

Malnutrition, Frailty, and Sarcopenia in Patients With Cirrhosis: 2021 Practice Guidance by the American Association for the Study of Liver Diseases.

Title: Malnutrition, Frailty, and Sarcopenia in Patients With Cirrhosis: 2021 Practice Guidance by the American Association for the Study of Liver Diseases.

Publication year: 2021

Journal: Hepatology (Baltimore, Md.)

Authors: Department of Medicine, University of California, San Francisco, San Francisco, CA.

Society: European Respiratory Society

Origin country: International (Europe)

Target countries: Europe

DOI: 10.1002/hep.32049

PMID: 34233031

Source: <https://pubmed.ncbi.nlm.nih.gov/34233031/>

pmc Hepatology Hepatology 319 nihpa 8302946 Hepatology (Baltimore, Md.) 0270-9139 1527-3350 pmc-is-collection-domain yes pmc-collection-title NIHPA Author Manuscripts PMC9134787 PMC9134787.1 9134787 9134787 NIHMS1802221 34233031 10.1002/hep.32049 NIHMS1802221 NIHMS1802221 1 Article Malnutrition, Frailty, and Sarcopenia in Patients With Cirrhosis: 2021 Practice Guidance by the American Association for the Study of Liver Diseases Lai Jennifer C <http://orcid.org/0000-0003-2092-6380> 1 # Tandon Puneeta 2 # Bernal William 3 Tapper Elliot B <http://orcid.org/0000-0002-0839-1515> 4 Ekong Udeme <http://orcid.org/0000-0002-3312-112X> 5 Dasarathy Srinivasan 6 Carey Elizabeth J 7 1 Department of Medicine, University of California, San Francisco, San Francisco, CA. 2 Division of Gastroenterology (Liver Unit), University of Alberta, Edmonton, Alberta, Canada. 3 Liver Intensive Therapy Unit, Institute of Liver Studies, Kings College Hospital, London, UK. 4 Division of Gastroenterology, University of Michigan, Ann Arbor, MI. 5 Georgetown University School of Medicine, Medstar Georgetown Transplant Institute, Washington, DC. 6 Department of Gastroenterology and Hepatology, Inflammation and Immunity, Lerner Research Institute, Cleveland Lerner Research Institute, Cleveland Clinic, Cleveland, OH. 7 Division of Gastroenterology and Hepatology, Mayo Clinic in Arizona, Phoenix, AZ. ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO: Jennifer C. Lai, M.D., M.B.A., Department of Medicine, University of California, San Francisco 513 Parnassus Avenue, UCSF Box 0538, San Francisco, CA 94143, Tel.: 415-476-2777, Jennifer.lai@ucsf.edu # Contributed equally.

9 2021 74 3 408482 1611 1644 12 05 2022 01 09 2022 01 09 2022 27 05 2022 28 08 2024 This file is available for text mining. It may also be used consistent with the principles of fair use under the copyright law. Erratum 74 6 11 11 2021 3563 3563 Hepatology (Baltimore, Md.) PMC9178552 34762312 pmc-status-qastatus 0 pmc-status-live yes pmc-status-embargo no pmc-status-released yes pmc-prop-open-access no pmc-prop-olf no pmc-prop-manuscript yes pmc-prop-open-manuscript yes pmc-prop-legally-suppressed no pmc-prop-has-pdf yes pmc-prop-has-supplement no pmc-prop-pdf-only no pmc-prop-suppress-copyright no pmc-prop-is-real-version no pmc-prop-is-scanned-article no pmc-prop-preprint no pmc-prop-in-epmc yes Purpose and Scope of This Practice Guidance This is the first American Association for the Study of Liver Diseases (AASLD) practice guidance on the management of malnutrition, frailty, and sarcopenia in patients with cirrhosis. This guidance represents the consensus of a panel of experts after a thorough review and vigorous debate of the literature published to date, incorporating clinical experience and common sense to fill in the gaps when appropriate. Our goal was to offer clinicians pragmatic recommendations that could be implemented immediately in clinical practice to target malnutrition, frailty, and sarcopenia in this

population.

This AASLD guidance document differs from AASLD guidelines, which are supported by systematic reviews of the literature, formal rating of the quality of the evidence and strength of the recommendations, and, if appropriate, meta-analysis of results using the Grading of Recommendations Assessment Development and Evaluation system. In contrast, this guidance was developed by consensus of an expert panel and provides guidance statements based on formal review and analysis of the literature on the topics, with oversight provided by the AASLD Practice Guidelines Committee at all stages of guidance development. The AASLD Practice Guidelines Committee chose to perform a guidance on this topic because a sufficient number of randomized controlled trials (RCTs) were not available to support the development of a guideline.

Cirrhosis is a major predisposing condition for the development of malnutrition, frailty, and sarcopenia. Multiple, yet complementary, definitions of these conditions exist in the published domain outside of the field of hepatology; but consensus definitions have not yet been established by the AASLD for patients with cirrhosis. Furthermore, there has been ambiguity related to operationalization of these constructs in clinical practice. To address this, we offer definitions of the theoretical constructs of malnutrition, frailty, and sarcopenia as commonly represented in all populations, partnered with operational definitions, developed by consensus, to facilitate pragmatic implementation of these constructs in clinical practice as applied to patients with cirrhosis (Table 1).

Malnutrition is a clinical syndrome that results from “an imbalance (deficiency or excess) of nutrients that causes measurable adverse effects on tissue/body form (body shape, size, composition) or function, and/or clinical outcome.” (1) Key to this definition is the recognition that malnutrition represents a spectrum of nutritional disorders across the entire range of body mass index (BMI)—from underweight to obese. By this definition, malnutrition leads to adverse physical effects, which, in patients with cirrhosis, are commonly manifested phenotypically as frailty or sarcopenia.

Frailty has most commonly been defined as a clinical state of decreased physiologic reserve and increased vulnerability to health stressors, a definition that has its roots in the field of geriatrics. (2) However, the weight of evidence available to date in patients with cirrhosis has focused predominantly on one component of frailty: physical frailty. Although this representation deviates somewhat from the classic “geriatric” definition of frailty as a global construct, physical frailty represents clinical manifestations of impaired muscle contractile function that are commonly reported by patients with cirrhosis such as decreased physical function, decreased functional performance, and disability.

Sarcopenia has been defined by the European Working Group on Sarcopenia as “a progressive and generalized skeletal muscle disorder associated with an increased likelihood of adverse outcomes including falls, fractures, disability, and mortality,” combining both muscle mass and muscle strength or muscle performance in its definition. (3) However, the majority of studies in patients with cirrhosis have investigated sarcopenia using measures of muscle mass alone. Therefore, based on the evidence available to date on patients with cirrhosis, we have developed a consensus definition for operationalization of sarcopenia in patients with cirrhosis as the phenotypic manifestation of loss of muscle mass.

Although we have, for the purposes of this guidance, developed separate operational definitions for malnutrition, frailty, and sarcopenia, we acknowledge that these three constructs are interrelated and in practice are often recognized simultaneously in an individual patient. For example, a patient with cirrhosis who presents to clinic with severe muscle wasting might be described as “malnourished,” “frail,” and “sarcopenic,” each descriptor conveying similar information about the patient’s poor clinical condition and prognosis. Despite the overlap of these three constructs in clinical practice, there is value in understanding each as a separate entity as well as the relationship between the three in order to develop tailored behavioral interventions and targeted

pharmacotherapies for these conditions.

Herein, we propose a conceptual framework for this relationship (Fig. 1). There are a number of factors that lead to malnutrition in patients with cirrhosis, which is challenging to identify at the bedside unless it manifests phenotypically as frailty and/or sarcopenia. Malnutrition is not the only factor that contributes to frailty and sarcopenia; other factors such as cirrhosis complications, other systems-related factors (e.g., systemic inflammation, metabolic dysregulation), physical inactivity, and environmental/organizational factors can contribute to frailty and/or sarcopenia within or independent of the malnutrition pathway. In addition, frailty and sarcopenia can contribute to each other—impaired muscle contractile function can accelerate loss of muscle mass and vice versa. It is these clinical phenotypes—frailty and sarcopenia—that ultimately lead to adverse health outcomes including hepatic decompensation, increased health care use, worse health-related quality of life, adverse posttransplant outcomes, and increased overall risk of death.

Here, we describe the factors that have been shown to contribute to frailty and sarcopenia in patients with cirrhosis. We acknowledge that these factors are, in some cases, interrelated; but for the purposes of ease of clinical implementation, we have categorized these factors broadly as (1) malnutrition, (2) cirrhosis-related, (3) other systems-related, (4) physical inactivity, and (5) environmental/organizational factors.

Reduced oral intake results from many factors including early satiety, anorexia, nausea and vomiting, dysgeusia, diet unpalatability (e.g., low sodium or low potassium), impaired level of consciousness, free water restriction, and frequent fasting due to procedures and hospitalizations. (5) Excess oral intake is a root cause of obesity and is influenced by a variety of biological, sociocultural, and psychological factors. (6) Many patients with cirrhosis have limited knowledge about disease self-management, including nutrition therapy. (7 , 8) Inadequate food knowledge/preparation skills and food insecurity can impact dietary intake—through either reduced or excess intake—across the spectrum of nutritional disorders from undernutrition to obesity. (7 - 9)

Malabsorption leads to high rates of micronutrient deficiency in patients with cirrhosis. Factors leading to impaired macronutrient intake and absorption also contribute to deficiency of many micronutrients. In particular, folate, thiamine, zinc, selenium, vitamin D, and vitamin E deficiencies have been reported in patients with alcohol-associated liver disease; and fat-soluble vitamin deficiencies have been well documented in patients with cholestatic liver disease. (10 - 14) Several of these micronutrients have a strong link with frailty or sarcopenia. Vitamin D deficiency is associated with impaired muscle contractile function in the general population. (15) Although studies evaluating the role of vitamin D deficiency on frailty and sarcopenia in patients with cirrhosis are lacking, vitamin D deficiency is prevalent in patients with cirrhosis (16 - 18) and may contribute to the development and progression of frailty in this population. Deficiency of zinc, a cofactor in the urea cycle that metabolizes ammonium, is associated with HE, frailty, and sarcopenia in patients with cirrhosis. (19 - 21) Magnesium deficiency occurs because of malabsorption of magnesium in the small intestine and is exacerbated by diuretic use. Magnesium deficiency is associated with reduced cognitive performance as well as reduced muscle strength in adults with cirrhosis (22 - 24) and with increased bone resorption in children with cholestatic liver disease. (25)

Impaired nutrient uptake is multifactorial, resulting from malabsorption, maldigestion, and altered macronutrient metabolism. Cholestasis leads to alterations in the enterohepatic circulation of bile salts and maladaptation of bile salt regulation. This may result in elevated serum and tissue levels of potentially toxic bile salts as well as impaired metabolism and malabsorption of long-chain fatty acids and fat-soluble vitamin deficiency in both adults and children. (26 - 28) Other contributors to malabsorption and maldigestion in patients with cirrhosis include portosystemic shunting, pancreatic enzyme deficiency, bacterial overgrowth, altered intestinal flora, and enteropathy. (5) Altered macronutrient metabolism or “accelerated starvation” occurs as a result of reduced hepatic glycogen synthesis and storage during the postprandial state, an early shift from glycogenolysis to gluconeogenesis, fatty acid oxidation, and increased rates of whole-body protein breakdown. (29 ,

30) Hypermetabolism has been variably defined in the literature (e.g., resting energy expenditure [REE] + 1 SD or REE:REE predicted + 2SD). (31 , 32) With its associated catabolic state, hypermetabolism also contributes to the imbalance between intake and requirements, occurring in at least 15% of patients with cirrhosis without a clear correlation of hypermetabolism with disease severity or other predictors. (32 , 33)

Cirrhosis itself leads to frailty and sarcopenia through a number of pathways. At the pathophysiological level, the altered catabolic state in cirrhosis leads to an imbalance between energy needs and intake. Altered protein metabolism, particularly of branched-chain amino acids (BCAAs) that are essential for supporting glutamine synthesis and extrahepatic ammonia detoxification, results in reduced levels of circulating BCAAs, which leads to accelerated muscle breakdown. (34 - 36) Impaired hepatic ammonia clearance from loss of metabolic capacity, in combination with increased portosystemic shunting, increases systemic ammonia concentration with pathologic effects on the muscle. (37 - 39) Ammonia is myotoxic through mechanisms that include decreased protein synthesis, increased autophagy, proteolysis, and mitochondrial oxidative dysfunction in the skeletal muscle. Posttranslational modifications of contractile proteins with bioenergetic dysfunction result in muscle contractile dysfunction and loss of muscle mass. (40 - 42)

The etiology of liver disease has been associated with differences in the prevalence of sarcopenia. (43 , 44) For example, alcohol-associated liver disease has been associated with a particularly high prevalence of sarcopenia, affecting 80% of patients with decompensated cirrhosis—although sarcopenia was reported in approximately 60% of patients with cirrhosis from NASH, chronic HCV, and autoimmune hepatitis. (45) Patients with alcohol-associated cirrhosis display the most rapid rate of reduction in muscle areas compared with other etiologies. (43) Alcohol exposure increases muscle autophagy, inhibits proteasome activity, and decreases the anabolic hormone insulin-like growth factor 1. (46 - 48) Patients with cirrhosis secondary to NASH may be at increased risk of sarcopenia due to the additive effects of insulin resistance and chronic systemic inflammation. (49) Finally, cholestasis-predominant liver diseases, such as primary sclerosing cholangitis, lead to elevated serum bile acid levels that may induce skeletal muscle atrophy through the bile acid receptor G protein–coupled bile acid receptor 1 (or TGR5) that is expressed in healthy muscles. (50)

Complications of portal hypertension also contribute to malnutrition and muscle dysfunction. HE is associated with anorexia, reduced physical activity, and frequent hospitalizations. (37 , 51) Ascites contributes to anorexia, early satiety, increased REE, and limited physical activity. (52 , 53) Both HE and ascites are strongly associated with frailty. (54)

Circulating levels of inflammatory markers such as IL-1, IL-6, IL-10, C-reactive protein, and TNF- α are elevated in patients with cirrhosis. (55 , 56) Low-grade endotoxemia may result from increased gut permeability, from impaired hepatic clearance of lipopolysaccharide and portosystemic shunting, and potentially from cirrhosis-related changes in the gut microbiome. (57) This chronic systemic inflammation may promote the development of frailty, sarcopenia, and their subsequent complications through reduced muscle protein synthesis and increased protein degradation. (58 - 61)

Even in the absence of cirrhosis, chronic liver disease may lead to systemic inflammation and vulnerability to developing frailty and sarcopenia. Inflammatory cytokines are elevated in chronic HCV; eradication of HCV with antiviral agents results in a decrease of these markers. (62 , 63) Both alcohol-associated liver diseases and NAFLDs are also characterized by elevated systemic inflammatory markers. (64)

Further disruption of mediators of the “liver–muscle axis” may result from cirrhosis-related reduction in circulating levels of testosterone and changes in growth hormone secretion and sensitivity. (65) Low testosterone levels have been observed in male patients with cirrhosis and sarcopenia compared with patients who are nonsarcopenic. (66) Testosterone replacement resulted in

improvements in total lean body mass, (67) further supporting the role of low testosterone in the development and progression of sarcopenia.

Obesity has been associated with frailty and sarcopenia in patients with cirrhosis and is of increasing relevance given the rapidly rising prevalence of obesity-related liver diseases. (6 , 68 - 71) Obesity is associated with metabolic dysregulation, visceral fat accumulation, insulin resistance, and anabolic resistance. A strong link has been demonstrated between obesity and muscle loss in patients with cirrhosis, with nearly one third of patients with obesity and cirrhosis meeting criteria for sarcopenia by skeletal muscle index (SMI). (70) With regard to muscle function, obesity has not been associated with an increased rate of frailty, although one multicenter study of patients with cirrhosis awaiting liver transplantation did demonstrate a significant interaction between obesity and frailty on clinical outcomes: patients with a BMI ≥ 35 kg/m² who were frail experienced a 3-fold increased risk of waitlist mortality compared with similar-weight patients who were nonfrail. (68)

Consistent with the general population, there has been a rapid rise in the prevalence of cirrhosis in older adults. (72) In older adults with cirrhosis, a combination of primary (aging-related) and secondary (chronic disease-related) sarcopenia occurs simultaneously and has been referred to as “compound sarcopenia.” (73) In hospitalized patients, compound sarcopenia was associated with higher odds of death (OR, 1.06; 95% CI, 1.04-1.08) and greater resource use (OR, 1.10; 95% CI, 1.04-1.08) than patients with cirrhosis but without compound sarcopenia. (73)

Physical inactivity and sedentary behavior are common in patients with cirrhosis and are associated with frailty and sarcopenia as well as mortality. (74 - 76) In one small study of 53 liver transplant candidates, participants spent 76% of their waking hours in sedentary time and completed a mean of only 3,000 steps per day. (76) Physical inactivity was significantly higher among liver transplant candidates who experienced waitlist mortality than in those who experienced other outcomes on the waitlist (e.g., transplant, removed for social reasons, or still waiting). (75) In a survey of liver transplant candidates and their caregivers, only 60% of patients and caregivers reported feeling that their clinicians “encouraged exercise,” (77) suggesting that one possible barrier to engaging in physical activity is the patient-provider communication around the benefits of physical activity.

There are no prospective longitudinal studies evaluating the direct role of physical inactivity on progressive frailty and/or sarcopenia. However, a number of trials have demonstrated a benefit of interventions to increase physical activity (in combination with nutritional counseling) on muscle function, muscle mass, and functional capacity. (78 - 82) These studies suggest that physical inactivity may, in part, contribute to decline in muscle function and/or muscle mass.

Social determinants of health—that is, where we live, learn, work, and play (83) —also play a role in the development of malnutrition, frailty, and sarcopenia. Health literacy is primarily governed by socioeconomic factors and is associated with physical frailty among liver transplant candidates. (84) Food insecurity owing to social factors such as poverty, isolation, or limited access to nutritious food is associated with advanced liver disease in patients with NAFLD. (85) Financial strain may limit caregiver presence in the home, resulting in limited monitoring, limited supervision for physical activity, and less attentive management of cirrhosis complications (e.g., timely lactulose therapy for HE). Conversely, increased patient needs impact caregiver productivity and earning potential. Some caregivers of patients with cirrhosis lose employment, (86) potentially worsening financial strain and thus the ability to provide adequate nutrition and management of cirrhosis complications that contribute to malnutrition.

Factors at the local, community, and national levels can exacerbate the development of malnutrition, frailty, and sarcopenia in this population. Community-level barriers to access to nutritious food may accelerate the development of all of these factors, including obesity, in some populations and drive adverse outcomes. In pediatric liver transplant recipients, neighborhood deprivation, an administrative metric of socioeconomic status, has been shown to be independently associated with mortality. (87) Given the complexity of managing patients with cirrhosis, there may

be insufficient time during clinical visits to devote to identifying factors and developing strategies to target the contributing causes. Although a referral to, or comanagement with, a registered dietitian with expertise in managing patients with advanced liver disease is ideal, some health care systems may not offer this resource or allow for longitudinal follow-up to assess for response to treatment recommendations. Furthermore, there may be confusion about which provider is responsible for management (e.g., primary care physician, hepatologist, registered dietitian), despite the importance of a multimodal, multidisciplinary approach.

