Sarcopenia in end-stage liver disease and after liver transplantation

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Abstract

Sarcopenia occurs in 30-70% of patients with end-stage liver disease and is associated with inferior pre- and post-liver transplant outcomes such as prolonged intubation times, long intensive care and hospitalization times, heightened risk of post-transplant infection, reduced health-related quality of life, and increased rates of mortality. The pathogenesis of sarcopenia is multifactorial and involves biochemical disturbances such as hyperammonemia, low serum concentrations of branched-chain amino acids (BCAAs) and low serum levels of testosterone, as well as chronic inflammation, inadequate nutritional status, and physical inactivity. Prompt recognition and accurate assessment of sarcopenia are critical and require imaging, dynamometry, and physical performance testing for the assessment of its subcomponents: muscle mass, muscle strength, and muscle function, respectively. Liver transplantation mostly fails to reverse sarcopenia in sarcopenic patients. In fact, some patients develop de novo sarcopenia after undergoing liver transplantation. The recommended treatment of sarcopenia is multimodal and includes a combination of exercise therapy and complementary nutritional interventions. Additionally, new pharmacological agents (e.g. myostatin inhibitors, testosterone supplements, and ammonia-lowering therapy) are under investigation in preclinical studies. Here, we present a narrative review of the definition, assessment, and management of sarcopenia in patients with end-stage liver disease prior to and after liver transplantation. (Acta gastroenterol. belg., **2023,** 86, **323-334**).

Keywords: Muscle quantity/quality, muscle strength, physical performance, liver disease.

Sarcopenia: more than loss of muscle mass

The term "sarcopenia", derived from the Greek words 'sarx' (flesh) and 'penia' (loss), was first introduced by Irwin Rosenberg in 1989 to describe a decrease in skeletal muscle mass (1). Although primarily described as a disease of the elderly, sarcopenia may occur earlier in life as a consequence of chronic conditions such as malignancy, organ failure such as End-Stage Liver Disease (ESLD), or inflammatory disease. Primary sarcopenia is defined as loss of skeletal muscle mass, strength, and function due to aging. Secondary sarcopenia denotes these changes as a result to underlying disease (2).

Over the last two to three decades, insights from different expert groups have led the definition of sarcopenia to evolve (2-6). Initially, the diagnosis of sarcopenia was exclusively based on the detection of a low muscle mass. However, as muscle function (strength or performance) became consistently recognized as a more reliable predictor of adverse health outcomes than muscle mass (7), in 2010 the European Working Group on Sarcopenia in Older People (EWGSOP) decided that muscle function should be included as an equally important criterium in the definition of sarcopenia (2). Later, in the 2019 revised definition (EWGSOP2 definition), poor muscle strength replaced low muscle mass as the primary characteristic of sarcopenia; additionally, muscle mass was specified to include both muscle quantity as well as muscle quality (4), which referred to micro- and macroscopic changes in muscle architecture and composition, as well as to muscle function delivered per unit of muscle mass (8). According to the EWGSOP2 operational definition (Table 1), sarcopenia is considered '*probable*' if poor muscle strength is present. The diagnosis of sarcopenia is '*confirmed*' if there is additional documentation of low muscle quantity or quality. If the criteria of low muscle strength, low muscle quantity or quality, and low physical performance are all met, sarcopenia is considered '*severe*'.

Sarcopenia is associated with an increased likelihood of adverse health outcomes including heightened fall risk, physical disability, loss of independence, morbidity, and mortality (9,10). Due to their similarities in etiology and definitions, considerable clinical overlap exists between the syndromes sarcopenia and the so-called frailty syndrome. Frailty describes a clinical state with multi-system impairment in one or more functional domains (physical, psychological, cognitive, and social), causing an increased vulnerability to stressors (11). The physical frailty phenotype is defined by presence of three of five of the following criteria: unintentional weight loss, exhaustion, physical inactivity, decreased handgrip strength, and slow walking speed (12). Sarcopenia can be considered as a risk factor for and the main component of the physical frailty phenotype (12,13). Sarcopenia do not take social, cognitive or psychological factors into account (13).

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Table 1. — **Operational definition of sarcopenia of EWGSOP2 2019 (4)**

Sarcopenia	Criteria		
Probable	Low muscle strength		
Confirmed	Low muscle strength	Low muscle quantity or quality	
Severe	Low muscle strength	Low muscle quantity or quality	Low physical performance

Table 2. — **Potential tools for assessing skeletal muscle mass, strength, and physical performance**

Muscle **quantity/quality**	**Skeletal muscle strength**	**Physical performance**
CT	Hand grip strength	6MWT
MRI	Knee flexion/extension strength	Gait speed test
DEXA	Maximal inspiratory and expiratory pressure	Timed up-and-go Test
BIA		Balance tests
Ultrasound imaging		SPPB

BIA, Bioelectrical Impedance Analysis; CT, Computed Tomographic; DEXA, Dual-Energy X-ray Absorptiometry; MRI, Magnetic Resonance Imaging; SPPB, Short Physical Performance Battery; 6MWT, 6Minute Walk Test.

