



Sarcopenia and frailty in decompensated cirrhosis

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Summary

In patients with decompensated cirrhosis, sarcopenia and frailty are prevalent. Although several definitions exist for these terms, in the field of hepatology, sarcopenia has commonly been defined as loss of muscle mass, and frailty has been broadly defined as the phenotypic manifestation of the loss of muscle function. Prompt recognition and accurate assessment of these conditions are critical as they are both strongly associated with morbidity, mortality, poor quality of life and worse post-liver transplant outcomes in patients with cirrhosis. In this review, we describe the complex pathophysiology that underlies the clinical phenotypes of sarcopenia and frailty, their association with decompensation, and provide an overview of tools to assess these conditions in patients with cirrhosis. When available, we highlight data focusing on patients with acutely decompensated cirrhosis, such as inpatients, as this is an area of unmet clinical need. Finally, we discuss management strategies to reverse and/or prevent the development of sarcopenia and frailty, which include adequate nutritional intake of calories and protein, as well as regular exercise of at least moderate intensity, with a mix of aerobic and resistance training. Key knowledge gaps in our understanding of sarcopenia and frailty in decompensated cirrhosis remain, including best methods to measure muscle mass and function in the inpatient setting, racial/ethnic variation in the development and presentation of sarcopenia and frailty, and optimal clinical metrics to assess response to therapeutic interventions that translate into a reduction in adverse outcomes associated with these conditions.

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Introduction

The last decade has seen a surge in research establishing sarcopenia and frailty as prevalent complications that predict morbidity and mortality in cirrhosis. As these complications are potentially modifiable with early identification and therapy, it is essential that clinicians understand what sarcopenia and frailty are, how they are measured, their role in prognosis and decompensation, their proposed pathophysiological basis, and recommended treatment strategies. In this review, we discuss the evidence supporting each of these areas and provide recommendations for future research in the field. To date, the literature on sarcopenia and frailty in cirrhosis has not clearly delineated patients with decompensated cirrhosis from those with compensated disease. Herein, we highlight the available information for decompensated cirrhosis when data are available. We also provide a conceptual framework for the overlap between sarcopenia and frailty as inter-related phenotypes.

Prevalence and overlap of sarcopenia and frailty

The prevalence of sarcopenia and frailty in cirrhosis ranges from 40–70%^{1,2} and 18–43%^{3,4} respectively (Table 1), depending on the population evaluated, the methods of assessment, and the operational

definitions used. In broad terms, frailty in cirrhosis has focused on physical frailty and has been operationalised as impaired muscle function, while sarcopenia has been operationalised as impaired muscle mass. This common connection to muscle naturally results in an overlap between these conditions, and in the factors that contribute to their development (Fig. 1). While the loss of muscle function can lead to loss of muscle mass and vice versa (Table 1), these conditions can occur in isolation. In several studies, cirrhosis-related complications have been more prevalent in patients with sarcopenia or frailty (Table 1).

Operational definitions and methods of assessment

Sarcopenia

Distinct from the geriatric literature that considers muscle function and muscle mass to define sarcopenia, in cirrhosis, most studies have operationalised sarcopenia as loss of muscle mass. Various indirect and direct techniques such as anthropometry, bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry (DXA), ultrasound, MRI and CT have been applied to quantify muscle mass in decompensated cirrhosis (Fig. 2).

Keywords: Body composition; Muscle mass; Muscle function; Survival; End-stage liver disease; Liver transplant; Computed tomography.

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Key point

Sarcopenia and physical frailty are common, inter-related complications in decompensated cirrhosis.



Within the clinical setting, mid-arm muscle circumference is readily accessible, but its use in decompensated cirrhosis is limited by high inter-observer variability and a stronger prognostic relevance in compensated patients.^{5,6} The Royal Free Hospital Subjective Global Assessment tool incorporates mid-arm muscle circumference alongside body mass index and dietary intake, and although time consuming, it is promising as an independent predictor of mortality⁷ and post-transplant outcomes⁸ in decompensated patients. Tools such as BIA and whole body DXA have traditionally had limited use in decompensated cirrhosis as they are affected by fluid status. For DXA, the use of appendicular skeletal muscle (particularly arm muscle) may help to circumvent this issue.^{9,10} Ultrasound is another promising, non-invasive, bedside tool for which there is data in compensated cirrhosis¹¹ and critical care,^{12,13} with evidence that suggests that muscle measurements are not influenced by hydration status.¹⁴ However, studies in decompensated patients are required.

Cross-sectional imaging assessment by CT or MRI^{15,16} is the most well-validated, accurate and objective sarcopenia assessment tool.^{2,17} Its routine use in the clinical setting is limited by radiation exposure, the potential for renal injury, high cost, and the need for specialised interpretation. Within the research setting, cross-sectional imaging studies have dominated the literature. Although much has been learned, heterogeneity exists around the choice of skeletal muscle measures and uncertainty exists about how these measures should be applied across different ethnic/racial groups. These problems are not unique to cirrhosis. A review of over 70 GI-oncology CT-sarcopenia studies identified 19 distinct cut-offs, and a higher incidence of sarcopenia in Asian populations if Western cut-offs were used.¹⁸ In cirrhosis, the most commonly evaluated muscle measures have included the total skeletal muscle index (SMI) at L3, the cross-sectional area and the index and thickness of psoas or paraspinal muscles. While studies from Asia^{19,20} and Europe^{21,22} have identified transverse psoas muscle thickness²¹ and paraspinal muscles index²² as independent predictors of mortality, in a recent North American collaboration, the psoas muscle index was a poor predictor of waitlist mortality when compared to the SMI.²³ The same collaboration identified L3 SMI mortality thresholds in 396 North American patients (ascites in 61%): SMI <50 cm²/m² in males and <39 cm²/m² in females.²⁴ Interestingly, although these cut-offs have been validated in subsequent work, a recent single centre study of 355 patients determined that they were not predictive of waitlist mortality.²⁵ This brings up the important point that contextual factors (in this case, high transplant rates and low model for end-stage liver disease scores) can influence the predictive value of SMI.

More information is also required about the validity of these cut-offs across ethnic/racial groups. A recent systematic review and meta-analysis demonstrated higher sarcopenia-related mortality in Asian participants (hazard ratio [HR] 2.45; 95% CI 1.44–4.16; *p* = 0.001) compared to Western participants (HR 1.45; 95% CI 1.002–2.09; *p* <0.05).²⁶ Although the North American collaboration cut-offs for sarcopenia²⁷ are the most validated and widely used criteria, further research is encouraged. It is unlikely that there will be a universal prognostic cut-off or single optimal site of measurement for all populations. In this situation, cut-offs based on continental norms, or the evaluation of SMI measures as a continuous variable may offer an advantage over a single global cut-off.