Tools to assess frailty as a multidimensional construct (e.g., global frailty) or its individual components (e.g., physical frailty, disability, functional status) that have been studied in adults or children with cirrhosis are listed in Table 2 . (115 - 128) The tools are organized in the table from subjective, survey-based tools assessed by the patient, caregiver, or clinician to objective, performance-based assessments. The majority of these tools have been studied in the ambulatory setting only, underscoring the original “geriatric” construct of frailty as a chronic state of decreased physiologic reserve. However, the strong prognostic value of the two tools that have been studied in the acute care setting—activities of daily living (ADLs) and Karnofsky Performance Status (KPS)—highlights the pragmatic need for tools to measure the effects of frailty and sarcopenia in patients with acute cirrhosis complications.

Some scales have validated thresholds to grade the severity of frailty. Specifically, patients can be categorized as having high, moderate, or low performance status using KPS thresholds of 80-100, 50-70, or 10-40, respectively. (88 , 89) The Liver Frailty Index also has established cut-points to define robust (Liver Frailty Index < 3.2), prefrail (Liver Frailty Index 3.2-4.3), and frail (Liver Frailty Index $\geq$ 4.4). (90 , 91) Poor performance according to some scales (e.g., ADLs), however, suggests a greater burden of functional deficits than others (e.g., walk speed). The only tools that have also evaluated the associations between longitudinal assessments and outcomes in patients with cirrhosis are the KPS scale and the Liver Frailty Index. (88 , 92)

When it comes to assessing frailty in children, the well-established tools for assessment of frailty in adults are challenging to administer given the need for participation in the tests (either by survey or by performance) and consideration of age-related and sex-related norms. However, a few studies have demonstrated that the concept of frailty has clear applicability to children with chronic liver disease. The traditional Fried frailty phenotype, developed in older adults and validated in patients with cirrhosis of all ages, has been modified for children. (93) Although assessment of frailty was feasible in this cohort of children 5-17 years of age, the majority of children undergoing liver transplantation are too young to use the Modified Fried Frailty Instrument (median age 18 years), highlighting the need to derive an objective pediatric frailty assessment tool for children < 2 years of age. One promising metric is the Lansky Play-Performance Scale, a measure of global functional status developed for children with cancer aged 1-16 years, which can be assessed by the patient, caregiver, or clinical provider. (94) Gaps remain in the measurement of muscle contractile function among those < 1 year of age.

Frailty is common among patients with cirrhosis; its prevalence increases with liver disease severity. Estimates of frailty prevalence in this population have varied because of the use of a number of different tools to capture impaired muscle contractile function. Among patients with cirrhosis in the ambulatory setting, the reported prevalence of frailty has ranged from 17% to 43%. (54 , 75 , 95 , 96) Among hospitalized patients with cirrhosis, the prevalence of frailty is as high as 38% for inpatients with HE (and 18% for those without HE) when measured as disability using the ADL tool. (97 , 98) Rates of frailty have been reported to be as high as 68% when measured as impaired performance status using the KPS scale. (89) Using the Modified Fried Frailty Instrument, 24% of children with chronic liver disease met the criteria for frailty, with rates as high as 46% among children with more advanced/end-stage liver disease. (93)

Frailty worsens in the majority of patients with cirrhosis over time. (88 , 92) Among patients awaiting liver transplantation in the United States, < 20% displayed improved or stable KPS scores. (88) After liver transplantation, at least 90% experience some improvement in their KPS scores,

with a median improvement of 20% by 1 year posttransplant. (88) Frailty, as measured by the Liver Frailty Index, improved in only 16% of 1,093 patients with cirrhosis awaiting liver transplantation during a median follow-up time of 10.6 months on the waitlist. (92) At 3, 6, and 12 months after liver transplantation, Liver Frailty Index scores worsened from pretransplant values in 59%, 41%, and 32% of patients, respectively. Only 20% of patients achieved functional “robustness” as defined by a Liver Frailty Index score of ≤ 3.2 by 1 year after liver transplantation. (99)

Frailty has been strongly linked with mortality in both the ambulatory and acute care settings as well as the posttransplant setting. (54 , 75 , 88 , 89 , 92 - 94 , 96 , 97 , 100 - 108) For example, frailty, by the Liver Frailty Index, was associated with a nearly 2-fold increased adjusted risk of death in a study of > 1,000 ambulatory patients with cirrhosis awaiting liver transplantation at 9 US centers (sub-HR, 1.82; 95% CI, 1.31-2.52). (54) In another study including 734 hospitalized patients with cirrhosis, disability, as assessed by the need for some assistance with three or more ADLs, was associated with a nearly 2-fold increased adjusted odds of 90-day mortality (OR, 1.83; 95% CI, 1.05-3.20). (97) In the posttransplant setting, compromised functional performance, by the KPS score, was associated with higher HRs for death after liver transplantation (for KPS 50%-70%: HR, 1.18; 95% CI, 1.13-1.24; for KPS 10%-40%: HR, 1.43; 95% CI, 1.35-1.52). (88)

Importantly, changes in frailty over time—both worsening and improvement—are informative of mortality risk. (88 , 92) Among 1,093 patients with cirrhosis at eight US sites, each 0.1 unit change in the Liver Frailty Index over 3 months was associated with a 2-fold increased hazard of waitlist mortality (HR, 2.04; 95% CI, 1.35-3.09), independent of baseline frailty and Model for End-Stage Liver Disease-Sodium (MELD-Na) score. Cumulative rates of waitlist mortality at 6 months were 12.1% among those who experienced severe worsening compared with 7% among those who remained stable. Although this was a purely observational study, it is worth noting that those who displayed improved frailty scores demonstrated a 6-month cumulative incidence of waitlist mortality of only 0.6%, suggesting the potential benefit of interventions targeting frailty to reduce mortality in this population. (92)

Baseline frailty measures have been linked with outcomes other than mortality. These outcomes include metrics of health care use in both ambulatory patients (e.g., unplanned hospitalizations, health care costs, recovery of physical function after liver transplantation) and hospitalized patients (e.g., readmissions, prolonged length of stay, discharge to a rehabilitation facility). (89 , 97 , 99 , 105 , 109) Furthermore, frailty is strongly associated with patient-reported outcomes, including development of falls, depression, disability, and global health-related quality of life. (109 - 114)

Methods to assess muscle mass in patients with cirrhosis are detailed in Table 3 . (171 - 178)

CT imaging is currently the gold standard for assessment of muscle mass in cirrhosis, but cost and exposure to ionizing radiation make routine use of CT solely for the purpose of detecting sarcopenia impractical in many clinical settings. (129) However, when abdominal CT imaging is performed for clinical reasons—such as in patients with HCC or for surgical planning (e.g., transplant, hepatectomy)—muscle mass measurement can be obtained from clinical scans using readily available quantitative morphomics software. (130) Muscle mass is conventionally reported as the SMI, calculated as the total skeletal muscle area at L3 normalized to height. (131) Total psoas muscle area has also been studied in patients with cirrhosis (along with psoas muscle index, calculated as total psoas muscle area normalized to height) but has been shown to be less strongly correlated with total body protein as determined by dual-energy X-ray absorptiometry (DEXA) than skeletal muscle area. (132) Furthermore, psoas muscle index led to greater misclassification of mortality risk in adult patients with cirrhosis when compared with SMI. (133) Quantitative morphomics by MRI is less well studied in patients with cirrhosis but offers the same theoretical advantages as CT-based measures of muscle mass (and is often more costly and less readily available in resource-limited settings). (134)

Measures of muscle mass other than cross-sectional imaging have been studied in patients with cirrhosis. Assessment of fat-free mass by bioelectrical impedance analysis (BIA), including segmental BIA, has been shown to modestly correlate with muscle mass and is associated with mortality in patients with cirrhosis. (71 , 135 - 140) Fluid retention impacts the reliability of lean body mass estimates by BIA. (141) Phase angle measurements have good reliability in patients with cirrhosis, even among those with ascites. (136) Availability of BIA devices for routine clinical practice is currently limited, although availability of portable BIA devices may increase the acceptability of BIA measures of body composition. Other methods to assess muscle mass, such as DEXA scanning or anthropometrics, may be more available in some practice settings worldwide but have limitations in patients with cirrhosis due to fluid retention in certain body compartments. (138 , 142 - 145) Anthropometrics, although valuable in pediatric populations, (146) are vulnerable to high interobserver variability and the inability to distinguish different body compartments (lean versus fat mass), which is of particular relevance given increasing rates of obesity in populations with cirrhosis. (142)

Sarcopenia assessment is particularly useful in the pediatric population because muscle contractile function can be difficult to assess in young children. Measures of muscle mass can provide an objective measure of growth because anthropometric measures such as weight, BMI, midarm circumference, triceps skin fold thickness, and serum markers such as albumin are often confounded by concurrent ascites, peripheral edema, and organomegaly. (147 - 149) This is particularly relevant in infants, for whom ascites limits the value of standard anthropometric measurements. Similar to adults, CT imaging with quantitative morphomics provides the most accurate assessment of muscle mass, with more data supporting the use of total psoas muscle versus total skeletal muscle mass, including reference values for children aged 1-16 years. (147 , 150 - 152) Longitudinal measurements, including rate of change, are even more relevant given the dynamic changes with development in children.

Sarcopenia is common in adults with cirrhosis, affecting 30%-70% of patients with end-stage liver disease. (153) Similar to the general population, there are strong sex-based differences in the prevalence of sarcopenia, with 21% of women and 54% of men with cirrhosis awaiting liver transplantation meeting criteria for sarcopenia by SMI in one large multicenter study. (131) The degree of muscle loss correlates with severity of liver disease in men but not women. (154) In children, sarcopenia has been reported in 17%-40% of those with end-stage liver disease. (151 , 155 , 156)

Studies investigating sarcopenia in patients with cirrhosis have largely focused on muscle mass assessments in the ambulatory setting. Sarcopenia has been shown to be a robust predictor of a wide spectrum of outcomes in adults with cirrhosis both with and without HCC. (70 , 73 , 131 , 142 , 147 , 151 , 154 , 157 - 165) These outcomes have included not only mortality both before and after liver transplantation (131 , 160 , 161) but also hepatic decompensation, (166) reduced quality of life, (167) increased risk of infection, (157) and prolonged hospitalization. (44 , 73 , 168) In a meta-analysis of 3,803 liver transplant candidates across 19 studies in partly overlapping cohorts published between 2000 and 2015, "sarcopenia," as defined by a wide range of CT-assessed skeletal muscle mass cut-points, was associated with a pooled HR of 1.72 (95% CI, 0.99-3.00) for waitlist mortality and 1.84 (95% CI, 1.11-3.05) for posttransplant mortality. (159) A separate North American multicenter cohort of nearly 400 patients with cirrhosis listed for liver transplantation identified SMI cut-points to predict waitlist mortality: $< 39 \text{ cm}^2/\text{m}^2$ in women and $< 50 \text{ cm}^2/\text{m}^2$ in men. (131 , 169) These SMI cut-points were further validated in a separate cohort of all White patients. (131 , 169) Although the original derivation cohort consisted of patients with liver transplants in the ambulatory setting at five centers in North America, it predominantly consisted of non-Hispanic and Hispanic White patients, so additional validation in more diverse cohorts is warranted to evaluate the prognostic value of SMI across all populations. Most studies to date have used a static measure of sarcopenia, but recent data suggest that sarcopenia is progressive and that dynamic measures of rate of muscle loss from serial/longitudinal measures are predictors of clinical outcomes. (43)

In children with end-stage liver disease, sarcopenia has been associated with adverse outcomes including growth failure, hospitalizations, infections, and motor delay. (151 , 155 , 156)

“Sarcopenic obesity” refers to the state of decreased muscle mass in the setting of increased fat mass. This phenotype presents a unique clinical challenge in that it can be difficult to detect without dedicated testing because fat mass can mask underlying muscle wasting. (6) The prevalence of sarcopenic obesity in patients with cirrhosis ranges from 20% to 35%. (70 , 71 , 139) NAFLD has been shown to be a strong risk factor for sarcopenic obesity, even after adjustment for metabolic comorbidities. (69 , 170) Sarcopenic obesity, defined as low sex-adjusted SMI and BMI ≥ 25 kg/m², is an independent risk factor for mortality in patients with cirrhosis. (70 , 139) Rates of sarcopenic obesity are likely to increase as cirrhosis related to NAFLD increases.

Measures of muscle mass, particularly by cross-sectional imaging, have the advantage of being objective, reliable, and more easily reproducible than measures of muscle function. However, despite the prognostic importance of sarcopenia in patients with cirrhosis, its clinical use is currently hampered by the lack of inexpensive, safe, and readily available tests for assessment. On the other hand, many tools to assess frailty can be administered quickly in the ambulatory setting and at low cost and, perhaps most importantly, can be repeated at follow-up intervals. Furthermore, measures of muscle contractile function may be more closely associated than measures of muscle mass, with additional patient-reported outcomes including depression and the ability to complete basic life activities. (98 , 111 , 113 , 179 , 180)

For the purposes of clinical practice, one tool does not fit all. The choice of whether to measure frailty or sarcopenia (or both) depends on the specific clinical scenario and resources available. Given the ease, low cost, and repeatability of frailty metrics, we recommend routine assessment of frailty using a standardized tool—from which there are many to choose (Table 2)—in all ambulatory patients with cirrhosis. Assessment of muscle mass, on the other hand, may be useful in select groups, especially those in whom measures of frailty are unobtainable or unreliable. Such groups may include hospitalized patients, who often cannot perform performance-based tests of muscle contractile function. In this setting, preserved muscle mass may be an indicator of underlying physiologic reserve and suggest high potential for reversal of the patient’s acute presentation. Children with end-stage liver disease represent another subgroup in whom assessment of muscle mass may be more useful than measures of muscle contractile function given the limitations of performance-based testing in very young individuals (including infants).

For the purposes of research, frailty and sarcopenia represent important and complementary endpoints because they are robust and consistent predictors of outcomes in patients with cirrhosis. Given that the pathophysiology of sarcopenia in patients with cirrhosis is better elucidated than frailty, (57) sarcopenia may offer more precise mechanistic targets for drug development. In addition, assessment of muscle mass does not require active patient participation and therefore may be more appropriate as a research tool in patients who are critically ill and immobilized (e.g., on mechanical ventilation). However, frailty has the advantage of directly measuring how an individual functions and correlating strongly with how the individual feels, so frailty may be a more direct measure of a patient’s quality of life than sarcopenia. For these reasons, we recommend the inclusion of both frailty and sarcopenia as complementary endpoints in research studies.

Ideally, all patients with cirrhosis would receive intensive efforts to preserve muscle mass and contractile function on diagnosis of cirrhosis, but we recognize that this is not practical in most clinical settings given resource limitations. In an effort to guide the greatest resource allocation to those with the greatest need, we have grounded our recommendations within a classic three-level framework for disease prevention and health promotion, with each level representing different aims at different stages of disease requiring increasing intensities of assessment and action (Fig. 2). “Primary prevention” refers to routine screening to identify patients with sarcopenia or frailty. “Secondary prevention” refers to the initiation of therapy in patients diagnosed with sarcopenia or frailty. “Tertiary prevention” refers to the intensification of therapy in patients with sarcopenia or frailty not responding to first-line therapy. The ultimate goal is to prevent the occurrence of adverse

health outcomes attributable to malnutrition, frailty, and sarcopenia.

Using this framework, we have developed a clinical practice algorithm for screening, assessment, and management of malnutrition, frailty, and sarcopenia in patients with cirrhosis (Fig. 3). Key to this algorithm is the importance of reassessment of malnutrition risk, frailty, and sarcopenia—whether it be rescreening for the development or evaluating for worsening of these conditions. Although definitive intervals for reassessment have not been established in the literature, there are three points that have informed our recommendations for reassessment intervals. First, rates of frailty and sarcopenia increase with worsening liver disease severity, so patients with decompensated cirrhosis should be assessed more frequently than those with compensated cirrhosis. Second, clinical trials of interventions that target muscle dysfunction, such as testosterone, (67) nocturnal nutritional supplementation (181) or exercise, (79 , 80) evaluated outcomes at intervals no shorter than 8 weeks but as long as 3, 6, and 12 months. Third, the recent International Conference of Frailty and Sarcopenia Research consensus guidelines on frailty screening and management in primary care recommended screening for frailty (in the general geriatric population) on an annual basis. (182) Based on these points, we recommend that reassessment of malnutrition risk (refer to the “Screening for Malnutrition Risk” section), frailty, and sarcopenia occurs at least annually for patients with well-compensated disease but as frequently as every 8-12 weeks among those with decompensated cirrhosis and/or those undergoing active management for malnutrition, frailty, and sarcopenia.

Ideally, a multidisciplinary team, consisting of the patient's primary care provider, gastroenterologist/hepatologist, registered dietitian, certified exercise physiologist/physical therapist, and health behavior specialist—especially ones with expertise in managing patients with serious medical conditions, including advanced liver disease—would be involved with each level of management; but this may not be feasible in many practice settings. At a minimum, a patient should be referred to a registered dietitian and a certified exercise physiologist/physical therapist if malnutrition, frailty, and/or sarcopenia are progressive despite primary and secondary preventive efforts.

Given the interdependence of malnutrition, frailty, and sarcopenia in patients with cirrhosis, interventions that target one condition likely impact the other two conditions as well. Here, we provide pragmatic guidance for the management of malnutrition, frailty, and sarcopenia in patients with cirrhosis (Fig. 4). This information was intended for medical providers who are not specialists in nutrition or exercise to engage in primary and secondary prevention efforts (Fig. 2).

Multiple tools to screen for malnutrition have been evaluated in patients with cirrhosis. (183 - 187) Of these, the Royal Free Hospital Nutrition Prioritizing Tool (RFH-NPT) has been the most consistently associated with a diagnosis of malnutrition. (185 - 187) Patients are classified into three nutritional risk categories (low, moderate, and high) based on a combination of (1) presence of acute hepatitis or need for enteral nutritional support; (2) low BMI, unexplained weight loss, or maintenance of volitional nutritional intake; and (3) whether fluid overload interferes with ability to eat. Patients at high risk for malnutrition based on the RFH-NPT classification system have been shown to experience worse clinical outcomes including reduced survival, worsened liver function, and reduced quality of life. (187) Improvement in the RFH-NPT has been associated with improved survival. (187)

When possible, the cause of underlying chronic liver disease should be addressed. Eradication of chronic HCV is associated with a reduction in systemic inflammation, although levels of inflammatory biomarkers among individuals with advanced fibrosis remained elevated above levels measured in individuals who are not infected with HCV. Alcohol-associated skeletal myopathy may be partially reversible with alcohol cessation. (188) Although the exact mechanisms linking NAFLD with sarcopenia and sarcopenic obesity are not well understood, the shared pathophysiologic processes of chronic inflammation and insulin resistance (that lead to both NAFLD and sarcopenia) suggest that interventions targeting NAFLD have the potential to prevent muscle loss.

