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Review Article

Clinical relevance of skeletal muscle abnormalities in patients with cirrhosis

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ABSTRACT

Recent advances in body composition evaluation have demonstrated abnormalities in skeletal muscle in patients with cirrhosis. Sarcopenia (severe muscle depletion) and myosteatosis (pathological fat accumulation in muscle) are prevalent muscle abnormalities in patients with cirrhosis that confer poor prognosis. Sarcopenia has become a well-defined factor for adverse clinical outcomes pre- and post-liver transplantation and emerging evidence has suggested the prognostic significance of myosteatosis in predicting mortality and overt hepatic encephalopathy in patients with cirrhosis. Advances in the understating of these muscle abnormalities might help improve therapeutic interventions to correct them and potentially improve outcomes of patients with cirrhosis. Moreover, inclusion of these muscle abnormalities within the current organ allocation policies might lead to a better mortality risk assessment in patients awaiting liver transplant and even to a decrease in the rates of futile liver transplants.

This review summarizes the current knowledge regarding the modalities to evaluate skeletal muscle abnormalities in cirrhosis, the incidence and clinical impact of these abnormalities in cirrhosis; existing and potential novel therapeutic strategies are also discussed.

1. Introduction

Skeletal muscle abnormalities, including sarcopenia (severe muscle depletion) and myosteatosis (pathological fat accumulation in muscle), are common in patients with cirrhosis. Computed tomography (CT) assessment of body composition is an objective and reliable approach to identify muscle abnormalities. Sarcopenia is an independent predictor of adverse clinical outcomes in cirrhosis, such as hepatic encephalopathy [1], waitlist mortality [2–6], longer hospital stay and higher frequency of infection following liver transplantation (LT) [7–9], increased health care cost [10], and post-LT mortality [4,11].

The model for end stage liver disease (MELD) is the most frequently used system worldwide to prioritize patients with cirrhosis for LT. However, muscle abnormalities are not included in this allocation system and, therefore, patients with these muscle abnormalities may be under prioritized [5,12].

In the general population, muscle loss starts to occur in the fifth decade of life at the rate of 1% per year up to age 70, and increases to 1.5% per year afterwards [13]. Two fold higher rates of muscle loss have been observed in patients with cirrhosis and, notably, elevations above 3% per year significantly increase the risk of mortality [14]. The prevalence of sarcopenia in patients with cirrhosis is expected to be 40–70% [15]. Discrepancies in the prevalence of these muscle abnormalities between studies might result from divergent criteria for definition (values below 5th percentile of age and gender-matched normal population or optimal cut-points for the mortality discriminations), outcome of interest and study population. Cut-points derived from cancer populations have frequently been applied to evaluate survival in patients with cirrhosis or prediction of post-LT outcomes. However, applicability of those body mass index (BMI)-dependent cut-offs in the cirrhotic population is debatable due to the fluid retention in the majority of patients with cirrhosis. Comparison between studies is also limited due to conflicting outcomes, such as overall mortality in patients assessed for LT, mortality on waitlist in patients listed for LT, post-LT mortality in patients having received LT, short *versus* long-term outcomes, which limited the development of generalized definitions. This review summarizes the existing information on skeletal muscle abnormalities in patients with cirrhosis, focusing on the frequency, factors associated and clinical implication of these abnormalities. It also provides insight into future research on how reversing these muscle abnormalities may help to improve outcomes in patients with cirrhosis and circumvent futile LT.

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Table 1
Skeletal muscle indices used for sarcopenia diagnosis in patients with cirrhosis.

Skeletal muscle mass indices	Abbreviation	Muscle included	Landmark	Software
Skeletal Muscle Index	SMI	Total cross sectional areas of psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis (Normalized to height)	Third lumbar vertebrate (L3)	• SliceOmatic • MATLAB • ImageJ • Non-commercial software tool developed at the Erasmus MC University Medical Centre
Psoas Muscle Index	PMI	Sum of the areas of the 2 psoas (Normalized to height)	• Mid fourth lumbar vertebrate • Close to the intervertebral disk between the level of the third and fourth lumbar vertebra	• Leonardo Workstation using oncocare • Myrian XP-Liver 1.14.1
Total Psoas Area	TPA	Total psoas areas	Fourth lumbar vertebra (L4)	• MATLAB
Psoas Muscle Area	PMA	Sum of the areas of the 2 psoas	• Mid fourth lumbar vertebrate • Close to the intervertebral disk between the level of the third and fourth lumbar vertebra	• Myrian XP-Liver 1.14.1
Transversal Psoas Muscle Thickness	TPMT	Right psoas muscle	Umbilicus	• NA

NA: not applicable.

