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Review

Sarcopenia; An Endemic in the Times of Pandemic in Liver Transplantation

Hamid Ullah [1], Sara Iqbal [2,*], Blanca Lizaola-Mayo [2], Elizabeth Carey [2]

1. Division of Internal Medicine, University of Mississippi, Jackson, Mississippi, USA; E-Mail: hamid.ullah1@gmail.com
2. Transplant Center, Mayo Clinic, Phoenix, AZ, USA; E-Mails: iqbal.sara@mayo.edu; Lizaola-Mayo.Blanca@mayo.edu; carey.elizabeth@mayo.edu

* **Correspondence:** Sara Iqbal; E-Mail: iqbal.sara@mayo.edu

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Abstract

Liver transplantation (LT) has grown monumentally in the last 40 years. Sarcopenia has emerged as an independent factor associated with increased mortality in patients with end stage liver disease. In this review we aim to shed light upon recent developments in assessment, clinical implications, management of sarcopenia in patients requiring a liver transplant. We also bring attention to the impact of COVID-19 pandemic on sarcopenia which ranges from the disease pathology to the unprecedented preventive measures taken during this time. Assessment tools to risk stratify and assess the degree of COVID related deconditioning in patients with end stage liver disease is an exigency. Management of sarcopenia requires a multifarious approach to address nutritional factors, exercise and pharmacotherapy. We may have to shift gears to focus on more rigorous rehabilitation and nutritional techniques during the times of pandemic. Future studies should evaluate whether recovery of sarcopenia with nutritional management in combination with an exercise program is sustainable and whether that improvement in muscle mass leads to an improvement in clinical outcomes. Data regarding long term and short-term effects of COVID 19 pandemic, to

form assessment tools that aim to identify patients who can benefit from multimodal prehabilitation and rehabilitation, is required.

Keywords
Sarcopenia; COVID-19; liver transplant; liver frailty Index; 6 MWT

1. Introduction

Liver transplantation (LT) has grown monumentally in the last 40 years. The learning curve has been steep but we continue to hone our skills in fields pertaining to recipient selection, organ procurement, matching and post transplant management. Sarcopenia has more recently emerged as an independent factor associated with increased mortality in patients with end stage liver disease. Advent of COVID-19 has not only magnified the predisposition towards development of sarcopenia due to the social restrictions but data is also emerging regarding direct effects of the virus on muscle health.

Sarcopenia, described as the disproportionate loss of muscle mass, is frequently seen in patients with advanced liver disease with prevalence before and after LT ranging between 14% and 78% and between 30% and 100%, respectively [1]. The definition of sarcopenia has evolved from loss of muscle mass into remnant muscle strength. Even in the presence of multiple definitions of sarcopenia in the literature, low muscle mass, irrespective of how it is measured, is a powerful indicator of clinically relevant adverse outcomes, including poor quality of life [2], hepatic decompensation [3], mortality in patients with cirrhosis on the LT wait list [4-6], longer hospital and intensive care unit stay [5, 7], higher incidence of infection following LT [5, 8], higher overall health care cost [9] and post-LT mortality [10]. Loss of muscle mass on cross-sectional imaging has been associated with increased mortality, morbidity, physical disability and poor quality of life both before and after LT [8, 11, 12]. In this review we aim to discuss latest developments including identification, assessment, clinical implications and management of sarcopenia in liver transplant recipients in the light of prevailing pandemic.