A strong theoretical basis exists for the management of frailty and sarcopenia with agents that lower circulating blood ammonia concentration or reduce its production. In an animal model, combined use of rifaximin and L-ornithine L-aspartate lowered plasma and muscle ammonia concentrations and improved muscle mass and function. (189) These data raise the possibility that agents used to manage HE may have a role in prevention and treatment of sarcopenia as well. However, data specifically evaluating the benefit of HE management strategies on muscle contractile function or muscle mass in patients with cirrhosis are lacking. Carnitine plays a key role in mitochondrial fatty acid oxidation, a process impaired by ammonia and central to mitochondrial function and energy metabolism. In small studies, administration of L-carnitine was associated with dose-related lowering of blood ammonia levels, a lower rate of muscle loss, reversal of existing sarcopenia, and increased levels of physical activity (190 - 192) However, a recent systematic review did not show benefit of acetyl-L-carnitine for the treatment of HE, (193) so its availability for the management of frailty and/or sarcopenia in clinical practice may be limited.

Medical therapy of fluid retention should be optimized as ascites and edema lead to early satiety, limit exercise capacity, and compromise mobility. In some patients, therapeutic paracentesis may improve anorexia, satiety, caloric intake, and exercise tolerance as well as reduce REE. (52 , 53 , 194) Use of loop diuretics in patients with cirrhosis and ascites has been associated with loss of muscle mass, although this finding is limited to one study and has not been confirmed in other cohorts (and its use must be balanced against the risk of poorly controlled fluid retention). (195)

Placement of a transjugular intrahepatic portosystemic shunt (TIPS) in patients with portal hypertensive complications has been associated with marked improvement in body composition with gain of lean body mass, lower visceral fat, and an increase in total and fat-free muscle mass. (134 , 196 - 199) However, failure to increase muscle mass after TIPS is seen in up to one third of patients and is associated with increased mortality; baseline sarcopenia is a strong risk factor for failure to improve muscle mass after TIPS. (134 , 197) There is currently no evidence supporting the use of TIPS explicitly for the management of frailty and/or sarcopenia, although TIPS placement for standard indications (e.g., ascites, variceal bleed) may offer indirect benefits to the patient in the form of improvement in muscle mass.

Liver transplantation is associated with improvement of frailty and sarcopenia in some, but not all, liver transplant recipients and often not to levels of age-matched and sex-matched norms. (99 , 101 , 168 , 200 - 203) In a prospective study that included 118 liver transplant recipients without HCC, the proportion of patients who were frail (Liver Frailty Index score ≥ 4.5) decreased from 29% pretransplant to 9% at 12 months after transplant, but only 30% met criteria for "robust" by a Liver Frailty Index <3.2 . (99) Rates of improvement were related to the severity of pretransplant frailty, (99) highlighting a need both for pretransplant interventions to prevent or minimize frailty and for mechanisms to identify and transplant patients before they become severely frail. With respect to sarcopenia, two separate studies including 53 and 40 liver transplant recipients demonstrated rates of improvement in muscle mass between 25% and 34% after liver transplantation; however, one of the studies demonstrated that 26% developed new-onset sarcopenia after liver transplant but did not identify any specific predictors of posttransplant muscle loss. (201 , 203) Similar to our recommendations regarding TIPS, liver transplantation may offer indirect benefits to improving frailty and/or sarcopenia in recipients but cannot be recommended specifically for the treatment of these two conditions.

Although frailty and/or sarcopenia may improve after liver transplantation in some patients, both pretransplant frailty and sarcopenia are associated with adverse outcomes, including mortality after liver transplantation. (88 , 99 , 160 - 163 , 204) When considering the presence of frailty or sarcopenia in the assessment of a patient's candidacy for liver transplantation, we recommend the use of objective, standardized metrics for frailty and/or sarcopenia for transplant decision-making. However, in the absence of data demonstrating specific thresholds of objective metrics of frailty or sarcopenia that balance risk of waitlist with posttransplant mortality, we do not recommend using frailty or sarcopenia as absolute contraindications against liver transplantation.

A personalized nutrition “prescription” should be provided to all patients with cirrhosis that is tailored to current nutritional status (i.e., a patient who meets criteria for frailty or sarcopenia should receive more intensive nutritional support to reach their targets than a patient who does not meet these criteria for malnutrition). Reassessment of nutritional intake should be repeated at regular intervals, with more frequent intervals reserved for those meeting criteria for frailty or sarcopenia at baseline and/or displaying worsening impairment of muscle contractile function or mass. If clinical deterioration or lack of improvement occurs despite target calorie and protein intake, additional causes should be considered, barriers addressed, and the nutrition prescription refined.

One of the most important elements of developing a personalized intake prescription is to calculate the patient's REE. Indirect calorimetry using a metabolic cart is the gold standard for measuring actual REE but is not widely available in all practice settings. Use of handheld calorimeters, a relatively inexpensive option to measure REE, has been validated in patients with cirrhosis to quantify REE and can be used at the bedside with high reliability in measuring REE (based on the gold standard of metabolic cart indirect calorimetry). (205 , 206) In the absence of indirect calorimetry, predictive equations (e.g., Harris-Benedict, Mifflin-St. Jeor) can be used to estimate an individual's daily energy expenditure; but there is considerable interindividual variation in measured versus predicted values of REE. (33)

Studies evaluating energy expenditure in patients with cirrhosis have demonstrated that total energy expenditure ranges from 28 to 38 kcal/kg/day. (207 - 210) Based on these data, current nutrition guidelines for patients with chronic liver diseases and/or cirrhosis recommend a weight-based daily caloric intake of at least 35 kcal/kg/day. (211 - 213) In patients with fluid retention, dry weight can be estimated using subjective assessments based on either (1) postparacentesis weight or (2) subtracting a percentage of weight based on the amount of fluid retention (mild, 5%; moderate, 10%; severe, 15%; additional 5% taken off with bilateral pedal edema to the knees). (211) Although data are lacking on actual energy use among patients with cirrhosis across the spectrum of BMI, there is increasing acceptance of the need for BMI-adjusted energy intake goals. In light of this, weight-based energy intake recommendations may be modified to 25-35 kcal/kg/day for individuals with BMI 30-40 kg/m² and 20-25 kcal/kg/day for individuals with BMI $\geq$ 40 kg/m². (213) Further research is required to evaluate the accuracy of weight-based equations across BMI strata. Until that time, given their ease of use in a busy clinical practice for patients who are nonhospitalized and patients who are clinically stable, we support using BMI-adjusted, weight-based energy intake calculations to develop personalized daily caloric targets when indirect calorimetry is not available and use of predictive equations (e.g., Harris-Benedict) is not practical.

Sodium restriction may reduce the palatability of food, representing a barrier to adequate nutrition intake. In a study of 120 outpatients with cirrhosis and ascites, only 31% were adherent to a 2-g-sodium diet, and adherent patients had a 20% lower daily caloric intake. (9) When patients are prescribed a sodium-restricted diet, it should be balanced with educational resources that offer suggestions to improve diet palatability. Liberalization of sodium restriction should be considered if the patient is unable to maintain nutritional targets because of diet unpalatability.

Studies dating as far back as the 1980s have established that patients with cirrhosis have increased protein needs. (210 , 214 - 216) In these studies, a positive protein balance was achieved above a protein intake of 1.2 g/kg/day (214 , 216) ; another study in patients with cirrhosis demonstrated the ability to use up to 1.8 g/kg/day of protein (210) A small randomized clinical trial of 30 hospitalized patients with cirrhosis and HE who received either protein restriction (0 g/day for the first 3 days, then gradual increase to 1.2 g/kg/day for the next 2 days) versus a normal-protein diet of 1.2 g/kg/day demonstrated accelerated protein catabolism in the protein-restricted group with no difference in evolution of HE between the two groups. (217) Based on these data, we recommend a protein intake of 1.2-1.5 g/kg/day for adults with cirrhosis because it is safe, does not worsen HE, and minimizes protein loss compared with lower protein doses. (217 , 218) For children with cirrhosis, protein intake of up to 4 g/kg/day has been shown to be safe and effective at improving anthropometrics (based on a single study with 10 children). (219) Although the existing literature

lacks consistency on whether the weight on which to calculate protein targets should be measured, dry, or ideal body weight, we recommend using ideal body weight (based on height) for pragmatic reasons.

Data evaluating the effect of the type of protein on nutritional status in patients with cirrhosis are limited. Several studies have demonstrated the benefits of vegetable and casein-based protein diets over meat protein diets to reduce HE. (220 - 222) In light of the limited evidence on malnutrition and the fact that meat may be a staple protein source for many patients, we currently do not recommend limiting the intake of meat-based protein sources. However, patients should be encouraged to consume protein from a diverse range of sources, including vegetable and dairy products when possible.

Some studies support the use of BCAA supplementation (e.g., leucine, isoleucine, and valine) in the management of cirrhosis-related complications, primarily HE, some of which evaluated the effect of BCAAs on nutritional status. (223 - 226) Two studies have demonstrated a reduction in clinical events and an improvement in quality of life with longer-term use of BCAAs. (223 , 225) However, in a meta-analysis of 16 RCTs evaluating BCAA supplementation (either orally or i.v.) in patients with HE, BCAAs had no effect on mortality, quality of life, or nutritional parameters (227) Children with chronic cholestatic liver disease have significantly higher BCAA requirements than healthy children. (228) One RCT of children with end-stage liver disease demonstrated benefit of BCAA-enriched nutritional support over a standard formula with respect to midarm muscular circumference (MAMC) and triceps skinfold thickness, but this study included only 12 children (229) Given that BCAAs are naturally present in protein-containing foods, we do not recommend long-term BCAA supplementation beyond recommended protein intake targets from a diverse range of protein sources.

Several other amino acid-based treatments have been studied in patients with cirrhosis, but there is currently insufficient patient-level evidence to definitively support their use for management of malnutrition, frailty, or sarcopenia in this population. These include β -hydroxy- β -methylbutyrate (a metabolite of leucine), (230 , 231) acetyl-L-carnitine (an amino acid that has been shown to reduce blood ammonia levels), (193) and L-ornithine L-aspartate (a combination of two endogenous amino acids that reduces blood ammonia levels). (232)

Timing of nutritional intake is essential to manage nutritional status in patients with cirrhosis. Prolonged periods of fasting should be avoided in cirrhosis, with evidence supporting the benefits on muscle mass of an early morning breakfast, late evening snack, and intake of small, frequent meals and snacks every 3-4 hours while awake. (181 , 233 , 234) A landmark study randomized 103 patients to daytime or nighttime supplemental nutrition of 710 kcal/day who otherwise had isocaloric, isonitrogenous diets. (181) Although most sustained in the Child-Turcotte-Pugh A patients, significant improvement in total body protein and fat-free mass was demonstrated in patients receiving nocturnal supplementation across all Child-Turcotte-Pugh classes. A diverse range of late-night snack options have been evaluated in the literature, with snacks varying from 149 to 710 kcal with varying carbohydrate and protein composition. (233) Given the range of personal habits regarding timing of regular food intake and preferences for types of snacks, we suggest a personalized approach to providing patients with recommendations on the timing of additional snacks (e.g., early breakfast versus late-evening snack) as well as snack content (e.g., protein bar, rice ball, yogurt).

A retrospective study of 75 patients with cirrhosis and known esophageal varices who underwent enteric tube placement demonstrated that 15% of patients experienced a gastrointestinal bleed within 48 hours of placement. (235) Higher MELD-Na score was a strong predictor of gastrointestinal bleeding. On the other hand, in a study of 14 outpatients with cirrhosis, continuous feeding through an enteric tube was associated with significant improvement of ascites, need for paracenteses, and handgrip strength without any reported complications. (236) Percutaneous gastrostomy placement is associated with a high risk of complications and mortality in patients with cirrhosis. (237) Based on these data, we recommend considering an enteric tube only in patients

who have failed a trial of oral supplementation; we strongly advise against placement of percutaneous feeding devices in patients with cirrhosis and ascites.

In patients who are overweight/obese with compensated cirrhosis, weight loss of 5%-10% has been associated with reduced disease progression and reduction of portal hypertension (238) but the effects of intentional weight loss on nutritional parameters, muscle contractile function, and muscle mass are less well studied. In a study of 160 dieting older adults without liver disease, intentional weight loss was associated with decreases in lean mass and bone mineral density; but this was mitigated by resistance training. (239) Given the evidence supporting the role of adequate protein intake in the preservation of overall nitrogen balance (see the " Protein Intake " section), we advise caution when recommending weight loss in patients with decompensated cirrhosis or known sarcopenic obesity. (6) If weight loss through caloric restriction must be prescribed in patients with cirrhosis for clinical reasons (e.g., to reduce NASH progression, for transplant listing), we recommend (1) ensuring adequate protein intake (1.2-1.5 g/kg/day) and (2) combination with an exercise program.

Existing meta-analyses of nutritional supplementation in hospitalized patients with cirrhosis have not been able to demonstrate an impact on mortality. (240 , 241) However, a subgroup analysis of three studies evaluating oral nutritional supplementation alone demonstrated a benefit in mortality in hospitalized patients with cirrhosis (risk ratio, 0.40; 95% CI, 0.18-0.90). (241) The benefit of oral supplementation is further supported by an RCT of patients hospitalized with severe acute alcohol-associated hepatitis in which enteral versus oral supplementation did not offer a benefit in mortality but adequate oral intake (defined as ≥ 22 kcal/kg/day)—regardless of mode of administration—reduced mortality by 67% (0.19-0.57) compared with patients who consumed < 22 kcal/kg/day. One study conducted at a single Veterans Affairs medical center demonstrated that a cirrhosis-specific nutrition education intervention targeted to physicians and dieticians involved in caring for inpatients with cirrhosis resulted in increased nutritional intake and reduction in 90-day hospital readmissions. (243) We recommend that all hospitalized patients with cirrhosis receive formal consultation by a registered dietician within 24 hours of admission or, if not possible, with the RFH-NPT. (213) Barriers to oral intake (e.g., fasting time, HE, nausea) should be promptly identified and addressed. In patients who screen positive for malnutrition in whom barriers have been addressed and who are unable to meet their nutrition targets through oral intake alone, enteral nutrition should be considered within 48-72 hours of hospital admission. (244 , 245) One common barrier is prolonged periods of fasting that result from frequent nil per os (NPO) orders for procedures; strategies to minimize this fasting period or frequency of NPO orders (e.g., prebedtime snack, early-morning snack if the procedure will be in the late afternoon, consider advancing diet rapidly when there is no indication for NPO status) should be implemented.

In the intensive care unit (ICU) population, limited cirrhosis-specific data are available to guide energy targets. Indirect calorimetry is the gold standard for determining total energy requirements in this setting. However, given the limited availability of indirect calorimetry in many hospital settings, predictive or weight-based estimations of energy needs may be used, recognizing the potential underestimation of energy needs in light of the dynamic metabolic requirements and fluid overload in patients with cirrhosis who are acutely ill. (244) In patients who are critically ill, it is generally recommended to use higher protein goals, targeting 1.2-2.0 g/kg/day. (244 , 246 , 247) Again, the literature is not clear whether these recommendations are based on dry or ideal body weight; therefore, we recommend using ideal body weight for pragmatic purposes.

For hospitalized patients with cirrhosis who are unable to meet energy needs through oral intake alone, enteral feeding should be considered (time course has not been established in the literature); for those who are critically ill and unable to maintain volitional intake, enteral feeding should be initiated within 24-48 hours of ICU admission. A meta-analysis of 21 RCTs comparing early versus delayed enteral nutrition in all patients who are critically ill (including those with cirrhosis) demonstrated a significant reduction in mortality (relative risk, 0.70; 95% CI, 0.49-1.00) and infectious morbidity (relative risk, 0.74; 95% CI, 0.58-0.93) among those receiving early enteral nutrition versus delayed enteral nutrition or standard of care. (244) In one RCT of 136 patients with

severe alcohol-associated hepatitis randomized (1:1) to intensive enteral nutritional support versus oral supplementation, enteral feeding had to be discontinued early in 49% of patients and was associated with three (4%) serious adverse events that were determined to be related to the intervention (one aspiration pneumonia, one decompensated diabetes, one severe worsening of HE); mortality benefit of supplemental nutrition was demonstrated only in patients ≥ 21.5 kcal/kg body weight/day, regardless of intervention arm. In two studies of early enteral feeding in patients with cirrhosis admitted with an esophageal variceal hemorrhage, placement of a nasogastric feeding tube was associated with a 10%-33% rate of rebleeding. (235 , 248)

Data around the use of parenteral nutrition in cirrhosis are limited, but meta-analyses in the general critically ill population have reported a higher incidence of hyperglycemia and sepsis (but an improvement in mortality when compared with patients receiving enteral nutrition). (249 , 250) Parenteral nutrition should be considered as a second-line option to enteral nutrition in patients who are unable to meet their nutritional requirements by oral intake alone and is strongly preferable to no nutritional supplementation in patients who are hospitalized and meet criteria for frailty or sarcopenia.

Vitamin and mineral deficiencies are common in cirrhosis regardless of etiology of liver disease and are particularly prevalent in patients with advanced disease, cholestasis, or acute illness. (251 , 252) Routine assessment for micronutrient deficiencies and appropriate repletion are recommended in patients with cirrhosis. (253) Recommendations for repletion of certain micronutrients that have been better studied in patients with cirrhosis are detailed in Table 4 . (255 - 261) There is little evidence to guide longer-term maintenance dosing once deficiency has been corrected. Decisions for use of longer-term maintenance dosing will depend on assessment of whether the patient remains at nutritional risk (e.g., still consuming alcohol or with low oral intake).

However, because vitamin and mineral status may not be regularly assessed in clinical practice because of competing demands from other cirrhosis complications (e.g., management of protein-calorie malnutrition, ascites, HE, etc.)—and multivitamin supplementation is inexpensive and essentially free of side effects—we support a pragmatic approach of an empiric course of oral multivitamin supplementation in patients with cirrhosis who display any evidence of frailty or sarcopenia, as has been proposed in the general population. (254)

Physical activity–based interventions have been shown to improve muscle contractile function and muscle mass as well as cardiopulmonary function and quality of life in patients with cirrhosis. (78 - 81 , 238 , 262 - 265) The caveat to interpretation of these studies in this population is that they have been limited by small sample size and inclusion of primarily well-compensated patients.

There are three general principles to consider when recommending activity-based interventions for patients with cirrhosis: (1) assess frailty and/or sarcopenia with a standardized tool, (2) recommend a combination of aerobic and resistance exercises, and (3) tailor recommendations based on the physical assessment and reassessments.

Assess frailty and/or sarcopenia with a standardized tool. This should occur at baseline and longitudinally to assess response to the intervention. Improvement in frailty has been associated with lower rates of mortality compared with worsening of frailty in patients with decompensated cirrhosis. (92) Data are lacking on the potential benefits of changes in sarcopenia.