2. Definition of sarcopenia

The Greek origins of the term are *sarx* for 'flesh' and *penia* for 'loss' and the term was first adopted by Rosenberg in 1989 [16]. Age-related sarcopenia was initially defined in the elderly and is a term denoting a reduced amount of skeletal muscle, generally described as lean appendicular mass normalized to height squared > two standard deviations below that typical of healthy young adults [17]. Since then, sarcopenia has been gradually adopted in the clinical setting as low muscle mass that leads to negative effects on function and clinical outcomes.

Primary (age-related) and secondary (disease, nutrition or activity-related) have been suggested as sarcopenia categories [18] by The European Working Group on Sarcopenia in Older People (EWGSOP); however, it may not be feasible to distinguish between primary and secondary sarcopenia in some clinical settings, including patients with cirrhosis. Although there is still a lack of consensus on the definition of sarcopenia, EWGSOP and the special interest group (SIG) on cachexia-anorexia recommend considering the presence of both low muscle mass and functional deterioration (strength or performance) [18,19] as part of the sarcopenia definition, in order to provide a practical description. In an attempt to build a more comprehensive term, three conceptual stages of sarcopenia, *i.e.*, presarcopenia (low muscle mass), sarcopenia (low muscle mass with low strength or performance), severe sarcopenia (low muscle mass with both low strength and impaired performance) have been proposed by EWGSOP [18], which excludes age per se from the definition of sarcopenia [20].

In cirrhosis, sarcopenia has been identified as a predominant and life-threatening complication, described by progressive loss of skeletal muscle mass and strength, which has become of great interest over the past few years. In the fields of hepatology and liver transplantation, the term "sarcopenia" has mainly focused on adverse clinical outcomes related to low muscle mass.

3. Modalities to evaluate muscle characteristics in cirrhosis

Lack of a standardized definition for sarcopenia in cirrhosis may arise from various quantitative measurements of muscle mass by indirect and direct techniques, such as anthropometry, bioelectrical impedance (BIA), dual-energy X-ray absorptiometry (DXA), ultrasound (US), magnetic resonance imaging (MRI) and computed tomography (CT), which have been applied to diagnose sarcopenia in cirrhosis. Comparability between studies might be limited due to restricted ability of some of these techniques to provide a direct estimate of muscle mass. Moreover, the accuracy of some of these techniques, such as BIA by fluid retention, DXA by muscle water and fibrotic accumulation especially in the elderly, might be questioned. Reliable tools comprising diagnostic CT and MRI are a routine part of LT assessment in most LT centers, to screen for hepatocellular carcinoma (HCC) and to assess the vascular and biliary anatomy. Importantly, validity across techniques should be established in order to reach a consensus between different techniques and their associated cut-points. Sensitivity and specificity of techniques to capture longitudinal changes are inevitable criteria for predicting patients' long-term outcomes.

Standard-of-care CT imaging has been widely used to predict outcomes in patients with cirrhosis. Skeletal muscle cross-sectional area and radiodensity can be estimated on a single slice CT using a pre-defined Hounsfield Units (HU) range of −29 HU to 150 HU [21]. Use of non-contrast *versus* contrast-enhanced CT scans does not seem to be a major concern for skeletal muscle cross sectional quantification and consequently for sarcopenia identification. However, skeletal muscle radiodensity was significantly increased in the arterial and portal-venous phase compared to the non-contrast phase CTs [22,23]. Diverse software programs, including SliceOmatic, ImageJ, FatSeg, OsiriX, have been applied to quantify abdominal skeletal muscle cross-sectional area (Table 1), which demonstrated tremendous agreement [24].