2. Modalities to Evaluate Muscle Mass in the Liver Transplant Candidate

Sarcopenia has been assessed through a variety of modalities including muscle mass quantification, including anthropometry, bioelectrical impedance analysis, dual-energy X-ray absorptiometry (DEXA), ultrasound, magnetic resonance imaging (MRI), and computed tomography (CT). DEXA scan is considered safe, inexpensive and is readily available and reproducible with a low radiation exposure however limited by its inability to differentiate water from muscle; therefore, affected by lower limb edema which is commonly present in decompensated liver disease [13]. It was also found to have weak concordance with CT [14]. Similar limitations are found with bioelectrical impedance analysis [15]. Anthropometry specifically mid-arm muscle circumference (MAMC) has been cost effectively used in out-patients to assess repeated measures of muscle mass. MAMC has reliable intra-/inter-observer agreement when performed by trained individuals [16] and has been shown to predict mortality in patients with cirrhosis and those after LT [17]. Studies have

shown that MAMC poorly correlates with CT and MRI. Ultrasound is also a safe and inexpensive study with high intraobserver and interobserver reliability but is limited by indeterminate reproducibility [18]. CT and MRI easily differentiate main body compartments, i.e., muscle, visceral, and subcutaneous adipose tissue in a fast and accurate manner. These tests are not affected by the presence of ascites or edema however cost of procedure and radiation in case of CT are the main limitations for these modalities [18, 19]. We do advocate for using CT as the preferred means of assessment for sarcopenia due to multitude of reasons as discussed prior along with it being the most studied modality based on previously published reports on sarcopenia in liver transplant patients [6, 5, 8, 18, 20, 21] and also a frequent imaging modality for common clinical indications (i.e malignancy screening, vasculature assessment). When assessing sarcopenia by SMI on an abdominal CT scan, there does not appear to be a large difference between measurements at L3 versus L4 vertebrae [22]. There is scarce data evaluating these modalities in different ethnicities and rarely accounts for gender disparities in sarcopenia [23]. Sarcopenic obesity (SO) is another understated challenge reported in 20-40% of patients awaiting liver transplant [24]. A decrease of 30% in 1 year post LT survival is noted in living donor LT patients with SO patients when compared with non-sarcopenic obesity [25]. Interestingly recent literature research has shown that SO patients had a lower incidence of neurological, surgical, respiratory, and cardiovascular complications compared with those with sarcopenia alone [1].

3. Assessment of Muscle Strength and Function

Multiple measures of muscle strength and function have been described including six minute walk testing (SMWT) [26, 27], hand grip dynamometry, Karnofsky Performance Status (KPS) [18, 28], Short physical performance battery (SPPB) [29], gait speed [30] and cardiopulmonary exercise test (CPET) [31, 32]. These tests can be quickly performed with little to no expense however due to the complex nature of the disease it is difficult to ascertain the cause of suboptimal performance when confounding comorbidities exist for example cardiopulmonary limitations. Even though we do not have an expert consensus on which modality to use in the assessment of liver transplantation, studies highlight independent association of functional measures including 6MWT as a significant predictor of waitlist mortality when compared to sarcopenia described on the bases of SMI [27].

4. Liver Frailty Index

Lai et al coined Liver Frailty Index (LFI) in 2017 [33] from a cohort of 536 patients with ESLD this was based on Fried Frailty Index [34] and Short physical performance battery (SPPB) [35]. It consists of dominant hand grip strength (HGS), time to do 5 chair stands and time holding 3 balance positions (feet side by side, semi-tandem and tandem). LFI is liver disease-specific that can then be categorised into frail, pre-frail and robust and assessed longitudinally. Independent of cirrhosis related decompensation [36] it has shown to be a good predictor of LT waiting list mortality, hospital admissions [37], post LT mortality [38] and acute cellular rejection [39]. To standardize LFI and make it a unit of clinical comparisons, validation in acute worsening of liver disease, inpatient population, data from other countries and its response to treatment interventions is required. Expert opinion from American Society of Transplant in 2019 emphasised that frailty should not be used as the sole criterion for delisting a patient for liver transplantation, but rather should be considered one of many criteria when evaluating transplant candidacy and suitability [40].