Recommend a combination of aerobic and resistance exercises. Activity-based interventions in patients with cirrhosis have ranged in duration from 8 to 64 weeks. (266) Exercise prescriptions can be guided by principles of frequency, intensity, time, and type, as detailed in the management toolbox (Fig. 4) and adapted from the American College of Sports Medicine. (267) Although the type of exercise (e.g., aerobic only or combination aerobic and resistance training) has varied in these studies, the general consensus is that the optimal activity-based intervention should include a combination of aerobic and resistance training. The theoretical framework for this recommendation

is that aerobic training may address impaired muscular endurance and cardiopulmonary fitness, whereas resistance training specifically addresses skeletal muscle strength and mass. (263) Data on what constitutes an adequate level of aerobic activity in patients with cirrhosis are limited, although it is reasonable to follow Centers for Disease Control guidelines to achieve 150-300 minutes of moderate to vigorous intensity exercise per week and muscle-strengthening exercises at least 2 days per week. (268) The use of technology, including fitness trackers, can provide more accurate and objective data on an individual's actual physical activity better than self-report alone. (76) Smartphone-based fitness apps designed for persons with cirrhosis may have a role in facilitating increased exercise and activity in patients with cirrhosis. (269)

Tailor recommendations based on baseline assessment and reassessments . This includes modifying the intensity of the physical activity intervention based on the presence of frailty and/or sarcopenia. (270) It also includes adapting recommendations based on risk for adverse events related to increased mobility, such as musculoskeletal injury and falls. (271) Studies evaluating activity-based interventions in patients with cirrhosis to date have demonstrated a good safety profile of exercise, (238 , 272 , 273) but most studies to date have primarily included patients with well-compensated cirrhosis. A number of unanswered questions regarding an exercise program in cirrhosis remain, including the duration, time of day, and impact of concurrent exercise on responses. (274) Notwithstanding these, it is prudent for patients to optimize their portal hypertensive complications (e.g., ascites control, variceal prophylaxis, optimal HE therapies) before initiating an activity-based program.

In one study of 101 male patients with cirrhosis and low testosterone (defined as total testosterone < 12 nmol/L or free testosterone < 230 pmol/L), testosterone replacement increased muscle mass, decreased fat mass, and improved glucose metabolism. (67) The anabolic effect of testosterone on muscle may be related to suppression of muscle cell apoptosis and myostatin production. (275) However, exogenous testosterone is also associated with increased risk for HCC and thrombophilia. Testosterone therapy may be indicated for some men with cirrhosis, but the risk/benefit profile must be individualized. For men with a personal or family history of HCC, prostate cancer, or thrombophilia, the risk of testosterone replacement may outweigh potential benefits.

In patients with cirrhosis, frailty and sarcopenia are prevalent and lethal. The last decade has welcomed a large body of literature solidifying the importance of frailty and sarcopenia on outcomes in patients with cirrhosis and has brought with it exciting opportunities for future research. Although the possibilities are endless, we highlight three that we believe are the most urgently needed:

Standardized, feasible assessment of frailty and sarcopenia in diverse populations of patients with cirrhosis with respect to sex/gender, race/ethnicity, and clinical acuity . The literature has been lacking on detailed comparisons of frailty and sarcopenia by not only biological sex but also self-identified gender. Cohorts should be enriched with patients of diverse racial/ethnic backgrounds to better understand variation in racial/ethnic differences in manifestations of malnutrition, frailty, and sarcopenia and the implications on clinical outcomes. Lastly, more studies are needed in patients with decompensated cirrhosis, particularly those who are acutely ill.

Longitudinal assessment of frailty and sarcopenia. This includes evaluation of the natural progression as well as predictors of accelerated decline. Studies evaluating any treatments in this population (e.g., antiviral agents, alcohol abstinence, management of ascites, TIPS, liver transplantation) should also investigate the impact of those interventions on muscle function and muscle mass.

Development of therapeutics and multimodal strategies targeting frailty and sarcopenia. Frailty and sarcopenia are measurable and clinically significant. The objective measurement of these conditions enables a field of research focused on reversing or slowing their consequences. This will require collaboration across many disciplines, including hepatology, surgery, nutrition, and physiotherapy; but it will also require collaboration across industries, including academia and

pharmaceutical and biotechnology firms. One essential step for the development of therapeutics is certification by the Food and Drug Administration of clinically meaningful endpoints of frailty and sarcopenia.

The authors are grateful for the valuable contributions of the AASLD Practice Guideline Committee (PGC), particularly Barry Schlansky. Members of the PGC include George Ioannou (chair), Rabab Ali, Scott W. Biggins, Roniel Cabrera, Henry Chang, Michael F. Chang, David S. Goldberg, Ruben Hernaez, Binu John, Patricia D. Jones, W. Ray Kim (board liaison), Cynthia Levy, Jeff McIntyre, Jessica L. Mellinger, Mindie H. Nguyen, Nadia Ovchinsky, Mary E.M. Rinella (board liaison), Anjana A. Pillai, Daniel S. Pratt, Hugo R. Rosen, Barry Schlansky, Matthew J. Stotts, Christopher J. Sonnenday, Lisa B. VanWagner, and Elizabeth C. Verna.

Supported by the American Association for the Study of Liver Diseases. Dr. Lai is partially supported by R01 AG059183 and R21 AG067554. Srinivasan Dasarathy is partially supported by NIH RO1 GM119174; RO1 DK113196; P50 AA024333; RO1 AA021890; 3U01AA026976 - 03S1; UO1 AA 026976; R56HL141744;UO1 DK061732; 5U01 DK062470-17S2.

Potential conflict of interest: Dr. Lai received grants from Axcella and Lipocine. Dr. Bernal advises Versantis.

American Association for the Study of Liver Diseases

Model for End-Stage Liver Disease-Sodium

Royal Free Hospital Nutrition Prioritizing Tool

transjugular intrahepatic portosystemic shunt.

10.1016/j.clnu.2006.02.007 . 16697086 2) Morley JE , Vellas B , Abellan van Kan G , Anker SD , Bauer JM , Bernabei R , Frailty consensus: a call to action . J Am Med Dir Assoc 2013 ; 14 : 392 – 397 . 23764209 10.1016/j.jamda.2013.03.022 PMC4084863 3) Cruz-Jentoft AJ , Bahat G , Bauer J , Boirie Y , Bruyère O , Cederholm T , Sarcopenia: revised European consensus on definition and diagnosis . Age Ageing 2019 ; 48 : 16 – 31 . 10.1093/ageing/afy169 . 30312372 PMC6322506 4) World Health Organization . Malnutrition . https://www.who.int/health-topics/malnutrition#tab=tab_1 . Accessed June 15, 2020 . 5) Bunchorntavakul C , Reddy KR . Review article: malnutrition/sarcopenia and frailty in patients with cirrhosis . Aliment Pharmacol Ther 2020 ; 51 : 64 – 77 . 10.1111/apt.15571 . 31701570 6) Eslamparast T , Montano-Loza AJ , Raman M , Tandon P . Sarcopenic obesity in cirrhosis—the confluence of 2 prognostic titans . Liver Int 2018 ; 38 : 1706 – 1717 . 10.1111/liv.13876 . 29738109 7) Volk ML , Fisher N , Fontana RJ . Patient knowledge about disease self-management in cirrhosis . Am J Gastroenterol 2013 ; 108 : 302 – 305 . 10.1038/ajg.2012.214 . 23459041 PMC3819196 8) Beg S , Curtis S , Shariff M . Patient education and its effect on self-management in cirrhosis: a pilot study . Eur J Gastroenterol Hepatol 2016 ; 28 : 582 – 587 . 10.1097/MEG.0000000000000579 . 27015016 9) Morando F , Rosi S , Gola E , Nardi M , Piano S , Fasolato S , Adherence to a moderate sodium restriction diet in outpatients with cirrhosis and ascites: a real-life cross-sectional study . Liver Int 2015 ; 35 : 1508 – 1515 . 10.1111/liv.12583 . 24811138 10) Wu J , Meng QH . Current understanding of the metabolism of micronutrients in chronic alcoholic liver disease . World J Gastroenterol 2020 ; 26 : 4567 – 4578 . 10.3748/wjg.v26.i31.4567 . 32884217 PMC7445863 11) Sanvisens A , Zuluaga P , Pineda M , Fuster D , Bolao F , Juncà J , Folate deficiency in patients seeking treatment of alcohol use disorder . Drug Alcohol Depend 2017 ; 180 : 417 – 422 . 10.1016/j.drugalcdep.2017.08.039 . 28988003 12) Lewis MJ . Alcoholism and nutrition: a review of vitamin supplementation and treatment . Curr Opin Clin Nutr Metab Care 2020 ; 23 : 138 – 144 . 10.1097/MCO.0000000000000622 . 31977336 13) Phillips JR , Angulo P , Petterson T , Lindor KD . Fat-soluble vitamin levels in patients with primary biliary cirrhosis . Am J Gastroenterol 2001 ; 96 : 2745 – 2750 . 11569705 10.1111/j.1572-0241.2001.04134.x 14) Jorgensen RA , Lindor KD , Sartin JS , LaRusso NF ,

Wiesner RH . Serum lipid and fat-soluble vitamin levels in primary sclerosing cholangitis . *J Clin Gastroenterol* 1995 ; 20 : 215 – 219 . 10.1097/00004836-199504000-00011 . 7797830 15) Holick MF Vitamin D deficiency . *N Engl J Med* 2007 ; 357 : 266 – 281 . 10.1056/NEJMra070553 . 17634462 16) Arteh J , Narra S , Nair S . Prevalence of vitamin D deficiency in chronic liver disease . *Dig Dis Sci* 2009 ; 55 : 2624 – 2628 . 10.1007/s10620-009-1069-9 . 19960254 17) Kubesch A , Quenstedt L , Saleh M , Rüschenbaum S , Schwarzkopf K , Martinez Y , Vitamin D deficiency is associated with hepatic decompensation and inflammation in patients with liver cirrhosis: a prospective cohort study . *PLoS One* 2018 ; 13 : e0207162 . 10.1371/journal.pone.0207162 . 30408125 PMC6224127 18) Guo G-Y , Shi Y-Q , Wang L , Ren X , Han Z-Y , Guo C-C , Serum vitamin D level is associated with disease severity and response to ursodeoxycholic acid in primary biliary cirrhosis . *Aliment Pharmacol Ther* 2015 ; 42 : 221 – 230 . 10.1111/apt.13244 . 25982180 19) Riggio O , Merli M , Capocaccia L , Caschera M , Zullo A , Pinto G , Zinc supplementation reduces blood ammonia and increases liver ornithine transcarbamylase activity in experimental cirrhosis . *Hepatology* 1992 ; 16 : 785 – 789 . 10.1002/hep.1840160326 . 1505922 20) Nishikawa H , Yoh K , Enomoto H , Iwata Y , Sakai Y , Kishino K , Serum zinc level is associated with frailty in chronic liver diseases . *J Clin Med* 2020 ; 9 : 1570 . 10.3390/jcm9051570 . PMC7290657 32455875 21) Nishikawa H , Enomoto H , Yoh K , Iwata Y , Sakai Y , Kishino K , Serum zinc concentration and sarcopenia: a close linkage in chronic liver diseases . *J Clin Med* 2019 ; 8 : 336 . 10.3390/jcm8030336 . PMC6462961 30862022 22) Rocchi E , Borella P , Borghi A , Paolillo F , Pradelli M , Farina F , Zinc and magnesium in liver cirrhosis . *Eur J Clin Invest* 1994 ; 24 : 149 – 155 . 10.1111/j.1365-2362.1994.tb00980.x . 8033947 23) Aagaard NK , Andersen H , Vilstrup H , Clausen T , Jakobsen J , Dørup I . Muscle strength, Na, K-pumps, magnesium and potassium in patients with alcoholic liver cirrhosis—relation to spironolactone . *J Intern Med* 2002 ; 252 : 56 – 63 . 10.1046/j.1365-2796.2002.01008.x . 12074739 24) Aagaard NK , Andersen H , Vilstrup H , Clausen T , Jakobsen J , Dørup I . Decreased muscle strength and contents of Mg and Na, K-pumps in chronic alcoholics occur independently of liver cirrhosis . *J Intern Med* 2003 ; 253 : 359 – 366 . 10.1046/j.1365-2796.2003.01100.x . 12603504 25) Heubi JE , Higgins JV , Argao EA , Sierra RI , Specker BL . The role of magnesium in the pathogenesis of bone disease in childhood cholestatic liver disease: a preliminary report . *J Pediatr Gastroenterol Nutr* 1997 ; 25 : 301 – 306 . 10.1097/00005176-199709000-00010 . 9285381 26) Maillette de Buy Wenniger L , Beuers U . Bile salts and cholestasis . *Dig Liver Dis* 2010 ; 42 : 409 – 418 . 10.1016/j.dld.2010.03.015 . 20434968 27) Yu R , Wang Y , Xiao Y , Mo L , Liu A , Li D , Prevalence of malnutrition and risk of undernutrition in hospitalised children with liver disease . *J Nutr Sci* 2017 ; 6 : e55 . 10.1017/jns.2017.56 . 29152259 PMC5672325 28) Venu M , Martin E , Saeian K , Gawrieh S . High prevalence of vitamin A deficiency and vitamin D deficiency in patients evaluated for liver transplantation . *Liver Transpl* 2013 ; 19 : 627 – 633 . 10.1002/lt.23646 . 23495130 PMC3667969 29) Owen OE , Reichle FA , Mozzoli MA , Kreulen T , Patel MS , Elfenbein IB , Hepatic, gut, and renal substrate flux rates in patients with hepatic cirrhosis . *J Clin Invest* 1981 ; 68 : 240 – 252 . 10.1172/JCI110240 . 7251861 PMC370791 30) Owen OE , Trapp VE , Reichard GA , Mozzoli MA , Moctezuma J , Paul P , Nature and quantity of fuels consumed in patients with alcoholic cirrhosis . *J Clin Invest* 1983 ; 72 : 1821 – 1832 . 10.1172/JCI111142 . 6630528 PMC370471 31) Madden AM , Morgan MY . Resting energy expenditure should be measured in patients with cirrhosis, not predicted . *Hepatology* 1999 ; 30 : 655 – 664 . 10.1002/hep.510300326 . 10462371 32) Peng S , Plank LD , McCall JL , Gillanders LK , McIlroy K , Gane EJ . Body composition, muscle function, and energy expenditure in patients with liver cirrhosis: a comprehensive study . *Am J Clin Nutr* 2007 ; 85 : 1257 – 1266 . 17490961 10.1093/ajcn/85.5.1257 33) Eslamparast T , Vandermeer B , Raman M , Gramlich L , Den Heyer V , Belland D , Are predictive energy expenditure equations accurate in cirrhosis? *Nutrients* 2019 ; 11 : 334 . 10.3390/nu11020334 . PMC6412603 30720726 34) Mullen KD , Denne SC , McCullough AJ , Savin SM , Bruno D , Tavill AS , Leucine metabolism in stable cirrhosis . *Hepatology* 1986 ; 6 : 622 – 630 . 10.1002/hep.1840060412 . 3089896 35) Yamato M , Muto Y , Yoshida T , Kato M , Moriwaki H . Clearance rate of plasma branched-chain amino acids correlates significantly with blood ammonia level in patients with liver cirrhosis . *Int Hepatol Commun* 1995 ; 3 : 91 – 96 . 10.1016/0928-4346(94)00159-3 . 36) Montanari A , Simoni I , Vallisa D , Trifirò A , Colla R , Abbiati R , Free amino acids in plasma and skeletal muscle of patients with liver cirrhosis . *Hepatology* 1988 ; 8 : 1034 – 1039 . 10.1002/hep.1840080509 . 3417224 37) Vilstrup H , Amodio P , Bajaj J , Cordoba J , Ferenci P , Mullen KD , Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the Study of Liver