A study by Englesbe et al. was the first application of CT in cirrhosis to evaluate sarcopenia using the cross-sectional area of the psoas muscle, which found an association between psoas muscle area and post-LT mortality [25]. Subsequent studies evaluating patients assessed for LT, used CT cut-points for sarcopenia associated with higher mortality risk derived from skeletal muscle index (SMI) in cancer patients [9,26]. In order to standardize cut-points for sarcopenia, Carey et al., recently defined sarcopenia as SMI < 50 cm^2/m^2 in males and <39 cm^2/m^2 in female patients listed for LT in North America centers [27]. CT measured SMI calculated as total muscle area at the third lumbar vertebra (L3), normalized to height, is a strong surrogate of whole body muscle mass [28] and can be applied as a reliable marker of whole body muscularity. Defined in this way, sarcopenia was mainly delineated as sex specific SMI values associated with mortality that were independent of age and MELD score [27].

Apart from SMI, various psoas muscle measurements, including cross sectional area [25,29], index [30] and thickness [3], have been applied to predict mortality risk in patients with cirrhosis. It has been recently reported that psoas muscle index has limited performance to identify patients with higher waitlist mortality risk in cirrhosis. Consequently, SMI has been identified as a more complete and robust measurement compared to the psoas muscle index [31].

Figure one illustrates the total skeletal muscle and psoas muscle estimation at L3 from two male patients with cirrhosis. Fig. 1A, B presents a sarcopenic patient who had low SMI ($40\,cm^2/m^2$) and psoas muscle index of seven cm^2/m^2 whereas Fig. 1C, D shows a patient with a high SMI ($65\,cm^2/m^2$) and psoas muscle index of seven cm^2/m^2. Overall, CT image analysis is an opportunistic body composition assessment and, therefore, inclusion of a low-dose CT at L3 as part of LT assessment should be considered in the future to develop and validate the consistent criteria for sarcopenia identification.

4. Clinical significance of sarcopenia

Sarcopenia is related to severe adverse clinical outcomes in patients with cirrhosis. However, a standardized threshold for sarcopenia that can be used in clinical practice in patients with cirrhosis is lacking. Absence of such criteria is a major obstacle in sarcopenia inclusion within organ allocation criteria in the LT setting. This emphasizes the need to develop standardized cut-point values for sarcopenia that can be adopted in LT centers widely.

In patients with cirrhosis, sarcopenia has been shown to be associated with various adverse outcomes pre and post-LT. Besides mortality [32–35], sarcopenia was repeatedly associated with increased risk of infection and increased length of hospitalization [6–9]. Mortality associated SMI cut-offs derived from cancer populations were applied as threshold criteria for sarcopenia in previous single center studies [12,32–35]. A multicentre study of almost 400 patients determined the threshold values that correlate best with waitlist mortality in patients with cirrhosis. Using SMI < $50\,cm^2/m^2$ in males and <$39\,cm^2/m^2$ in females patients listed for LT, sarcopenia was observed in 50% of male patients and 33% of female patients [27]. Higher mortality observed in sarcopenic patients with cirrhosis seems to be related to sepsis rather than liver failure [32]. Data regarding the influence of existing pre-LT sarcopenia on post-LT outcomes is also emerging. Recently, a SMI value <$48\,cm^2/m^2$ showed discriminative performance for predicting post-LT mortality in acutely ill men undergoing urgent evaluation and LT [36]. A major research gap remains regarding the influence of sarcopenia in patients with cirrhosis that persists following LT on long-term outcomes. Therefore, prospective evidence is needed to validate the predictive value of muscle abnormalities as independent prognostic factors of long-term outcomes in patients with cirrhosis.

Sarcopenia is difficult to evaluate in patients with high BMI. Sarcopenic obesity, which is the concurrent presence of sarcopenia and obesity, has been observed in 20%–35% of patients with cirrhosis [37]. Although the prognostic significance of sarcopenic obesity in cirrhosis has not been widely investigated, studies found that sarcopenic obesity was associated with higher mortality in patients with cirrhosis [38], patients with HCC [39], as well as HCC recurrence in patients who underwent hepatectomy for HCC, of which 51% had cirrhosis [40].

