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Original article

Skeletal muscle mass in patients with end-stage liver disease: Not only muscle size but especially muscle quality matters in relation to physical fitness

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SUMMARY

Background: Physical fitness is an important modifiable factor related to quality of life. Sarcopenia and myosteatosis are associated with morbidity and mortality in patients with end-stage liver disease (ESLD). However, their relationship with physical fitness has not been established yet. Therefore, the main purpose of this study was to investigate the association between both low skeletal muscle index (SMI) and myosteatosis with physical fitness in patients with ESLD.

Methods: In this retrospective cross-sectional cohort study, a cohort of patients with ESLD who were evaluated for liver transplantation (LT) was included. Physical fitness was reflected by cardiorespiratory fitness (CRF) and skeletal muscle strength, as measured by the 6-min walking distance (6MWD) and handgrip strength (HGS), respectively. Both were included in routine LT evaluation. Skeletal Muscle Index (SMI) and Muscle Radiation Attenuation (MRA) were evaluated based on the routine abdominal computed tomography. Linear and logistic regression analyses were performed.

Results: Out of the 130 patients 94 (72%) were male, mean age was 56 ± 11 years. Myosteatosis was significantly associated with low 6MWD as percentage of predicted (β = −12.815 (CI -24.608 to −1.022, p-value 0.034)) as well as with low absolute 6MWD (<250 m) (OR 3.405 (CI 1.134–10.220, p-value 0.029)). No association was found between SMI and/or myosteatosis with HGS, or between SMI and 6MWD.

Conclusion: In contrast to SMI, myosteatosis is associated with low CRF. Neither low SMI nor myosteatosis was associated with skeletal muscle strength. Therefore physical exercise training might be especially beneficial for LT candidates with myosteatosis.

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1. Introduction

Skeletal muscle mass and function in patients with end-stage liver disease (ESLD) are main points of interest and some literature suggests that they should be included in the Model of End stage Liver Disease (MELD) score to better predict the risk of short-term mortality and prioritize patients for liver transplantation (LT) [1]. Lower protein synthesis, metabolic abnormalities and malnutrition affect the balance between protein synthesis and breakdown, and therefore affect the degree of muscle depletion [2]. Myosteatosis is defined as fat accumulation in the skeletal muscle, and is a key factor affecting lower muscle quality. Fat accumulation in the muscle tissue increases with age and adiposity, but is also very common in patients with ESLD [3].

Both skeletal muscle area (SMA) and myosteatosis (i.e. low skeletal muscle density as a parameter of muscle quality) can be measured with imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI) and are related to prognosis in liver cirrhosis [4–6]. In severe sarcopenia, muscle mass, muscle function and muscle strength are decreased [4]. A European study stated that 36% of patients with cirrhosis had

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Abbreviations

6MWD	6-min walking distance
6MWT	6-min walking test
BMI	Body Mass Index
CI	Confidence Interval
CRF	Cardiorespiratory Fitness
ESLD	End-Stage Liver Disease
HCC	Hepatocellular Carcinoma
HGS	Handgrip Strength
LT	Liver Transplantation
MELD	Model of End stage Liver Disease
MRA	Muscle Radiation Attenuation
OR	Odds Ratio
SMA	Skeletal Muscle Area
SMI	Skeletal Muscle Index
SMM	Skeletal Muscle Mass

sarcopenia and 31% had so-called pre-sarcopenia [7]. Insight into the prevalence of myosteatosis in patients with ESLD is scarce, but it seems to be over 50% [8].

The association between both sarcopenia and myosteatosis with morbidity and mortality has been described in a limited number of studies in ESLD [4,9]. Studies shown that there is an inverse association between increased fat infiltration in the muscle area and a decreased quantified muscle area, suggesting that fat infiltration is not driven by loss of muscle mass alone. Changes in muscle tissue, for example myosteatosis, might result in reduced muscle function and decreased functional performance [10,11]. Muscle function and strength, reflected by gait speed and handgrip strength (HGS) are associated with dropping out of the waiting list for LT due to a declining health status [12]. Surprisingly, despite the fact that myosteatosis and sarcopenia are associated with several negative outcomes in LT candidates, the association between myosteatosis with parameters of physical fitness has not been studied yet.