Assessment of sarcopenia

According to EWGSOP2 definition, the presence and degree of severe sarcopenia is assessed by comprehensive evaluation of three parameters, being muscle quantity/quality, muscle strength, and physical performance (4). As shown in Table 2, a variety of testing tools are available.

Assessment of muscle mass

Computed Tomographic (CT) and Magnetic Resonance Imaging (MRI) scans are recommended by EWGSOP2 (4) and are currently considered the gold standard methods to quantify skeletal muscle mass (14-16). The Lumbar-3 Skeletal Muscle Index (L3 SMI), defined as the cumulative cross-sectional area of all skeletal muscles at the L3 vertebra, normalized for body surface (cm^2/m^2), has been investigated as a measure for sarcopenia (Table 2). The recommended L3 SMI cut-off values for defining sarcopenia in patients with ESLD who are awaiting liver transplantation are <50 cm^2/m^2 for men and <39 cm^2/m^2 for women (17). However, whereas the L3 SMI measures 7 distinct muscles (the psoas, quadratus lumborum, erector spinae, transversus abdominis, rectus abdominis, external oblique, and internal oblique muscles), the isolated assessment of the Psoas Muscle Area (PMA) is considered more user-friendly, and has a higher accuracy in predicting 1-year survival after liver transplantation (18) and may therefore be the preferred method.

Dual-Energy X-ray Absorptiometry (DEXA) scan, Bioelectrical Impedance Analysis (BIA), and ultrasound (US) can also be used to assess muscle mass and present specific advantages such as whole-body visualization (DEXA), lack of radiation burden (BIA and US), and low health care cost (BIA and US). However, relative to CT imaging, the use of DEXA, followed by the use of BIA and US seems to be increasingly less accurate in defining muscle mass (19,20).

Assessment of muscle strength

The current gold standard for diagnosing low muscle strength is the measurement of hand grip strength (4) with a hand dynamometer (21). According to the EWGSOP2, the threshold to define hand-grip weakness is <27 kg in men, and <16 kg in women (4). A dynamometric leg extension strength test, which measures the maximal isometric and/or isokinetic strength of the quadriceps muscle, is recommended to assess the lower body strength (22).

Assessment of muscle performance

According to EWGSOP2, the standard-of-care tools for the assessment of the severity of sarcopenia include the Short Physical Performance Battery (SPPB) test, the timed up-and-go test, and gait speed test. The SPPB is an objective tool to assess the physical function of the lower extremity (23) an consists of 3 timed tasks for the evaluation of patients' balance, gait, and strength: a balance task (ability to stand for 10 seconds with feet in 3 different positions (together side-by-side, semi-tandem, and tandem)), a timed 4 meter walk at usual pace, and a timed 5-fold chair-stand test (time to rise 5 times from a chair) (24). The SPPB possesses an excellent test-retest reliability (25). To date, in clinical and research settings the SPPB is frequently used as a screening test for frailty syndrome (26). The measurement of gait speed, such as a 4 meter usual walking speed test, has been documented to perform almost equally to SPPB in predicting disability (27), and holds the advantage of being a less time-consuming test. A single cut-off gait speed of ≤0.8 m/s is recommended by EWGSOP2 as an indicator of severe sarcopenia (4).

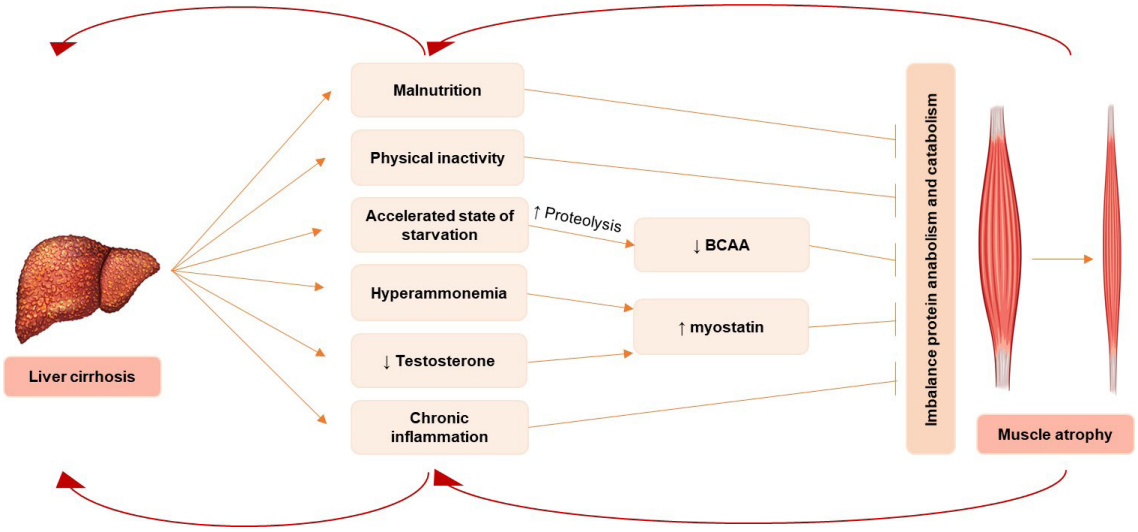

Figure 1. — Liver-muscle axis: possible mechanisms of the interaction between liver cirrhosis and sarcopenia. BCAA, Branched chain amino acids.

