51% (n=102 patients) of the population when

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diagnosis of obesity was based on BMI (BMI-SO), in 76.5% (n=153 patients) when diagnosis of obesity was based on BF% (BF%-SO) and in 34.5% (n=69 patients) when diagnosed based on AIM-SO score. The prevalence of the main metabolic comorbidities was 28.1% for T2D, 49.5% for dyslipidemia and 36.9% for arterial hypertension (AH). Regarding laboratory findings, these are presented in **Table 1**. Finally, data from elastography, showed a mean CAP at 287.79 dB/m and liver stiffness at 6.95 kPa. The remaining characteristics of the sample population are presented in **Table 1**.

Table 1. Main demographic, clinical and laboratory characteristics of the population.

	Total participants (n=200)
Age, years	55.86 (± 13.69)
Sex, males, n (%)	91 (45.5%)
Comorbidities	
T2D, n (%)	55 (28.1)
AH, n (%)	72 (36.9)
Dyslipidemia, n (%)	98 (49.5)
Obesity (BMI), (%)	113 (56.5%)
Obesity (BF%), (%)	185 (92.5%)
Low ALM/W	160 (80%)
WC, cm	105.07 (± 13.54)
BMI, kg/m^2	31.70 (± 5.68)
BF%	43.41 (± 7.06)
ALM/W, (%)	23.84 (± 4.24)
AIMSO score	0.40 ± 0.13
BMI-SO, n (%)	102 (51%)
BF%-SO, n (%)	153 (76.5%)
SO based on AIM-SO score, n (%)	69 (34.5%)
HbA1c (%)	5.91 (± 0.80)
Glu, mg/dl	93.18 (± 23.59)
Insulin, μU/ml	16.10 (± 12.20)
HOMA-IR	3.92 (± 3.73)
Total cholesterol, mg/dl	190.53 (± 40.85)
HDL cholesterol, mg/dl	52.12 (± 13.07)
LDL cholesterol, mg/dl	111.71 (± 36.49)
Triglycerides, mg/dl	127.30 ± 58.29
AST, U/L	30.00 (± 21.09)
ALT, U/L	39.63 (± 36.83)
γ-GT, U/L	61.13 (± 74.03)
25(OH)VitD, ng/ml	24.98 (± 10)
Ferritin, ng/ml	158.72 (± 177.54)
Hormonal status	
FSH, mIU/ml	46.30 (± 51.56)
LH, mIU/ml	15.56 (± 13.97)

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DHEAS, μg/dl	147.58 (± 130.02)
SHBG, nmol/L	44.87 (± 21.52)
Testo, ng/ml	6.78 (± 52.93)
Free Testo, ng/ml	0.21 (± 1.97)
Δ4, ng/ml	0.91 (± 0.8)
Severity of liver disease	
FIB-4	1.19 (± 0.90)
CAP, dB/m	287.79 (± 41.37)
Liver stiffness, kPa	6.95 (± 5.07)
Functional performance tests	
SPPB	10.98 (± 1.21)
LFI	3.82 (± 0.58)

Continuous variables expressed as mean (SD) and categorical variables as number of individuals n (percentage of the sample, %). Abbreviations: T2D: type 2 diabetes, AH: arterial hypertension, BMI: body mass index, BF%: body fat percentage, ALM/W: appendicular lean mass-to-weight ratio, SO: sarcopenic obesity, WC: waist circumference, HbA1c: hemoglobin A1c, Glu: fasting glucose, HOMA-IR: homeostatic model assessment of insulin, HDL: high density lipoprotein, LDL: low-density lipoprotein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GT: gamma-glutamyl transferase, 25(OH)VitD: 25-hydroxy-vitamin D, FSH: follicle-stimulating hormone, LH: luteinizing hormone, DHEAS: dehydroepiandrosterone sulfate, SHBG: sex hormone-binding globulin, Testo: testosterone, Δ4: Δ4 androstenedione, FIB-4: fibrosis-4 index, CAP: controlled attenuation parameter, SPPB: short physical performance battery, LFI: liver frailty index.

3.2. Main Characteristics of Patients Correlated with SO Phenotypes

3.2.1. SO Diagnosed Based on BMI & ALM/W (BMI-SO)

Patients with, compared to those without BMI-SO, had more frequently AH (44.5% vs. 28.7%, p = 0.022) and higher BMI (34.05 vs. 27.85 kg/m², p <0.001), WC (110 vs. 97 cm, p <0.001) and BF% (48.95% vs. 38.45%, p <0.001). In addition, the former group had higher levels of fasting Glu (88 vs. 86 mg/dl, p=0.030), insulin (14.6 vs. 11.3 μU/l, p<0.001), HOMA-IR index (3.25 vs. 2.57, p<0.001), total cholesterol (194 vs. 178.5 mg/dl, p=0.043), LDL cholesterol (114.5 vs. 101.5, p=0.040) and triglycerides (126.5 vs. 107 mg/dl, p=0.044). Regarding severity of liver disease, participants with BMI-SO had worse steatosis based on CAP values (292.5 vs. 270 dB/m, p <0.001), while they had poorer physical performance based on SPPB (11 vs. 12, p = 0.002) (**Table 2).** In multivariate logistic regression analysis, WC (OR: 1.085, 95% C.I.: 1.047-1.125, p<0.001) and total cholesterol (OR: 1.017, 95% C.I.: 1.007-1.027, p=0.001) were the only factors independently associated with the presence of BMI-SO, but only WC had relatively good discriminative ability (AUC: 0.77, 95%C.I.: 0.71-0.82). The findings were similar when men and women were evaluated separately.