The main purpose of this study is to investigate the association between both skeletal muscle index (SMI) (i.e. muscle quantity) and myosteatosis (i.e. muscle quality) on the one hand with on the other hand physical fitness parameters (cardiorespiratory fitness (CRF) and skeletal muscle strength) in LT candidates. Our hypothesis is that both SMI and myosteatosis are associated with physical fitness.

2. Materials and methods

2.1. Study design

The present study is a retrospective single center cohort study including consecutive patients evaluated for LT in the Leiden University Medical Center (LUMC) between January 2018 and December 2020. Part of this evaluation is a nutritional assessment by a dietician, a consultation by a physical therapist and an abdominal CT scan. Inclusion criteria for this study were patients >18 years and diagnosed with ESLD. Exclusion criteria were evaluations for re-transplantations and multiple organ transplantations, patients evaluated for LT elsewhere, or who had an interval between LT evaluation by dietician and physical therapist and CT scan of more than three months. During the LT evaluation, which consisted of one week hospitalization during which all required examinations were performed, nutritional assessment was examined by a dietician including assessment of dietary intake, food related problems and body composition. The physical therapist examined the physical function, physical fitness and self-reported level of weekly physical activity. Based on our sample size calculation ($\alpha = 0.05$, $1-\beta = 0.80$), 85 participants were required to reach sufficient statistical power. The sample size calculation was performed on the outcome 6MWD. The mean 6MWD in pre-liver transplant patients was 369 ± 122 m, which was reported in the study of Carey et al. [13] A clinically relevant difference was 14–30 m [14]. This study was approved with a non-WMO declaration by the Medical Ethical Committee of the LUMC (G20.137) and was compatible with the latest version of the Declaration of Helsinki.

2.2. Measurements

Patient characteristics as age (years), sex (male/female), etiology of the liver disease, Child Pugh score, MELD score, body mass (kg), body mass index (BMI) (kg/m^2), percentage of weight loss in the prior three-six months before LT evaluation (%) were collected from the electronic patient files (Chipsoft, HiX). Complications as ascites, hepatic encephalopathy and the prevalence of hepatocellular carcinoma (HCC) were reported. Body composition was analyzed with CT, were contrast enhanced, 5 mm slice and 120 kV and in the portal venous phase, and this abdominal CT was part of the standard examinations for evaluation for LT. Analyses were performed with SliceOmatic (Tomovision Canada) by an experienced and trained researcher and registered dietician (C.L.). To obtain the body composition, SMA was measured by the surface of skeletal muscle at the third lumbar vertebra in cm^2 (−29–+150 Hounsfield Unit (HU)). MRA, a measurement of muscle density, was defined as the mean HU of the SMA surface (mean HU). SMA was divided by squared height to calculate the Skeletal Muscle Index (SMI) [15]. The following muscle areas were included: psoas, erector spinae, quadratus, lumborum, transversus abdominis, external and internal obliques, and rectus abdominis muscles, because of the validation of this specific muscle areas as measurement of whole-body muscle mass [16]. Sex specific cut-off values for SMI and MRA were used to define low SMI and myosteatosis. For male, SMI < 43 cm^2/m^2 in BMI < 24.9 kg/m^2 and SMI < 53 cm^2/m^2 in BMI > 25 kg/m^2 was defined as low SMI and in female SMI < 41. The cut-off value of myosteatosis was in both male and female a mean HU < 41 in patients with a BMI < 24.9 kg/m^2 and a mean HU < 33 for patients BMI > 25 kg/m^2 [17].