The timed up-and-go test is also widely used in clinical practice for the measurement of functional performance of the lower extremity (28). This test measures the time taken by an individual to stand up from a chair, walk a distance of 3 meters at their usual pace, turn, walk back, and sit down (28,29). The timed up-and-go test also has a high test-retest reliability (29,30).

Sarcopenia in end-stage liver disease: prevalence and clinical relevance

The prevalence of sarcopenia in ESLD is high. In patients with liver cirrhosis, the reported rates range between 30% and 70% (9,31-37), with the large variability probably reflecting the variation in the used diagnostic criteria and definitions. A recent meta-analysis indicated that patients with alcohol-associated liver disease have a higher prevalence of sarcopenia compared to those with other liver disease etiologies (49.6%, 95% CI: 42.9%-56.3%, n =1219 versus 33.4%, 95% CI: 27.4%-39.6%, n = 2166, p<0.001) (38).

The mechanisms of sarcopenia in liver cirrhosis are complex and multifactorial (Figure 1) (39-41). In the human body, skeletal muscle is the largest protein storage site. Skeletal muscle mass is maintained by the balance between catabolism and anabolism of muscle protein. In ESLD, this balance is disturbed due to decreased anabolism and enhanced catabolism, with skeletal muscle atrophy as a result. There is a complex crosstalk between the liver and the muscle mass. Common drivers of this liver-muscle axis that contribute to sarcopenia in cirrhosis include biochemical disturbances such as hyperammonemia, low branched-chain amino acids (BCAAs), and low testosterone levels, as well as chronic inflammation, inadequate nutritional status and physical inactivity (39,42-45).

Sarcopenia in ESLD is associated with a poor prognosis (33,46). A growing body of evidence has shown that mortality on the liver transplant waiting list is significantly higher in sarcopenic than in non-sarcopenic patients (9,14,17,18,31-34,37,47-51). For example, the study of Lai et al., who analyzed the impact of deficient muscle function on waiting list mortality in 309 liver transplantation candidates, showed that patients with a <10 SPPB score had a 45% increased risk of mortality while on the waiting list (50). Additionally, Lai et al. found that for every 1 kg increase in grip strength, every 0.1 meter/second increase in gait speed, and every 1 second decrease in chair stand, the risk of waiting list mortality decreased with 11%, 28%, and 17%, respectively (p<0.01) (50). Similar observations were reported by Wang *et al.,* who documented waiting list mortality to be associated with grip strength (hazard ratio (HR), 0.74; 95% confidence interval (95% CI), 0.59-0.92; P=0.008), with SPPB (HR, 0.89; 95% CI, 0.82-0.97;P=0.01), and with muscle quality as assessed by skeletal muscle attenuation, which is inversely related to increased macroscopic fat infiltration of the muscle (HR, 0.77; 95% CI, 0.63-0.95; P=0.02) (49). Studies further showed muscle function to have a stronger correlation with waiting list mortality than muscle mass, suggesting that assessment of muscle function is clinically more useful than measurement of muscle mass in patients with ESLD awaiting liver transplantation (49,51).

Despite the existing awareness of the negative effects of sarcopenia on the health outcomes in ESLD patients, sarcopenia is not included in current prognostic models as the Model for End-Stage Liver Disease (MELD) score. Recent studies revealed that inclusion of sarcopenia indices in the MELD score has a stronger association with waiting list mortality, relative to the current prognostic scoring systems, which are based exclusively on laboratory parameters (Table 3). The improvement in predicting waiting list mortality prediction was seen primarily in patients with low MELD scores, who are typically considered to have a good prognosis (34,52).

Table 3. — **Performance of the traditional and the modified MELD score (with inclusion of sarcopenia) in predicting waiting list mortality**

References	Modified MELD score	Assessment of sarcopenia	Association with waiting list mortality
Tandon *et al.* (34)	MELD-sarcopenia	L3-SMI	The presence of sarcopenia was associated with increased mortality in patients with low MELD scores (<15; log-rank P=0.02) but not in patients with higher MELD scores (≥15;P=0.59)
Montano-Loza *et al.* (51)	MELD-sarcopenia	L3-SMI	Inclusion of sarcopenia assessment within MELD improved significantly the prediction of 3-month mortality in patients with MELD<15 (0.85 vs. 0.69, P = 0.02) and refractory ascites (0.74 vs. 0.71, P=0.01) compared with MELD
Durand *et al.* (31)	MELD-psoas	PMA	The discrimination of MELD-psoas score (0.82; 95% CI, 0.64-0.93) was superior to that of the MELD score

L3-SMI: Skeletal Muscle Index at L3 region; PMA: Psoas Muscle Area (= Transversal Psoas Muscle Thickness (TPMT) measured on a Computed Tomography (CT) image at the level of the umbilicus).