Diseases and the European Association for the Study of the Liver . *Hepatology* 2014 ; 60 : 715 – 735 . 25042402 10.1002/hep.27210 38) Shawcross DL , Wright GAK , Stadlbauer V , Hodges SJ , Davies NA , Wheeler-Jones C , Ammonia impairs neutrophil phagocytic function in liver disease . *Hepatology* 2008 ; 48 : 1202 – 1212 . 10.1002/hep.22474 . 18697192 39) Shalimar Sheikh MF , Mookerjee RP , Agarwal B , Acharya SK , Jalan R . Prognostic role of ammonia in patients with cirrhosis . *Hepatology* 2019 ; 70 : 982 – 994 . 10.1002/hep.30534 . 30703853 40) Chen HW , Dunn MA . Muscle at risk: the multiple impacts of ammonia on sarcopenia and frailty in cirrhosis . *Clin Transl Gastroenterol* 2016 ; 7 : e170 . 10.1038/ctg.2016.33 . 27228401 PMC4893684 41) Dasarathy S , Hatzoglou M . Hyperammonemia and proteostasis in cirrhosis . *Curr Opin Clin Nutr Metab Care* 2018 ; 21 : 30 – 36 . 10.1097/MCO.0000000000000426 . 29035972 PMC5806198 42) Davuluri G , Allaway A , Thapaliya S , Rennison JH , Singh D , Kumar A , Hyperammonaemia-induced skeletal muscle mitochondrial dysfunction results in cataplerosis and oxidative stress . *J Physiol* 2016 ; 594 : 7341 – 7360 . 10.1113/JP272796 . 27558544 PMC5157075 43) Welch N , Dasarathy J , Runkana A , Penumatsa R , Bellar A , Reen J , Continued muscle loss increases mortality in cirrhosis: impact of aetiology of liver disease . *Liver Int* 2020 ; 40 : 1178 – 1188 . 10.1111/liv.14358 . 31889396 PMC7195232 44) Vural A , Attaway A , Welch N , Zein J , Dasarathy S . Skeletal muscle loss phenotype in cirrhosis: a nationwide analysis of hospitalized patients . *Clin Nutr* 2020 ; 39 : 3711 – 3720 . 10.1016/j.clnu.2020.03.032 . 32303380 PMC7541467 45) DiMartini A , Cruz RJ , Dew MA , Myaskovsky L , Goodpaster B , Fox K , Muscle mass predicts outcomes following liver transplantation . *Liver Transpl* 2013 ; 19 : 1172 – 1180 . 10.1002/lt.23724 . 23960026 PMC4382961 46) Thapaliya S , Runkana A , McMullen MR , Nagy LE , McDonald C , Prasad SVN , Alcohol-induced autophagy contributes to loss in skeletal muscle mass . *Autophagy* 2014 ; 10 : 677 – 690 . 10.4161/auto.27918 . 24492484 PMC4091154 47) Bousquet-Dubouch M-P , Nguen S , Bouyssie D , Burlet-Schiltz O , French SW , Monsarrat B , Chronic ethanol feeding affects proteasome-interacting proteins . *Proteomics* 2009 ; 9 : 3609 – 3622 . 10.1002/pmic.200800959 . 19609968 PMC2766596 48) Lang CH , Frost RA , Svanberg E , Vary TC . IGF-I/IGFBP-3 ameliorates alterations in protein synthesis, eIF4E availability, and myostatin in alcohol-fed rats . *Am J Physiol Endocrinol Metab* 2004 ; 286 : E916 – E926 . 10.1152/ajpendo.00554.2003 . 14749210 49) Bhanji RA , Narayanan P , Allen AM , Malhi H , Watt KD . Sarcopenia in hiding: the risk and consequence of underestimating muscle dysfunction in nonalcoholic steatohepatitis . *Hepatology* 2017 ; 66 : 2055 – 2065 . 10.1002/hep.29420 . 28777879 50) Abrigo J , Gonzalez F , Aguirre F , Tacchi F , Gonzalez A , Meza MP , Cholic acid and deoxycholic acid induce skeletal muscle atrophy through a mechanism dependent on TGR5 receptor . *J Cell Physiol* 2021 ; 236 : 260 – 272 . 10.1002/jcp.29839 . 32506638 51) Tapper EB , Aberasturi D , Zhao Z , Hsu CY , Parikh ND . Outcomes after hepatic encephalopathy in population-based cohorts of patients with cirrhosis . *Aliment Pharmacol Ther* 2020 ; 51 : 1397 – 1405 . 10.1111/apt.15749 . 32363684 PMC7266029 52) Aql BA , Scolapio JS , Dickson RC , Burton DD , Bouras EP . Contribution of ascites to impaired gastric function and nutritional intake in patients with cirrhosis and ascites . *Clin Gastroenterol Hepatol* 2005 ; 3 : 1095 – 1100 . 10.1016/S1542-3565(05)00531-8 . 16271340 53) Dolz C , Raurich JM , Ibáñez J , Obrador A , Marsé P , Gayá J . Ascites increases the resting energy expenditure in liver cirrhosis . *Gastroenterology* 1991 ; 100 : 738 – 744 . 10.1016/0016-5085(91)80019-6 . 1993495 54) Lai JC , Rahimi RS , Verna EC , Kappus MR , Dunn MA , McAdams-DeMarco M , Frailty associated with waitlist mortality independent of ascites and hepatic encephalopathy in a multicenter study . *Gastroenterology* 2019 ; 156 : 1675 – 1682 . 10.1053/j.gastro.2019.01.028 . 30668935 PMC6475483 55) Ebadi M , Bhanji RA , Mazurak VC , Montano-Loza AJ . Sarcopenia in cirrhosis: from pathogenesis to interventions . *J Gastroenterol* 2019 ; 54 : 845 – 859 . 10.1007/s00535-019-01605-6 . 31392488 PMC6759678 56) Santetti D , de Albuquerque Wilasco MI , Dornelles CTL , Werlang ICR , Fontella FU , Kieling CO , Serum proinflammatory cytokines and nutritional status in pediatric chronic liver disease . *World J Gastroenterol* 2015 ; 21 : 8927 – 8934 . 10.3748/wjg.v21.i29.8927 . 26269683 PMC4528036 57) Dasarathy S , Merli M . Sarcopenia from mechanism to diagnosis and treatment in liver disease . *J Hepatol* 2016 ; 65 : 1232 – 1244 . 10.1016/j.jhep.2016.07.040 . 27515775 PMC5116259 58) Arroyo V , García-Martínez R , Salvatella X . Human serum albumin, systemic inflammation, and cirrhosis . *J Hepatol* 2014 ; 61 : 396 – 407 . 10.1016/j.jhep.2014.04.012 . 24751830 59) Albillos A , Lario M , Álvarez-Mon M . Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance . *J Hepatol* 2014 ; 61 : 1385 – 1396 . 10.1016/j.jhep.2014.08.010 . 25135860 60) Dalle S , Rossmeislova L ,

Koppo K . The role of inflammation in age-related sarcopenia . *Front Physiol* 2017 ; 8 : 1045 . 10.3389/fphys.2017.01045 . 29311975 PMC5733049 61) Soysal P , Stubbs B , Lucato P , Luchini C , Solmi M , Peluso R , Inflammation and frailty in the elderly: a systematic review and meta-analysis . *Ageing Res Rev* 2016 ; 31 : 1 – 8 . 10.1016/j.arr.2016.08.006 . 27592340 62) Nishitsuji H , Funami K , Shimizu Y , Ujino S , Sugiyama K , Seya T , Hepatitis C virus infection induces inflammatory cytokines and chemokines mediated by the cross talk between hepatocytes and stellate cells . *J Virol* 2013 ; 87 : 8169 – 8178 . 10.1128/JVI.00974-13 . 23678168 PMC3700210 63) Saraiva GN , Rosário NFd , Medeiros T , Leite PEC , Lacerda GdS , Andrade TGd , Restoring inflammatory mediator balance after sofosbuvir-induced viral clearance in patients with chronic hepatitis C . *Mediators Inflamm* 2018 ; 2018 : 8578051 . 10.1155/2018/8578051 29977152 PMC5994301 64) Gao B , Tsukamoto H . Inflammation in alcoholic and nonalcoholic fatty liver disease: friend or foe? *Gastroenterology* 2016 ; 150 : 1704 – 1709 . 10.1053/j.gastro.2016.01.025 . 26826669 PMC4887345 65) Dasarathy S The pathogenesis of physical frailty and sarcopenia . In: Tandon P , Montano-Loza AJ , eds. *Frailty and Sarcopenia in Cirrhosis* . Cham, Switzerland : Springer International Publishing ; 2020 : 33 – 53 . 10.1007/978-3-030-26226-6_4 . 66) Moctezuma-Velázquez C , Low G , Mourtzakis M , Ma M , Burak KW , Tandon P , Association between low testosterone levels and sarcopenia in cirrhosis: a cross-sectional study . *Ann Hepatol* 2018 ; 17 : 615 – 623 . 10.5604/01.3001.0012.0930 . 29893704 67) Sinclair M , Grossmann M , Hoermann R , Angus PW , Gow PJ . Testosterone therapy increases muscle mass in men with cirrhosis and low testosterone: a randomised controlled trial . *J Hepatol* 2016 ; 65 : 906 – 913 . 10.1016/j.jhep.2016.06.007 . 27312945 68) Haugen CE , McAdams-DeMarco M , Verna EC , Rahimi RS , Kappus MR , Dunn MA , Association between liver transplant wait-list mortality and frailty based on body mass index . *JAMA Surg* 2019 ; 154 : 1103 – 1109 . 10.1001/jamasurg.2019.2845 . 31509169 PMC6739734 69) Kashiwagi K , Takayama M , Fukuhara K , Shimizu-Hirota R , Chu P-S , Nakamoto N , A significant association of non-obese non-alcoholic fatty liver disease with sarcopenic obesity . *Clin Nutr ESPEN* 2020 ; 38 : 86 – 93 . 10.1016/j.clnesp.2020.05.025 . 32690183 70) Montano-Loza AJ , Angulo P , Meza-Junco J , Prado CMM , Sawyer MB , Beaumont C , Sarcopenic obesity and myosteatosis are associated with higher mortality in patients with cirrhosis . *J Cachexia Sarcopenia Muscle* 2015 ; 7 : 126 – 135 . 10.1002/jcsm.12039 . 27493866 PMC4864157 71) Nishikawa H , Nishiguchi S . Sarcopenia and sarcopenic obesity are prognostic factors for overall survival in patients with cirrhosis . *Intern Med* 2016 ; 55 : 855 – 856 . 10.2169/internalmedicine.55.6298 . 27086795 72) Orman ES , Roberts A , Ghabril M , Nephew L , Desai AP , Patidar K , Trends in characteristics, mortality, and other out-comes of patients with newly diagnosed cirrhosis . *JAMA Netw Open* 2019 ; 2 : e196412 . 10.1001/jamanetworkopen.2019.6412 . 31251379 PMC6604080 73) Welch N , Attaway A , Bellar A , Alkhafaji H , Vural A , Dasarathy S . Compound sarcopenia in hospitalized patients with cirrhosis worsens outcomes with increasing age . *Nutrients* 2021 ; 13 : 659 . 10.3390/nu13020659 . 33670535 PMC7923160 74) Hayashi F , Matsumoto Y , Momoki C , Yuikawa M , Okada G , Hamakawa E , Physical inactivity and insufficient dietary intake are associated with the frequency of sarcopenia in patients with compensated viral liver cirrhosis . *Hepatol Res* 2013 ; 43 : 1264 – 1275 . 10.1111/hepr.12085 . 23489325 75) 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 . 10.1111/ajt.12762 . 24935609 PMC4107151 76) Dunn MA , Josbeno DA , Schmotzer AR , Tevar AD , DiMartini AF , Landsittel DP , The gap between clinically assessed physical performance and objective physical activity in liver transplant candidates . *Liver Transpl* 2016 ; 22 : 1 – 22 . 10.1002/lt.24506 . 27348200 77) Chascsa DM , Lai JC , Dunn MA , Montano-Loza AJ , Kappus MR , Dasarathy S , Patient and caregiver attitudes and practices of exercise in candidates listed for liver transplantation . *Dig Dis Sci* 2018 ; 63 : 3290 – 3296 . 10.1007/s10620-018-5271-5 . 30178285 PMC6532051 78) Román E , Torrades MT , Nadal MJ , Cárdenas G , Nieto JC , Vidal S , Randomized pilot study: effects of an exercise programme and leucine supplementation in patients with cirrhosis . *Dig Dis Sci* 2014 ; 59 : 1966 – 1975 . 10.1007/s10620-014-3086-6 . 24599772 79) Román E , García-Galcerán C , Torrades T , Herrera S , Marín A , Doñate M , 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 . 10.1371/journal.pone.0151652 . 27011355 PMC4807034 80) Zenith L , Meena N , Ramadi A , Yavari M , Harvey A , Carbonneau M , 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. e2 . 10.1016/j.cgh.2014.04.016 . 24768811 81) Kruger C , McNeely ML , Bailey RJ , Yavari M , Abiralde JG , Carbonneau M , Home exercise training improves exercise capacity in cirrhosis patients: role of exercise adherence . Sci Rep 2018 ; 8 : 99 . 10.1038/s41598-017-18320-y . 29311671 PMC5758716 82) Hiraoka A , Michitaka K , Kiguchi D , Izumoto H , Ueki H , Kaneto M , Efficacy of branched-chain amino acid supplementation and walking exercise for preventing sarcopenia in patients with liver cirrhosis . Eur J Gastroenterol Hepatol 2017 ; 29 : 1416 – 1423 . 10.1097/MEG.0000000000000986 . 29016470 83) Centers for Disease Control and Prevention . Social determinants of health: Know what affects health . <https://www.cdc.gov/socialdeterminants/index.htm> . Accessed August 16, 2020 . 84) Bittermann T , Dwinnells K , Chadha S , Wolf MS , Olthoff KM , Serper M . Low health literacy is associated with frailty and reduced likelihood of liver transplant listing: a prospective cohort study . Liver Transpl 2020 ; 26 : 1409 – 1421 . 10.1002/lt.25830 . 32567232 PMC8809114 85) Golovaty I , Tien PC , Price JC , Sheira L , Seligman H , Weiser SD . Food insecurity may be an independent risk factor associated with nonalcoholic fatty liver disease among low-income adults in the United States . J Nutr 2020 ; 150 : 91 – 98 . 10.1093/jn/nxz212 . 31504710 PMC6946902 86) Bajaj JS , Wade JB , Gibson DP , Heuman DM , Thacker LR , Sterling RK , The multi-dimensional burden of cirrhosis and hepatic encephalopathy on patients and caregivers . Am J Gastroenterol 2011 ; 106 : 1646 – 1653 . 10.1038/ajg.2011.157 . 21556040 PMC3989143 87) Wadhwani SI , Beck AF , Bucuvalas J , Gottlieb L , Kotagal U , Lai JC . Neighborhood socioeconomic deprivation is associated with worse patient and graft survival following pediatric liver transplantation . Am J Transplant 2020 ; 20 : 1597 – 1605 . 10.1111/ajt.15786 . 31958208 PMC7261648 88) Thuluvath PJ , Thuluvath AJ , Savva Y . Karnofsky performance status before and after liver transplantation predicts graft and patient survival . J Hepatol 2018 ; 69 : 818 – 825 . 10.1016/j.jhep.2018.05.025 . 29883596 89) Tandon P , Reddy KR , O'Leary JG , Garcia-Tsao G , Abiralde JG , Wong F , A Karnofsky performance status-based score predicts death after hospital discharge in patients with cirrhosis . Hepatology 2017 ; 65 : 217 – 224 . 10.1002/hep.28900 . 27775842 90) Lai JC , Covinsky KE , Dodge JL , Boscardin WJ , Segev DL , Roberts JP , Development of a novel frailty index to predict mortality in patients with end-stage liver disease . Hepatology 2017 ; 66 : 564 – 574 . 10.1002/hep.29219 . 28422306 PMC5519430 91) Kardashian A , Ge J , McCulloch CE , Kappus MR , Dunn MA , Duarte-Rojo A , Identifying an optimal liver frailty index cutoff to predict waitlist mortality in liver transplant candidates . Hepatology 2020 ; 73 : 1132 – 1139 . 10.1002/hep.31406 . 32491208 PMC7710552 92) Lai JC , Dodge JL , Kappus MR , Dunn MA , Volk ML , Duarte-Rojo A , Changes in frailty are associated with waitlist mortality in patients with cirrhosis . J Hepatol 2020 ; 73 : 575 – 581 . 10.1016/j.jhep.2020.03.029 . 32240717 PMC7438309 93) Lurz E , Quammie C , Englesbe M , Alonso EM , Lin HC , Hsu EK , Frailty in children with liver disease: a prospective multicenter study . J Pediatr 2018 ; 194 : 109 – 115.e4 . 10.1016/j.jpeds.2017.10.066 . 29478492 94) Perito ER , Bucuvalas J , Lai JC . Functional status at listing predicts waitlist and posttransplant mortality in pediatric liver transplant candidates . Am J Transplant 2018 ; 19 : 1 – 21 . 10.1111/ajt.15203 . PMC6482090 30506640 95) Tapper EB , Konerman M , Murphy S , Sonnenday CJ . Hepatic encephalopathy impacts the predictive value of the Fried Frailty Index . Am J Transplant 2018 ; 18 : 2566 – 2570 . 10.1111/ajt.15020 . 30019835 PMC6166663 96) Tandon P , Tangri N , Thomas L , Zenith L , Shaikh T , Carbonneau M , A rapid bedside screen to predict unplanned hospitalization and death in outpatients with cirrhosis: a prospective evaluation of the Clinical Frailty Scale . Am J Gastroenterol 2016 ; 111 : 1759 – 1767 . 10.1038/ajg.2016.303 . 27481305 97) Tapper EB , Finkelstein D , Mittelman MA , Piatkowski G , Lai M . Standard assessments of frailty are validated predictors of mortality in hospitalized patients with cirrhosis . Hepatology 2015 ; 62 : 584 – 590 . 10.1002/hep.27830 . 25846824 PMC4768731 98) Tapper EB , Baki J , Parikh ND , Lok AS . Frailty, psychoactive medications, and cognitive dysfunction are associated with poor patient-reported outcomes in cirrhosis . Hepatology 2019 ; 69 : 1676 – 1685 . 10.1002/hep.30336 . 30382584 PMC6438757 99) Lai JC , Segev DL , McCulloch CE , Covinsky KE , Dodge JL , Feng S . Physical frailty after liver transplantation . Am J Transplant 2018 ; 18 : 1986 – 1994 . 10.1111/ajt.14675 . 29380529 PMC6066446 100) Samoylova ML , Covinsky KE , Haftek M , Kuo S , Roberts JP , Lai JC . Disability in patients with end-stage liver disease: results from the functional assessment in liver transplantation study . Liver Transpl 2017 ; 23 : 292 – 298 . 10.1002/lt.24684 . 27884053 PMC5325797 101) Thuluvath PJ , Thuluvath AJ , Savva Y , Zhang T . Karnofsky performance status following liver transplantation in patients with multiple organ failures and probable acute-on-chronic liver failure . Clin Gastroenterol Hepatol 2020 ; 18 : 234 – 241 .