Physical fitness was measured by CRF and a by general skeletal muscle strength. CRF was measured with the 6 min walking distance (6MWD). General skeletal muscle strength was reflected by the HGS (JAMAR Handgrip Dynamometer; Sammons Preston Rolyan, Bolingbrook, IL). Both tests were performed during usual care by an experienced physical therapist during the evaluation for LT. The 6MWT was performed under monitoring of rest and peak heart rate (HR_{rest} and HR_{peak}, respectively; beats per minute) and peripheral oxygenation saturation (SpO2) measured with pulse oximetry (OxiMax N-65, Tyco Healthcare Group L.P., Nellcor Puritan Bennett Division, Pleasanton, CA, USA) [18]. The HGS was measured conform a previously published protocol, using the highest value of the strongest hand [19]. 6MWD and HGS were measured and presented in meters and kilograms, respectively, and as percentage (%) of predicted based on sex and aged specific normative values [20,21]. Based on previous research, a 6MWD cut off of 250 m was used to define low 6MWD [13,22]. A HGS of <85% of values specific for age and sex was defined as low HGS as suggested by Norman et all [23].

2.3. Statistical analysis

Statistical analysis was performed with Statistical Package for the Social Sciences version 26 (SPSS, Chicago IL, USA). Descriptive results were shown as mean and standard deviation when

continuous, or as frequency and percentage when categorical variables. To study the difference in 6MWD and HGS between the normal SMI and low-SMI, the myosteatosis and non-myosteatosis groups, a linear regression analysis was performed for both the relationship between MRA and SMI groups with HGS and 6MWD. Missing outcomes of 6MWD due to medical reasons (for example if a person was unable to walk) were scored as 25% of predicted, which corresponds to the lowest predicted score based on complete cases. Regression coefficient (β), corresponding 95% confidence intervals (CI) and p-values were reported. To study the difference between the patients with low SMI, without low SMI, with myosteatosis, without myosteatosis and with low 6MWD or low HGS (all as dichotomous variable), logistic regression analysis was performed based on cut off values used for clinical care by the dietician or physical therapist. Odds Ratio's (OR) and corresponding confidence intervals and p-values were reported. Because of the high number of missing values in 6MWD and HGS, we performed a sensitivity analysis with only complete cases. All analyses were adjusted for sex and age. A p-value below 0.05 was considered statistically significant.

3. Results

In total, 152 patients were included in this study. Twenty-two patients (14.5%) were excluded, leaving 130 patients for analysis. Reasons for exclusion are presented in Fig. 1. Patient characteristics of the study population are shown in Table 1. The majority of the study population was male (N = 94, 72.3%) and mean age was 56 ± 11 years. The most common etiology of the liver disease was post-alcoholic liver disease, followed by viral liver disease (hepatitis B and C) and cholestatic liver diseases. Based on the cut-off values for SMI and MRA, 46 patients (35.4%) had low SMI and 27 patients (20.8%) had myosteatosis. Seventeen patients (13.1%) had both low SMI and myosteatosis. Mean time between CT scan and LT evaluation was 1 ± 17 days (range −55–86 days). There was no statistically significant difference in mean SMI (P = 0.233), but the patients with missing data had a significant lower MRA (P < 0.05) compared to the non-missing patients (supplementary file).

3.1. 6 minute walking distance

The mean walking distance for the total population was 467 ± 116 m. 24 patients (19%) had a 6MWD <250 m. 6MWD HR_{peak} was 94 ± 21 bpm, and heart rate response (HR_{peak} minus HR_{rest}) was 20 ± 14 bpm. The 6MWD was missing in 39 patients (30%). These missing data were not missing at random (Supplemental Table), since half of the missing group was not able to perform the test due to medical reasons (N = 19, 15%). Other reasons for missing were: no available consultation by a physical therapist (N = 7, 6%) or non-declared (N = 13, 10%). A statistically significant association was found between the presence of myosteatosis and 6MWD (% of predicted) with β = −12.388 (CI −23.939 to −0.837, p-value 0.036) and β = −12.815 (CI −24.608 to −1.022, p-value 0.034) in the crude and adjusted analyses, respectively. There was no statistically significant difference in 6MWD (% of predicted) between patients with low SMI compared to the normal SMI group or between patients with both low SMI and myosteatosis compared to normal group. Results are shown in Table 2.

Presence of myosteatosis was associated with low 6MWD (OR, 3.405; CI 1.134–10.220; p-value 0.029) as is shown in Table 3. No statistically significant difference in 6MWD was found between the SMI groups. Sensitivity analysis confirmed the association between low 6MWD and myosteatosis (OR, 7.277; CI 1.056–50.127; p-value 0.044) as shown in Tables 4 and 5.