Frailty

As originally defined in the field of geriatrics, frailty is a distinct biologic syndrome of decreasing physiologic reserve and increasing vulnerability to health stressors.²⁸ “Global” frailty results from multi-dimensional derangements across one or a combination of physiologic systems including musculoskeletal, cardiovascular, neurologic, endocrine, and/or immune systems. In patients with decompensated cirrhosis, hepatic-specific factors (e.g. protein synthetic dysfunction, ammonia-associated muscle toxicity, and encephalopathy-related physical inactivity) are often the dominant drivers of the frail phenotype that manifest as loss of muscle function (physical frailty). Therefore, the tools that have gained broader acceptance in hepatology clinics and research settings focus largely on assessing loss of muscle function.

A number of tools have been evaluated. Tests of global frailty have included the frailty index, clinical frailty scale, and the hospital frailty risk score.^{3,29,30} Metrics of *physical* frailty/performance have been assessed using the liver frailty index, Fried frailty phenotype, short physical performance battery (SPPB), activities of daily living (ADL), Karnofsky performance status (KPS), 6-minute walk test (6MWT), and short gait speed as a single measure, or grip strength as a single measure.^{31–37} Each of these tests, with the exception of ADL and KPS, are performance-based metrics^{33,34,37} and necessitate active patient participation in testing. This can limit their use in severely decompensated or acutely ill populations, in whom muscle mass testing may be of greater clinical utility. Whether the construct of frailty, which was originally conceptualised in the field of geriatrics as a *chronic* biologic state of decreased physiologic reserve, is truly applicable in the setting of acute illness such as acutely decompensated cirrhosis or acute-on-chronic liver failure (ACLF) remains to be seen.

Future directions:

- Establish the trajectory, predictors and overlap of muscle mass and muscle function decline.

Table 1. The prevalence of sarcopenia and frailty in patients with decompensated cirrhosis.

Study	Patient population	Prevalence of sarcopenia	Prevalence of frailty	Differences in the: Prevalence of cirrhosis complications and *Child-Pugh/MELD scoring according to sarcopenia or frailty status
Montano-Loza <i>et al.</i> , 2015 ²	669 patients with cirrhosis Outpatient	45% Sarcopenic CT-measured L3 SMI	n.a.	Ascites (72%): In 78% of sarcopenic vs. 67% of non-sarcopenic ($p = 0.001$) Hepatic encephalopathy (38%): In 49% of sarcopenic vs. 29% of non-sarcopenic ($p < 0.001$) *Child-Pugh ($p < 0.001$) and MELD score ($p = 0.001$) higher in sarcopenic vs. non-sarcopenic
Cron <i>et al.</i> , 2016 ⁴	542 patients with ESLD referred for LT Outpatient and inpatient 86% White	n.a.	43% Frail Five-component Fried Frailty Index ≥ 3	Ascites (52%): In 63% of frail vs. 55% of non-frail ($p = 0.08$) Hepatic encephalopathy (41%): 51% of frail vs. 39% of non-frail ($p = 0.003$) *MELD score higher in frail vs. non-frail ($p < 0.001$)
Tandon <i>et al.</i> , 2016 ³	300 patients with cirrhosis 81% White Outpatient	n.a.	18% Frail Clinical frailty scale >4	Ascites (28%): 52% in frail vs. 22% in non-frail ($p < 0.001$) *Child-Pugh score higher in frail vs. non-frail ($p < 0.001$)
Aby <i>et al.</i> , 2018 ¹²¹	146 Patients with NASH or cryptogenic cirrhosis Outpatient 36% White 29% Hispanic	62% Sarcopenic Psoas area measured at the L3 (CT or MRI of the abdomen and pelvis)	n.a.	Ascites (79%): 80% of sarcopenic vs. 77% of non-sarcopenic ($p = 0.68$) Hepatic encephalopathy (56%): 57% of sarcopenic vs. 55% of non-sarcopenic ($p = 1.0$) *No significant difference in MELD scores between sarcopenic and non-sarcopenic patients
Lai <i>et al.</i> , 2018 ¹²²	529 patients with cirrhosis Outpatient 58% Non-Hispanic White 25% Hispanic White	n.a.	No prevalence reported (Continuous Index) Liver Frailty Index (grip, chair stands, balance)	Ascites: Mild/Moderate (27%) Refractory (7%) Hepatic esitively associated with the presence of ascites and hepatic encephalopathy *Data not available regarding differences in Child-Pugh and MELD scores across non-frail vs. frail patients
Bhanji <i>et al.</i> , 2019 ³⁰	265 adult patients evaluated and listed for LT with a primary diagnosis of NASH and ALD Outpatient	NASH: 22% ALD: 47% CT-measured L3 SMI	NASH: 49% ALD: 34% Rockwood frailty index	No significant difference in the prevalence of decompensation between sarcopenic and non-sarcopenic No significant difference in the prevalence of decompensation between frail and non-frail *No significant difference in Child-Pugh and MELD scores between sarcopenic/non-sarcopenic and frail/non-frail patients

ALD, alcohol-related liver disease; ESLD, end-stage liver disease; L3, third lumbar vertebra; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; n.a., no assessment; SMI, skeletal muscle index.

- Identify the best tools to diagnose sarcopenia/frailty in patients who are ambulatory, hospitalised with acute illness, hospitalised with critical illness.
- Identify normal values of muscle mass and function across demographics (e.g. age, sex, and race/ethnicity) and disease severity (e.g. decompensated cirrhosis, ACLF), including cross-sectional imaging and other promising bedside tools (e.g. ultrasound).

Pathophysiological basis of sarcopenia and frailty

Sarcopenia

Despite the high clinical significance, there have been few preclinical and human mechanistic studies on skeletal muscle responses in cirrhosis.^{38,39} Contributing pathophysiological factors include hepatocellular necrosis with cytokine release, host biomolecules including danger-associated and pathogen-associated molecular patterns (DAMPs, PAMPs), the vascular consequences of cirrhosis with portosystemic shunting resulting in hyperammonaemia and endotoxemia, and the underlying aetiology of liver disease (ethanol, cholestasis, insulin resistance).³⁸ These perturbations in cirrhosis contribute to anabolic resistance, a state in which physiological anabolic stimuli including nutrients and physical activity

do not elicit the expected increase in protein synthesis and decrease in proteolysis (Fig. 3). Even though most mechanistic studies have been reported in compensated patients, similar pathophysiological abnormalities, though more severe, have been reported in decompensated cirrhosis and ACLF.^{40,41}

Skeletal muscle protein homeostasis

Made up of both structural and contractile proteins, skeletal muscle is the largest storage site for protein in humans. Muscle mass is maintained by a balance between protein synthesis and proteolysis (protein homeostasis or proteostasis). The major proteolytic pathways in the muscle include the ATP-dependent ubiquitin proteasome pathway (UPP), the lysosomal autophagy pathway and the calcium-dependent calpain pathway.⁴² Metabolic tracer studies, as well as molecular signalling and organelle function, demonstrate reduced muscle protein synthesis and increased autophagic proteolysis in cirrhosis.⁴³ Muscle protein synthesis is primarily regulated by 2 factors: i) myostatin, a transforming growth factor β superfamily member and ii) locally synthesised insulin like growth factor 1 (mechanogrowth factor).^{38,44} Downstream signalling pathway components including the mammalian target or rapamycin complex 1 (mTORC1) and its target molecules, energy sensor, AMP kinase, and eukaryotic initiation factor components are responsible for protein synthesis and regulation of autophagic proteolysis.