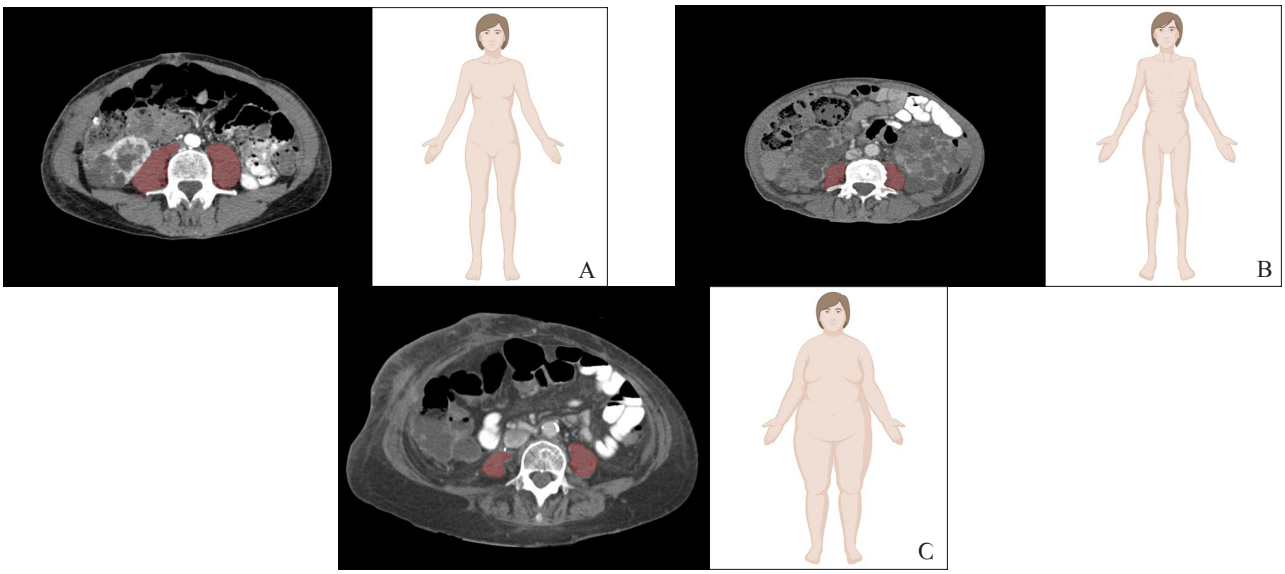

Figure 2. — Cross-sections of psoas muscles on computed tomography 2A. in a non-sarcopenic non-obese patient; 2B. in a sarcopenic patient; 2C. in a patient with sarcopenic obesity. Created with Biorender®.

Strikingly, studies show that the negative impact of sarcopenia on health outcomes of ESLD patients extends beyond liver transplantation, and reportedly include prolonged intubation times (53), prolonged intensive care unit stay (53), overall hospitalization times (53,54), and post-transplant infections (53-55). Additionally, out or 7 studies, all but one (54) found that pre-transplant sarcopenia was associated with an increased risk of post-transplant mortality (Table 4) (48,52,53,55-58).

Sarcopenia can co-exist with obesity and is referred to as sarcopenic obesity or sarcobesity. It is a condition where poor muscle strength and low muscle mass are associated with excessive adipose tissue (Figure 2) (59). Currently, no standardized criteria are used to define sarcopenic obesity, due to inadequate diagnosis of both obesity and sarcopenia individually. Adiposity is mostly assessed by the use of the body mass index (BMI) (60). According to the criteria of World Health Organisation, a BMI ≥30 kg/m^2 is considered as obesity (61). A recent position statement on obesity (62) has claimed to focus also on the body fat composition, in addition to excess bodyweight alone, as there is evidence that excess visceral adiposity and visceral-to-subcutaneous adipose tissue ratio are strongly correlated with the deleterious effects of obesity, including cardiometabolic risk and the development of NASH, above and beyond BMI (60,63-65). Based on this knowledge, Alalwan et al. proposed a new diagnostic criterion for "obesity-phenotype oriented" sarcopenic obesity (i.e., sarcopenic visceral-obesity or sarcopenic subcutaneous-obesity) (66). Due to the obesity epidemic, the prevalence of sarcopenic obesity in patients undergoing liver transplantation has increased and currently ranges between 13% and 33% (59). A complex crosstalk exists between skeletal muscle, liver, and adipose tissue (67). Through reduced adiponectin production and increased leptin production, adipose tissue may stimulate sarcopenia and induce fibrogenesis in the liver. Skeletal muscle on the other

Table 4. — **The impact of pre-transplant sarcopenia on clinical outcomes after liver transplantation**