Table 2. Comparison of patients with and without BMI-SO.

	Without BMI-SO n = 98 (49%)	**With BMI-SO n = 102 (51%)**	**p-value**
Age, years	55 (46.25 - 64.75)	59.50 (50.25 - 66.75)	0.740
Sex, male, n (%)	48 (48.98)	43 (42.16)	0.333
Cormobidities			
T2D, n (%)	23 (24.2%)	32 (31.6%)	0.245

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AH, n (%)	27 (28.7%)	45 (44.5%)	**0.022**
Dyslipidemia, n (%)	53 (54.6%)	45 (44.5%)	0.156
WC, cm	97 (90.25 - 103)	110 (103 - 119)	**<0.001**
BMI, kg/m²	27.85 (26.22 - 29.17)	34.05 (33 - 37.35)	**<0.001**
BF%	38.45 (34.62 - 45.07)	48.95 (42.1 - 50.5)	**<0.001**
ALM/W, (%)	25.42 (22.3 - 28.81)	21.6 (20.06 - 25.14)	**<0.001**
HbA1c (%)	5.65 (5.4 - 6.1)	5.7 (5.4 - 6)	0.159
Glu, mg/dl	86 (78.25 - 98.75)	88 (81.25 - 102.5)	**0.030**
Insulin, μU/ml	11.3 (7.3 - 18.32)	14.6 (11.52 - 20.65)	**<0.001**
HOMA-IR	2.57 (1.31 - 4.13)	3.25 (2.27 - 5.09)	**<0.001**
Total cholesterol, mg/dl	178.5 (153.25 - 206.5)	194 (166.25 - 226)	**0.043**
HDL cholesterol, mg/dl	52.97 (± 13.15)	51.27 (± 13.00)	0.380
LDL cholesterol, mg/dl	101.5 (79 - 134.75)	114.5 (87.75 - 144.5)	**0.040**
Triglycerides, mg/dl	107 (79 - 138)	126.5 (93 - 161.25)	**0.044**
AST, U/L	23 (20 - 29)	21 (18 - 31.75)	0.958
ALT, U/L	28 (19 - 43.75)	24.5 (18.25 - 38.75)	0.375
γ-GT, U/L	31 (21 - 78.75)	25 (17.25 - 67)	0.794
25(OH)VitD, ng/ml	24.5 (19.05 - 31.8)	24.5 (19.2 - 30.7)	0.876
Ferritin, ng/ml	111 (62.2 - 202)	104 (62.8 - 160)	0.511
Hormonal status			
FSH, mIU/ml	11.4 (6.87 - 66.25)	41.1 (8.28 - 85.5)	0.227
LH, mIU/ml	6.78 (3.18 - 22.3)	14.3 (4.31 - 27.5)	0.060
DHEAS, μg/dl	121.35 (63.5 – 214)	105 (55.82 – 180.5)	0.644
SHBG, nmol/L	46.69 (± 20.09)	43.07 (± 22.82)	0.261
Testo, ng/ml	2.96 (0.22 - 4.61)	0.46 (0.13 - 4.09)	0.055
Free Testo, ng/ml	0.021 (0.003 - 0.08)	0.009 (0.002 - 0.07)	0.694
Δ4, ng/ml	0.75 (0.38 - 1.07)	0.54 (0.3 - 0.92)	0.531
Severity of liver disease			
FIB-4	0.98 (0.71 – 1.43)	1.04 (0.68 – 1.40)	0.731
CAP, dB/m	270 (249.5 – 283)	292.5 (262.25 – 337.5)	**<0.001**
Liver stiffness, kPa	5.42 (4.81 – 6.71)	5.63 (4.7 – 6.45)	0.347
Functional performance tests			
SPPB	12 (11 – 12)	11 (10 – 12)	**0.002**
LFI	3.83 (3.39 – 4.18)	3.84 (3.47 – 4.29)	0.284

Continuous variables expressed as mean (SD) or median with interquartile range (IQR: 25th - 75th percentile) and categorical variables as number of individuals n (percentage of the sample, %). Abbreviations: T2D: type 2 diabetes, AH: arterial hypertension, BMI: body mass index, BF%: body fat percentage, ALM/W: appendicular lean mass-to-weight ratio, SO: sarcopenic obesity, WC: waist circumference, HbA1c: hemoglobin A1c, Glu: fasting glucose, HOMA-IR: homeostatic model assessment of insulin, HDL: high density lipoprotein, LDL: low-density lipoprotein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GT: gamma-glutamyl transferase, 25(OH)VitD: 25-hydroxy-vitamin D, FSH: follicle-stimulating hormone, LH: luteinizing hormone, DHEAS: dehydroepiandrosterone sulfate, SHBG: sex hormone-binding globulin, Testo: testosterone, Δ4: Δ4

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androstenedione, FIB-4: fibrosis-4 index, CAP: controlled attenuation parameter, SPPB: short physical performance battery, LFI: liver frailty index.