Mediators of the liver-muscle axis

There are a number of potential mediators of the liver-muscle axis that contribute to sarcopenia in cirrhosis. These include hyperammonaemia, endotoxemia, and endocrine abnormalities including decreased testosterone levels and insulin resistance. Of these, the literature supporting the role of hyperammonaemia is strongest.⁴⁵ Ammonia is a cytotoxic metabolite generated during amino acid catabolism, gut microbial metabolism, and purine breakdown.⁴⁶ Physiologically, ammonia disposal occurs in the hepatocytes via ureagenesis. This process is impaired in cirrhosis due to hepatocyte dysfunction and portosystemic shunting.⁴⁷ Even though encephalopathy is the most well-known consequence of hyperammonaemia, there is increasing evidence that the skeletal muscle uptake of ammonia is increased in cirrhosis with signalling and metabolic consequences.^{45,48,49} The mechanistic role of testosterone and growth hormone-related increases in protein synthesis and muscle mass have been recognised in cirrhosis.⁵⁰ There is also increasing evidence that ethanol, an aetiological factor for liver disease, directly and indirectly (by aggravating muscle hyperammonaemia) contributes to more severe sarcopenia than observed in other forms of liver disease.^{51,52} Of interest, particularly in the setting

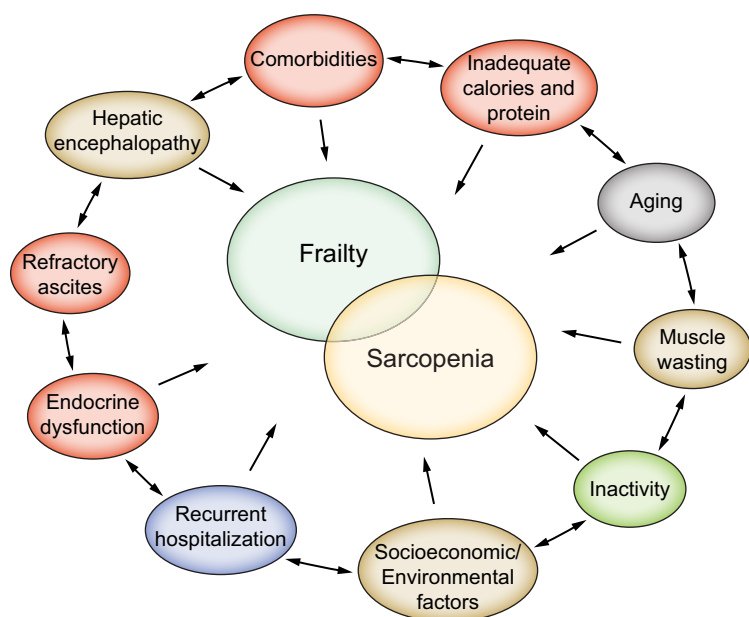


Fig. 1. The conceptual overlap between frailty, sarcopenia, and their contributing factors. The common connection of impaired muscle health in the definitions of frailty and sarcopenia in patients with cirrhosis naturally results in an overlap in the factors that contribute to their development. The contributing factors can independently contribute to frailty or sarcopenia or both (centripetal arrows from the outer circle); the effect of these factors on the development of frailty or sarcopenia or both may further be potentiated by the effect of the factors on each other (bidirectional arrows in the outer circle).

of decompensated cirrhosis and ACLF, is the potential contribution of endotoxemia-mediated muscle proteolysis and decreased protein synthesis, especially during sepsis and infection.³⁸ Other mediators including mitochondria-derived factors, PAMPs and DAMPs may also contribute to dysregulated proteostasis, but their mechanistic relevance and contributions have not been reported in cirrhosis.

Molecular perturbations

Recent bioinformatics analyses of unbiased transcriptomic and proteomic data show impaired mRNA translation, ribosome and mitochondrial dysfunction, and free radical disposal during hyperammonaemia.⁵³ Similar observations have been reported in response to ethanol across multiple regulatory pathways.⁵⁴ Initial reports in pre-clinical and human muscle tissue showed that hyperammonaemia causes transcriptional upregulation of myostatin, a transforming growth factor β superfamily member that downregulates mTORC1 signalling and increases AMPK α 2 phosphorylation, both of which result in decreased protein synthesis and increased autophagic proteolysis.^{48,55} Subsequent studies in rodents and myotube models of hyperammonaemia show a unique hyperammonaemic stress response characterised by impaired mTORC1 signalling and increased phosphorylation of eukaryotic initiation factor 2 α with decreased protein synthesis.^{46,56} A hyperammonaemic stress response that shares some components of amino acid deficiency and others from an unfolded protein response causes sarcopenia via both phosphorylation of eukaryotic initiation factor 2 α (eIF2 α) and decreased mTORC1 signalling.⁵⁶ Skeletal muscle ammonia transport is enhanced by ethanol, aggravating adverse muscle responses to hyperammonemia.⁵¹ In skeletal muscle from patients and preclinical models, the UPP is either not activated or inactivated, while autophagic flux – representing the major proteolytic pathway – is increased.^{57,58} Recent data suggest that the effects of hyperammonaemia on muscle may be context and species dependent.⁵⁹ Further studies are required to assess these effects with a view to developing targeted therapies.

