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

Academic Editor: Haval Shirwan

Special Issue: Current Opinion in Organ Transplantation

OBM Transplantation
2021, volume 5, issue 3
doi:10.21926/obm.transplant.2103149

Received: March 31, 2021
Accepted: July 13, 2021
Published: July 20, 2021

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  | Leucine                  | 7.5 g/day typically in        | Included in many nutritional supplements     |
|                         |                          | divided doses with additional|                                              |
|                         |                          | amino acids                  |                                              |
| Tsien et al. 2015 [83] | 2-hydroxymethyl butyrate| 1 g tid                      | Metabolite of leucine                       |
|                         |                          |                               | Nutritional supplement                      |
| Holeccek et al., 2017  |                          |                               | with anticatabolic action                    |
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 |

| 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.

**References**

1. Ooi PH, Hager A, Mazurak VC, Dajani K, Bhargava R, Gilmour SM, et al. Sarcopenia in chronic liver disease: Impact on outcomes. Liver Transplant. 2019; 25: 1422-1438.
2. Norman K, Kirchner H, Lochs H, Pirlich M. Malnutrition affects quality of life in gastroenterology patients. World J Gastroenterol. 2006; 12: 3380-3385.
3. Alvares-da-Silva MR, da Silveira TR. Comparison between handgrip strength, subjective global assessment, and prognostic nutritional index in assessing malnutrition and predicting clinical outcome in cirrhotic outpatients. Nutrition. 2005; 21: 113-117.
4. Durand F, Buyse S, Francoz C, Laouénan C, Bruno O, Belghiti J, et al. Prognostic value of muscle atrophy in cirrhosis using psoas muscle thickness on computed tomography. J Hepatol. 2014; 60: 1151-1157.
5. Montano-Loza AJ, Duarte-Rojo A, Meza-Junco J, Baracos VE, Sawyer MB, Pang JX, et al. Inclusion of sarcopenia within MELD (MELD-sarcopenia) and the prediction of mortality in patients with cirrhosis. Clin Transl Gastroenterol. 2015; 6: e102.
6. DiMartini A, Cruz RJ, Dew MA, Myaskovsky L, Goodpaster B, Fox K, et al. Muscle mass predicts outcomes following liver transplantation. Liver Transplant. 2013; 19: 1172-1180.
7. Masuda T, Shirabe K, Ikekami T, Harimoto N, Yoshizumi T, Soejima Y, et al. Sarcopenia is a prognostic factor in living donor liver transplantation. Liver Transplant. 2014; 20: 401-407.
8. Krell RW, Kaul DR, Martin AR, Englesbe MJ, Sonnenday CJ, Cai S, et al. Association between sarcopenia and the risk of serious infection among adults undergoing liver transplantation. Liver Transplant. 2013; 19: 1396-1402.
9. van Vugt JL, Buettner S, Alferink LJ, Bossche N, de Bruin RW, Darwish Murad S, et al. Low skeletal muscle mass is associated with increased hospital costs in patients with cirrhosis listed for liver transplantation-a retrospective study. Transpl Int. 2018; 31: 165-174.
10. Kaido T, Ogawa K, Fujimoto Y, Ogura Y, Hata K, Ito T, et al. Impact of sarcopenia on survival in patients undergoing living donor liver transplantation. Am J Transplant. 2013; 13: 1549-1556.
11. Periyalwar P, Dasarathy S. Malnutrition in cirrhosis: Contribution and consequences of sarcopenia on metabolic and clinical responses. Clin Liver Dis. 2012; 16: 95-131.