Study	Sample size	Follow-up period	Assessment method of sarcopenia	Post-operative outcome parameter	Association
Englesbe *et al.* (55)	163	3 years after LT	Quantity of muscle mass (psoas area)	Post-transplant mortality	Strong association between psoas area and post-transplant mortality (HR = 3.7/1,000 mm^2 decrease in psoas area; p<0.0001)
Hamaguchi *et al.* (47)	200	80 months after LT	1. Quantity of muscle mass (PMI) 2. Quality of muscle mass (intramuscular adipose tissue content)	Post-transplant mortality	Low PMI (OR=3.635, P<0.001) and high intramuscular adipose tissue content (OR=3.898, P<0.001) were independent risk factors for death after transplantation
Kaido *et al*. (56)	72	1 year after LT	1. Quantity of muscle mass 2. Muscle strength (grip strength)	Post-transplant survival	Overall survival rates were lower in patients with sarcopenia than those without sarcopenia (P<0.001)
Kalafateli *et al.* (52)	232	1 year after LT	Quantity of muscle mass (L3-PMI)	1. Post-transplant 2. mortality 3. Length of post-transplant 4. hospitalization 5. In-hospital infection 6. Mechanical ventilation duration >24h 7. ICU stay >5 days	1. Low L3-PMI was significantly associated with higher 12 month mortality risk (OR = 0.996) 2. L3-PMI (OR = 0.996) was an independent predictor for a hospital stay >20 days 3. No association found 4. No association found 5. No association found
Masuda et al. (54)	204	5 years after LT	Quantity of muscle mass (PMI)	1. Post-transplant survival 2. Postoperative sepsis	1. Patients with sarcopenia showed significantly worse overall survival in comparison with patients without sarcopenia (P=0.02) 2. The rate of post operative sepsis was significant increased in patients with sarcopenia (17.7%) compared to patients without sarcopenia (7.4%) (P=0.03)
Kuo *et al.* (57)	126	5.1 years	Quantity of muscle mass (L3 SMI)	Post-transplant mortality	SMI was associated with post-transplant mortality (hazard ratio [HR] = 0.96 per cm^2/m^2, 95% CI 0.92-0.99). Patients with SMI ≤ $48cm^2/m^2$ versus >$48cm^2/m^2$ experienced higher rates of death at 1 year (86% versus 95%) and 3 years (73% versus 95%) (P= 0.01)
Montano-Loza *et al.* (14)	248	52±3 months after LDLT	Quantity of muscle mass (L3 SMI)	1. Length of hospital stay 2. Infections after liver transplantation 3. Post-transplant mortality	1. Sarcopenic patients had longer hospital stays in comparison with nonsarcopenic patients (4064 versus 2563 days; P=0.005) 2. Sarcopenic patients had a higher frequency of bacterial infections after liver transplantation (26% versus 15%,P=0.04) in comparison with nonsarcopenic patients 3. No association found with increased mortality

HR: Hazard Ratio; ICU: Intensive Care Unit; LT: Liver Transplantation; L3 SMI: L3 Skeletal Muscle Index; OR: Odds Ratio; PMI: Psoas Muscle Index.

hand secretes myokines that influence adipose mass, fat deposition in the liver, muscle metabolism, and insulin sensitivity (67). Since sarcopenia and obesity share common pathophysiologic mechanisms, they may act synergistically, and cause a greater negative impact on health outcomes than either obesity or sarcopenia alone (47,68,69). In a recent meta-analysis of 1515 liver transplant, pre-transplant sarcopenic obesity was associated with an increased overall post-transplant mortality -relative to non-sarcopenic and non-obese patients- at short-, intermediate-, and long-term follow-up (RR = 2.06, 95% CI: 1.28-3.33; RR = 1.67, 95% CI: 1.10-2.51; and RR = 2.08, 95% CI: 1.10-3.93, respectively) (59). Studies in other populations showed that sarcopenic obesity is also associated with other negative health consequences, such as increased risk of disability, institutionalization, metabolic diseases, and cardiovascular diseases, compared to sarcopenia or obesity alone (68). Limited research exist on the impact of ectopic accumulation of fat in the muscle, or myosteatosis, in the setting of liver transplantation. The absolute amount of intramuscular fat can be estimated on the basis of the decrease in skeletal muscle density on CT and MRI. Four studies looked into the impact of myosteatosis both before and after liver transplantation and found that patients with myosteatosis had the lowest

survival rates (69-72). Pathological cut-offs for skeletal muscle density index, however, are still not yet defined.

Sarcopenia after liver transplantation

A small number of studies have examined the natural post-transplant evolution of pre-existing (pre-transplant) sarcopenia (15,57,71,73-76). Interestingly, in successfully transplanted liver recipients, despite complete restoration of liver function, sarcopenia does not improve in a statistically significant or clinically relevant manner. Moreover, some patients develop *de novo* sarcopenia after undergoing liver transplantation (15,57,71,75-77). The pathophysiologic mechanisms of persistent and newly developed sarcopenia after liver transplantation are not well understood. The use of immunosuppressive agents, repeated hospitalizations, post-transplant infections, renal failure, physical inactivity, inadequate nutritional intake, and pre-transplant non-resolving changes in muscle mass, are potential factors contributing to the new onset of, or the failure to reverse pre-transplant sarcopenia (78). Pravisani *et al.* found that intensive care unit hospitalization time, biliary complications, pre-transplant sarcopenia, and the presence of sarcopenia one month after transplantation were predictive for long-term sarcopenia after transplantation (76).

Few studies have investigated the association between post-transplant (persistent or new onset) sarcopenia and post-transplant clinical outcome (75,76). Pravisani *et al.* showed that new-onset sarcopenia is a negative predictor of overall post-transplant survival (HR: 9.08, P=0.001) (76). Jeon *et al.* also found an association between new-onset sarcopenia and post-transplant mortality risk (HR: 10.53, P=0.024) (75). This association was not present when persistent pre-transplant sarcopenia was included in the analysis (75) suggesting that newly developed sarcopenia during the perioperative period has a greater negative impact on the survival of liver transplant patients than persistent sarcopenia (75).