5. Impact of Sarcopenia in LT

Sarcopenia, irrespective of how it's defined and measured, has significant clinical implications for patients awaiting LT including increased mortality [5, 41], poor quality of life [2], hepatic decompensation [3] and their post transplant period including longer hospitalization, intensive care requirements, increased risk of infection along with higher 1 year post LT mortality [6, 10, 38, 39, 42]. It is however important to note that the North American Working Group and American Society of Transplant recommends that sarcopenia should not be the sole criterion for declining or delisting candidates for LT [40, 43]. Sarcopenia when added to the MELD score was associated with improved prediction of mortality in patients with cirrhosis especially in the patient cohort with low MELD scores [5]. It has been proposed to prioritize these patients before they develop extreme muscle wasting. This has not yet qualified as a prevalent practice. Keeping in mind the robust effect was seen in MELD score less than 15 and lack of a threshold value for sarcopenia poses a significant limitation in its use as a risk stratification tool or practice guidance. A more holistic approach to transplant candidacy is advised including an objective metric of sarcopenia along with a patient's medical, physical, functional, and psychosocial factors.

Knowledge regarding implications of sarcopenia may assist clinicians in addressing the elephant in the room earlier in the transplant evaluation. It may help provide appropriate counselling to patients regarding his pre and post LT risks. This information may help motivate patients to seek appropriate interventions with regards to nutrition and exercise and also opt for living donor LT or higher-risk donor livers.

6. Pandemic and Its Effects on Sarcopenia

COVID-19 has had a profound impact on sarcopenia which stems not just from disease pathology but also the surrounding preventive actions opted worldwide to curtail the infection. COVID-19 pandemic has led to a devastating global impact requiring implementation of unprecedented measures in order to halt the spread of infection. Travel bans, quarantine, isolation and social distancing [44, 45] have led to reduction in physical activity and increase in sedentary lifestyle [46] which are associated with loss of muscle mass [47]. Decreased social interaction and physical activity may lead to increased levels of stress and anxiety which are reported to increase markers of muscle atrophy [48, 49]. Psychological stressors and limited access to food pave the way for poor dietary choices, commonly opting for fast foods containing low protein and high fat and sugar content [50, 51]. Our concerns, not yet validated, are worsening of fatty liver disease alongside metabolic syndromes and increase in sarcopenic obesity in cirrhotics.

The ability of COVID-19 to cause chronic illness, sarcopenia and physical deconditioning may be underestimated. Myalgia, lethargy and anorexia in the setting of anosmia and dysgeusia can have the potential to exacerbate muscle weakness. It has now become clear that survivors of COVID-19 are at increased risk of acute sarcopenia with worsening muscle insufficiency, defined by decline in muscle function and/or quantity within six months, usually following a stressor event [52-55]. Mechanisms of acute sarcopenia with COVID-19 include direct injury, as SARS-CoV-2 enters host cells via the angiotensin-converting enzyme 2 (ACE2) receptors found on skeletal muscle surfaces [54, 56, 57] and indirect pathways such as increased serum concentrations of inflammatory cytokines including interleukin 6 (IL-6) and Tumour Necrosis Factor Alpha (TNF-α) along with use of

steroids and muscle relaxants during management of disease which may all have a detrimental effect on muscle protein synthesis [52, 58]. TNF-α also decreases messenger Ribonucleic Acid (mRNA) translational efficiency causing anabolic resistance, which requires higher protein intake to stimulate muscle protein synthesis [52].

Obesity is described as an adverse prognostic factor during the pandemic. It is associated with systemic inflammation, which may exacerbate the effects of acute illness upon muscle metabolism. Sarcopenic obesity may also be associated with ectopic deposition of fat and intramyocellular lipid deposition, thus affecting the quality of muscle [59].

It is safe to assume that the overall impact of all the factors mentioned above is magnified in patients with end stage liver disease. Assessment of frailty has taken a new meaning during the pandemic. It would be worthwhile to look into the impact of SARS CoV-2 infection along with its sequelae on the present frailty measures used for assessment of sarcopenia.

7. Management of Sarcopenia

Management of sarcopenia requires a multifaceted approach. Clinician awareness in recognizing the impact of sarcopenia and the potential to modify that impact is the first step towards the path of management. Early counselling performed by clinicians during the pandemic may help mitigate some effects of sarcopenia by motivating patients to seek prehabilitation and follow standard operating procedures (SOPs). Objective assessment of sarcopenia may help monitor for further deterioration or improvement even though there is scarce data that improving muscle mass and function increases survival pre- and post-LT [60, 61].