3.2.2. SO Diagnosed Based on BF% & ALM/W (BF%-SO)

Patients with, compared to those without BF%-SO, were older (59 vs 47 years, p =0.003) and more frequently women (59.5% vs 38.3% women, p =0.011), while they had higher prevalence of AH (40.9% vs 23.9%, p = 0.036). In addition, the former group had higher BMI (32.4 vs 26.6 kg/m², p <0.001), WC (104 vs 93 cm, p <0.001) and BF% (45.8 % vs 34.8%, p <0.001), while they had greater levels of fasting Glu (88 vs 82 mg/dl, p =0.005), insulin (13.7 vs 9.68 μU/ml, p =0.001), HOMA-IR index (3.17 vs 1.7, p <0.001) and triglycerides (121 vs 104 mg/dl, p =0.040). Regarding hormonal profile, the patients with BF%-SO, compared to those without BF%-SO, had higher levels of FSH (45.4 vs 8.63 mIU/ml, p <0.001), LH (16.9 vs 4.78 mIU/ml, p <0.001), while they had lower levels of DHEAS (103 vs 166 μg/dl, p =0.028). In relation to severity of liver disease, individuals with BF%-SO had worse steatosis based on CAP values (280 vs 268 dB/m, p =0.013), while they had poorer physical performance based on both SPPB (11 vs 12, p =0.041) and LFI (3.9 vs 3.62, p =0.004) (**Table 3).** In multivariate logistic regression analysis, DHEAS (OR: 0.97, 95% C.I.: 0.96-0.98, p=0.04) and WC (OR: 1.035, 95% C.I.: 1.005-1.065, p=0.022) were the only factors independently associated with BF%-SO, although both had relatively low discriminative ability (AUC: 0.65, 95%C.I.: 0.61-0.69 and AUC: 0.68, 95%C.I.: 0.62-0.73, respectively). After adjusting for Δ4 androstenedione and testosterone, DHEAS (OR: 0.96, 95% C.I.: 0.94-0.98, p =0.03) and WC (OR: 1.042, 95% C.I.: 1.007-1.061, p =0.031) were again independently associated with BF%-SO.

Table 3. Comparison of patients with and without BF%-SO.

	Without BF%-SO n = 47 (23.5%)	**With BF%-SO n = 153 (76.5%)**	**p-value**
Age, years	47 (37 – 56)	59 (52 – 67)	**0.003**
Sex, male, n (%)	29 (61.7%)	62 (40.5)	**0.011**
Cormobidities			
T2D, n (%)	10 (21.7%)	45 (30%)	0.275
AH, n (%)	11 (23.9%)	61 (40.9%)	**0.036**
Dyslipidemia, n (%)	21 (44.7%)	77 (51%)	0.450
WC, cm	93 (90 - 107)	104 (97.5 - 113)	**<0.001**
BMI, kg/m²	26.6 (24.8 - 28.7)	32.4 (28.95 - 35.05)	**<0.001**
BF%	34.8 (32.9 - 38.9)	45.8 (40.2 - 50.1)	**<0.001**
ALM/W, (%)	28.98 (27.73 - 30.11)	22.4 (20.5 - 25.62)	**<0.001**
HbA1c (%)	5.4 (5.3 - 6.1)	5.7 (5.4 - 6.05)	0.168
Glu, mg/dl	82 (72 - 92)	88 (81 - 102.5)	**0.005**
Insulin, μU/ml	9.68 (6.91 - 18)	13.7 (9.62 - 19)	**0.001**
HOMA-IR	1.7 (1.21 - 3.84)	3.17 (1.83 - 4.67)	**<0.001**
Total cholesterol, mg/dl	181 (148 - 226)	191 (160.5 - 223.5)	0.216
HDL cholesterol, mg/dl	47 (42.3 - 62.1)	51.5 (43.5 - 62.25)	0.558
LDL cholesterol, mg/dl	103 (78 - 145)	110 (84.5 - 142)	0.507
Triglycerides, mg/dl	104 (71 - 136)	121 (92.5 - 148)	**0.040**
AST, U/L	23 (20 - 33)	22 (19 - 30)	0.757