Sarcopenia in patients with cirrhosis has classically been related to mortality in both sexes; however, there is mounting evidence that male sex predisposes to higher frequency and increased mortality risk related to sarcopenia [41]. The reason for the sex differences in sarcopenia frequency and mortality risk in cirrhosis has not been clarified. The metabolic pattern that drives muscle loss in male patients with cirrhosis is similar to other chronic inflammatory systemic diseases [42] and, therefore, impaired glycogen synthesis due to hepatic damage and diminished energy availability may partially explain muscle loss in male patients.

Previous studies have demonstrated poor correlation between muscle mass and MELD score, and therefore they evaluated the inclusion of sarcopenia within the MELD score. Inclusion of muscles mass assessed by CT within the MELD scores demonstrated improvement in mortality prediction [5,12]. Importantly, the presence of sarcopenia was comparable to adding 10 points to the MELD score [5]. However, discriminative performance of MELD-sarcopenia score was mainly observed in patients with low MELD score. In addition, a model including sarcopenia, MELD score, age, and presence of hepatic encephalopathy prior to listing showed better discriminative performance in predicting three-month mortality on waiting-list [12]. Multicentric prospective studies are warranted to determine whether sarcopenic patients with lower MELD score may benefit from expedited LT.

5. Management of sarcopenia in cirrhosis

Management of sarcopenic patients requires an integrated approach of nutrition and exercise. Nutritional screening and assessments should be implemented in all patients with cirrhosis to identify presence and degree of malnutrition. Subjective global assessment (SGA) is considered the gold standard for diagnosing malnutrition; however, assessment of sarcopenia by CT is a more efficient method to predict adverse outcomes in patients with cirrhosis compared to the SGA [43]. Besides nutrition and physical activity, other approaches such as hormone replacement therapies and nutritional supplementation are suggested strategies to improve muscle mass in cirrhosis [44].

Nutritional management of patients with cirrhosis includes three major components including sufficient energy intake, adequate protein intake and avoiding prolonged fasting periods. Daily protein intake of 1.2–1.5 gr/kg and energy intake of at least 35 kcal/kg in non-obese patients (BMI < $30\,kg/m^2$) have been recommended by recent European Association for the Study of the Liver (EASL) Clinical Practice Guidelines on nutrition in chronic liver disease. Protein intake of 1.2–1.5 gr/kg is recommended to reverse sarcopenia and preclude loss of muscle in patients with sarcopenia and liver cirrhosis. In obese patients with cirrhosis, a moderate decrease in calorie intake (−500 to 800 kcal/d) is recommended. Patients with hepatic encephalopathy can tolerate normal protein intake; however, favoring consumption of vegetables and dairy protein is recommended. Only in patients with severe overt hepatic encephalopathy and gastrointestinal bleeding, protein restriction might be needed for just a very short period of time [44].

Very low (<0.8 g/kg/d) and low (0.8–1.2 g/kg/d) protein intake was observed in 76% of patients on a LT waiting list. Very low protein intake was independently associated with the finding of moderate or severe malnutrition according to the subjective global assessment (SGA B or C) and wait-list mortality. Autoimmune liver diseases and worsening hepatic function were the main predictors of very low protein intake [45].

Patients awaiting LT are recommended to avoid fasting longer than six hours. Long periods of fasting can be avoided by taking small, frequent meals, especially a late-night snack. The ideal calorie and composition of late-night snacks has not been determined, however a late-night snack containing 50gr complex carbohydrate [46] or a branched-chain amino acid (BCAA) enriched snack have shown some beneficial impact on clinical outcomes [47]. Although the later has shown better capacity, the optimal composition of BCAA has not been identified. Consumption of a nighttime supplement in patients with cirrhosis could lead to the elevation in fat free