12. Mazzarelli C, Viganò R, Perricone G, Vangeli M, Gasperi AD, Mazza E, et al. Sarcopenia in liver transplant candidates. Dig Liver Dis. 2020; 52: e66.
13. Belarmino G, Gonzalez MC, Sala P, Torrinhas RS, Andraus W, D’Albuquerque LA, et al. Diagnosing sarcopenia in male patients with cirrhosis by dual-energy X-ray absorptiometry estimates of appendicular skeletal muscle mass. J Parenter Enter Nutr. 2018; 42: 24-36.
14. Giusto M, Lattanzi B, Albanese C, Galtieri A, Farcomeni A, Giannelli V, et al. Sarcopenia in liver cirrhosis: The role of computed tomography scan for the assessment of muscle mass compared
with dual-energy X-ray absorptiometry and anthropometry. Eur J Gastroenterol Hepatol. 2015; 27: 328-334.
15. Hara N, Iwasa M, Sugimoto R, Mifuji-Moroka R, Yoshikawa K, Terasaka E, et al. Sarcopenia and sarcopenic obesity are prognostic factors for overall survival in patients with cirrhosis. Intern Med. 2016; 55: 863-870.
16. Morgan MY, Madden AM, Soulsby CT, Morris RW. Derivation and validation of a new global method for assessing nutritional status in patients with cirrhosis. Hepatology. 2006; 44: 823-835.
17. Alberino F, Gatta A, Amodio P, Merkel C, Di Pascoli L, Boffo G, et al. Nutrition and survival in patients with liver cirrhosis. Nutrition. 2001; 17: 445-450.
18. Tandon P, Low G, Mourtzakis M, Zenith L, Myers RP, Abraldes JG, et al. A model to identify sarcopenia in patients with cirrhosis. Clin Gastroenterol Hepatol. 2016; 14: 1473-1480.
19. Praktiknjo M, Book M, Luetkens J, Pohlmann A, Meyer C, Thomas D, et al. Fat-free muscle mass in magnetic resonance imaging predicts acute-on-chronic liver failure and survival in decompensated cirrhosis. Hepatology. 2018; 67: 1014-1026.
20. Meza-Junco J, Montano-Loza AJ, Baracos VE, Prado CM, Bain VG, Beaumont C, et al. Sarcopenia as a prognostic index of nutritional status in concurrent cirrhosis and hepatocellular carcinoma. J Clin Gastroenterol. 2013; 47: 861-870.
21. Carey EJ, Lai JC, Wang CW, Dasarathy S, Lobach I, Montano-Loza AJ, et al. A multicenter study to define sarcopenia in patients with end-stage liver disease. Liver Transplant. 2017; 23: 625-633.
22. Shen W, Punyanitya M, Wang ZM, Gallagher D, St.-Onge MP, Albu J, et al. Total body skeletal muscle and adipose tissue volumes: Estimation from a single abdominal cross-sectional image. J Appl Physiol. 2004; 97: 2333-2338.
23. Ebadi M, Tandon P, Mocetzuma-Velazquez C, Ghosh S, Baracos VE, Mazurak VC, et al. Low subcutaneous adiposity associates with higher mortality in female patients with cirrhosis. J Hepatol. 2018; 69: 608-616.
24. Montano-Loza AJ, Angulo P, Meza-Junco J, Prado CM, Sawyer MB, Beaumont C, et al. Sarcopenic obesity and myosteatosis are associated with higher mortality in patients with cirrhosis. J Cachexia Sarcopenia Muscle. 2016; 7: 126-135.
25. Kamo N, Kaido T, Hamaguchi Y, Okumura S, Kobayashi A, Shirai H, et al. Impact of sarcopenic obesity on outcomes in patients undergoing living donor liver transplantation. Clin Nutr. 2019; 38: 2202-2209.
26. Faustini-Pereira JL, Homcher-Galant L, Garcia E, de Mello BA, Marroni CA. Exercise capacity of cirrhotic patients with hepatopulmonary syndrome. Ann Hepatol. 2015; 14: 361-368.
27. Yadav A, Chang YH, Carpenter S, Silva AC, Rakela J, Aqel BA, et al. Relationship between sarcopenia, six-minute walk distance and health-related quality of life in liver transplant candidates. Clin Transplant. 2015; 29: 134-141.
28. Malinis MF, Chen S, Allore HG, Quagliarello VJ. Outcomes among older adult liver transplantation recipients in the model of end stage liver disease (MELD) era. Ann Transplant. 2014; 19: 478-487.