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ALT, U/L	31 (21 - 47)	25 (18 - 40)	0.961
γ-GT, U/L	32 (21 - 79)	25 (18 - 68.5)	0.622
25(OH)VitD, ng/ml	22 (16.85 – 29.05)	25 (19.9 - 31.6)	0.306
Ferritin, ng/ml	114 (43.75 - 213.5)	108 (65.3 - 162)	0.915
Hormonal status			
FSH, mIU/ml	8.63 (5.72 - 14.9)	45.4 (8.45 - 85.5)	**<0.001**
LH, mIU/ml	4.78 (2.83 - 10.8)	16.9 (4.34 - 27.4)	**<0.001**
DHEAS, μg/dl	166 (101 - 299)	103 (54.2 - 179.5)	**0.028**
SHBG, nmol/L	41.3 (25.9 - 52.7)	42.9 (30.45 - 58)	0.482
Testo, ng/ml	3.74 (0.25 - 4.53)	0.48 (0.18 - 4.32)	0.138
Free Testo, ng/ml	0.05 (0.003 - 0.1)	0.006 (0.002 - 0.07)	0.085
Δ4, ng/ml	0.8 (0.35 - 1.21)	0.56 (0.3 - 0.96)	0.235
Severity of liver disease			
FIB-4	0.89 (0.61 - 1.13)	1.06 (0.77 - 1.47)	0.126
CAP, dB/m	268 (246 - 284)	280 (256 - 322.5)	**0.013**
Liver stiffness, kPa	5.61 (4.93 - 7.1)	5.45 (4.67 - 4.35)	1.000
Functional performance tests			
SPPB	12 (11 - 12)	11 (10 - 12)	**0.041**
LFI	3.62 (3.3 - 3.97)	3.9 (3.5 - 4.28)	**0.004**

Continuous variables expressed as mean (SD) or median with interquartile range (IQR: 25th - 75th percentile) and categorical variables as number of individuals n (percentage of the sample, %). Abbreviations: T2D: type 2 diabetes, AH: arterial hypertension, BMI: body mass index, BF%: body fat percentage, ALM/W: appendicular lean mass-to-weight ratio, SO: sarcopenic obesity, WC: waist circumference, HbA1c: hemoglobin A1c, Glu: fasting glucose, HOMA-IR: homeostatic model assessment of insulin, HDL: high density lipoprotein, LDL: low-density lipoprotein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GT: gamma-glutamyl transferase, 25(OH)VitD: 25-hydroxy-vitamin D, FSH: follicle-stimulating hormone, LH: luteinizing hormone, DHEAS: dehydroepiandrosterone sulfate, SHBG: sex hormone-binding globulin, Testo: testosterone, Δ4: Δ4 androstenedione, FIB-4: fibrosis-4 index, CAP: controlled attenuation parameter, SPPB: short physical performance battery, LFI: liver frailty index.

Further analyzing differences by gender, men with, compared to those without BF%- SO, were older (56.23 vs 47.93 years, p = 0.017) and had higher AH prevalence (45.2% vs 17.2%, p =0.009). In addition, the former group had higher BMI (32.77 vs 27.21 kg/m², p <0.001), WC (108 vs 99.5 cm, p <0.001) and BF% (37.75% vs 33.65%, p <0.001), while they had greater levels of fasting Glu (88 vs 81 mg/dl, p =0.021), insulin (14.5 vs 9.72 μU/ml, p =0.005), HOMA-IR index (3.2 vs 2.03, p =0.002), LDL cholesterol (121.06 vs 104.78 mg/dl, p = 0.031) and FIB-4 (1.14 vs 0.89, p =0.004). Regarding hormonal profile, men with BF%-SO had lower DHEAS levels (117.5 vs 217.5 μg/dL, p = 0.028), regarding to those without BF%-SO. Multivariate analysis confirmed the findings in the total cohort, since again DHEAS (OR: 0.95, 95% C.I.: 0.91-0.99, p=0.03; after adjustment, OR: 0.94, 95% C.I.: 0.89-0.99, p=0.04) and WC (OR: 1.072, 95% C.I.: 1.015-1.083, p=0.02; after adjustment, OR:1.066, 95% C.I.: 1.022-1.081, p=0.04) were independently associated with BF%-SO.

Women with, compared to those without BF%-SO had higher BMI (33.2 vs 26.3 kg/m², p <0.001), WC (104.61 vs 91.12 cm, p <0.001) and BF% (49.19% vs 40.91%, p <0.001), while, regarding hormonal profile, no significant difference was found. In relation to severity of liver disease, women with BF%-SO had worse steatosis based on CAP values (277 vs 255 dB/m, p = 0.013), while they had poorer

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physical performance based on LFI (4.06 vs 3.69, p =0.018) (**Table 4**). In multivariate analysis, WC was the only factor independently associated with BF%-SO (OR: 1.15, 95% C.I.: 1.092-1.221, p=0.01)

Table 4. Comparison of patients with and without BF%-SO, by gender.