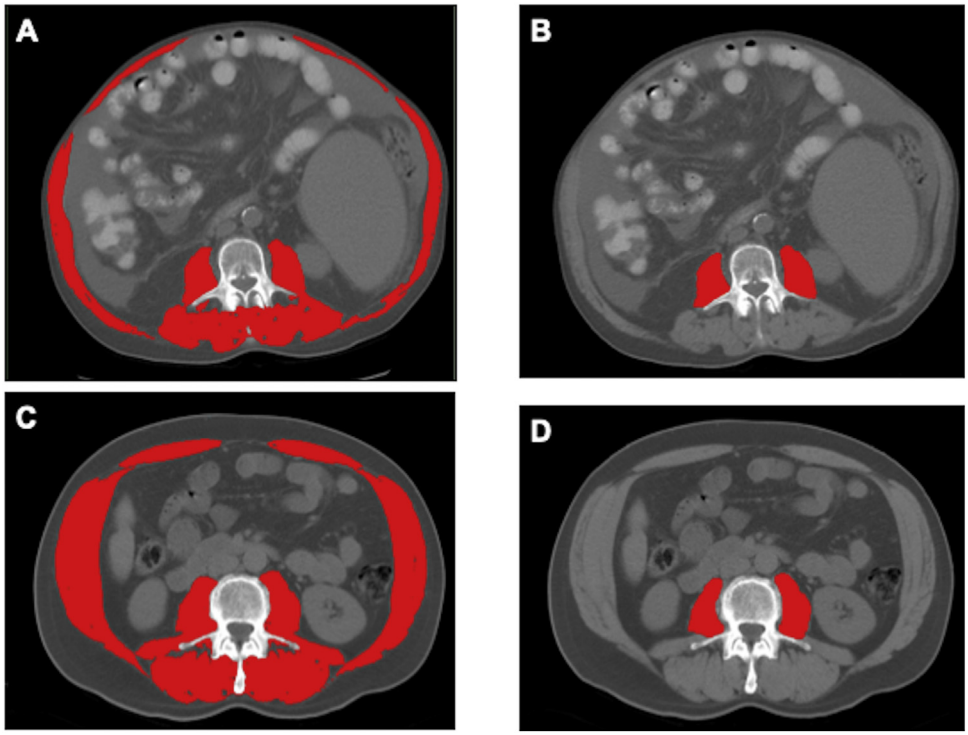

Fig. 1. (A–D). Abdominal computed tomography images taken at the 3rd. Lumbar vertebra to quantify total muscle and psoas muscle areas in cirrhosis. Abdominal computed tomography images taken at the 3rd lumbar vertebra were used to evaluate the L3 SMI and psoas muscle index. Red color designates skeletal muscles. Fig. 1(A, B) presents a patient who had low SMI (40 cm^2/m^2) and psoas muscle index of seven cm^2/m^2, whereas Fig. 1C, D shows a patient with high SMI (65 cm^2/m^2) and psoas muscle index of seven cm^2/m^2.

mass and total body protein stores [48]. Regardless of the type and composition of the late evening snack, this supplementary nutrition reduced lipid oxidation and improved nitrogen balance [47].

In patients with cirrhosis, routine physical activity is required to prevent sarcopenia. Type and duration of physical exercise are important to consider in patients with cirrhosis and patients should go through screening for varices and the required variceal prophylaxis prior to initiate exercise. Overall, moderate intensity exercise for at least 30 min per day, 3–5 times per week is recommended. Physical exercise should start with a short-term warm-up (5–10 min) and end with a stretching/cool-down phase (5–10 min) [49]. Although a combination of resistance and aerobic exercise is recommended, resistance exercise is more effective in reversing sarcopenia [50].

Various pharmacological and nutritional interventions have been suggested to reverse sarcopenia in geriatric and cancer populations, however evidence is emerging in cirrhosis. Among nutritional supplements, BCAAs have attracted intensive attention in recent years, especially due to diminished serum concentration of BCAAs in cirrhosis. In fact, amino acids in plasma have been associated with survival in patients with cirrhosis. Specifically, the branched-chain and aromatic amino acids (Fischer's ratio) are associated with prognosis [51].