Organelle dysfunction

Ribosomal biogenesis is decreased during hyperammonaemia, aggravating signalling responses.⁵³ The decreased ribosomal content and biogenesis in hyperammonaemia is mediated by impaired β -catenin-cMYC signalling. The effect of other mediators and aetiological factors on ribosomal biogenesis is yet to be studied. Both hyperammonaemia and ethanol impair mitochondrial oxidative function via inhibition of components of the electron transport chain, leakage of electrons, generation of free radicals and oxidative tissue injury. Even though muscle mitochondrial mass is

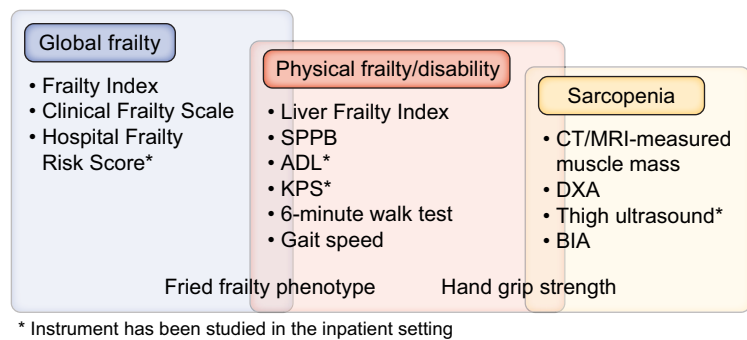


Fig. 2. Tools that have been studied in patients with cirrhosis to quantify multi-dimensional (global) frailty, physical frailty, and sarcopenia. Tools to measure frailty and sarcopenia in patients with cirrhosis. This fig. represents the tools to operationalise the constructs of frailty and sarcopenia that have been studied in patients with cirrhosis. While each of the instruments was originally developed to capture a specific construct (e.g., global frailty, physical frailty, or sarcopenia), in practice, overlap exists and the selection of the instrument used for either clinical or research is influenced by pragmatic concerns. ADL, activities of daily living; BIA, bioelectrical impedance analysis; DXA, dual energy X-ray absorptiometry; KPS, Karnofsky performance status; SPPB, short physical performance battery.

not altered during hyperammonaemia and ethanol exposure, functional abnormalities result in decreased responses to various substrates and reduced ATP synthesis.^{54,60} Endotoxemia also results in ribosomal and mitochondrial dysfunction similar to the effects of hyperammonaemia, but the relevance in cirrhosis is not yet known.^{61,62}

Metabolic abnormalities

Non-ureagenic skeletal muscle ammonia disposal involves cataplerosis (loss of tricarboxylic acid cycle intermediates) of α -ketoglutarate (α KG) with increased glutamate and glutamine synthesis.^{56,60} Substrate preferences are altered in cirrhosis and hyperammonaemia promotes partitioning of the essential amino acid, L-leucine into the mitochondria for oxidation instead of being retained in the cytosol for translational regulation or as a substrate for peptide chain elongation.⁶³ Transcriptional upregulation of the leucine exchanger SLC7A5 (LAT1) in the muscle promotes glutamine-leucine exchange, explaining the elevated plasma glutamine and reduced L-leucine levels in cirrhosis and revealing a potential therapeutic target.⁵⁶ There is emerging data that intermediary metabolites (succinate, α KG) can regulate signalling molecules and pathways⁶⁴ and help to explain the molecular-metabolic interactions during hyperammonaemia.

Hormonal changes

Sarcopenia is associated with decreased testosterone in males. Androgen receptor binding sites have been identified on the myostatin promoter. The increased myostatin levels in cirrhosis can be explained by the decreased inhibition by testosterone.⁶⁵ The limited therapeutic responses to testosterone may be explained by an increase in peripheral aromatase activity with portosystemic

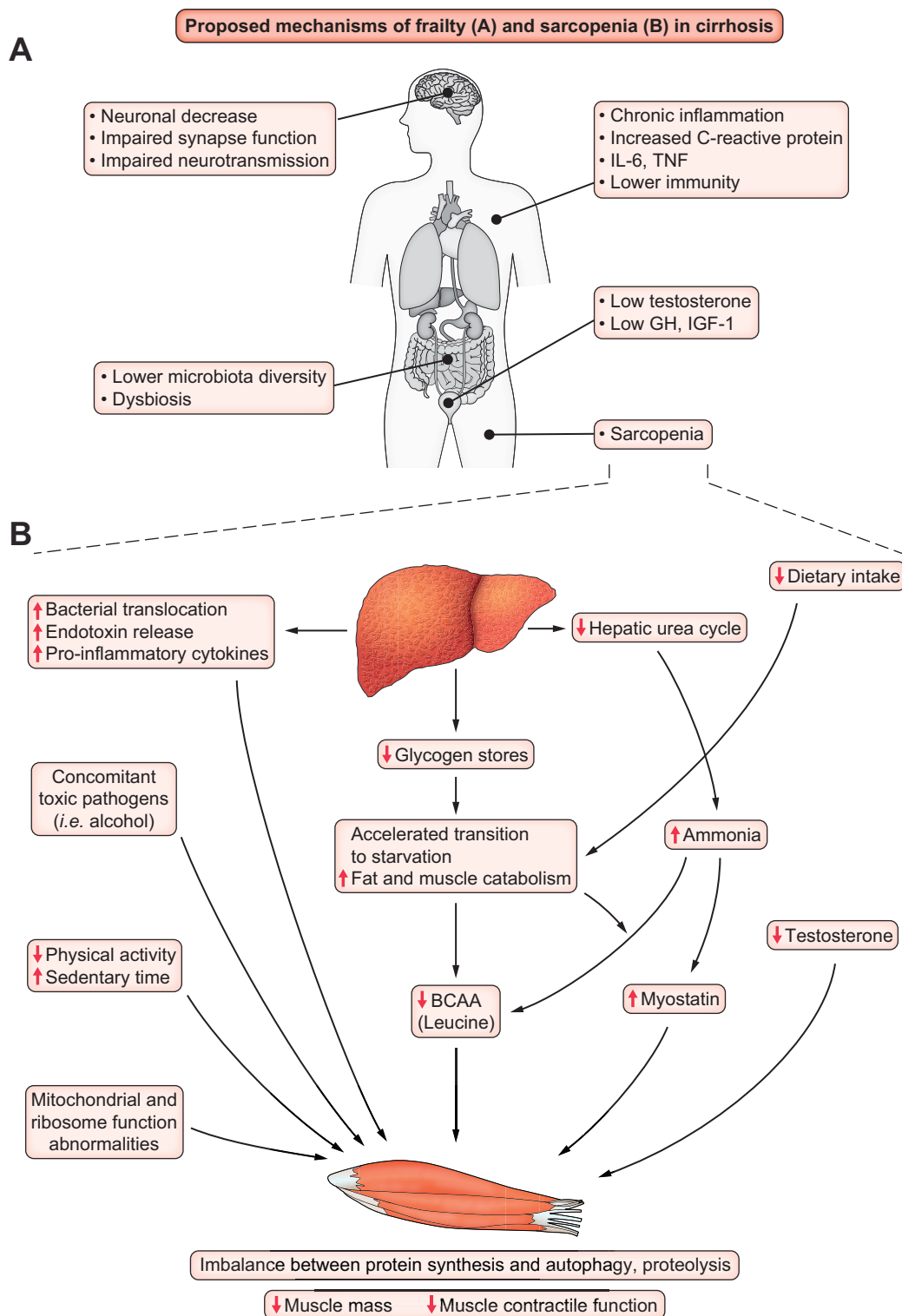


Fig. 3. Proposed mechanisms of frailty and sarcopenia in cirrhosis. (A) Common drivers of frailty are present in aging and decompensated cirrhosis. Hepatic encephalopathy, sarcopenia, altered gut microbiota and bacterial translocation, endotoxemia and exacerbation of chronic inflammation are associated with liver decompensation and contribute to the general frailty phenotype. (B) Multiple mechanisms contribute to sarcopenia in cirrhosis. These include physical inactivity, a lack of adequate energy sources due to reduced dietary intake, low glycogen deposits and a rapid transition to fasting metabolism. Endotoxemia, chronic inflammation and toxic substances such as alcohol also contribute. Low testosterone levels may contribute in male patients. Molecular mechanisms are detailed in the Pathogenesis section. BCAA, branched chain amino acid.