Treatment of sarcopenia

Various therapeutic strategies have been developed, according to the different factors involved in the pathogenesis of sarcopenia. In order to target the multifactorial pathophysiology, a multimodal intervention is recommended (Figure 3). Currently, the recommended primary treatment for sarcopenia includes the combination of exercise therapy with nutritional therapy (79,80).

Physical exercise

It is strongly recommended to prescribe an exercise intervention that in itself is multimodal and involves aerobic exercise, muscle strengthening, balance improvement, and flexibility exercises, to counteract sarcopenia and its associated clinical impact (Figure 4).

Resistance training is the most effective physical exercise strategy to induce muscle hypertrophy and improve muscle strength (81,82). The activation of anabolic signals, stimulated by resistance training, leads to a muscle protein synthesis (83). Resistance training does not only increase skeletal muscle mass and strength, but also improves physical performance with improvement of balance (84-86). Aerobic training is recommended as it generates improvements in cardiopulmonary fitness and muscular endurance (87,88). Additionally, aerobic training has favorable effects on body composition with reduction of adipose tissue, including a reduction of intramuscular adipose tissue, which is especially beneficial for obese sarcopenic patients (84,89,90). Literature shows that aerobic and/or strength training have beneficial effects on health-related quality of life (91,92). Balance and flexibility training increases independency and reduces the fall risk (93,94). This is important, as ESLD patients and liver transplant recipients have a heightened fall risk as well as a high risk to develop osteoporosis and associated fragility fractures (95,96). Therefore, it recommended for a multimodal exercise program for sarcopenic patients to include balance and flexibility training.

Physical training can be challenging for patients with ESLD because of potential comorbidities, such as hepatic encephalopathy, cirrhotic cardiomyopathy, chronotropic incompetence, hepatopulmonary syndrome, portopulmonary hypertension, ascites, and anemia. Training programs should be tailored to the individual patient and their evolving physical abilities. Before starting with exercise therapy, it is advisable to optimize the patient's medical condition, including treatment of comorbidities. Furthermore, it is recommended for any patient with chronic disease to start at low intensity and to progress slowly (97,98). Especially for decompensated ESLD patients and for early post-transplant patients, exercise sessions should be monitored and supervised by an exercise physiologist or physiotherapist, preferably someone who has expertise in managing patients with liver disease and associated comorbidities.

Not only is organized exercise therapy important, but patients should also be advised to be generally physically active in their day-to-day life. Exercise is different from physical activity as it is defined as "a subcategory of physical activity that is planned, performed on a repeated basis over an extended period of time, and purposeful in improving physical fitness, performance, and health" (99). Physical activity is defined as "any bodily movement produced by skeletal muscles that results in energy expenditure" (100). The World Health Organization (WHO) has developed specific guidelines on physical activity and sedentary behavior for people suffering from chronic conditions or disability (99). The recommendations include the implementation of regular aerobic activities (≥150 or ≥75 minutes per week at moderate or vigorous intensity, respectively), muscle strengthening activities (2-3 sessions per week),