29. Lai JC, Feng S, Terrault NA, Lizaola B, Hayssen H, Covinsky K. Frailty predicts waitlist mortality in liver transplant candidates. Am J Transplant. 2014; 14: 1870-1879.
30. Dunn MA, Josbeno DA, Tevar AD, Rachakonda V, Ganesh SR, Schmotzer AR, et al. Frailty as tested by gait speed is an independent risk factor for cirrhosis complications that require hospitalization. Am J Gastroenterol. 2016; 111: 1768-1775.
31. Ney M, Haykowsky MJ, Vandermeer B, Shah A, Ow M, Tandon P. Systematic review: Pre- and post-operative prognostic value of cardiopulmonary exercise testing in liver transplant candidates. Aliment Pharmacol Ther. 2016; 44: 796-806.
32. Bernal W, Martin-Mateos R, Lipcsey M, Tallis C, Woodsford K, McPhail MJ, et al. Aerobic capacity during cardiopulmonary exercise testing and survival with and without liver transplantation for patients with chronic liver disease. Liver Transplant. 2014; 20: 54-62.
33. Lai JC, Covinsky KE, Dodge JL, Boscardin WJ, Segev DL, Roberts JP, et al. Development of a novel frailty index to predict mortality in patients with end-stage liver disease. Hepatology. 2017; 66: 564-574.
34. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: Evidence for a phenotype. J Gerontol A. 2001; 56: M146-M157.
35. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: Association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol. 1994; 49: M85-M94.
36. Lai JC, Rahimi RS, Verna EC, Kappus MR, Dunn MA, McAdams-DeMarco M, et al. Frailty associated with waitlist mortality independent of ascites and hepatic encephalopathy in a multicenter study. Gastroenterology. 2019; 156: 1675-1682.
37. Sinclair M, Poltavskiy E, Dodge JL, Lai JC. Frailty is independently associated with increased hospitalisation days in patients on the liver transplant waitlist. World J Gastroenterol. 2017; 23: 899-905.
38. Lai JC, Segev DL, McCulloch CE, Covinsky KE, Dodge JL, Feng S. Physical frailty after liver transplantation. Am J Transplant. 2018; 18: 1986-1994.
39. Fozouni L, Mohamad Y, Lebsack A, Freise C, Stock P, Lai JC. Frailty is associated with increased rates of acute cellular rejection within 3 months after liver transplantation. Liver Transplant. 2020; 26 :390-396.
40. Lai JC, Sonnenday CJ, Tapper EB, Duarte-Rojo A, Dunn MA, Bernal W, et al. Frailty in liver transplantation: An expert opinion statement from the American society of transplantation liver and intestinal community of practice. Am J Transplant. 2019; 19: 1896-1906.
41. van Vught JL, Levolger S, de Bruin RW, van Rosmalen J, Metselaar HJ, IJzermans JN. Systematic review and meta-analysis of the impact of computed tomography-assessed skeletal muscle mass on outcome in patients awaiting or undergoing liver transplantation. Am J Transplant. 2016; 16: 2277-2292.
42. Kuo SZ, Ahmad M, Dunn MA, Montano-Loza AJ, Carey EJ, Lin S, et al. Sarcopenia predicts post-transplant mortality in acutely ill men undergoing urgent evaluation and liver transplantation. Transplantation. 2019; 103: 2312-2317.
43. Carey EJ, Lai JC, Sonnenday C, Tapper EB, Tandon P, Duarte-Rojo A, et al. A north American expert opinion statement on sarcopenia in liver transplantation. Hepatology. 2019; 70: 1816-1829.
44. Parmet WE, Sinha MS. Covid-19 - the law and limits of quarantine. N Engl J Med. 2020; 382: e28.
45. Sjödin H, Wilder-Smith A, Osman S, Farooq Z, Rocklöv J. Only strict quarantine measures can curb the coronavirus disease (COVID-19) outbreak in Italy, 2020. Euro Surveill. 2020; 25: 2000280.