shunting and hyperammonaemia.⁵⁰ Whether myostatin responds to testosterone supplementation in cirrhosis is not yet known. Abnormal growth hormone secretory patterns also occur in cirrhosis and growth hormone binding sites have been identified on the myostatin promoter.^{65,66} Additionally, growth hormone can stimulate the muscle anabolic molecule, insulin like growth factor 1, that activates the mTORC1 signalling pathway. Increased circulating angiotensin in cirrhosis,⁶⁷ especially in patients with non-alcoholic fatty liver disease, has the potential to bind to the angiotensin receptor on skeletal muscle and cause increased proteolysis.

Endotoxemia/inflammation

Systemic endotoxemia, due to alterations in the gut microbiome and a disrupted gastrointestinal mucosal barrier, activates Toll-like receptors expressed on muscle, leading to a reduction in protein synthesis and increased proteolysis, both of which result in sarcopenia.³⁸ Additionally, increased circulating interleukin (IL)-6 also contributes to dysregulated protein homeostasis and sarcopenia.⁶⁸ Tumour necrosis factor- α promotes activation of the transcription factor NF- κ B which leads to transcriptional activation of MuRF1, atrogin1, and protein degradation,⁶⁹ as well as potentially contributing to muscle atrophy in cirrhosis.⁷⁰ Of interest, it has been hypothesised that the systemic inflammatory response that occurs during ACLF is an energetically expensive process, requiring reallocation of nutrients to fuel immune activation, potentially contributing to muscle mass loss.⁷¹

Systemic hypermetabolism, accelerated starvation

Systemic hypermetabolism and reduced caloric intake also aggravate dysregulated proteostasis and sarcopenia.⁷² Cirrhosis is a state of accelerated starvation with increased proteolysis and fatty acid oxidation, but the underlying mediator(s) of these metabolic responses have not yet been identified.^{73,74} Human studies have shown that a low respiratory quotient is associated with reduced muscle area.⁷³

Frailty

Multiple pathophysiologic factors have been found to contribute to frailty in the elderly, including disturbances in muscle proteostasis, the immune system, chronic inflammation,⁷⁵ neurologic alterations,⁷⁶ microbiota modifications⁷⁷ and endocrine alterations.⁷⁸ Interestingly, many of these changes are also described in patients with decompensated cirrhosis and may help us to understand why frailty occurs at an earlier age in cirrhosis (Fig. 3). To our knowledge, there has been no cirrhosis-specific data in this area. The predominant model for animal frailty testing has been aged animals. In recent years, new animal models of frailty have been proposed,⁷⁹ including the

Il10 homozygous knockout mouse (*Il10*^{tm/tm}) demonstrating a frail phenotype associated with chronic inflammation and reduced muscle strength,⁸⁰ that may have relevance to cirrhosis. The development of rodent frailty assessment tools may also advance our understanding of the pathophysiology of frailty^{81,82} in future work.

Future directions

- Explore the contribution/hierarchy/synergy of mediators of the liver-muscle axis (e.g. hyperammonaemia, endotoxemia, endocrine abnormalities, additional factors) to sarcopenia in decompensated cirrhosis/ACLF.
- Identify the pathophysiological factors associated with physical frailty in cirrhosis.
- Explore whether the pathophysiological mechanisms of sarcopenia and frailty act independently or synergistically in patients with decompensated cirrhosis/ACLF.
- Use information gained about the pathophysiology of sarcopenia and frailty to identify new therapeutic targets.

The relationship between sarcopenia/frailty and prognosis (including decompensation and death)

Both sarcopenia and frailty are more prevalent in patients with evidence of hepatic decompensation (Table 1) and are independently associated with a full range of adverse outcomes in patients with decompensated cirrhosis.

Sarcopenia has consistently been shown to be a key predictor of reduced quality of life,⁸³ mortality both pre-^{2,17} and post-LT,⁸⁴ longer hospital and intensive care unit stays,⁸⁵ a higher incidence of infection following LT,^{85,86} and higher overall health care costs.⁸⁷ Sarcopenia, as measured by CT⁸⁸ or MRI-based imaging,^{16,89} has also been identified as a predictor of decompensation itself, including development of ACLF⁹⁰ and decompensation after transjugular intrahepatic portosystemic shunt (TIPS) placement.⁸⁹ In particular, studies have shown a strong relationship between sarcopenia and hepatic encephalopathy (HE),^{91,92} likely due to reduced capacity for extrahepatic ammonia removal by muscle among those with muscle depletion. Supporting this, sarcopenia is almost 2-fold more prevalent in patients with overt HE compared to those without HE (53 vs. 32%, $p < 0.001$).⁹² Moreover, sarcopenia predicts post-procedure HE in patients undergoing TIPS,⁹³ and improvements in sarcopenia post-TIPS (>10%) are associated with fewer episodes of overt HE after TIPS.⁹⁴

In outpatients with cirrhosis, physical frailty (as defined as a liver frailty index ≥ 4.5), increases the adjusted risk of waitlist mortality 1.9x compared to non-frail patients (95% CI 1.4–2.6)³¹. Other assessments using the Fried frailty phenotype, SPPB,

Key point

Our understanding of the pathophysiological basis of sarcopenia and physical frailty is in evolution. Sarcopenia has been linked to factors including cytokine release, endotoxemia, hyperammonaemia and low testosterone levels (males).

Table 2. Studies evaluating the association between sarcopenia and frailty in patients with cirrhosis.