3.2. Handgrip strength

The mean HGS was 40 ± 12 kg and 26 ± 7 kg for male and female, respectively. Based on the sex and age specific norm values, 38% (N = 49) of patients had a HGS < 85%. There was no statistically significant association between SMI, myosteatosis or both low SMI and myosteatosis on the one hand and HGS on the other hand as presented in Tables 2 and 3. Sensitivity analysis with only complete cases confirmed these findings.

4. Discussion

To the best of our knowledge, this is the first study investigating the association between low SMI and myosteatosis on the one hand with physical fitness parameters on the other hand in patients with ESLD waiting for LT. We found that patients with myosteatosis had a lower walking distance (as percentage of predicted) compared to patients with normal MRA. The odds for having a 6MWD <250 m were significantly higher in patients with myosteatosis compared to the patients without myosteatosis. Low SMI was not associated with decreased CRF. Furthermore, presence of myosteatosis and/or low SMI were both not associated with general skeletal muscle strength, reflected by the HGS.

The results of this study are in line with the results of Yadav et al., where there was no association between sarcopenia and 6MWD. In contradiction to our findings, Wang et al. found a significant correlation of both SMI and MRA with HGS, but the

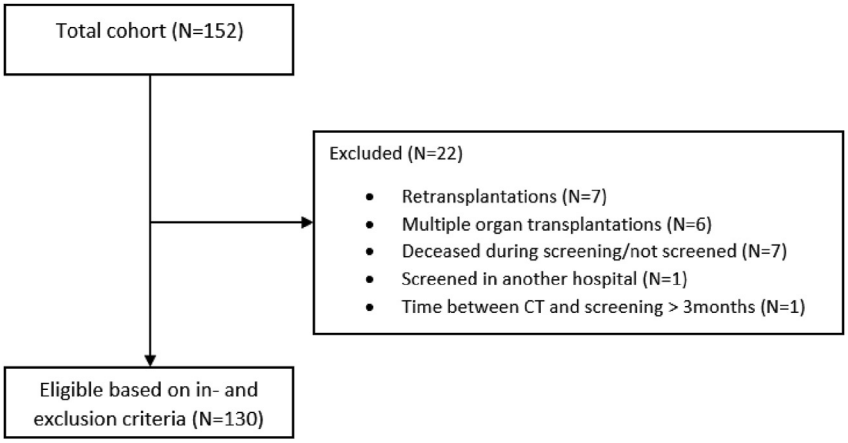

Fig. 1. Flowchart of patient inclusion.

Table 1
Population characteristics.