Lifestyle modifications including abstinence from alcohol and smoking are advised across the board to all patients with end stage liver disease irrespective of etiology. Optimizing glycemic control may also help in reversing sarcopenia [62], keeping in mind hyperinsulinaemic state causes catabolism.

The International Society for Hepatic Encephalopathy and Nitrogen Metabolism Consensus provides BMI-stratified target caloric recommendations based on an ideal body weight (also corrected for fluid retention) [63]. For nonobese individuals (BMI < 30 kg/m2) optimal daily energy intake of at least 35 kcal/kg of actual body weight corrected for fluid retention is recommended. In obese patients, a moderately hypocaloric diet (with a reduction of 500 to 800 kcal/day) has been suggested [64]. Protein target of 1.5 g/kg/day is recommended with further increase up to 2.0 g/kg/day in cases of severe hepatic decompensation [64] and SARs COV-19 infection [65]. Protein restriction is no longer necessary in patients with hepatic encephalopathy [66]. Patients with end stage liver disease are susceptible to accelerated muscle catabolism during prolonged periods of starvation and in an attempt to shorten the overnight fasting period they are advised to eat a snack shortly before bedtime and avoid skipping breakfast [64, 67].

Multiple studies to date have demonstrated that exercise improves muscle mass and function, function, 6 minute walk test (6 MWT) and quality of life in patients with compensated and decompensated cirrhosis [68-70] in the absence of an evidence based collaborative recommendation. Even though large studies aiming to look at the survival benefit are needed, it is generally recommended that a combination 3 days/week aerobic and 2 days/week of resistance exercises be performed at moderate-high intensity whilst awaiting LT [71]. We bring special attention towards patients recovering from COVID-19 who may require enhanced physiotherapy.

Taking into consideration that current policies mandate isolation for these patients, mobilization can be considered within COVID-19 pods. Provision of strength training equipment in COVID-19 units will help to build a supportive environment focused around rehabilitation [52].

Pharmacotherapeutic interventions are of great interest and serve as promising potential for growth. Summary of a few interventions is provided in Table 1. Myostatin is a secreted protein that functions as a potent negative regulator of skeletal muscle growth. Interventions focused on its disruption via neutralising antibodies in skeletal muscle may slow down muscle breakdown [72, 73]. There is ongoing research to target myostatin signalling in skeletal muscle in hopes to improve muscle mass and function. Modified myostatin propeptide to block myostatin [74] and a soluble ActRIIB receptor Fc fusion protein [75] have been looked into for this purpose. Promising results in older adults have been reported for muscle mass and function through direct inhibition of myostatin. However, functional measures of strength (handgrip, isometric leg strength) and endurance (6-minute walking distance) were not affected which limits their use in patients with end stage liver disease.

Selective Androgen Receptor Modulators (SARMs) demonstrate anabolic activity in muscle and bone, but unlike testosterone and other androgens it minimally affects growth of the prostate and other secondary sexual organs [76]. MK-0773 treatment has shown increase in lean body mass but did not improve muscular strength or physical performance [77].

Hyperammonemia contributes to abnormal skeletal muscle proteostasis. It is uncertain whether ammonia-lowering treatment improves proteostasis or reverses sarcopenia even though improvement in grip strength and skeletal muscle growth is reported in a preclinical study [78]. Use of L-ornithine L-aspartate (LOLA) has been supported by several randomized clinical trials and meta-analyses, improvement in skeletal muscle growth and function has also been reported however adequately powered, well-controlled trials are required to demonstrate that LOLA monotherapy provides an effective agent for the prevention and treatment of sarcopenia in these chronic liver diseases [79, 80].

Table 1 Abbreviations: bid, twice daily; IM, intramuscularly; RCT, randomized clinical trial; tid, three times a day [43].