Study	Patient population	Sarcopenia assessment	Frailty assessment	Sarcopenia and frailty association	Main finding
Yadav <i>et al.</i> ⁹⁷	213 patients listed for liver transplant	CT	6MWD	A poor correlation between sarcopenia (SMI) and 6MWD existed ($r = 0.19$, $p = 0.007$) A poor correlation between sarcopenia (SMI) and 6MWD existed ($r = 0.19$, $p = 0.007$) Poor correlation between SMI and 6MWD ($r = 0.19$, $p = 0.007$)	6MWD appears to be a more useful prognostic indicator than the presence of sarcopenia. 6MWD appears to be a more useful prognostic indicator than the presence of sarcopenia. 6MWD appears to be a more useful prognostic indicator than the presence of sarcopenia. 6MWD appears to be a more useful prognostic indicator than the presence of sarcopenia. 6MWD was the main predictor of waitlist mortality
Wang <i>et al.</i> ⁹⁸	292 liver transplant candidates	CT	6MWD appears to be a more useful prognostic indicator than the presence of sarcopenia. SPPB	6MWD appears to be a more useful prognostic indicator than the presence of sarcopenia. No correlation between SPPB and SMI in men ($\rho = 0.09$; $p = 0.24$) or women ($\rho = 0.07$; $p = 0.50$)	SPPB was associated with waitlist mortality.
Sinclair <i>et al.</i> ⁹⁹	145 men referred for liver transplant	CT DEXA	Handgrip strength	The correlation between CT muscle mass and handgrip strength was present but weak (τ , 0.24; $p < 0.001$). Handgrip strength was modestly correlated with DEXA-measured APLM (τ , 0.34; $p < 0.001$) and DEXA-measured LM of arms (τ , 0.39; $p < 0.001$). Correlation between CT muscle mass and handgrip strength was weak (τ , 0.24; $p < 0.001$). Correlation between DEXA total LM and handgrip strength was modest (τ , 0.38; $p < 0.001$) and DEXA-measured APLM (τ , 0.34; $p < 0.001$).	Handgrip strength combined with MELD score was superior for the prediction of waitlist mortality
Dang <i>et al.</i> ¹²³	180 patients with cirrhosis evaluated for liver transplant	CT	6MWT	Weak correlation between SMI and 6MWT ($r=0.022$; $p = 0.003$).	Sarcopenia and low 6MWT (<489 m) were independently associated with mortality. Patients who had both sarcopenia and low 6MWT had the worst prognosis

6MWT, 6-minute walk test; DEXA, dual-energy X-ray absorptiometry; DEXA total LM, DEXA total lean mass; DEXA-measured APLM, DEXA-measured appendicular lean mass; SMI, skeletal muscle index; SPPB, short physical performance battery.

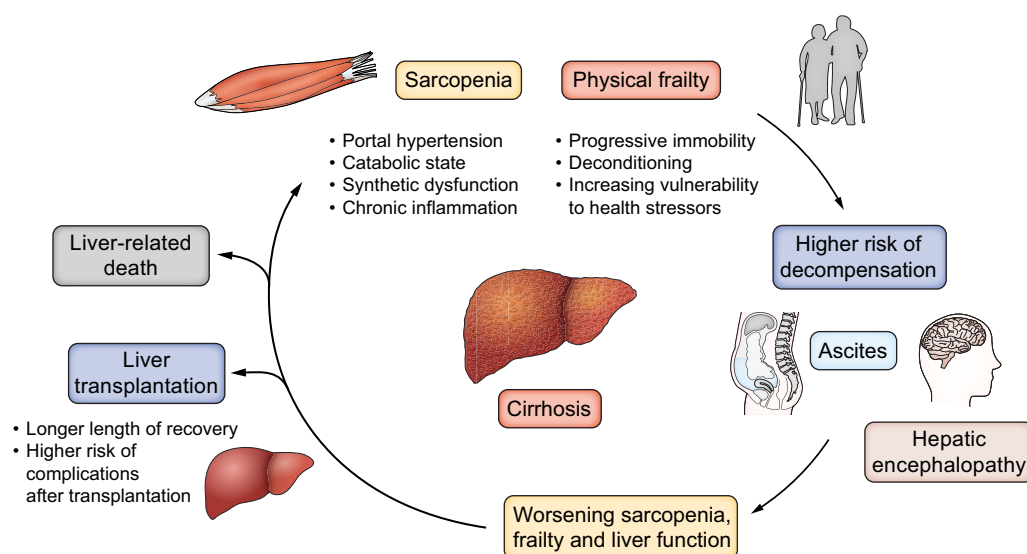


Fig. 4. Potential mechanisms of sarcopenia and physical frailty and their association with a higher risk of decompensation in patients with cirrhosis. Sarcopenia and frailty are present in 40–70% and 18–43% of patients with cirrhosis. The main factors associated with these conditions include portal hypertension, a catabolic state, synthetic dysfunction, chronic inflammation, progressive immobility and deconditioning. Sarcopenia and frailty are associated with an increased risk of liver decompensation related complications, including ascites, hepatic encephalopathy and infection. Liver decompensation may also increase the risk of worsening both sarcopenia and frailty. Post-transplantation, both conditions are associated with an increased risk of morbidity and mortality.

6MWT, and gait speed have demonstrated similar associations with death.^{32,35,36,95} Ambulatory assessments using the clinical frailty scale, frailty index, Fried frailty phenotype, and short gait speed predicted future hospitalisations and length of hospitalised days.^{3,30,36,95} Only 2 instruments, ADL and KPS, have been studied in hospitalised patients with cirrhosis: loss of ability to complete ADL was associated with an adjusted risk of 90-day mortality after discharge (HR 1.83, 95% CI 1.05–3.20), and each 10-point improvement in KPS score was associated with a 30% reduction in the odds of death 30 days after discharge (95% CI 20–40%).^{33,37} Furthermore, longitudinal changes in the liver frailty index predicted outcomes in patients with decompensated cirrhosis – a 0.1 unit increase in the liver frailty index per 3 months was associated with a 2-fold higher risk of death/delisting (95% CI 1.4–3.1).⁹⁶

A few studies evaluated *both* sarcopenia and frailty in a single study, all in outpatients being evaluated for liver transplantation (Table 2).^{97–99} Although they are inter-related constructs, these studies have demonstrated low correlations between the 2 conditions, suggesting that metrics of sarcopenia and metrics of frailty may capture different risks in this patient population. Further investigations are essential to better understand the relationship between sarcopenia and frailty.

A bidirectional relationship between these conditions is plausible (Fig. 4). For example, factors that occur with decompensation and ACLF, such as anorexia, ascites, HE and pro-inflammatory

cytokine release can result in higher energy consumption, reduced nutritional intake and physical inactivity, increasing the risk of sarcopenia and frailty developing (and worsening). Further research will add granularity to the potential mechanisms of sarcopenia and frailty and their association with increased risk of decompensation in patients with cirrhosis (Fig. 4).

Future directions:

- Evaluate the course of sarcopenia and frailty during decompensation/ACLF. Explore if/how sarcopenia/frailty may contribute to the process of decompensation/ACLF.
- Identify if there is a difference between chronic frailty (measured in stable, ambulatory patients) vs. acute frailty (measured in acutely ill patients) in terms of their associations with clinically relevant outcomes.
- Explore the prognostic implications of a more global, multi-dimensional concept of frailty (common place in the aging literature) compared to the single dimension of physical frailty.