10.1016/j.cgh.2019.03.016 . 30885883 102) Bernal W , Martin-Mateos R , Lipcsey M , Tallis C , Woodsford K , Mcphail MJ , Aerobic capacity during cardiopulmonary exercise testing and survival with and without liver transplantation for patients with chronic liver disease . *Liver Transpl* 2013 ; 20 : 54 – 62 . 10.1002/lt.23766 . 24136710 103) Wallace D , Cowling TE , Walker K , Suddle A , Gimson A , Rowe I , The impact of performance status on length of hospital stay and clinical complications following liver transplantation . *Transplantation* 2020 Oct 8 . 10.1097/TP.0000000000003484 . [Epub ahead of print] 33044430 104) Wallace D , Cowling T , McPhail MJ , Brown SE , Aluvihare V , Suddle A , Assessing the time-dependent impact of performance status on outcomes after liver transplantation . *Hepatology* 2020 ; 72 : 1341 – 1352 . 10.1002/hep.31124 . 31968130 105) Dunn MA , Josbeno DA , Tevar AD , Rachakonda V , Ganesh SR , Schmotzer AR , Frailty as tested by gait speed is an independent risk factor for cirrhosis complications that require hospitalization . *Am J Gastroenterol* 2016 ; 111 : 1768 – 1775 . 10.1038/ajg.2016.336 . 27575708 106) 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 . 10.3748/wjg.v23.i5.899 . 28223735 PMC5296207 107) Carey EJ , Steidley DE , Aqel BA , Byrne TJ , Mekeel KL , Rakela J , Six-minute walk distance predicts mortality in liver transplant candidates . *Liver Transpl* 2010 ; 16 : 1373 – 1378 . 10.1002/lt.22167 . 21117246 108) Prentis JM , Manas DMD , Trenell MI , Hudson M , Jones DJ , Snowden CP . Submaximal cardiopulmonary exercise testing predicts 90-day survival after liver transplantation . *Liver Transpl* 2012 ; 18 : 152 – 159 . 10.1002/lt.22426 . 21898768 109) Tapper EB , Zhao L , Nikirk S , Baki J , Parikh ND , Lok AS , Incidence and bedside predictors of the first episode of overt hepatic encephalopathy in patients with cirrhosis . *Am J Gastroenterol* 2020 ; 115 : 2017 – 2025 . 10.14309/ajg.0000000000000762 . 32773463 PMC7853725 110) Tapper EB , Derstine B , Baki J , Su GL . Bedside measures of frailty and cognitive function correlate with sarcopenia in patients with cirrhosis . *Dig Dis Sci* 2019 ; 64 : 3652 – 3659 . 10.1007/s10620-019-05713-4 . 31292783 111) Cron DC , Friedman JF , Winder GS , Thelen AE , Derck JE , Fakhoury JW , Depression and frailty in patients with end-stage liver disease referred for transplant evaluation . *Am J Transplant* 2016 ; 16 : 1805 – 1811 . 10.1111/ajt.13639 . 26613640 112) Derck JE , Thelen AE , Cron DC , Friedman JF , Gerebics AD , Englesbe MJ , Quality of life in liver transplant candidates . *Transplantation* 2015 ; 99 : 340 – 344 . 10.1097/TP.0000000000000593 . 25606782 113) Lai JC , Dodge JL , McCulloch CE , Covinsky KE , Singer JP . Frailty and the burden of concurrent and incident disability in patients with cirrhosis: a prospective cohort study . *Hepatol Commun* 2020 ; 4 : 126 – 133 . 10.1002/hep4.1444 . 31909360 PMC6939546 114) Tapper EB , Nikirk S , Parikh N , Zhao L . Falls are common, morbid, and predictable in patients with cirrhosis . *J Hepatol* 2021 Apr 19 . 10.1016/j.jhep.2021.04.012 . [Epub ahead of print] PMC8380639 33887359 115) Kremer WM , Nagel M , Reuter M , Hilscher M , Michel M , Kaps L , Validation of the Clinical Frailty Scale for the prediction of mortality in patients with liver cirrhosis . *Clin Transl Gastroenterol* 2020 ; 11 : e00211 . 10.14309/ctg.0000000000000211 . 32764204 PMC7386350 116) Orman ES , Ghabril M , Chalasani N . Poor performance status is associated with increased mortality in patients with cirrhosis . *Clin Gastroenterol Hepatol* 2016 ; 14 : 1189 – 1195.e1 . 10.1016/j.cgh.2016.03.036 . 27046483 PMC4955687 117) Dolgin NH , Martins PNA , Movahedi B , Lapane KL , Anderson FA , Bozorgzadeh A . Functional status predicts postoperative mortality after liver transplantation . *Clin Transplant* 2016 ; 30 : 1403 – 1410 . 10.1111/ctr.12808 . 27439897 118) Hsu C-Y , Lee Y-H , Hsia C-Y , Huang Y-H , Su C-W , Lin H-C , Performance status in patients with hepatocellular carcinoma: determinants, prognostic impact, and ability to improve the Barcelona Clinic Liver Cancer system . *Hepatology* 2013 ; 57 : 112 – 119 . 10.1002/hep.25950 . 22806819 119) Jacob M , Copley LP , Lewsey JD , Gimson A , Rela M , van der Meulen JHP . Functional status of patients before liver transplantation as a predictor of posttransplant mortality . *Transplantation* 2005 ; 80 : 52 – 57 . 10.1097/01.TP.0000163292.03640.5C . 16003233 120) Jo HB , Lee JK , Kang HW , Kim JH , Lim YJ , Koh M-S , Safety and effectiveness of midazolam for cirrhotic patients undergoing endoscopic variceal ligation . *Turk J Gastroenterol* 2018 ; 29 : 448 – 455 . 10.5152/tjg.2018.17589 . 30249560 PMC6284641 121) Vouche M , Habib A , Ward TJ , Kim E , Kulik L , Ganger D , Unresectable solitary hepatocellular carcinoma not amenable to radiofrequency ablation: multicenter radiology-pathology correlation and survival of radiation segmentectomy . *Hepatology* 2014 ; 60 : 192 – 201 . 10.1002/hep.27057 . 24691943 122) Álvares-da-Silva MR , Reverbel da Silveira T . 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 . 10.1016/j.nut.2004.02.002 . 15723736 123) Wang CW , Feng S , Covinsky KE , Hayssen H , Zhou L-Q , Yeh BM , A comparison of muscle function, mass, and quality in liver transplant candidates . *Transplantation* 2016 ; 100 : 1692 – 1698 . 10.1097/TP.0000000000001232 . 27314169 PMC4962324 124) Haugen CE , McAdams-DeMarco MA , Verna EC , Association between liver transplant wait-list mortality and frailty based on body mass index . *JAMA Surg* . 2019 ; 154 1103 – 1109 . 31509169 10.1001/jamasurg.2019.2845 PMC6739734 125) Haugen CE , McAdams-DeMarco M , Holscher CM , Ying H , Gurakar AO , Garonzik-Wang J , Multicenter study of age, frailty, and waitlist mortality among liver transplant candidates . *Ann Surg* 2020 ; 271 : 1132 – 1136 . 10.1097/SLA.0000000000003207 . 30672803 PMC6639152 126) Lai JC , Ganger DR , Volk ML , Dodge JL , Dunn MA , Duarte-Rojo A , Association of frailty and sex with wait list mortality in liver transplant candidates in the Multicenter Functional Assessment in Liver Transplantation (FrAILT) Study . *JAMA Surg* 2021 ; 156 : 256 – 262 . 10.1001/jamasurg.2020.5674 . 33377947 PMC7774043 127) Skladany L , Drotarova Z , Vnencakova J , Jancekova D , Molcan P , Koller T . Applicability and prognostic value of frailty assessment tools among hospitalized patients with advanced chronic liver disease . *Croat Med J* 2021 ; 62 : 8 – 16 . 10.3325/cmj.2021.62.8 . 33660956 PMC7976891 128) 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 . 10.1111/apt.13771 . 27539029 129) Carey EJ , Lai JC , Sonnenday C , Tapper EB , Tandon P , Duarte-Rojo A , A North American expert opinion statement on sarcopenia in liver transplantation . *Hepatology* 2019 ; 70 : 1816 – 1829 . 10.1002/hep.30828 . 31220351 PMC6819202 130) Paris MT , Tandon P , Heyland DK , Furberg H , Premji T , Low G , Automated body composition analysis of clinically acquired computed tomography scans using neural networks . *Clin Nutr* 2020 ; 39 : 3049 – 3055 . 10.1016/j.clnu.2020.01.008 . 32007318 PMC7374050 131) Carey EJ , Lai JC , Wang CW , Dasarathy S , Lobach I , Montano-Loza AJ , A multicenter study to define sarcopenia in patients with end-stage liver disease . *Liver Transpl* 2017 ; 23 : 625 – 633 . 10.1002/lt.24750 . 28240805 PMC5762612 132) Wells CI , McCall JL , Plank LD . Relationship between total body protein and cross-sectional skeletal muscle area in liver cirrhosis is influenced by overhydration . *Liver Transpl* 2019 ; 25 : 45 – 55 . 10.1002/lt.25314 . 30040184 133) Ebadi M , Wang CW , Lai JC , Dasarathy S , Kappus MR , Dunn MA , Poor performance of psoas muscle index for identification of patients with higher waitlist mortality risk in cirrhosis . *J Cachexia Sarcopenia Muscle* 2018 ; 9 : 1053 – 1062 . 10.1002/jcsm.12349 . 30269421 PMC6240754 134) Praktijnjo M , Book M , Luetkens J , Pohlmann A , Meyer C , Thomas D , Fat-free muscle mass in magnetic resonance imaging predicts acute-on-chronic liver failure and survival in decompensated cirrhosis . *Hepatology* 2018 ; 67 : 1014 – 1026 . 10.1002/hep.29602 . 29059469 135) Pirlich M , Schutz T , Spachos T , Ertl S , Weis M , Lochs H , Bioelectrical impedance analysis is a useful bedside technique to assess malnutrition in cirrhotic patients with and without ascites . *Hepatology* 2000 ; 32 : 1208 – 1215 . 10.1053/jhep.2000.20524 . 11093726 136) Ruiz-Margáin A , Xie JJ , Román-Calleja BM , Pauly M , White MG , Chapa-Ibargüengoitia M , Phase angle from bioelectrical impedance for the assessment of sarcopenia in cirrhosis with or without ascites . *Clin Gastroenterol Hepatol* 2020 Sep 2 . 10.1016/j.cgh.2020.08.066 . [Epub ahead of print] 32890753 137) Fernando Gomes Romeiro L , Augusti S . Nutritional assessment in cirrhotic patients with hepatic encephalopathy . *World J Hepatol* 2015 ; 7 : 2940 – 2954 . 10.4254/wjh.v7.i30.2940 . 26730273 PMC4691697 138) Hara N , Iwasa M , Iwata K , Miyachi H , Tanaka H , Takeo M , Value of the extracellular water ratio for assessment of cirrhotic patients with and without ascites . *Hepatol Res* 2009 ; 39 : 1072 – 1079 . 10.1111/j.1872-034X.2009.00546.x . 19619257 139) Hara N , Iwasa M , Sugimoto R , Mifuji-Moroka R , Yoshikawa K , Terasaka E , Sarcopenia and sarcopenic obesity are prognostic factors for overall survival in patients with cirrhosis . *Intern Med* 2016 ; 55 : 863 – 870 . 10.2169/internalmedicine.55.5676 . 27086797 140) Viertel M , Bock C , Reich M , Löser S , Plauth M . Performance of CT-based low skeletal muscle index, low mean muscle attenuation, and bioelectric impedance derived low phase angle in the detection of an increased risk of nutrition related mortality . *Clin Nutr* 2019 ; 38 : 2375 – 2380 . 10.1016/j.clnu.2018.10.018 . 30415908 141) Bellafronte NT , Diani LM , Vega-Piris L , Cuadrado GB , Chiarello PG . Comparison between dual-energy X-ray absorptiometry and bioelectrical impedance for body composition measurements in adults with chronic kidney disease: a cross-sectional, longitudinal, multi-treatment analysis . *Nutrition* 2021 ; 82 : 111059 . 10.1016/j.nut.2020.111059 . 33341596 142) Giusto M , Lattanzi B ,

Albanese C , Galtieri A , Farcomeni A , Giannelli V , 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 . 10.1097/MEG.0000000000000274 . 25569567 143) Labio ED , Del Rosario DB , Strasser SI , McCaughan GW , Crawford BA . Effect of ascites on bone density measurement in cirrhosis . *J Clin Densitom* 2007 ; 10 : 391 – 394 . 10.1016/j.jocd.2007.07.001 . 17703977 144) Lindqvist C , Brismar TB , Majeed A , Wahlin S . Assessment of muscle mass depletion in chronic liver disease: dual-energy X-ray absorptiometry compared with computed tomography . *Nutrition* 2019 ; 61 : 93 – 98 . 10.1016/j.nut.2018.10.031 . 30703575 145) Sinclair M , Hoermann R , Peterson A , Testro A , Angus PW , Hey P , Use of dual X-ray absorptiometry in men with advanced cirrhosis to predict sarcopenia-associated mortality risk . *Liver Int* 2019 ; 39 : 1089 – 1097 . 10.1111/liv.14071 . 30746903 146) WHO Multicentre Growth Reference Study Group . Reliability of anthropometric measurements in the WHO Multicentre Growth Reference Study . *Acta Paediatr Suppl* 2007 ; 450 : 38 – 46 . 10.1111/j.1651-2227.2006.tb02374.x . 16817677 147) Mangus RS , Bush WJ , Miller C , Kubal CA . Severe sarcopenia and increased fat stores in pediatric patients with liver, kidney, or intestine failure . *J Pediatr Gastroenterol Nutr* 2017 ; 65 : 579 – 583 . 10.1097/MPG.0000000000001651 . 28604513 148) Squires RH , Ng V , Romero R , Ekong U , Hardikar W , Emre S , Evaluation of the pediatric patient for liver transplantation: 2014 practice guideline by the American Association for the Study of Liver Diseases, American Society of Transplantation and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition . *Hepatology* 2014 ; 60 : 362 – 398 . 10.1002/hep.27191 . 24782219 149) Young S , Kwarta E , Azzam R , Sentongo T . Nutrition assessment and support in children with end-stage liver disease . *Nutr Clin Pract* 2013 ; 28 : 317 – 329 . 10.1177/0884533612474043 . 23466471 150) Grutters LA , Pennings JP , Bruggink JLM , Viddeleer AR , Verkade HJ , de Kleine RHJ , Body composition of infants with biliary atresia: anthropometric measurements and computed tomography-based body metrics . *J Pediatr Gastroenterol Nutr* 2020 ; 71 : 440 – 445 . 10.1097/MPG.0000000000002859 . 32694399 151) Ooi PH , Thompson-Hodgetts S , Pritchard-Wiart L , Gilmour SM , Mager DR . Pediatric sarcopenia: a paradigm in the overall definition of malnutrition in children? *JPEN* 2020 ; 44 : 407 – 418 . 10.1002/jpen.1681 . 31328301 152) Lurz E , Patel H , Lebovic G , Quammie C , Woolfson JP , Perez M , Paediatric reference values for total psoas muscle area . *J Cachexia Sarcopenia Muscle* 2020 ; 11 : 405 – 414 . 10.1002/jcsm.12514 . 31920002 PMC7113526 153) Mazurak VC , Tandon P , Montano-Loza AJ . Nutrition and the transplant candidate . *Liver Transpl* 2017 ; 23 : 1451 – 1464 . 10.1002/lt.24848 . 29072825 154) Tandon P , Ney M , Irwin I , Ma MM , Gramlich L , Bain VG , Severe muscle depletion in patients on the liver transplant wait list: its prevalence and independent prognostic value . *Liver Transpl* 2012 ; 18 : 1209 – 1216 . 10.1002/lt.23495 . 22740290 155) Ooi PH , Mazurak VC , Bhargava R , Dunichand-Hoedl A , Romero RA , Gilmour SM , Myopenia and reduced subcutaneous adiposity in children with liver disease are associated with adverse outcomes . *JPEN* 2020 July 25 . 10.1002/jpen.1963 . [Epub ahead of print] 32710565 156) Woolfson JP , Perez M , Chavhan GB , Johara FT , Lurz E , Kamath BM , Sarcopenia in children with end-stage liver disease on the transplant waiting list . *Liver Transpl* 2021 ; 27 : 641 – 651 . 10.1002/lt.25985 . 33460522 PMC8248423 157) Montano-Loza AJ , Meza-Junco J , Prado CMM , Lieffers JR , Baracos VE , Bain VG , Muscle wasting is associated with mortality in patients with cirrhosis . *Clin Gastroenterol Hepatol* 2012 ; 10 : 166 – 173.e1 . 10.1016/j.cgh.2011.08.028 . 21893129 158) Belarmino G , Gonzalez MC , Sala P , Torrinhas RS , Andraus W , D'Albuquerque LAC , Diagnosing sarcopenia in male patients with cirrhosis by dual-energy X-ray absorptiometry estimates of appendicular skeletal muscle mass . *JPEN* 2018 ; 42 : 24 – 36 . 10.1177/0148607117701400 . 28402708 159) van Vugt JLA , Levolger S , de Bruin RWF , van Rosmalen J , Metselaar HJ , IJzermans JNM . 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 . 10.1111/ajt.13732 . 26813115 160) Englesbe MJ , Patel SP , He K , Lynch RJ , Schaubel DE , Harbaugh C , Sarcopenia and mortality after liver transplantation . *J Am Coll Surg* 2010 ; 211 : 271 – 278 . 10.1016/j.jamcollsurg.2010.03.039 . 20670867 PMC2914324 161) Kaido T , Ogawa K , Fujimoto Y , Ogura Y , Hata K , Ito T , Impact of sarcopenia on survival in patients undergoing living donor liver transplantation . *Am J Transplant* 2013 ; 13 : 1549 – 1556 . 10.1111/ajt.12221 . 23601159 162) Hamaguchi Y , Kaido T , Okumura S , Fujimoto Y , Ogawa K , Mori A , Impact of quality as well as

quantity of skeletal muscle on outcomes after liver transplantation . *Liver Transpl* 2014 ; 20 : 1413 – 1419 . 10.1002/lt.23970 . 25088484 163) Kuo SZ , Ahmad M , Dunn MA , Montano-Loza AJ , Carey EJ , Lin S , Sarcopenia predicts posttransplant mortality in acutely ill men undergoing urgent evaluation and liver transplantation . *Transplantation* 2019 ; 103 : 2312 – 2317 . 10.1097/TP.0000000000002741 . 30985575 PMC6783339 164) Marasco G , Serenari M , Renzulli M , Alemanni LV , Rossini B , Pettinari I , Clinical impact of sarcopenia assessment in patients with hepatocellular carcinoma undergoing treatments . *J Gastroenterol* 2020 ; 55 : 927 – 943 . 10.1007/s00535-020-01711-w . 32748172 PMC7519899 165) Hari A , Berzigotti A , Štabuc B , Caglevi N . Muscle psoas indices measured by ultrasound in cirrhosis—preliminary evaluation of sarcopenia assessment and prediction of liver decompensation and mortality . *Dig Liver Dis* 2019 ; 51 : 1502 – 1507 . 10.1016/j.dld.2019.08.017 . 31547952 166) Tapper EB , Zhang P , Garg R , Nault T , Leary K , Krishnamurthy V , Body composition predicts mortality and decompensation in compensated cirrhosis patients: a prospective cohort study . *JHEP Rep* 2020 ; 2 : 100061 . 10.1016/j.jhepr.2019.11.005 . 32039402 PMC7005567 167) Ando Y , Ishigami M , Ito T , Ishizu Y , Kuzuya T , Honda T , Sarcopenia impairs health-related quality of life in cirrhotic patients . *Eur J Gastroenterol Hepatol* 2019 ; 31 : 1550 – 1556 . 10.1097/MEG.0000000000001472 . 31206408 168) Montano-Loza AJ , Meza-Junco J , Baracos VE , Prado CMM , Ma M , Meeberg G , Severe muscle depletion predicts post-operative length of stay but is not associated with survival after liver transplantation . *Liver Transpl* 2014 ; 20 : 640 – 648 . 10.1002/lt.23863 . 24678005 169) Georgiou A , Papatheodoridis GV , Alexopoulou A , Deutsch M , Vlachogiannakos I , Ioannidou P , Validation of cutoffs for skeletal muscle mass index based on computed tomography analysis against dual energy X-ray absorptiometry in patients with cirrhosis: the KIRRHOS study . *Ann Gastroenterol* 2020 ; 33 : 80 – 86 . 10.20524/aog.2019.0432 . 31892802 PMC6928470 170) Carias S , Castellanos AL , Vilchez V , Nair R , Dela Cruz AC , Watkins J , Nonalcoholic steatohepatitis is strongly associated with sarcopenic obesity in patients with cirrhosis undergoing liver transplant evaluation . *J Gastroenterol Hepatol* 2016 ; 31 : 628 – 633 . 10.1111/jgh.13166 . 26399838 PMC6615558 171) Kalafateli M , Mantzoukis K , Choi Yau Y , Mohammad AO , Arora S , Rodrigues S , Malnutrition and sarcopenia predict post-liver transplantation outcomes independently of the Model for End-Stage Liver Disease score . *J Cachexia Sarcopenia Muscle* 2016 ; 8 : 113 – 121 . 10.1002/jcsm.12095 . 27239424 PMC4864202 172) Kobayashi K , Maruyama H , Kiyono S , Ogasawara S , Suzuki E , Ooka Y , Application of transcutaneous ultrasonography for the diagnosis of muscle mass loss in patients with liver cirrhosis . *J Gastroenterol* 2018 ; 53 : 652 – 659 . 10.1007/s00535-017-1378-2 . 28821966 173) Tandon M , Singh H , Singla N , Jain P , Pandey CK . Tongue thickness in health vs cirrhosis of the liver: prospective observational study . *World J Gastrointest Pharmacol Ther* 2020 ; 11 : 59 – 68 . 10.4292/wjgpt.v11.i3.59 . 32844044 PMC7416379 174) Tandon P , Mourtzakis M , Low G , Zenith L , Ney M , Carbonneau M , Comparing the variability between measurements for sarcopenia using magnetic resonance imaging and computed tomography imaging . *Am J Transplant* 2016 ; 16 : 2766 – 2767 . 10.1111/ajt.13832 . 27093434 175) Strauss BJ , Gibson PR , Stroud DB , Borovnicar DJ , Xiong DW , Keogh J . Total body dual X-ray absorptiometry is a good measure of both fat mass and fat-free mass in liver cirrhosis compared to “gold-standard” techniques . *Ann N Y Acad Sci* 2000 ; 904 : 55 – 62 . 10865710 10.1111/j.1749-6632.2000.tb06421.x 176) Wang NC , Zhang P , Tapper EB , Saini S , Wang SC , Su GL . Automated measurements of muscle mass using deep learning can predict clinical outcomes in patients with liver disease . *Am J Gastroenterol* 2020 ; 115 : 1210 – 1216 . 10.14309/ajg.0000000000000662 . 32467506 PMC7415547 177) Kim G , Kang SH , Kim MY , Baik SK . Prognostic value of sarcopenia in patients with liver cirrhosis: a systematic review and meta-analysis . *PLoS One* 2017 ; 12 : e0186990 . 10.1371/journal.pone.0186990 . 29065187 PMC5655454 178) Lurz E , Patel H , Frimpong RG , Ricciuto A , Kehar M , Wales PW , Sarcopenia in children with end-stage liver disease . *J Pediatr Gastroenterol Nutr* 2018 ; 66 : 222 – 226 . 10.1097/MPG.0000000000001792 . 29356766 179) Foster C , Baki J , Nikirk S , Williams S , Parikh ND , Tapper EB . Comprehensive health-state utilities in contemporary patients with cirrhosis . *Hepatol Commun* 2020 ; 4 : 852 – 858 . 10.1002/hep4.1512 . 32490321 PMC7262287 180) Derck JE , Thelen AE , Cron DC , Friedman JF , Gerebics AD , Englesbe MJ , Quality of life in liver transplant candidates: frailty is a better indicator than severity of liver disease . *Transplantation* 2015 ; 99 : 340 – 344 . 10.1097/TP.0000000000000593 . 25606782 181) Plank LD , Gane EJ , Peng S , Muthu C , Mathur S , Gillanders L , Nocturnal nutritional supplementation improves total body protein status of patients with liver cirrhosis: a randomized 12-month trial . *Hepatology* 2008 ;