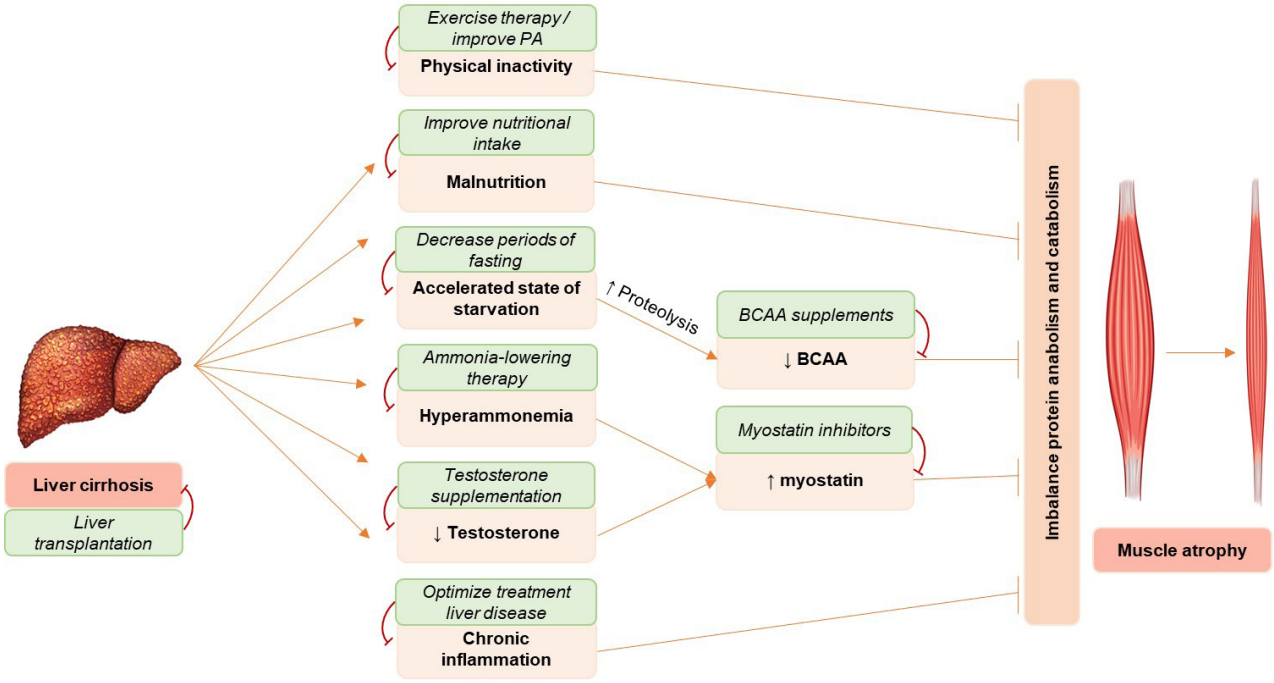

Figure 3. — Multimodal treatment strategies to target the multifactorial pathophysiology of sarcopenia.

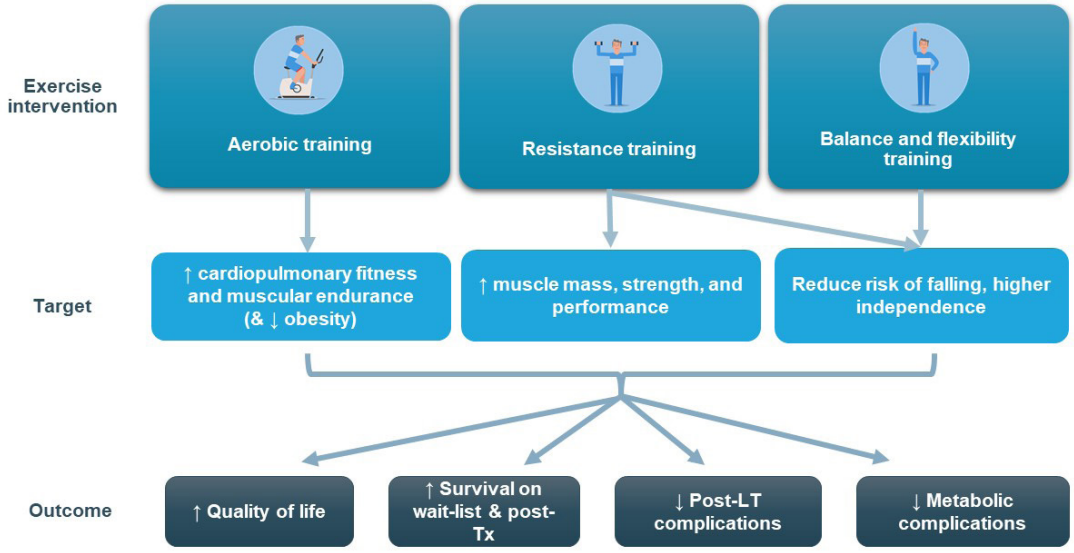

Figure 4. — Multimodal exercise intervention.

and postural balance exercises (≥2-3 sessions per week) (99,101). Importantly, the WHO guidelines also emphasize the benefits of practicing *any* form of physical activity, even if the aforementioned recommendations are out of reach. By simply becoming more physically active, clinically relevant health benefits can be obtained (102). Many ESLD patients lead a sedentary and physically inactive life. They are among the most sedentary of all patients with chronic disease (103). After transplantation, the physical activity level of liver transplant recipients generally improves, but it still fails to meet the physical activity guidelines and falls below that of the general population (104).

Nutritional therapy

Inadequate nutritional intake is one of the key factors in the development of sarcopenia. The design of nutritional strategies for sarcopenia should focus on optimal caloric and protein intake, to allow skeletal muscle mass to grow, and/or to prevent muscle mass to decline.

Protein intake

Most patients with cirrhosis are in a catabolic state and suffer from protein depletion. Sarcopenic cirrhotic patients, including those with sarcopenic obesity,

may require a higher daily protein intake than what is recommended for healthy adults [the recommended dietary allowance for an average adult is 0.8 g protein per kg body weight per day (g/kg/day) (105)], in conjunction with physical exercise to achieve muscle replenishment (106,107). Recent guidelines for the treatment of sarcopenic cirrhotic patients recommend a protein intake of 1.5 g/kg/day (106,108,109), provided renal function is normal. According to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines for nutrition in kidney diseases 2020 a low-protein diet, providing 0.55-0.60 g or 0.6-0.8 g dietary protein/kg body weight/day, is recommended for non-dialysis patients with chronic kidney disease stages 3-5 without or with diabetes, respectively (110). In metabolically stable adults with chronic kidney disease stage 5 on hemodialysis or peritoneal dialysis, irrespective of diabetes, a dietary protein intake of 1.0-1.2 g/kg body weight per day is recommended to maintain a stable nutritional status (110). These recommendations are based on expert opinion and with limited high-quality studies (111). A diverse range of protein sources should be used, including animal- and plant-based products (109). Studies have shown that increased protein intake (1.2-1.8 g/kg/day) prevents muscle wasting in cirrhotic patients and is generally well tolerated and safe without exacerbating hepatic encephalopathy in cirrhotic patients (112-114). Some studies support the use of branched chain amino acids (BCAA) supplementation (at 0.25 g/kg/day) as these promote muscle protein synthesis (106,115-118) and lead to better health outcomes, including improved quality of life and increased survival rate, in cirrhotic patients (119-121). However, to date, BCAA supplementation is not recommended in any form, other than as part of an overall daily target of protein, which naturally contain BCAAs (109).