Therapy

Based on the pathophysiological mechanisms that contribute to sarcopenia/frailty, the potential therapies for these conditions are presented in Fig. 5. These include the restoration of liver function through optimal management of the underlying

Key point

There are multiple knowledge gaps in our understanding of sarcopenia and physical frailty in decompensated cirrhosis that require further evaluation, including the potential impact of these conditions on the course of decompensation. What is clear is that they are independent predictors of increased morbidity, mortality and reduced quality of life.

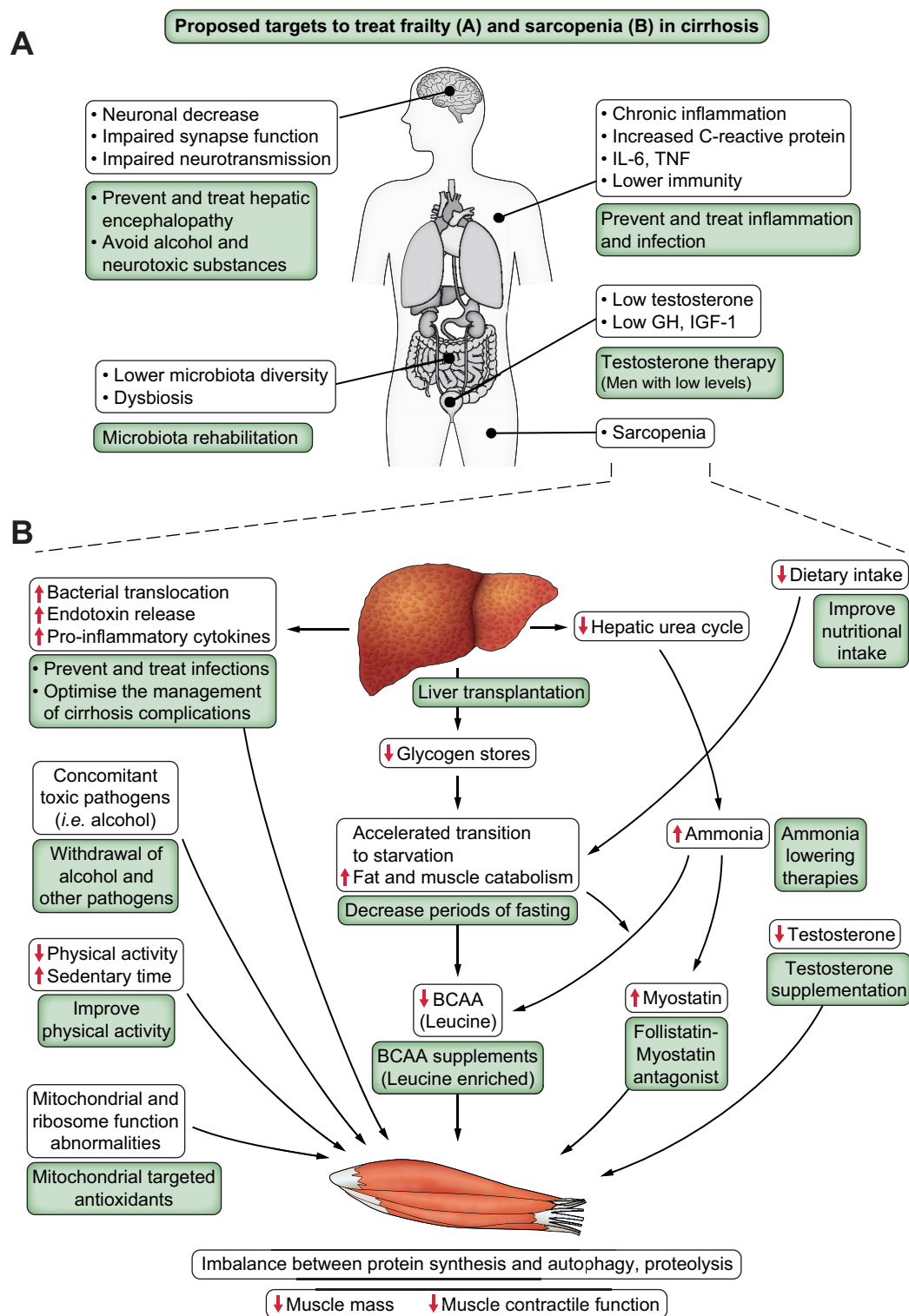


Fig 5. Proposed therapeutic strategies for the treatment of frailty and sarcopenia in cirrhosis. (A) Potential therapeutic strategies to treat frailty in cirrhosis. At the current time (apart from sarcopenia based therapies), these therapies have not been evaluated in experimental studies or in patients. (B) Potential therapeutic strategies to treat sarcopenia in cirrhosis. At the current time, evidence for most of these strategies is based on a small number of experimental or human-based studies. Larger prospective interventional studies are required to determine whether the findings in molecular studies can be translated to patients. See more details in the section on Pathogenesis and the section on Therapy. BCAA, branched chain amino acid.



Fig 6. Summary of therapies for sarcopenia and frailty^{124,125}. BCAA, branched chain amino acid; HCC, hepatocellular carcinoma; RCT, randomised controlled trial.

disease aetiology (e.g. abstinence from alcohol, antiviral therapy), optimal management of liver-related complications (e.g. infection, ascites, variceal bleeding, hepatic encephalopathy), and liver transplantation when required. Nutrition, exercise and hormonal replacement therapy (men) are dealt with more extensively in the manuscript as several clinical studies have been performed to assess their possible efficacy.

Nutrition therapy

General Importance of nutrition therapy

All patients with decompensated disease should receive dietary counselling and educational

resources.¹⁰⁰ Although existing meta-analyses of nutritional supplementation in hospital have not been able to demonstrate an impact on mortality,¹⁰¹ this may in part be related to the inclusion of studies with a very short intervention duration or patients with very advanced liver disease. A recent quality improvement intervention in hospitalised patients with cirrhosis was associated with increased nutritional intake and a reduction in 90-day hospital readmissions, supporting the impact of such strategies in this population.¹⁰² A randomised-controlled trial (RCT) reported on a 6-month intervention promoting dietary intake at guideline-based targets using educational

materials and monthly dietician visits in outpatients with decompensated cirrhosis and minimal HE. A significant improvement in minimal HE, muscle mass/strength and quality of life was observed in the intervention group.¹⁰³

Calorie prescription

There is considerable inter-individual variation in measured vs. predicted values of resting energy expenditure¹⁰⁴ with 45% of traditional predictive equations estimating energy requirements to within 90–110% of the measured resting energy expenditure.¹⁰⁴ Therefore, when available, indirect calorimetry should be used to determine resting energy expenditure. Caloric intake recommendations are provided in Fig. 6. Weight loss in the setting of decompensated cirrhosis or sarcopenic obesity must be approached with caution¹⁰⁵ – caloric reduction should occur under the guidance of a dietitian, with protein intake maintained¹⁰⁵ and concurrent resistance activity prescribed.