Author	Intervention	Dosing	Comment
Corey et al., 2014 [81]	Cholecalciferol	2000 IU/day Deficiency	Deficiency common in cirrhosis
Davuluri et al., 2016 [82] Tsien et al. 2015 [83]	Leucine	7.5 g/day typically in divided doses with additional amino acids	Included in many nutritional supplements
Holecek et al., 2017 [84]	2-hydroxymethyl butyrate	1 g tid	Metabolite of leucine Nutritional supplement with anticatabolic action

Sinclair et al., 2016 [85]	Testosterone in androgen-deficient men	Testosterone undecanoate 1,000 mg IM, schedule per RCT; or transdermal gel 50 mg/day [86]	Gel preferred for sustained physiologic levels, concerns for thrombosis and prostate cancer
Ohara et al., 2018 [87]	L-carnitine	1,000 mg/day or bid	Essential nutrient for fatty acid metabolism One fourth is synthesized in the kidney and liver

Ace inhibitors seem to have beneficial effects on preventing sarcopenia [88]. There is evidence that they do not cause increased COVID-19 risk or mortality [89]. Future studies are required focusing on its use in patients with COVID-19 infection and end stage liver disease patients to identify risks and benefits.

There is dire need of developing potential treatment options that may prevent or reverse sarcopenia as exercise and nutrition may not always be feasible especially in bed ridden patients during the pandemic.

8. Conclusion

Sarcopenia, endemic in patients with end stage liver disease, has been explored vigorously in the last few years. There are still clinical research questions that merit further consideration which include formulation of assessment tools that can help clinicians recognize sarcopenia and follow the progression. Once consensus regarding reliable and reproducible objective tools with clear threshold values is reached, this can be further extrapolated to the effects of COVID-19 infection and collateral effects of the pandemic in patients with advanced liver disease. Realizing the ability of SARS-CoV-2 to cause physical decline is multifactorial and complex, it is related to periods of convalescence, anxiety, poor dietary choices, reduced appetite, chronic cardiorespiratory symptoms, social isolation, and reduced access to physical activity. The impact of physical deconditioning related to liver disease and COVID-19 pandemic +/- infection should be carefully assessed in patients planned to undergo liver transplantation surgeries. Peri operative risk should be further studied in this highly susceptible group and management approach should be tailored accordingly to identify not only the best timing of surgery but also to initiate timely and focussed prehabilitation and counselling.

Author Contributions

Content was written and researched by Drs Hamid Ullah, Sara Iqbal and Blanca Lizaola-Mayo. Abstract, Introduction, Modalities for assessment, Impact of sarcopenia on LT, management, effects of Pandemic and conclusion was completed by Dr Hamid Ullah. LFI, muscle strength and function, management of sarcopenia, effects of pandemic and conclusion was completed by Dr Sara Iqbal. Muscle strength and function, pandemic changes, LFI and reviewer comment changes was

completed by Dr Blanca Lizaola-Mayo. The whole manuscript was supervised and corrected by Dr Elizabeth Carey.

Competing Interests

The authors whose names are listed above have no affiliations with or involvement in any organization or entity with financial or non financial interest in the subject matter or materials discussed in the manuscript.

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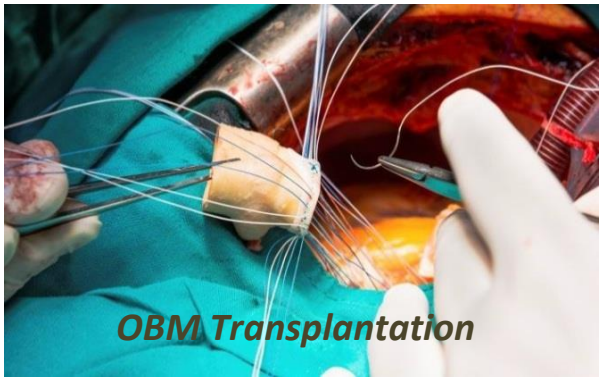

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