Caloric intake

For non-obese ESLD patients, most recent guidelines suggest a daily energy intake of 35 kcal/kg/day (106,122,123). However, individual characteristics such as gender, age, body composition, and lifestyle variably influence a patient's daily energy expenditure, and consequently demands inter-individual variations in the requirement of energy intake (124). Also, a subset of cirrhotic patients is known to be hypermetabolic and to have a resting energy expenditure that is higher than predictions would suggest (125). Therefore, if available, indirect calorimetry should be performed to determine the patient's resting energy expenditure and provide a personalized caloric intake recommendation (39,109).

In sarcopenic obese patients, a hypocaloric diet (i.e. deficit of 500-800 kcal/day) under the guidance of a dietician is recommended. It is necessary for the hypocaloric diet to include adequate protein intake (>1.5 g proteins/kg/day) to achieve weight loss whilst minimizing concomitant muscle loss (106,122,123).

Due to their impaired glycogen storage, patients with liver cirrhosis show an early onset of gluconeogenesis after short-term fasting (126). It is therefore advised to keep periods of starvation short, by consuming late-evening snacks and splitting the caloric and protein intake into multiple, frequent and small meals (106,108,109,116,122). Late-evening carbohydrate snacking has been shown to improve protein metabolism in liver cirrhosis patients (127-130).

Micronutrient supplementation

Cirrhotic patients are susceptible to the development of severe deficiencies in micronutrients, such as zinc, vitamin D, A, E, K, and magnesium. A routine assessment of micronutrient deficiencies and appropriate repletion are recommended in patients with liver cirrhosis (109).

Due to its ammonia-lowering capacity, zinc has been postulated as a potential therapeutic agent for sarcopenia (131). In patients with cirrhosis, zinc deficiency has been shown to be an independent predictor for sarcopenia (132) and oral zinc supplementation has been proven to improve liver function in patients with liver cirrhosis (131). However, to our knowledge, the therapeutic effect of oral zinc supplementation on sarcopenia in cirrhosis has not been evaluated.

Vitamin D deficiency is associated with a decline in muscle mass, muscle strength, and poor physical performance (133). There is some evidence that vitamin D supplementation has a small positive impact on muscle strength, particularly in patients with low serum 25-hydroxyvitamin D levels (<30 ng/mL) (134,135). However, the effect of vitamin D supplementation in sarcopenic cirrhotic patients remains to be experimentally evaluated.

Pharmacological treatment

To date, there is no approved pharmacological treatment for sarcopenia (136). However, as summarized in Table 5, agents such as myostatin inhibitors, testosterone supplements, and ammonia-lowering therapy are at various stages of evaluation in preclinical studies. Currently, the safety and efficacy of these treatment options are still unknown, as no phase III and IV clinical trials are available (137).

Conclusion

Sarcopenia has a strong clinical impact on health outcomes in ESLD patients. It is a strong predictor of morbidity and mortality and is highly prevalent both before and after liver transplantation. However, in clinical practice of liver diseases and transplantation, the awareness of sarcopenia and its clinical impact in liver patients is still low. Routine assessment of sarcopenia is recommended, to allow for prompt recognition and treatment, not only to improve muscle mass, strength,

Table 5. — **Pharmacological strategies in development for treating sarcopenia**

Mechanism of action	Study population	Sample size	Effects
Myostatin inhibitors	>75 years, fallen in the past year	N=365	Appendicular lean body, stairs climbing time, chair rise with arms, and fast gait speed improved significantly from baseline to week 24 with differences between myostatin inhibitor and placebo of respectively 0.43 kg (p<0.0001), –0.46 s (p=0.093), –1.28 s (p=0.011), –4.15 s (p=0.054), and 0.05 m/s (p=0.088) (124)
Testosterone supplementation	Men with established cirrhosis and low serum testosterone	N=101	Significant increase of muscle mass (MAD +4.74kg, p=0.008), bone mass (MAD +0.08kg, p=0.009), and haemoglobin (MAD +10.2g/L, p=0.041) and significant reduction of fat mass (MAD -4.34kg, p<0.001) and HbA1c (MAD -0.35%, p=0.028) (125)
Ammonia-lowering therapy (L-ornithine L-aspartate, branch chain amino acids)	Portacaval anastomosis rats (a model of sarcopenia in hyperammonemia of portosystemic shunting)	N=16	Significant increase of lean body mass and grip strength (p<0.010) (126)

MAD: Mean Absolute Deviation.

and function, but also to improve patient outcomes. The absence of a consensus in the diagnosis of sarcopenia remains a challenge. Validation of techniques to evaluate sarcopenia in the liver disease and liver transplant population are warranted, as is a consensus definition of diagnostic criteria and cut-off values. Currently, physical exercise therapy and nutritional interventions are recommended as the most important components of the multimodal treatment approach to sarcopenia. Further understanding of the complex interplay between the liver, adipose and muscle tissues is needed to develop targeted therapies for sarcopenia.

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Conflict of interest

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Author's contributions

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