Protein prescription

Protein intake should not be restricted in decompensated cirrhosis.¹⁰⁶ 1.2–1.5 g/kg/day is a unanimous recommendation across guidelines in the area, with increased intake recommended in the critically ill^{100,100,107} (Fig. 6). The data to support branched chain amino acids (BCAAs) are less clear.³⁹ Selected studies have demonstrated a reduction in clinical events and an improvement in quality of life with the longer-term use of BCAAs.^{108,109} In a meta-analysis of 16 RCTs in patients with HE, BCAAs were associated with a beneficial impact on HE but no impact on mortality.¹¹⁰ Although further studies are required, most guidelines recommend BCAAs (0.25 g/kg/d)^{100,107} in patients who are protein intolerant or unable to achieve protein targets.

Timing of nutritional intake

Prolonged periods of fasting should be avoided in cirrhosis. The landmark study in the area by Plank *et al.* randomised 103 patients to daytime or nighttime oral supplemental nutrition of 710 kcal per day. Although most sustained in the Child-Pugh A patients, even decompensated patients demonstrated a significant improvement in total body protein and fat-free mass with night-time supplementation.¹¹¹ A diverse range of late night snack options have been evaluated in the literature, with snacks varying from 149 kcal to 710 kcal and varying carbohydrate and protein composition⁷⁴ (Fig. 6).

Exercise therapy

Exercise therapy in cirrhosis has been reviewed in detail in several recent reviews.^{112,113} Most of the available data is from patients with compensated cirrhosis without separate results in decompensated patients, and no data in hospitalised

patients. Exercise programmes ranging from 8–14 weeks in duration have resulted in improvements in peak exercise capacity (VO₂), muscle mass, muscle strength, the hepatic venous pressure gradient and quality of life and fatigue.^{112,113} If in keeping with their goals of care, all patients with decompensated cirrhosis should receive pre-exercise safety screens and an exercise prescription as detailed in Fig. 6. Drawing from experience with other compromised populations, resistance training is the focus of many programmes in patients with decompensated cirrhosis and significant deconditioning, with aerobic training introduced later. If falls are a major issue, initial emphasis is often placed on lower extremity strength and balance training.

Testosterone therapy

Testosterone levels are almost universally decreased in patients with decompensated liver disease.¹¹⁴ In the only 12-month RCT of 101 cirrhosis patients (80% decompensated) with low testosterone levels, Sinclair *et al.* demonstrated significant improvements in muscle mass, bone mineral mass and reductions in total fat mass in patients receiving testosterone therapy.¹¹⁵ Exclusion criteria included those >70 years of age, with hepatocellular carcinoma or other known malignancy, prostate disease, haematocrit >55%, estimated glomerular filtration rate <30 ml/min. Although this single RCT is promising, the widespread use of testosterone has been limited by concerns about hepatocellular carcinoma and venous thrombosis, and therefore it is not routinely prescribed.

Emerging therapies

As highlighted in the pathophysiology section and Fig. 5, several novel molecular and metabolic abnormalities have been identified as potential therapeutic targets in the skeletal muscle of patients with cirrhosis. In an experimental model of hyperammonaemia, rifaximin and L-ornithine L-aspartate lowered plasma and muscle ammonia concentrations and improved muscle mass. This was associated with decreased expression of myostatin, autophagy markers and reversal of the general control nonderepressible 2 (GCN2)/eIF2 α phosphorylation as well as mTORC1 signalling.¹¹⁶ Among BCAAs, data on the potential role of leucine-enriched BCAA supplementation (simultaneous mTORC1 activator and mitochondrial oxidative substrate)^{56,117} and its metabolite beta-hydroxy-beta-methylbutyrate is promising.¹¹⁸ Mitochondrial targeted antioxidants are another potential therapy to reverse oxidative dysfunction, decrease ATP content, and restore protein synthesis and muscle mass.⁵⁴ In a recent study, L-carnitine (1,000 mg/day) administration for more than 6 months suppressed skeletal muscle loss in patients with cirrhosis.¹¹⁹ The suppression was dose-dependent, with high-dose ($\geq 1,274$ mg/day) administration resulting in a reduction in serum

ammonia levels at 1 year.¹²⁰ In preclinical models, follistatin, an antagonist of myostatin, has been linked to reduced myostatin expression, increased muscle mass and protein synthesis. Further research is required before these therapies can be used in routine clinical practice.⁵⁵

Future directions

- Explore the reversibility of sarcopenia and frailty with adequately powered studies of nutrition and physical activity. Assess dose, intervention duration, predictors of response (e.g. inflammation, degree of liver dysfunction) and point of futility.
- Determine whether improvements in sarcopenia/frailty independently impact the course of liver disease or whether improvement is secondary to improvements in liver function.
- Determine more accurate methods for assessing total energy needs.
- Evaluate the impact of emerging (non-nutrition, non-physical activity) therapies.

Conclusions

In summary, sarcopenia and frailty are not only common, but also clinically significant conditions that occur in the life of a patient with decompensated cirrhosis. Although much has been uncovered, much remains to be clarified about these conditions – how best to diagnose them across distinct groups of patients, their pathophysiological basis, how/whether they mediate decompensation and optimal therapeutic strategies. The accumulating evidence will provide even more support to standardise the assessment and management of sarcopenia and frailty alongside other classic cirrhosis complications as a routine part of cirrhosis care.

Abbreviations

ACLF, acute-on-chronic liver failure; ADL, activities of daily living; BCAA, branched chain amino acids; BIA, bioelectrical impedance analysis; DXA, dual-

energy X-ray absorptiometry; eIF2 α , eukaryotic initiation factor 2 α ; HE, hepatic encephalopathy; IL, interleukin; KPS, Karnofsky performance status; mTORC1, mammalian target of rapamycin complex 1; RCT, randomised-controlled trial; SMI, skeletal muscle index; SPPB, short physical performance battery; TIPS, transjugular intrahepatic portosystemic shunt; UPP, ubiquitin proteasome pathway

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

All authors contributed equally for the compilation and selection of studies, and writing the different section of this manuscript. All authors contributed to development of tables and figures. All authors approved the final version.

Supplementary data

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Key point

Existing management strategies for sarcopenia and physical frailty centre on adequate nutritional intake, shortening the fasting period and physical activity in addition to optimal management of cirrhosis aetiology and its complications.

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