	Total (N = 130)	Male (N = 94)	Female (N = 36)	p-value
Sex (% male)	95 (72.3%)	–	–	
Age	56 ± 11	57 ± 9	53 ± 13	0.068
Primary liver disease				0.110
Post alcohol	40 (30.8%)	33 (35.1%)	7 (19.4%)	
NAFLD	18 (13.8%)	11 (11.7%)	7 (19.4%)	
Viral	22 (16.8%)	17 (18.1%)	5 (14.3%)	
AIH	12 (9.2%)	9 (9.6%)	3 (8.3%)	
Cholestatic	19 (14.6%)	13 (13.9%)	6 (17.1%)	
HCC	7 (5.3%)	4 (4.3%)	3 (8.3%)	
Other	12 (9.2%)	7 (7.4%)	5 (13.9%)	
Ethnicity				0.796
African	4 (3.1%)	2 (2.1%)	2 (5.6%)	
Asian	8 (6.2%)	6 (6.4%)	2 (5.6%)	
Caucasian	104 (80.0%)	75 (79.8%)	29 (80.6%)	
Hispanic	1 (0.8%)	1 (1.1%)	0 (0.0%)	
Other	13 (10.0%)	10 (10.6%)	3 (8.3%)	
Weight (kg)	84.73 ± 18.92	87.7 ± 16.43	76.7 ± 22.97	**<0.05**
Weight change (%)	−3.29 ± 9.93	−3.92 ± 10.57	−1.5 ± 7.72	0.296
BMI (kg/m^2)	27.6 ± 6.41	27.5 ± 5.08	27.8 ± 9.17	0.842
SMI (cm^2/m^2)	49.09 ± 9.17	50,61 ± 8.95	45.15 ± 8.65	**<0.05**
MRA (mean HU)	41.15 ± 7.64	41.42 ± 7.38	40.47 ± 8 0.31	0.553
6MWD (m)[a]	467 ± 116	468 ± 126	464 ± 80	0.877
% of predicted	74 ± 17	73 ± 18	77 ± 17	0.302
6MWD HR_{peak} (bpm)	94 ± 21 bpm	94 ± 22 bpm	92 ± 20 bpm	0.784
6MWD HR response	20 ± 14 bpm	20 ± 13 bpm	20 ± 16 bpm	0.953
HGS (KG)[b]	36 ± 12	40 ± 12	26 ± 7	**<0.05**
% of predicted	89 ± 25	88 ± 26	93 ± 24	0.274
Complications (yes)				
Ascites (%)	51 (39.2%)	34 (36.2%)	17 (47.2%)	0.131
HCC (%)	46 (35.4%)	36 (38.3%)	10 (27.8%)	0.329
HE (%)	26 (21.3)	19 (20.2%)	7 (19.4%)	0.904
MELD score	15.65 ± 6.93	15.01 ± 6.19	17.6 ± 8.73	0.123
Child Pugh score				0.167
CP-A	55 (42.3%)	43 (45.7%)	12 (33.3%)	
CP-B	47 (36.2%)	33 (35.1%)	14 (38.9%)	
CP-C	28 (21.5%)	18 (19.1%)	10 (27.8%)	

Data expressed as mean ± standard deviation or frequency and percentage (%). Abbreviations: 6MWD: 6 min walking distance, 6MWD HR response: 6MWD peak heart rate minus 6MWD resting heart rate, AIH: Auto-Immune Hepatitis, CP: Child Pugh, BMI: Body Mass Index, HGS: Hand Grip Strength, HCC: Hepatocellular Carcinoma, HE: Hepatic Encephalopathy, MRA: Muscle Radiation Attenuation, NAFLD: Non-Alcoholic Fatty Liver Disease, SMI: Skeletal Muscle Index. A p-value <0.05 was considered statistically significant.
[a] Data missing in 39 patients.
[b] Data missing in 11 patients.

Table 2
Linear regression model SMI and MRA on 6 min walking distance and hand-grip strength.

	6MWD as % normal value						HGS as % normal value					
	Crude model			Adjusted for age and sex			Crude model			Adjusted for age and sex		
	β	95% CI	P-value	β	95% CI	P-value	β	95% CI	P-value	β	95% CI	P-value
Low SMI (yes vs no)	−1.276	−11.528–8.977	0.805	−1.366	−11.979–9.247	0.779	−7.950	−18.167–2.267	0.126	−7.566	−18.196–3.065	0.161
Myosteatosis (yes vs no)	−12.388	−23.939–−0.837	**0.036**	−12.815	−12.101–−1.022	**0.034**	−6.385	−18.302–5.542	0.291	−7.178	−19.343–4.988	0.244
Low SMI and myoseatosis (yes vs no)	−8.323	−23.707–7.061	0.283	−9.289	−24.806–6.228	0.235	−13.968	−29.461–1.525	0.076	13.523	−29.348–2.301	0.093

Abbreviations: 6MWD: 6 min walking test, CI: confidence interval, MRA: Muscle Radiation Attenuation, SMI: Skeletal Muscle Index. A p-value <0.05 was considered statistically significant.

correlation was rather weak, suggesting that it is at least questionable whether SMI and MRA on the one hand and HGS on the other hand do reflect the same construct, i.e. general skeletal muscle strength [24]. In line with our findings, West et al. showed that myosteatosis is associated with reduced CRF in patients undergoing hepatobiliary and pancreatic surgery, while SMI was not [25]. This can be explained by the fact that CRF is an integrated resultant of the function of several organ systems such as the heart, blood and lungs in oxygen uptake and transport and the skeletal muscles (i.e. the mitochondria) in oxygen extraction, which highlights that it is not solely a resultant of muscle function [26]. In healthy muscle tissue, stimulation of the muscle fibers counteracts the accumulation of fat, preventing myosteatosis. However, fatty infiltration diminishes the ability to fully activate a muscle and lowers sensitivity to insulin, leading to an decreased effect of anabolic stimuli on skeletal muscle [27,28]. Impaired lipid (oxidative) metabolism, mitochondrial dysfunction and differentiation of muscle stem-cells are described as potential contributors to the

Table 3
Logistic regression model SMI and MRA on 6 min walking distance and handgrip strength.