	Men			**Women**		
	Patients without BF%-SO (n=29)	Patients with BF%-SO (n=62)	P- value	Patients without BF%-SO (n=18)	Patients with BF%-SO (n=91)	P- value
Age, years	47.93 (± 13.81)	56.23 (± 15.71)	**0.017**	54.94 (± 14.15)	58.31 (± 11.1)	0.265
Cormobidities						
T2D, n (%)	7 (24.1%)	17 (27.4%)	0.744	3 (16.6%)	28 (30.7%)	0.216
AH, n (%)	5 (17.2%)	28 (45.2%)	**0.009**	6 (33.3%)	33 (36.2%)	0.763
Dyslipidemia, n (%)	14 (48.3%)	28 (45.2%)	0.833	7 (38.8%)	49 (53.8%)	0.228
WC, cm	99.5 (90.75 - 107.25)	108 (100 - 119)	**<0.001**	91.12 (± 9.25)	104.61 (± 10.24)	**<0.001**
BMI, kg/m²	27.21 (± 3.81)	32.77 (± 5.02)	**<0.001**	26.3 (24.8 - 30.45)	33.2 (28.7 - 35.8)	**<0.001**
BF%	33.65 (32.05 - 35)	37.75 (36.67 - 42.5)	**<0.001**	40.91 (± 3.91)	49.19 (± 3.8)	**<0.001**
ALM/W, (%)	29.28 (28.85 - 30.31)	25.83 (23.79 - 27.13)	**<0.001**	27.42 (24.45 - 30.27)	21.14 (19.57 - 22.19)	**<0.001**
HbA1c (%)	5.4 (5.3 - 6.17)	5.6 (5.4 - 6.02)	0.296	5.8 (5.45 - 6.25)	5.8 (5.4 - 6.1)	0.509
Glu, mg/dl	81 (66.25 - 96.5)	88 (82.25 - 100.25)	**0.021**	89.24 (± 19.95)	97.14 (± 24.3)	0.211
Insulin, µU/ml	9.72 (7.18 - 14.15)	14.5 (10.27 - 24.02)	**0.005**	11.11 (± 7.53)	16.5 (± 12.49)	0.099
HOMA-IR	2.03 (1.15 - 3.12)	3.2 (1.94 -5.49)	**0.002**	2.6 (± 2.14)	4.22 (± 4.19)	0.148
Total cholesterol, mg/dl	176.61 (± 35.17)	191.29 (± 34.06)	0.073	174 (153 - 235)	180 (153 - 203)	0.912
HDL cholesterol, mg/dl	47.51 (± 10.32)	48.98 (± 12.06)	0.593	56.98 (± 13.51)	54.56 (± 13.64)	0.503
LDL cholesterol, mg/dl	104.78 (± 30.38)	121.06 (± 30.86)	**0.031**	95 (82 - 147.5)	100 (79 - 119)	0.484
Triglycerides, mg/dl	115 (68.75 - 129.25)	103.5 (90.75 - 159)	0.490	91 (64 - 160.5)	115 (91 - 137)	0.095
AST, U/L	22 (20 - 27.75)	23 (19 - 38.5)	0.306	22 (19.5 - 31.5)	22 (16 - 28)	0.805
ALT, U/L	30 (21 - 50.5)	36 (19.75 - 57)	0.860	21 (15.5 -32)	24 (16 - 31)	0.414

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γ-GT, U/L	32.5 (17.25 - 63.25)	37 (24.75 - 94)	0.490	32 (16.5 - 70.5)	24 (16 - 48)	0.449
25(OH)VitD, ng/ml	24.20 (± 10.05)	23.91 (± 9.01)	0.898	21.3 (13.15 - 28.2)	25.9 (19.2 - 33.6)	0.173
Ferritin, ng/ml	145.5 (46.9 - 280)	131 (79.17 - 212.5)	0.913	79.3 (33.75-152.5	86.9 (49.5 - 145)	0.335
Hormonal status						
FSH, mIU/mL	6.57 (3.73-6.57)	7.12 (4.96-16.92)	0.063	59.6 (10.5-65.72)	79.4 (46.55-95.62)	0.140
LH, mIU/mL	3.35 (2.58-6.14)	4.17 (3.14-6.81)	0.055	14.3 (6.11-25.35)	24.9 (16.92-32.27)	0.060
DHEAS, µg/dL	217.5 (152.25-331.30)	117.5 (76.22-137.5)	**0.028**	103 (45.67-171.5)	100 (54.1-151.25)	0.593
SHBG, nmol/L	37.86 (±17.28)	39.33 (±18.86)	0.739	50.73 (±22.6)	49.42 (±22.93)	0.834
Testosterone, ng/ml	4.43 (3.8-6.58)	4 (2.64-4.94)	0.062	0.18 (0.13-0.27)	0.19 (0.13-0.41)	0.068
Free testo, ng/ml	0.05 (0.004 - 0.1)	0.02 (0.002 - 0.069)	0.212	0.007 (0.003 - 0.11)	0.006 (0.002 - 0.07)	0.278
Δ4, ng/mL	0.83 (0.51-1.28)	0.61 (0.48-1.06)	0.683	0.9 (0.33-1.99)	0.58 (0.3-0.99)	0.330
Severity of liver disease						
FIB-4	0.89 (0.61 - 1.14)	1.14 (0.81 - 1.57)	**0.004**	1.04 (0.89 - 1.43)	1.02 (0.8 - 1.5)	0.188
CAP, dB/m	279.46 (± 34.8)	297.8 (± 45.54)	0.066	255 (233.5 - 269)	277 (254 - 298)	**0.013**
Liver stiffness, kPa	6.02 (5.27 - 7.44)	5.75 (4.98 - 6.66)	0.827	5 (4.55 -6.31)	5.3 (4.55 - 6.3)	0.603
Functional performance tests						
SPPB	12 (11 - 12)	12 (11 - 12)	0.211	12 (10.5 - 12)	11 (10 - 12)	0.286
LFI	3.48 (± 0.69)	3.69 (± 0.51)	0.171	3.69 (± 0.51)	4.06 (± 0.51)	**0.018**