Administration of oral nutritional supplements of BCAA at the dose of 12 g/day for two years in patients with decompensated cirrhosis improved event-free survival and quality of life [52]. In another study, BCAA supplementation (30 gr) was associated with mid-arm muscle circumference elevation and minimal hepatic encephalopathy improvement [53]. Among BCAAs, leucine has been well defined to confer superior benefit on mTOR (mammalian target of rapamycin) activation [54]. Administration of oral leucine (10 g/day), in conjunction with moderate physical exercise for 12 weeks, improved leg muscle mass and quality of life in patients with cirrhosis [55]. Larger randomized controlled trials in cirrhosis are required to establish the benefit of BCAAs, considering the dose, duration and compliance to the supplementation with and without exercise intervention on both prevention and treatment of sarcopenia in patients with cirrhosis.

Emerging evidence suggests that fish oil derived long chain n-3 PUFAs and their derived mediators can improve muscle mass and function in older adults [56] and in cancer cachexia [57]. Vitamin D has also shown some association with sarcopenia in geriatric population [58], however the impact of fish oil and vitamin D supplementation on sarcopenia incidence and treatment has not been investigated in patients with cirrhosis. L-Carnitine is a vital nutrient for fatty acid metabolism and almost one fourth of it is synthesized by the kidney and liver. Administration of L-Carnitine (1000 mg /day) for more than six months suppressed skeletal muscle loss in patients with cirrhosis [59].

In male patients with cirrhosis, lower testosterone levels were detected in sarcopenic compared to non-sarcopenic patients [60]. A one-year double-blinded, placebo-controlled trial of intramuscular testosterone administration to men with cirrhosis and low serum testosterone levels revealed significant improvement in muscle mass [61]. On the other hand, the presence of muscle abnormalities (sarcopenia and myosteatosis) independently increases the risk of hepatic encephalopathy and hyperammonemia [1]. Further, preclinical studies found some beneficial effects of ammonia lowering therapies on sarcopenia in cirrhosis [62]. The potential efficacy of these drug therapies to reverse sarcopenia highlights the need of clinical controlled trials.

6. Clinical implications of myosteatosis in cirrhosis

CT image-based analysis of body composition has revealed myosteatosis (pathological fat accumulation in skeletal muscle) as