	6MWD > 250 m vs < 250 m						HGS > 85% normal value vs < 85% normal value					
	Crude model			Adjusted for age and sex			Crude model			Adjusted for age and sex		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Low SMI (yes vs no)	0.606	0.208–1.768	0.359	0.768	0.248–2.373	0.646	2.056	0.909–4.650	0.084	2.113	0.903–4.945	0.084
Myosteatosis (yes vs no)	3.857	1.320–11.269	**0.014**	3.405	1.134–10.220	**0.029**	1.342	0.531–3.394	0.534	1.374	0.533–3.539	0.511
Low SMI and myoseatosis (yes vs no)	1.900	0.474–7.611	0.365	2.205	0.521–9.340	0.283	2.491	0.783–7.926	0.122	2.538	0.782–8.236	0.121

Abbreviations: 6MWD: 6 min walking test, CI: confidence interval, MRA: Muscle Radiation Attenuation, OR: Odds Ratio, SMI: Skeletal Muscle Index. A p-value <0.05 was considered statistically significant.

Table 4
Linear regression model SMI and MRA on 6 min walking distance and hand-grip strength–complete cases.

	6MWD as % normal value (N = 80)						HGS as % normal value (N = 103)					
	Crude model			Adjusted for age and sex			Crude model			Adjusted for age and sex		
	β	95% CI	P-value	β	95% CI	P-value	β	95% CI	P-value	β	95% CI	P-value
LOW SMI (yes vs no)	−5.965	−14.250–2.319	0.156	−3.734	−11.846–4.378	0.362	−7.950	−18.167–2.267	0.126	−7.566	−18.196–3.065	0.161
Myosteatosis (yes vs no)	−6.250	−16.461–3.961	0.227	−6.864	−16.578–2.849	0.163	−6.380	−18.302–5.542	0.291	−7.178	−19.343–4.988	0.244
Sarcopenia and myoseatosis (yes vs no)	−8.967	−22.178–4.244	0.179	−7.885	−20.793–5.024	0.225	−13.968	−29.461–1.525	0.076	−13.523	−29.348–2.301	0.093

Abbreviations: 6MWD: 6 min walking test, CI: confidence interval. MRA: Muscle Radiation Attenuation, SMI: Skeletal Muscle Index. A p-value <0.05 was considered statistically significant.

Table 5
Logistic regression model SMI and MRA on 6 min walking distance and handgrip strength–complete cases.

	6MWD > 250 m vs < 250 m (N = 80)						HGS > 85% normal value vs < 85% normal value (N = 103)					
	Crude model			Adjusted for age and sex			Crude model			Adjusted for age and sex		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Low SMI (yes vs no)	0.854	0.135–5.421	0.867	0.776	0.118–5.116	0.792	2.056	0.909–4.650	0.084	2.113	0.903–4.945	0.084
Myosteatosis (yes vs no)	6.923	1.049–45.689	**0.044**	7.277	1.056–50.127	**0.044**	1.342	0.531–3.394	0.534	1.374	0.533–3.539	0.511
Low SMI and myoseatosis (yes vs no)	3.800	0.475–30.419	0.208	3.149	0.383–25.891	0.286	2.491	0.783–7.926	0.122	2.538	0.782–8.236	0.121

Abbreviations: 6MWD: 6 min walking test, CI: confidence interval, MRA: Muscle Radiation Attenuation, OR: Odds Ratio, SMI: Skeletal Muscle Index. A p-value <0.05 was considered statistically significant.

development of myosteatosis in patients with ESLD [2,29]. Hence, myosteatosis is considered a measurement of the combination of skeletal muscle quality, muscle edema and structural changes, which is a broader concept than only skeletal muscle strength (which mainly depends on quantity, i.e. cross-sectional area). Impaired oxidative lipid metabolism might lead to muscle atrophy over time, which can potentially result in a muscle fiber type shift from type 2 (fast-twitch) to type 1 (slow-twitch) muscle cells, potentially affecting skeletal muscle strength. However, the exact effect of muscle fiber shift on development of myosteatosis is still unclear in patients with ESLD [2].