Continuous variables expressed as mean (SD) or median with interquartile range (IQR: 25th - 75th percentile) and categorical variables as number of individuals n (percentage of the sample, %). Abbreviations: T2D: type 2 diabetes, AH: arterial hypertension, BMI: body mass index, BF%: body fat percentage, ALM/W: appendicular lean mass-to-weight ratio, SO: sarcopenic obesity, WC: waist circumference, HbA1c: hemoglobin A1c, Glu: fasting glucose, HOMA-IR: homeostatic model assessment of insulin, HDL: high density lipoprotein, LDL: low-density lipoprotein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GT: gamma-glutamyl transferase, 25(OH)VitD: 25-hydroxy-vitamin D, FSH: follicle-stimulating hormone, LH: luteinizing hormone, DHEAS: dehydroepiandrosterone sulfate, SHBG: sex hormone-binding globulin, Testo: testosterone, Δ4: Δ4 androstenedione, FIB-4: fibrosis-4 index, CAP: controlled attenuation parameter, SPPB: short physical performance battery, LFI: liver frailty index.

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3.2.3. SO Diagnosed Based on AIM-SO Score

Patients with, compared to those without SO, based on AIM-SO score had higher WC (111 vs 100 cm, p <0.001), BMI (34.6 vs 30 kg/m², p <0.001), BF% (50.3% vs 39.7%, p <0.001) and lower values of ALM/W (21.15% vs 25.21%, p <0.001). In addition, the former group had higher LDL cholesterol levels (119.47 vs 107.58 mg/dl, p =0.043), while they had lower γ-GT (28 vs 36 U/L, p =0.027). In relation to severity of liver disease, individuals with AIM-SO had worse steatosis based on CAP values (289 vs 274 dB/m, p = 0.044), while they had poorer physical performance based on LFI (3.95 vs 3.81, p = 0.043) (**Table 5).** In multivariate analysis, WC was the only factor independently associated with AIM-SO (OR: 1.23, 95% C.I.: 1.082-1.345, p=0.02) with relatively good discriminative ability (AUC: 0.78, 95%C.I.: 0.73-0.84). The findings were similar when men and women were evaluated separately.

Table 5. Comparison of patients with and without SO - based on AIMSO score.

	Without SO n = 126 (63%)	**With SO n = 74 (37%)**	**p-value**
Age, years	55.77 (± 13.13)	56 (± 14.67)	0.909
Sex, male, n (%)	57 (45.2%)	34 (45.9%)	0.923
Comorbidities			
T2D, n (%)	35 (27.8%)	20 (27%)	0.802
AH, n (%)	43 (34.1%)	29 (39.2%)	0.608
Dyslipidemia, n (%)	66 (52.4%)	32 (43.25%)	0.174
WC, cm	100 (92 - 104)	111 (98 - 121)	**<0.001**
BMI, kg/m²	30 (± 5.1)	34.6 (± 5.47)	**<0.001**
BF%	39.7 (36.12 - 46.45)	50.3 (42.5 - 53.12)	**<0.001**
ALM/W, (%)	25.21 (21.68 - 28.04)	21.15 (19.77 - 24.02)	**<0.001**
HbA1c (%)	5.7 (5.3 - 6.1)	5.8 (5.4 - 5.9)	0.375
Glu, mg/dl	87 (79 - 95)	87 (82 - 101)	0.562
Insulin, μU/ml	13.3 (8.03 - 19.9)	13.5 (8.7 - 17.2)	0.981
HOMA-IR	3.09 (1.66 - 4.42)	3 (1.7 - 4.13)	0.872
Total cholesterol, mg/dl	186.12 (± 40.15)	198.24 (± 41.21)	0.053
HDL cholesterol, mg/dl	52.3 (± 13.36)	51.81 (± 12.63)	0.806
LDL cholesterol, mg/dl	107.58 (± 36.68)	119.47 (± 35.12)	**0.043**
Triglycerides, mg/dl	124.3 (± 61.35)	132.55 (± 52.55)	0.357
AST, U/L	23 (20 - 29)	22 (17 - 30)	0.14
ALT, U/L	25 (22 - 47)	23 (15 - 32)	0.12
γ-GT, U/L	36 (20 - 95)	28 (15 - 42)	**0.027**
25(OH)VitD, ng/ml	25.06 (± 10.12)	24.84 (± 9.85)	0.888
Ferritin, ng/ml	128 (80.5 - 209)	86.9 (65.3 - 155)	0.192
Hormonal status			
FSH, mIU/ml	21.4 (7.26 - 78.8)	41.1 (9.83 - 87.9)	0.131
LH, mIU/ml	12.02 (3.61 - 25.3)	10.7 (4.31 - 30.4)	0.109
DHEAS, μg/dl	115 (72.8 - 206)	102 (61.3 - 176)	0.610
SHBG, nmol/L	47.1 (30.8 - 60.3)	42.1 (26.1 – 53.3)	0.060
Testo, ng/ml	0.48 (0.19 – 3.98)	1.43 (0.14 - 4.41)	0.208