46. Ammar A, Brach M, Trabelsi K, Chtourou H, Boukhris O, Masmoudi L, et al. Effects of COVID-19 home confinement on eating behaviour and physical activity: Results of the ECLB-COVID19 international online survey. Nutrients. 2020; 12: 1583.

47. Breen L, Stokes KA, Churchward-Venne TA, Moore DR, Baker SK, Smith K, et al. Two weeks of reduced activity decreases leg lean mass and induces “anabolic resistance” of myofibrillar protein synthesis in healthy elderly. J Clin Endocrinol Metab. 2013; 98: 2604-2612.

48. Allen DL, McCall GE, Loh AS, Madden MC, Mehan RS. Acute daily psychological stress causes increased atrophic gene expression and myostatin-dependent muscle atrophy. Am J Physiol Regul Integr Comp Physiol. 2010; 299: R889-R898.

49. Kirwan R, McCullough D, Butler T, de Heredia FP, Davies IG, Stewart C. Sarcopenia during COVID-19 lockdown restrictions: Long-term health effects of short-term muscle loss. GeroScience. 2020; 42: 1547-1578.

50. Rauber F, da Costa Louzada ML, Steele EM, Millett C, Monteiro CA, Levy RB. Ultra-processed food consumption and chronic non-communicable diseases-related dietary nutrient profile in the UK (2008-2014). Nutrients. 2018; 10: 587.

51. Gibson EL. Emotional influences on food choice: Sensory, physiological and psychological pathways. Physiol Behav. 2006; 89: 53-61.

52. Welch C, Greig C, Masud T, Wilson D, Jackson TA. COVID-19 and acute sarcopenia. Aging Dis. 2020; 11: 1345-1351.

53. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: Revised European consensus on definition and diagnosis. Age Ageing. 2019; 48: 16-31.

54. Disser NP, De Micheli AJ, Schonk MM, Konnaris MA, Placentini AN, Edon DL, et al. Musculoskeletal consequences of COVID-19. J Bone Joint Surg. 2020; 102: 1197-1204.

55. Bagnato S, Boccagni C, Marino G, Prestandrea C, D’Agostino T, Rubino F. Critical illness myopathy after COVID-19. Int J Infect Dis. 2020; 99: 276-278.

56. Ferrandi PJ, Alway SE, Mohamed JS. The interaction between SARS-CoV-2 and ACE2 may have consequences for skeletal muscle viral susceptibility and myopathies. J Appl Physiol. 2020; 129: 864-867.

57. Casey P, Ang Y, Sultan J. COVID-19-induced sarcopenia and physical deconditioning may require reassessment of surgical risk for patients with cancer. World J Surg Oncol. 2021; 19: 8.

58. Lang CH, Frost RA, Nairn AC, MacLean DA, Vary TC. TNF-alpha impairs heart and skeletal muscle protein synthesis by altering translation initiation. Am J Physiol Endocrinol Metab. 2002; 282: E336-E347.

59. Batsis JA, Villareal DT. Sarcopenic obesity in older adults: Aetiology, epidemiology and treatment strategies. Nat Rev Endocrinol. 2018; 14: 513-537.

60. Tsien C, Shah SN, McCullough AJ, Dasarathy S. Reversal of sarcopenia predicts survival after a transjugular intrahepatic portosystemic stent. Eur J Gastroenterol Hepatol. 2013; 25: 85-93.