Although the prevalence of myosteatosis in patients with cirrhosis is over 50%, the current evidence regarding interventions to decrease myosteatosis is limited [8]. A study of Goodpaster et al. showed a beneficial effect of increasing physical activity on decreasing fat accumulation in the skeletal muscle in older adults [30]. Based on previous research by Bohannon et al., a change of 14.0–30.5 m in 6MWD is a clinically relevant difference [14]. This might suggest that, based on the regression coefficient for MRA, improving the MRA to a normal value with an exercise intervention might lead to a clinically relevant improvement of 6MWD in patients waiting for LT [14]. However, intervention studies regarding treatment of myosteatosis are rare. A systematic review of Ramírez-Velez et al. found that short-to-middle duration (mean 23 weeks, IQR 12–36 weeks, three-five sessions per week) supervised physical exercise therapy might be beneficial in improving the MRA in overweight or obese patients, but these findings are not yet confirmed in patients with chronic liver diseases or LT candidates [10].

This study has strengths and limitations. All measurements were performed in a standardized manner and performed by experienced dieticians and physical therapists. A CT scan was used, which is regarded as reference method for analyzing the body composition. Moreover, the sample size was calculated as more than accurate to answer our research question. However, due to the cross-sectional study design, no conclusions can be drawn regarding causality concerning the relation between myosteatosis and/or SMI and physical fitness outcome. Second, although we were informed about prior weight loss, as shown in Table 6, information regarding preceding changes in body composition prior to the LT evaluation were not available. It is plausible that a decreasing SMI or MRA can be the result of a catabolic state which might be associated with physical fitness. Third, there was a high number of missing data, especially for 6MWD. In about half of the missing 6MWD data cases, the reason for missing data was that the test was not possible due to the relatively strenuous physical

requirements of the walking test for the specific patients. These data were not missing at random and might therefore affect the results. However, these cases were assigned to the decreased 6MWD (<250 m) group in the logistic regression analysis, which partially corrects the possible selection bias issue concerning the non-randomly missing data. In the sensitivity analysis, the patients with missing data were excluded from analysis, but since these data were not missing at random, the results should be interpreted with caution. Additionally to this point, the mean HR_{peak} attained at the end of the 6MWD was relatively low (about 54% of predicted based on the mean age of the group), overall suggesting a submaximal effort, which might have lead to an underestimation of cardiorespiratory fitness in this population, possibly affecting the level of association with skeletal muscle parameters [31].

In conclusion, this study detected a sound association between myosteatosis and 6MWD in patients with ESLD. Presence of myosteatosis, reflected by MRA, was significantly associated with lower 6MWD and a higher odds ratio for 6MWD < 250 m. Assessment of myosteatosis, reflecting muscle quality, may help identifying patients who are at risk for the development of low CRF and guide interventions during the waiting period for LT, however, further studies are required to assess the clinical utility in cirrhosis. Based on the high prevalence of myosteatosis in patients waiting for LT and these findings, physical exercise training might be especially beneficial for patients with myosteatosis, although this should be confirmed prospectively in larger cohorts of LT candidates.

Author contribution

Daphne Bot: Participated in research design, writing the paper, performance of the research and data analysis.

Claudia Lucassen: Participated in research design, performance of the research and data analysis.

Maarten Werkman: Participated in research design, performance of the research.

Sylvia van Dijk: participated in the performance of the research.

Shirin Shahbazi Feshtali: participated in the performance of the research.

Maarten Tushuizen: Participated in research design, writing the paper, performance of the research and data analysis.

Bart van Hoek: Participated in research design, writing the paper, performance of the research and data analysis.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2023.04.005.

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