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Free Testo, ng/ml	0.006 (0.002 - 0.079)	0.025 (0.003 - 0.073)	0.969
Δ4, ng/ml	0.7 (0.39 - 1.34)	0.7 (0.3 – 0.9)	0.207
Severity of liver disease			
FIB-4	1.1 (0.83 - 1.57)	1.04 (0.72 - 1.2)	0.11
CAP, dB/m	274 (251 - 284)	289 (263 - 330)	**0.044**
Liver stiffness, kPa	5.7 (5.11 - 6.9)	5.6 (4.7 - 6.3)	0.15
Functional performance tests			
SPPB	11 (11 - 12)	11.5 (10 - 12)	0.143
LFI	3.81 (3.42 - 4.18)	3.95 (3.5 - 4.36)	**0.043**

Continuous variables expressed as mean (SD) or median with interquartile range (IQR: 25th - 75th percentile) and categorical variables as number of individuals n (percentage of the sample, %). Abbreviations: T2D: type 2 diabetes, AH: arterial hypertension, BMI: body mass index, BF%: body fat percentage, ALM/W: appendicular lean mass-to-weight ratio, SO: sarcopenic obesity, WC: waist circumference, HbA1c: hemoglobin A1c, Glu: fasting glucose, HOMA-IR: homeostatic model assessment of insulin, HDL: high density lipoprotein, LDL: low-density lipoprotein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GT: gamma-glutamyl transferase, 25(OH)VitD: 25-hydroxy-vitamin D, FSH: follicle-stimulating hormone, LH: luteinizing hormone, DHEAS: dehydroepiandrosterone sulfate, SHBG: sex hormone-binding globulin, Testo: testosterone, Δ4: Δ4 androstenedione, FIB-4: fibrosis-4 index, CAP: controlled attenuation parameter, SPPB: short physical performance battery, LFI: liver frailty index.

4. Discussion

This is the first study, to our knowledge, in which hormonal alterations and physical performance were evaluated in relation to SO in a MASLD population, using different diagnostic criteria for SO. Notably, among the hormones measured, DHEAS emerged as an independent factor associated with BF%-SO, while WC was consistently associated with SO across all definitions. In addition, we observed poorer results in functional tests in individuals with SO -an association not previously examined in patients with MASLD.

Our study attempted to assess the prevalence of SO in MASLD patients, part of the Greek population, using different diagnostic criteria, BMI and BF% for assessing obesity, and the recently proposed AIM-SO score. Most available studies in literature rely on a single SO definition, while many of them focus on Asian populations making comparisons with Caucasians more challenging [17]. According to our results, BF%-SO showed the highest prevalence reaching 76.5%, followed by BMI-SO at 51%, further declining to 34.5% when the AIM-SO score was used. These findings confirm the fluctuating prevalence of SO presented in other studies, depending on the diagnostic criteria used and the characteristics of the studied population. Indeed, studies using BF% derived from DEXA generally reported the highest SO prevalence [10,34,35], while BMI-based definitions consistently presented much lower values[36,37]. In addition, the relatively higher prevalence of SO that we found -76.5% when defined by BF%- may reflect population-specific differences in body composition, as our study, in contrast to others, included exclusively Caucasian individuals with MASLD [10,33].

As expected, SO patients had higher body weight, BMI and BF% compared to those without SO, although these findings were not entirely consistent in the AIM-SO-diagnosed group, suggesting that this criterion may identify a distinct SO phenotype, in which muscle mass and fat distribution are evaluated relative to each other rather than as absolute values. Like previous studies [10,31], we found that MASLD patients with SO more often had metabolic comorbidities, with AH being significantly more prevalent across all definitions. Moreover, regarding glycemic profile, patients with, compared to those without SO (based on BMI or BF%), had higher fasting glycemic levels and insulin resistance, as expressed by the HOMA-IR index, as well as more frequently dyslipidemia as

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expressed by higher cholesterol and/or triglycerides levels. These results are in accordance with the concept that insulin resistance along with lipotoxicity are key mechanisms in the liver-adipose-muscle axis, playing an essential role in the pathogenesis of both SO and MASLD [38].