61. Tsien C, Garber A, Narayanan A, Shah SN, Barnes D, Eghtesad B, et al. Post-liver transplantation sarcopenia in cirrhosis: A prospective evaluation. J Gastroenterol Hepatol. 2014; 29: 1250-1257.
62. Bhanji RA, Takahashi N, Moynagh MR, Narayanan P, Angirekula M, Mara KC, et al. The evolution and impact of sarcopenia pre- and post-liver transplantation. Aliment Pharmacol Ther. 2019; 49: 807-813.

63. Amodio P, Bemeur C, Butterworth R, Cordoba J, Kato A, Montagnese S, et al. The nutritional management of hepatic encephalopathy in patients with cirrhosis: International society for hepatic encephalopathy and nitrogen metabolism consensus. Hepatology. 2013; 58: 325-336.

64. European Association for the Study of the Liver. EASL clinical practice guidelines on nutrition in chronic liver disease. J Hepatol. 2019; 70: 172-193.

65. Hoffer LJ, Bistrian BR. Appropriate protein provision in critical illness: A systematic and narrative review. Am J Clin Nutr. 2012; 96: 591-600.

66. Córdoba J, López-Hellín J, Planas M, Sabin P, Sanpedro F, Castro F, et al. Normal protein diet for episodic hepatic encephalopathy: Results of a randomized study. J Hepatol. 2004; 41: 38-43.

67. Plank LD, Gane EJ, Peng S, Muthu C, Mathur S, Gillanders L, et al. Nocturnal nutritional supplementation improves total body protein status of patients with liver cirrhosis: A randomized 12-month trial. Hepatology. 2008; 48: 557-566.

68. Morkane CM, Kearney O, Bruce DA, Melikian CN, Martin DS. An outpatient hospital-based exercise training program for patients with cirrhotic liver disease awaiting transplantation: A feasibility trial. Transplantation. 2020; 104: 97-103.

69. Román E, García-Galcerán C, Torrades T, Herrera S, Marín A, Doñate M, et al. Effects of an exercise programme on functional capacity, body composition and risk of falls in patients with cirrhosis: A randomized clinical trial. PLoS One. 2016; 11: e0151652.

70. Zenith L, Meena N, Ramadi A, Yavari M, Harvey A, Carbonneau M, et al. Eight weeks of exercise training increases aerobic capacity and muscle mass and reduces fatigue in patients with cirrhosis. Clin Gastroenterol Hepatol. 2014; 12: 1920-1926.

71. Duarte-Rojo A, Ruiz-Margáin A, Montaño-Loza AJ, Macías-Rodríguez RU, Ferrando A, Kim WR. Exercise and physical activity for patients with end-stage liver disease: Improving functional status and sarcopenia while on the transplant waiting list. Liver Transplant. 2018; 24: 122-139.

72. Whittemore LA, Song K, Li X, Aghajanian J, Davies M, Girgenrath S, et al. Inhibition of myostatin in adult mice increases skeletal muscle mass and strength. Biochem Biophys Res Commun. 2003; 300: 965-971.

73. Hardee JP, Lynch GS. Current pharmacotherapies for sarcopenia. Expert Opin Pharmacother. 2019; 20: 1645-1657.

74. Bogdanovich S, Perkins KJ, Krag TO, Whittemore LA, Khurana TS. Myostatin propeptide-mediated amelioration of dystrophic pathophysiology. FASEB J. 2005; 19: 543-549.

75. Attie KM, Borgstein NG, Yang Y, Condon CH, Wilson DM, Pearsall AE, et al. A single ascending-dose study of muscle regulator ACE-031 in healthy volunteers. Muscle Nerve. 2013; 47: 416-423.

76. Gao WQ, Reiser PJ, Coss CC, Phelps MA, Kearbey JD, Miller DD, et al. Selective androgen receptor modulator treatment improves muscle strength and body composition and prevents bone loss in orchidectomized rats. Endocrinology. 2005; 146: 4887-4897.