48 : 557 – 566 . 10.1002/hep.22367 . 18627001 182) Ruiz JG , Dent E , Morley JE , Merchant RA , Beilby J , Beard J , Screening for and managing the person with frailty in primary care: ICFSR Consensus Guidelines . J Nutr Health Aging 2020 ; 24 : 920 – 927 . 10.1007/s12603-020-1492-3 . 33155616 PMC7597431 183) Boulhosa RSSB , Lourenço RP , Côrtes DM , Oliveira LPM , Lyra AC , de Jesus RP . Comparison between criteria for diagnosing malnutrition in patients with advanced chronic liver disease: GLIM group proposal versus different nutritional screening tools . J Hum Nutr Diet 2020 ; 33 : 862 – 868 . 10.1111/jhn.12759 . 32378264 184) Traub J , Bergheim I , Horvath A , Stadlbauer V . Validation of malnutrition screening tools in liver cirrhosis . Nutrients 2020 ; 12 : 1306 . 10.3390/nu12051306 . PMC7285209 32375271 185) Wu Y , Zhu Y , Feng Y , Wang R , Yao N , Zhang M , Royal Free Hospital-Nutritional Prioritizing Tool improves the prediction of malnutrition risk outcomes in liver cirrhosis patients compared with Nutritional Risk Screening 2002 . Br J Nutr 2020 ; 124 : 1293 – 1302 . 10.1017/S0007114520002366 . 32600494 PMC7656665 186) Georgiou A , Papatheodoridis GV , Alexopoulou A , Deutsch M , Vlachogiannakos I , Ioannidou P , Evaluation of the effectiveness of eight screening tools in detecting risk of malnutrition in cirrhotic patients: the KIRRHOS study . Br J Nutr 2019 ; 122 : 1368 – 1376 . 10.1017/S0007114519002277 . 31735186 187) Borhofen SM , Gerner C , Lehmann J , Fimmers R , Görtzen J , Hey B , The Royal Free Hospital-Nutritional Prioritizing Tool is an independent predictor of deterioration of liver function and survival in cirrhosis . Dig Dis Sci 2015 ; 61 : 1735 – 1743 . 10.1007/s10620-015-4015-z . 26725059 188) Peters TJ , Martin F , Ward K . Chronic alcoholic skeletal myopathy—common and reversible . Alcohol 1985 ; 2 : 485 – 489 . 10.1016/0741-8329(85)90120-X . 3161521 189) Kumar A , Davuluri G , Silva RNE , Engelen MPKJ , Ten Have GAM , Prayson R , Ammonia lowering reverses sarcopenia of cirrhosis by restoring skeletal muscle proteostasis . Hepatology 2017 ; 65 : 2045 – 2058 . 10.1002/hep.29107 . 28195332 PMC5444955 190) Hiramatsu A , Aikata H , Uchikawa S , Ohya K , Kodama K , Nishida Y , Levocarnitine use is associated with improvement in sarcopenia in patients with liver cirrhosis . Hepatol Commun 2019 ; 3 : 348 – 355 . 10.1002/hep4.1309 . 30859147 PMC6396356 191) Ohara M , Ogawa K , Suda G , Kimura M , Maehara O , Shimazaki T , L-Carnitine suppresses loss of skeletal muscle mass in patients with liver cirrhosis . Hepatol Commun 2018 ; 2 : 910 – 922 . 10.1002/hep4.1207 . PMC6078216 30094402 192) Malaguarnera M , Vacante M , Giordano M , Pennisi G , Bella R , Rampello L , Oral acetyl-L-carnitine therapy reduces fatigue in overt hepatic encephalopathy: a randomized, double-blind, placebo-controlled study . Am J Clin Nutr 2011 ; 93 : 799 – 808 . 10.3945/ajcn.110.007393 . 21310833 193) Martí-Carvajal AJ , Gluud C , Arevalo-Rodriguez I , Martí-Amarista CE . Acetyl-L-carnitine for patients with hepatic encephalopathy . Cochrane Database Syst Rev 2019 ; 2019 : CD011451 . 10.1002/14651858.CD011451.pub2 . PMC6353234 30610762 194) Makhoul NA , Mahran ZG , Sadek SH , Magdy DM , Makhoul HA . Six-minute walk test before and after large-volume paracentesis in cirrhotic patients with refractory ascites: a pilot study . Arab J Gastroenterol 2019 ; 20 : 81 – 85 . 10.1016/j.ajg.2019.05.009 . 31182343 195) Hanai T , Shiraki M , Miwa T , Watanabe S , Imai K , Suetsugu A , Effect of loop diuretics on skeletal muscle depletion in patients with liver cirrhosis: loop diuretics and muscle in cirrhosis . Hepatol Res 2019 ; 49 : 82 – 95 . 10.1111/hepr.13244 . 30156741 196) Allard JP , Chau J , Sandokji K , Blendis LM , Wong F . Effects of ascites resolution after successful TIPS on nutrition in cirrhotic patients with refractory ascites . Am J Gastroenterol 2001 ; 96 : 2442 – 2447 . 10.1111/j.1572-0241.2001.04051.x . 11513188 197) 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 . 23011041 10.1097/MEG.0b013e328359a759 198) Artru F , Miquet X , Azahaf M , Labreuche J , Ntandja Wandji LC , Sergeant G , Consequences of TIPSS placement on the body composition of patients with cirrhosis and severe portal hypertension: a large retrospective CT-based surveillance . Aliment Pharmacol Ther 2020 ; 52 : 1516 – 1526 . 10.1111/apt.16080 . 32931618 199) Benmassaoud A , Roccarina D , Arico F , Leandro G , Yu B , Cheng F , Sarcopenia does not worsen survival in patients with cirrhosis undergoing transjugular intrahepatic portosystemic shunt for refractory ascites . Am J Gastroenterol 2020 ; 115 : 1911 – 1914 . 10.14309/ajg.0000000000000959 . 33156111 200) Kaido T , Tamai Y , Hamaguchi Y , Okumura S , Kobayashi A , Shirai H , Effects of pretransplant sarcopenia and sequential changes in sarcopenic parameters after living donor liver transplantation . Nutrition 2017 ; 33 : 195 – 198 . 10.1016/j.nut.2016.07.002 . 27649861 201) Tsien C , Garber A , Narayanan A , Shah SN , Barnes D , Eghtesad B , Post-liver transplantation sarcopenia in cirrhosis: a prospective evaluation . J Gastroenterol Hepatol 2014 ; 29 : 1250 – 1257 . 10.1111/jgh.12524 . 24443785 PMC4024321 202)

Dasarathy S Posttransplant sarcopenia: an underrecognized early consequence of liver transplantation . *Dig Dis Sci* 2013 ; 58 : 3103 – 3111 . 10.1007/s10620-013-2791-x . 23912247 PMC4066193 203) Bergerson JT , Lee J-G , Furlan A , Sourianarayanan A , Fetzer DT , Tevar AD , Liver transplantation arrests and reverses muscle wasting . *Clin Transplant* 2015 ; 29 : 216 – 221 . 10.1111/ctr.12506 . 25557648 204) Bhanji RA , Takahashi N , Moynagh MR , Narayanan P , Angirekula M , Mara KC , The evolution and impact of sarcopenia pre– and post–liver transplantation . *Aliment Pharmacol Ther* 2019 ; 49 : 807 – 813 . 10.1111/apt.15161 . 30714184 205) Glass C , Hipskind P , Tsien C , Malin SK , Kasumov T , Shah SN , Sarcopenia and a physiologically low respiratory quotient in patients with cirrhosis: a prospective controlled study . *J Appl Physiol* 2013 ; 114 : 559 – 565 . 10.1152/jappphysiol.01042.2012 . 23288550 PMC3615594 206) Glass C , Hipskind P , Cole D , Lopez R , Dasarathy S . Handheld calorimeter is a valid instrument to quantify resting energy expenditure in hospitalized cirrhotic patients: a prospective study . *Nutr Clin Pract* 2012 ; 27 : 677 – 688 . 10.1177/0884533612446195 . 22668853 PMC4001821 207) Greco AV , Mingrone G , Benedetti G , Capristo E , Tataranni PA , Gasbarrini G . Daily energy and substrate metabolism in patients with cirrhosis . *Hepatology* 1998 ; 27 : 346 – 350 . 10.1002/hep.510270205 . 9462629 208) Guglielmi F , Panella C , Buda A , Budillon G , Caregaro L , Clerici C , Nutritional state and energy balance in cirrhotic patients with or without hypermetabolism: multicentre prospective study by the ‘Nutritional Problems in Gastroenterology’ Section of the Italian Society of Gastroenterology (SIGE) . *Dig Liver Dis* 2005 ; 37 : 681 – 688 . 10.1016/j.dld.2005.03.010 . 15978878 209) Riggio O , Angeloni S , Ciuffa L , Nicolini G , Attili AF , Albanese C , Malnutrition is not related to alterations in energy balance in patients with stable liver cirrhosis . *Clin Nutr* 2003 ; 22 : 553 – 559 . 10.1016/s0261-5614(03)00058-x . 14613758 210) Nielsen K , Kondrup J , Martinsen L , Døssing H , Larsson B , Stilling B , Long-term oral refeeding of patients with cirrhosis of the liver . *Br J Nutr* 1995 ; 74 : 557 – 567 . 10.1079/BJN19950158 . 7577893 211) European Association for the Study of the Liver . EASL clinical practice guidelines on nutrition in chronic liver disease . *J Hepatol* 2019 ; 70 : 172 – 193 . 10.1016/j.jhep.2018.06.024 . 30144956 PMC6657019 212) Plauth M , Bernal W , Dasarathy S , Merli M , Plank LD , Schütz T , ESPEN guideline on clinical nutrition in liver disease . *Clin Nutr* 2019 ; 38 : 485 – 521 . 10.1016/j.clnu.2018.12.022 . 30712783 PMC6686849 213) Amodio P , Bemeur C , Butterworth R , Cordoba J , Kato A , Montagnese S , The nutritional management of hepatic encephalopathy in patients with cirrhosis: International Society for Hepatic Encephalopathy and Nitrogen Metabolism Consensus . *Hepatology* 2013 ; 58 : 325 – 336 . 10.1002/hep.26370 . 23471642 214) Swart GR , van den Berg JWO , van Vuure JK , Rietveld T , Wattimena DL , Frenkel M . Minimum protein requirements in liver cirrhosis determined by nitrogen balance measurements at three levels of protein intake . *Clin Nutr* 1989 ; 8 : 329 – 336 . 10.1016/0261-5614(89)90008-3 . 16837309 215) Swart GR , van den Berg JWO , Wattimena JLD , Rietveld T , Van Vuure JK , Frenkel M . Elevated protein requirements in cirrhosis of the liver investigated by whole body protein turnover studies . *Clin Sci* 1988 ; 75 : 101 – 107 . 10.1042/cs0750101 . 3409620 216) Nielsen K , Kondrup J , Martinsen L , Stilling B , Wikman B . Nutritional assessment and adequacy of dietary intake in hospitalized patients with alcoholic liver cirrhosis . *Br J Nutr* 1993 ; 69 : 665 – 679 . 10.1079/BJN19930068 . 8329343 217) Córdoba J , López-Hellín J , Planas M , Sabín P , Sanpedro F , Castro F , Normal protein diet for episodic hepatic encephalopathy: results of a randomized study . *J Hepatol* 2004 ; 41 : 38 – 43 . 10.1016/j.jhep.2004.03.023 . 15246205 218) Gheorghe L , Iacob R , Vladan R , Iacob S , Gheorghe C . Improvement of hepatic encephalopathy using a modified high-calorie high-protein diet . *Rom J Gastroenterol* 2005 ; 14 : 231 – 238 . 16200232 219) Charlton CP , Buchanan E , Holden CE , Preece MA , Green A , Booth IW , Intensive enteral feeding in advanced cirrhosis: reversal of malnutrition without precipitation of hepatic encephalopathy . *Arch Dis Child* 1992 ; 67 : 603 – 607 . 10.1136/ad.67.5.603 . 1599297 PMC1793698 220) Uribe M , Marquez MA , Ramos GG , Ramos-Uribe MH , Vargas F , Villalobos A , Treatment of chronic portal–systemic encephalopathy with vegetable and animal protein diets: a controlled crossover study . *Dig Dis Sci* 1982 ; 27 : 1109 – 1116 . 10.1007/BF01391449 . 6756833 221) Bianchi GP , Marchesini G , Fabbri A , Rondelli A , Bugianesi E , Zoli M , Vegetable versus animal protein diet in cirrhotic patients with chronic encephalopathy. A randomized crossover comparison . *J Intern Med* 1993 ; 233 : 385 – 392 . 10.1111/j.1365-2796.1993.tb00689.x . 8068051 222) Jonung T , Jeppsson B , Åslund U , Nair BM . A comparison between meat and vegan protein diet in patients with mild chronic hepatic encephalopathy . *Clin Nutr* 1987 ; 6 : 169 – 174 . 10.1016/0261-5614(87)90052-5 . 223) Marchesini G , Bianchi G , Merli M , Amodio P , Panella C ,

Loguercio C , Nutritional supplementation with branched-chain amino acids in advanced cirrhosis: a double-blind, randomized trial . *Gastroenterology* 2003 ; 124 : 1792 – 1801 .
10.1016/S0016-5085(03)00323-8 . 12806613 224) Marchesini G , Dioguardi FS , Bianchi GP , Zoli M , Bellati G , Roffi L , Long-term oral branched-chain amino acid treatment in chronic hepatic encephalopathy. A randomized double-blind casein-controlled trial . *J Hepatol* 1990 ; 11 : 92 – 101 .
10.1016/0168-8278(90)90278-y . 2204661 225) Muto Y , Sato S , Watanabe A , Moriwaki H , Suzuki K , Kato A , Effects of oral branched-chain amino acid granules on event-free survival in patients with liver cirrhosis . *Clin Gastroenterol Hepatol* 2005 ; 3 : 705 – 713 .
10.1016/S1542-3565(05)00017-0 . 16206505 226) Plauth M , Egberts E-H , Hamster W , Török M , Müller PH , Brand O , Long-term treatment of latent portosystemic encephalopathy with branched-chain amino acids . *J Hepatol* 1993 ; 17 : 308 – 314 . 10.1016/S0168-8278(05)80210-7 .
8315258 227) Gluud LL , Dam G , Les I , Córdoba J , Marchesini G , Borre M , Branched-chain amino acids for people with hepatic encephalopathy . *Cochrane Database Syst Rev* 2015 : CD001939 . 10.1002/14651858.CD001939.pub2 . 26377410 228) Mager DR , Wykes LJ , Roberts EA , Ball RO , Pencharz PB . Branched-chain amino acid needs in children with mild-to-moderate chronic cholestatic liver disease . *J Nutr* 2006 ; 136 : 133 – 139 . 10.1093/jn/136.1.133 . 16365072
229) Chin SE , Shepherd RW , Thomas BJ , Cleghorn GJ , Patrick MK , Wilcox JA , Nutritional support in children with end-stage liver disease: a randomized crossover trial of a branched-chain amino acid supplement . *Am J Clin Nutr* 1992 ; 56 : 158 – 163 . 10.1093/ajcn/56.1.158 . 1609753
230) Gielen E , Beckwée D , Delaere A , De Breucker S , Vandewoude M , Bautmans I , Nutritional interventions to improve muscle mass, muscle strength, and physical performance in older people: an umbrella review of systematic reviews and meta-analyses . *Nutr Rev* 2021 ; 79 : 121 – 147 .
10.1093/nutrit/nuaa011 . 32483625 231) Singh SS , Kumar A , Welch N , Sekar J , Mishra S , Bellar A , Multiomics-identified intervention to restore ethanol-induced dysregulated proteostasis and secondary sarcopenia in alcoholic liver disease . *Cell Physiol Biochem* 2021 ; 55 : 91 – 116 .
10.33594/000000327 . 33543862 PMC8195260 232) Goh ET , Stokes CS , Sidhu SS , Vilstrup H , Gluud LL , Morgan MY . L-Ornithine L-aspartate for prevention and treatment of hepatic encephalopathy in people with cirrhosis . *Cochrane Database Syst Rev* 2018 : CD012410 .
10.1002/14651858.CD012410.pub2 . 29762873 PMC6494563 233) Tsien CD , McCullough AJ , Dasarathy S . Late evening snack: exploiting a period of anabolic opportunity in cirrhosis . *J Gastroenterol Hepatol* 2012 ; 27 : 430 – 441 . 10.1111/j.1440-1746.2011.06951.x . 22004479 234)
Vaisman N , Katzman H , Carmiel-Haggai M , Lusthaus M , Niv E . Breakfast improves cognitive function in cirrhotic patients with cognitive impairment . *Am J Clin Nutr* 2010 ; 92 : 137 – 140 .
10.3945/ajcn.2010.29211 . 20444959 235) Al-Obaid LN , Bazarbashi AN , Cohen ME , Kim J , Lei Y , Axelrad JE , Enteric tube placement in patients with esophageal varices: risks and predictors of postinsertion gastrointestinal bleeding . *JGH Open* 2020 ; 4 : 256 – 259 . 10.1002/jgh3.12255 .
32280774 PMC7144797 236) Vidot H , Bowen DG , Carey S , McCaughan GW , Allman-Farinelli M , Shackel NA . Aggressive nutrition intervention reduces ascites and frequency of paracentesis in malnourished patients with cirrhosis and ascites: ascites and frequency of paracentesis . *JGH Open* 2017 ; 1 : 92 – 97 . 10.1002/jgh3.12016 . 30483543 PMC6206992 237) Baltz JG , Argo CK , Al-Osaimi AMS , Northup PG . Mortality after percutaneous endoscopic gastrostomy in patients with cirrhosis: a case series . *Gastrointest Endosc* 2010 ; 72 : 1072 – 1075 . 10.1016/j.gie.2010.06.043 .
20855067 238) Berzigotti A , Albillos A , Villanueva C , Genescá J , Ardevol A , Agustín S , Effects of an intensive lifestyle intervention program on portal hypertension in patients with cirrhosis and obesity: the SportDiet study . *Hepatology* 2017 ; 65 : 1293 – 1305 . 10.1002/hep.28992 . 27997989
239) Villareal DT , Aguirre L , Gurney AB , Waters DL , Sinacore DR , Colombo E , Aerobic or resistance exercise, or both, in dieting obese older adults . *N Engl J Med* 2017 ; 376 : 1943 – 1955 .
10.1056/NEJMoa1616338 . 28514618 PMC5552187 240) Koretz RL , Avenell A , Lipman TO . Nutritional support for liver disease . *Cochrane Database Syst Rev* 2012 : CD008344 .
10.1002/14651858.CD008344.pub2 . 22592729 PMC6823271 241) Ney M , Vandermeer B , van Zanten SJV , Ma MM , Gramlich L , Tandon P . Meta-analysis: oral or enteral nutritional supplementation in cirrhosis . *Aliment Pharmacol Ther* 2013 ; 37 : 672 – 679 . 10.1111/apt.12252 .
23421379 242) Moreno C , Deltenre P , Senterre C , Louvet A , Gustot T , Bastens B , Intensive enteral nutrition is ineffective for patients with severe alcoholic hepatitis treated with corticosteroids . *Gastroenterology* 2016 ; 150 : 903 – 910.e8 . 10.1053/j.gastro.2015.12.038 . 26764182 243)
Reuter B , Shaw J , Hanson J , Tate V , Acharya C , Bajaj JS . Nutritional assessment in inpatients with cirrhosis can be improved after training and is associated with lower readmissions . *Liver*