Regarding liver enzymes (AST, ALT), no significant differences were noted among the groups with or without SO, although individuals with SO across all definitions exhibited significantly greater steatosis as indicated by CAP. These findings confirm previous reports [31] and they are consistent with the well-known observation that AST/ALT do not reflect the severity of steatosis. The stronger association between SO and liver steatosis likely reflects the shared pathophysiological background including central adiposity and insulin resistance which lead to fat accumulation in the liver. Regarding liver stiffness it did not appear to be meaningfully worse in the SO groups of our study, which may be explained by the fact that most of our patients had mild liver disease as indicated by low FIB-4 score values and liver stiffness.

Although SO and physical performance have been studied before, especially in older adults [39,40], their relationship had not been investigated in patients with MASLD. In our study, functional performance tests were found to be poorer based on SPPB scores in both BMI-SO and BF%-SO groups and on LFI in both BF%-SO and AIM-SO-based SO groups. Such observations suggest that functional impairment in SO may be present even in populations with predominantly preserved mobility, as seen in our outpatient cohort. Reduced physical performance is clinically important as it is linked to higher risk of frailty, falls and worse overall outcomes [41]. Therefore, detecting lower SPPB and LFI scores may represent an early manifestation of muscle dysfunction, while these simple functional tests might serve as valuable indicators of SO in MASLD patients who otherwise appear physically well.

Hormonal factors, such as testosterone, appear to be implicated in the pathogenesis of SO, influencing muscle mass and metabolic health [16]. In our study we evaluated for the first time not only total and free testosterone, but also DHEAS and Δ4 in the context of SO, and found that lower DHEAS levels were independently associated with the presence of BF%-SO. These findings were also confirmed in men when we performed a gender-specific analysis. DHEAS represents a key precursor that is converted to Δ4 and ultimately to testosterone [42,43], and thus alterations in this hormone may play an important pathogenetic role and serve as potential indicator of SO in individuals with MASLD.

Moreover, as seen in the multivariate analyses, WC emerged as the factor more consistently associated with SO across all definitions. A similar pattern was shown in the sex-specific sub-analyses, with WC acting as independent predictor in both men and women. These findings highlight the central role of abdominal fat accumulation in all forms of SO. From a pathophysiological perspective, the hypertrophic and dysfunctional adipose tissue represents a pro-inflammatory state and is responsible for cytokines secretion, such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) [44]. Such molecules not only trigger inflammatory pathways and hepatic fibrogenesis but also promote muscle catabolism, further exacerbate insulin resistance and interfere in the physiological function of the liver-adipose-muscle axis, ultimately contributing to SO and MASLD development [16]. Therefore, measuring and assessing WC in MASLD patients may serve as a potential simple routine screening tool to identify those with SO.

We acknowledge certain limitations in our study. First, the sample size was relatively small, while we mainly showed associations among SO and comorbidities and did not thoroughly explore causality in these relationships. Most of the participants had preserved mobility and had relatively mild liver disease with few cases of advanced fibrosis, thus perhaps over- or under-estimating the true prevalence and metabolic impact of SO in more advanced stages of MASLD. Nevertheless, our study has also several strengths, including the use of DEXA for assessing body composition, CAP to evaluate steatosis and liver stiffness to quantify fibrosis, while three different definitions were applied to define SO. More importantly, to our knowledge it represents the first study, in which physical performance/frailty was evaluated in MASLD patients with or without SO and where hormonal alterations were also explored in this population in relation to SO.

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5. Conclusions

In conclusion, SO prevalence among Caucasian patients with MASLD appears to be high, particularly when defined by BF% and is associated with greater hepatic steatosis and metabolic comorbidities, as well as poorer physical performance. Low DHEAS levels were associated with BF%-SO in the total population, as well as in men, but not in women, while WC was repeatedly found linked to SO regardless of definition. Our findings may help improve early recognition of SO in MASLD and ultimately enable more accurate clinical assessment and management of these patients.

Contributions: Niki G. Mourelatou analyzed data and wrote paper. Niki G. Mourelatou, Triada Bali, Magdalini Adamantou, Lampros Chrysavgis, Christos Chologkitas, Margarita Sarri, Dimitra Pavlopoulou and Dimitrios S. Karagiannakis collected data. Niki G. Mourelatou, Georgios Schinas, Theodoros Androutsakos and Georgia Sypsa analyzed data. Evangelos Cholongitas conceptualised and designed the study. George Papatheodoridis, Nikolaos Tentolouris, Anastasia N. Mavrogiannaki and Evangelos Cholongitas made critical revision of the article. All authors have approved the final draft of the manuscript for publication.

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