77. Papanicolaou DA, Ather SN, Zhu H, Zhou Y, Lutkiewicz J, Scott BB, et al. A phase IIA randomized, placebo-controlled clinical trial to study the efficacy and safety of the selective androgen receptor modulator (SARM), MK-0773 in female participants with sarcopenia. J Nutr Health Aging. 2013; 17: 533-543.
78. Kumar A, Davuluri G, Silva RN, Engelen MP, Ten Have GA, Prayson R, et al. Ammonia lowering reverses sarcopenia of cirrhosis by restoring skeletal muscle proteostasis. Hepatology. 2017; 65: 2045-2058.

79. Mittal VV, Sharma BC, Sharma P, Sarin SK. A randomized controlled trial comparing lactulose, probiotics, and L-ornithine L-aspartate in treatment of minimal hepatic encephalopathy. Eur J Gastroenterol Hepatol. 2011; 23: 725-732.

80. Butterworth RF. L-ornithine L-aspartate for the treatment of sarcopenia in chronic liver disease: The taming of a vicious cycle. Can J Gastroenterol Hepatol. 2019; 2019: 8182195.

81. Corey RL, Whitaker MD, Crowell MD, Keddis MT, Aqel B, Balan V, et al. Vitamin D deficiency, parathyroid hormone levels, and bone disease among patients with end-stage liver disease and normal serum creatinine awaiting liver transplantation. Clin Transplant. 2014; 28: 579-584.

82. Davuluri G, Krokowski D, Guan BJ, Kumar A, Thapaliya S, Singh D, et al. Metabolic adaptation of skeletal muscle to hyperammonemia drives the beneficial effects of L-leucine in cirrhosis. J Hepatol. 2016; 65: 929-937.

83. Tsien C, Davuluri G, Singh D, Allawy A, Ten Have GA, Thapaliya S, et al. Metabolic and molecular responses to leucine-enriched branched chain amino acid supplementation in the skeletal muscle of alcoholic cirrhosis. Hepatology. 2015; 61: 2018-2029.

84. Holeček M. Beta-hydroxy-beta-methylbutyrate supplementation and skeletal muscle in healthy and muscle-wasting conditions. J Cachexia Sarcopenia Muscle. 2017; 8: 529-541.

85. Sinclair M, Gow PJ, Grossmann M, Angus PW. Review article: Sarcopenia in cirrhosis--aetiology, implications and potential therapeutic interventions. Aliment Pharmacol Ther. 2016; 43: 765-777.

86. van Vugt JL, Alferink LJ, Buettner S, Gaspersz MP, Bot D, Darwish Murad S, et al. A model including sarcopenia surpasses the MELD score in predicting waiting list mortality in cirrhotic liver transplant candidates: A competing risk analysis in a national cohort. J Hepatol. 2018; 68: 707-714.

87. Ohara M, Ogawa K, Suda G, Kimura M, Maehara O, Shimazaki T, et al. L-carnitine suppresses loss of skeletal muscle mass in patients with liver cirrhosis. Hepatol Commun. 2018; 2: 906-918.

88. Delafontaine P, Yoshida T. The renin-angiotensin system and the biology of skeletal muscle: Mechanisms of muscle wasting in chronic disease states. Trans Am Clin Climatol Assoc. 2016; 127: 245-258.

89. Zhang P, Zhu LH, Cai JJ, Lei F, Qin JJ, Xie J, et al. Association of inpatient use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. Circ Res. 2020; 126: 1671-1681.
Enjoy *OBM Transplantation* by:

1. [Submitting a manuscript](http://www.lidsen.com/journals/transplantation)
2. [Joining in volunteer reviewer bank](http://www.lidsen.com/journals/transplantation)
3. [Joining Editorial Board](http://www.lidsen.com/journals/transplantation)
4. [Guest editing a special issue](http://www.lidsen.com/journals/transplantation)

For more details, please visit:
[http://www.lidsen.com/journals/transplantation](http://www.lidsen.com/journals/transplantation)