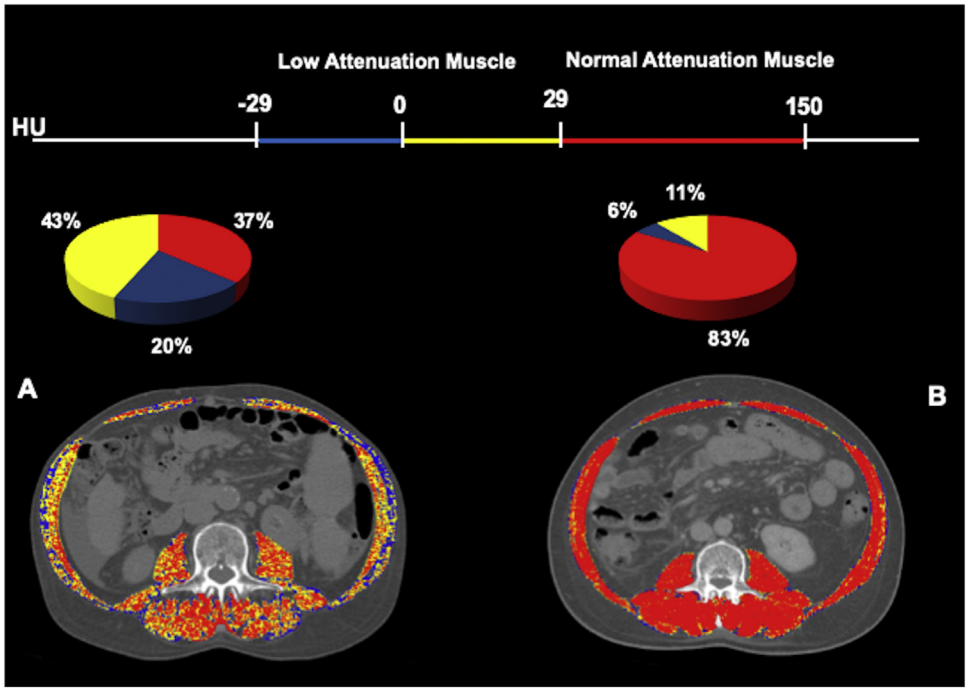

Fig. 2. (A, B). Computed tomography images used for the myosteatosis assessment in cirrhosis. Comparison of two patients with cirrhosis and similar BMI (≥25 kg/m^2). Attenuation ranges used for the analysis of normal attenuation (red), low attenuation region one (yellow), and low attenuation region two (dark blue) muscles are shown. (A) Patient with low muscle attenuation (20 Hounsfield Units, HU) with myosteatosis. (B) Patient with normal muscle attenuation (48 HU). More than 60% of the total muscle area in Fig. 2A is the area composed of low-radiodensity muscle, whereas for Fig. 2B, the areas of normal-radiodensity muscle is predominant (83%).

another radiologically-identified aberration in skeletal muscle. This reduced muscle radiation attenuation, defined as muscle radiodensity of <33 HU in patients with a BMI ≥ 25 and <41 in those with a BMI < 25, has repeatedly shown an association with adverse outcome in patients with malignant tumors [63]. However, a major gap remains regarding its prognostic significance in cirrhosis.

By applying cut-offs derived from a cancer population [64], myosteatosis was reported in 52% of patients with cirrhosis. The presence of myosteatosis was an independent predictor of shorter survival, which was mainly related to the deterioration in physical condition, rather than the severity of the liver disease. A longer intensive care unit stay was also observed in patients with myosteatosis [38]. Myosteatosis was one of the major features associated with hepatic encephalopathy in patients with cirrhosis, which was observed in 70% of patients with hepatic encephalopathy compared to 45% of patients without hepatic encephalopathy [1]. However, the efficacy of these BMI-dependent cut-offs derived from cancer populations is debatable in cirrhosis due to the presence of ascites.

In patients with myosteatosis, reduced muscle attenuation is displayed as an increase in the areas of low-radiodensity muscle (−29 to 0 HU and 1 to +29 HU) [65,66]. Fig. 2 highlights the muscle attenuation estimation at L3 from two male patients with cirrhosis. Fig. 2A represents a patient with myosteatosis who had low muscle attenuation (20 HU), whereas Fig. 2B shows a patient with a normal muscle attenuation or no-myosteatosis (48 HU). More than 60% of the total muscle area in Fig. 2A is composed of low-radiodensity muscle, whereas for Fig. 2B, the area of normal-radiodensity muscle is predominant (83%).

Major CT technical parameters, such as the use of intravenous contrast [67], have not been reported in previous studies assessing the association between myosteatosis and outcomes. Muscle and visceral adipose tissue radiodensity quantification is influenced by contrast medium administration [23]. Significant increase in muscle radiodensity following contrast administration [22,23] encourages the use of non-contrast images for myosteatosis identification. Further studies in patients with cirrhosis are required to determine various interactions between myosteatosis and sarcopenia.

7. Future directions

Objective assessment of skeletal muscle mass (quantity) and radiodensity (quality) has been practicable through radiological approaches. Skeletal muscle abnormalities including sarcopenia and myosteatosis (low attenuation on CTs) are associated with increased mortality and complications, such as hepatic encephalopathy in patients with cirrhosis. While skeletal muscle abnormalities constitue important prognostic factors, they are not integrated in conventional scores for prognosis in cirrhosis, such as the MELD or Child-Pugh scores, and the value of such an integration deserves approriate evaluation. Early identification of sarcopenia in patients with cirrhosis might provide us with the opportunity to develop preventive and treatment strategies to maintain muscle quantity, quality and, consequently, improve clinical outcomes in patients with cirrhosis.

At this moment, there is a need to improve criteria for CT-based evaluation of skeletal muscle abnormalities. Studies may require reporting whether unenhanced or contrast-enhanced CT images have been used to measure skeletal muscle radiodensity. This review emphasizes the necessity to conduct prospective longitudinal studies with a larger number of patients to overcome the difficulties in our present understanding of prognostic significance of skeletal muscle abnormalities in cirrhosis. This may lead to appropriate improvements in the current policy for organ allocation criteria in the LT setting. The efficacy of nutritional and pharmacological interventions in reversing muscle abnormalities should be investigated in controlled clinical trials.

Conflict of interest

None declared.

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