Transpl 2019 ; 25 : 1790 – 1799 . 10.1002/lt.25602 . 31301208 PMC7262968 244) McClave SA , Taylor BE , Martindale RG , Warren MM , Johnson DR , Braunschweig C , Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) . J Parenter Enter Nutr 2016 ; 40 : 159 – 211 . 10.1177/0148607115621863 26773077 245) McClave SA , DiBaise JK , Mullin GE , Martindale RG . ACG clinical guideline: nutrition therapy in the adult hospitalized patient . Am J Gastroenterol 2016 ; 111 : 315 – 334 . 10.1038/ajg.2016.28 . 26952578 246) Patel JJ , McClain CJ , Sarav M , Hamilton-Reeves J , Hurt RT . Protein requirements for critically ill patients with renal and liver failure . Nutr Clin Pract 2017 ; 32 (1 Suppl) : 101S – 111S . 10.1177/0884533616687501 . 28208022 247) Nanchal R , Subramanian R , Karvellas CJ , Hollenberg SM , Peppard WJ , Singbartl K , Guidelines for the management of adult acute and acute-on-chronic liver failure in the ICU: cardiovascular, endocrine, hematologic, pulmonary, and renal considerations . Crit Care Med 2020 ; 48 : e173 – e191 . 10.1097/CCM.0000000000004192 . 32058387 248) de Lédinghen V , Beau P , Mannant PR , Borderie C , Ripault MP , Silvain C , Early feeding or enteral nutrition in patients with cirrhosis after bleeding from esophageal varices? A randomized controlled study . Dig Dis Sci 1997 ; 42 : 536 – 541 . 10.1023/a:1018838808396 . 9073135 249) Peter JV , Moran JL , Phillips-Hughes J . A metaanalysis of treatment outcomes of early enteral versus early parenteral nutrition in hospitalized patients . Crit Care Med 2005 ; 33 : 213 – 220 ; discussion 260-261 . 10.1097/01.ccm.0000150960.36228.c0 . 15644672 250) Simpson F , Doig GS . Parenteral vs. enteral nutrition in the critically ill patient: a meta-analysis of trials using the intention to treat principle . Intensive Care Med 2005 ; 31 : 12 – 23 . 10.1007/s00134-004-2511-2 . 15592814 251) Cheung K , Lee SS , Raman M . Prevalence and mechanisms of malnutrition in patients with advanced liver disease, and nutrition management strategies . Clin Gastroenterol Hepatol 2012 ; 10 : 117 – 125 . 10.1016/j.cgh.2011.08.016 . 21893127 252) Himoto T , Masaki T . Current trends of essential trace elements in patients with chronic liver diseases . Nutrients 2020 ; 12 : 2084 . 10.3390/nu12072084 . PMC7400835 32674425 253) Kozeniecki M , Ludke R , Kerner J , Patterson B . Micronutrients in liver disease: roles, risk factors for deficiency, and recommendations for supplementation . Nutr Clin Pract 2020 ; 35 : 50 – 62 . 10.1002/ncp.10451 . 31840874 254) Sriram K , Lonchyna VA . Micronutrient supplementation in adult nutrition therapy: practical considerations . J Parenter Enteral Nutr 2009 ; 33 : 548 – 562 . 10.1177/0148607108328470 . 19454751 255) Johnson TM , Overgard EB , Cohen AE , DiBaise JK . Nutrition assessment and management in advanced liver disease . Nutr Clin Pract 2013 ; 28 : 15 – 29 . 10.1177/0884533612469027 . 23319353 256) Newsome PN , Beldan I , Moussa Y , Delahooke TE , Pouloupoulos G , Hayes PC , Low serum retinol levels are associated with hepatocellular carcinoma in patients with chronic liver disease . Aliment Pharmacol Ther 2000 ; 14 : 1295 – 1301 . 10.1046/j.1365-2036.2000.00849.x . 11012474 257) Schölmerich J , Löhle E , Kötting E , Gerok W . Zinc and vitamin A deficiency in liver cirrhosis . Hepatogastroenterology 1983 ; 30 : 119 – 125 . 6354899 258) Koop AH , Mousa OY , Pham LE , Corral-Hurtado JE , Pungpapong S , Keaveny AP . An argument for vitamin D, A, and zinc monitoring in cirrhosis . Ann Hepatol 2018 ; 17 : 920 – 932 . 10.5604/01.3001.0012.7192 . 30600288 259) Holick MF , Binkley NC , Bischoff-Ferrari HA , Gordon CM , Hanley DA , Heaney RP , Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline . J Clin Endocrinol Metab 2011 ; 96 : 1911 – 1930 . 10.1210/jc.2011-0385 . 21646368 260) Heubi JE , Hollis BW , Specker B , Tsang RC . Bone disease in chronic childhood cholestasis: vitamin D absorption and metabolism . Hepatology 1989 ; 9 : 258 – 264 . 10.1002/hep.1840090216 . 2783577 261) Altarelli M , Ben-Hamouda N , Schneider A , Berger MM . Copper deficiency: causes, manifestations, and treatment . Nutr Clin Pract 2019 ; 34 : 504 – 513 . 10.1002/ncp.10328 . 31209935 262) Macías-Rodríguez RU , Ilarraza-Lomelí H , Ruiz-Margáin A , Ponce-de-León-Rosales S , Vargas-Vorácková F , García-Flores O , Changes in hepatic venous pressure gradient induced by physical exercise in cirrhosis: results of a pilot randomized open clinical trial . Clin Transl Gastroenterol 2016 ; 7 : e180 . 10.1038/ctg.2016.38 . 27415618 PMC5543482 263) Aamann L , Dam G , Borre M , Drljevic-Nielsen A , Overgaard K , Andersen H , Resistance training increases muscle strength and muscle size in patients with liver cirrhosis . Clin Gastroenterol Hepatol 2020 ; 18 : 1179 – 1187.e6 . 10.1016/j.cgh.2019.07.058 . 31394282 264) Chen HW , Ferrando A , White MG , Dennis RA , Xie J , Pauly M , Home-based physical activity and diet intervention to improve physical function in advanced liver disease: a randomized pilot trial . Dig Dis Sci 2020 ; 65 : 3350 – 3359 . 10.1007/s10620-019-06034-2 . 31907774 265) Lai JC ,

Dodge JL , Kappus MR , Wong R , Mohamad Y , Segev DL , A multicenter pilot randomized clinical trial of a home-based exercise program for patients with cirrhosis: the Strength Training Intervention (STRIVE) . *Am J Gastroenterol* 2021 ; 116 : 717 – 722 . 10.14309/ajg.0000000000001113 . 33982941 PMC8178511 266) Williams FR , Berzigotti A , Lord JM , Lai JC , Armstrong MJ . Review article: impact of exercise on physical frailty in patients with chronic liver disease . *Aliment Pharmacol Ther* 2019 ; 50 : 988 – 1000 . 10.1111/apt.15491 . 31502264 267) Moore GE , Durstine JL , Painter PL , eds. *ACSM's Exercise Management for Persons with Chronic Diseases and Disabilities* . 4th ed. Champaign, IL : Human Kinetics ; 2016 . 268) US Department of Health & Human Services . Executive summary: physical activity guidelines for Americans . 2nd ed. https://health.gov/sites/default/files/2019-10/PAG_ExecutiveSummary.pdf . Published 2019 . Accessed April 23, 2021 . 269) Duarte-Rojo A , Bloomer PM , Rogers RJ , Hassan MA , Dunn MA , Tevar AD , Introducing EL-FIT (Exercise and Liver FITness): a smartphone app to prehabilitate and monitor liver transplant candidates . *Liver Transpl* 2021 ; 27 : 502 – 512 . 10.1002/lt.25950 . 33232547 PMC10251157 270) Lai JC , Sonnenday CJ , Tapper EB , Duarte-Rojo A , Dunn MA , Bernal W , 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 . 10.1111/ajt.15392 . 30980701 PMC6814290 271) Tandon P , Ismond KP , Riess K , Duarte-Rojo A , Al-Judaibi B , Dunn MA , Exercise in cirrhosis: translating evidence and experience to practice . *J Hepatol* 2018 ; 69 : 1164 – 1177 . 10.1016/j.jhep.2018.06.017 . 29964066 272) Lin FP , Ferrando AA , Dennis RA , Dunn MA , Kim WR , Duarte-Rojo A . Exercise-induced hyperammonemia does not precipitate overt hepatic encephalopathy . *Hepatology* 2020 ; 72 : 778 – 780 . 10.1002/hep.31148 . 31997375 273) Bandi J-C , García-Pagán JC , Escorsell A , François E , Moitinho E , Rodes J , Effects of propranolol on the hepatic hemodynamic response to physical exercise in patients with cirrhosis . *Hepatology* 1998 ; 28 : 677 – 682 . 10.1002/hep.510280312 . 9731558 274) Bellar A , Welch N , Dasarathy S . Exercise and physical activity in cirrhosis: opportunities or perils . *J Appl Physiol* 2020 ; 128 : 1547 – 1567 . 10.1152/jappphysiol.00798.2019 . 32240017 PMC7311690 275) Kovacheva EL , Hikim APS , Shen R , Sinha I , Sinha-Hikim I . Testosterone supplementation reverses sarcopenia in aging through regulation of myostatin, c-Jun NH 2-terminal kinase, Notch, and Akt signaling pathways . *Endocrinology* 2010 ; 151 : 628 – 638 . 10.1210/en.2009-1177 . 20022929 PMC2817626 FIG. 1. Factors contributing to malnutrition, frailty, and sarcopenia and the relationship between these three constructs. Cirrhosis-related and other systems-related factors, along with physical inactivity and environmental/organizational factors, contribute to malnutrition—which then leads to frailty and sarcopenia. These factors can also contribute directly to frailty and sarcopenia independently of malnutrition.

The three levels of disease prevention and health promotion as applied to management of malnutrition, frailty, and sarcopenia in patients with cirrhosis.

Algorithm for screening, assessment, and management of malnutrition, frailty, and sarcopenia in patients with cirrhosis.

Diagnostic and management toolboxes with specific tools to facilitate diagnosis and management of malnutrition, frailty, and sarcopenia in patients with cirrhosis.

Definitions for the Theoretical Constructs of Malnutrition, Frailty, and Sarcopenia and Consensus-Derived Operational Definitions Applied to Patients with Cirrhosis

Tools to Assess Frailty or Individual Frailty Components that have been Studied in Patients with Cirrhosis

Tools to Assess Muscle Mass that have been Studied in Patients with End-Stage Liver Disease

Micronutrient Supplementation in Cirrhosis

Ocular changes (e.g., xerophthalmia, night blindness)

Skin changes (e.g., hyperkeratosis, phrynoderma, poor wound healing)

In patients not responding to vitamin A replacement, consider replacing zinc as well (257 , 258)

Monitor levels with supplementation as there is risk of significant toxicity ($>120 \mu\text{g/dL}$)

Bone pain, muscle weakness, osteomalacia, anorexia, hair loss, poor wound healing

Therapeutic target 25-OH vitamin D $> 30 \text{ ng/mL}$

In children, supplementation with vitamin D 3 is more effective than vitamin D 2 because greater water solubility allows better absorption (260)

Give with calcium in those with low bone mineral density

Neurologic deficits (e.g., ataxia, peripheral neuropathy)

Deficiency is much less common than vitamins A and D

High doses antagonize vitamin A and adversely affect wound healing and platelet function

Bleeding, petechiae, purpura, ecchymosis

Prolongation of international normalized ratio

Not stored, so deficiencies occur rapidly

Route and dose of replacement regimen vary by clinical setting

Wernicke encephalopathy/Korsakoff syndrome

Thiamine measurement is not widely available

Dose and route according to deficiency syndrome and severity

Pellagra: dry skin and bright red tongue, gastrointestinal disturbance

Neurological symptoms; apathy, fatigue headache, memory loss, abnormal behavior

Blood levels are unreliable measures of deficiency

Hepatotoxicity possible from excess dosage

Oral changes (e.g., glossitis, ulcerations)

Parallel measurement of B 12 recommended

Oral changes (e.g., glossitis, ulcerations)

Neurologic (e.g., peripheral neuropathy, gait disturbance, cognitive impairment)

Patients with low gastric acid secretion or after ileal resection are at high risk for deficiency, and high doses may be required

Perifollicular petechiae, keratosis, ecchymosis

Requirements are increased in critical illness

Replacing zinc may result in normalization of vitamin A metabolism (257)

High doses may result in copper deficiency

Blood levels are only a crude index of whole-body zinc status

Skin changes: alopecia, dry skin, erythema

Bone marrow suppression: microcytic anemia, leukopenia, pancytopenia

Neurologic changes: neuropathies, ataxia

Blood copper level is a screening test for deficiency

Used to guide repletion strategies: confounded by inflammation (261)

Bariatric bypass surgery a risk factor for deficiency

All patients with cirrhosis should be assessed for frailty with a standardized tool both at baseline and longitudinally. 1a. There are insufficient data to recommend the use of one frailty tool over another. Instead, we recommend that selection of the standardized frailty tool in clinical practice should depend upon the relative need for efficiency versus objectivity of assessment within that clinical scenario. In patients with compensated cirrhosis, annual frailty assessment may be sufficient, whereas patients with decompensated cirrhosis may benefit from more frequent (every 3-6 months) assessment.

All patients with cirrhosis should be counseled on the risks and adverse clinical consequences of frailty regardless of their baseline frailty status.

Given the strong and consistent association between muscle mass and outcomes in both adults and children with cirrhosis, objective measures of muscle loss should be considered to assess risk for poor outcomes in patients with cirrhosis.

SMI as assessed by CT image analysis is recommended as the most consistent and reproducible method to quantify muscle mass in patients with cirrhosis. 4a There are currently insufficient data to support a bedside tool to assess muscle mass in patients with cirrhosis.

4b MRI measurement of skeletal muscle mass has not been validated in patients with cirrhosis but theoretically provides the same information on muscle mass as CT imaging.

Because of the risk of exposure to radiation, use of abdominal CT solely for the purpose of muscle mass measurement is not recommended for routine use; but quantification of skeletal muscle mass should be considered when an abdominal CT is obtained as part of clinical care or in patients in whom assessment of muscle contractile function is not practical or feasible (e.g., acutely ill patients, very young children).

In clinical settings, we recommend systematic assessment of frailty and/or sarcopenia in all patients with cirrhosis using a standardized instrument. 6a Frailty testing may be particularly useful in the ambulatory setting and when intermediate-term and long-term longitudinal assessments are needed to assess natural progression or response to treatment.

6b Sarcopenia testing may be particularly useful for patients in whom administration of tests of frailty is not feasible or is impractical (e.g., because of acute severe illness or inability to participate in testing such as in very young children).

In research studies of patients with cirrhosis, including clinical trials evaluating interventions related to malnutrition and/or muscle dysfunction, we recommend assessment of both frailty and sarcopenia, when possible, to more comprehensively capture the impact of interventions on these complementary endpoints.

All patients with cirrhosis should receive education, motivation, and behavioral skills support to reduce their risk of developing these conditions (primary prevention).

A positive frailty or sarcopenia screen should prompt evaluation for underlying etiologic risk factors and the development of an ambulatory personalized management plan (secondary prevention).

Reassessment of frailty or sarcopenia using the same standardized tool as baseline assessment should occur at least annually for patients with well-compensated disease but as frequently as every 8-12 weeks for those with decompensated cirrhosis and/or those undergoing active management for these conditions.

Patients with progressive frailty or sarcopenia despite initiation of secondary prevention efforts should undergo more intensive nutrition and exercise rehabilitation under the direct supervision of a registered dietitian and certified exercise physiologist/physical therapist (tertiary prevention).

Management should involve a multidisciplinary team consisting of the patient's primary care provider, gastroenterologist/hepatologist, registered dietitian, certified exercise physiologist/physical therapist, and health behavior specialist (if there is a concurrent mental health condition) when possible. However, if not available at all levels of prevention/health promotion, then at a minimum, referral to a registered dietitian and certified exercise physiologist/physical therapist is recommended at the tertiary prevention level.

Treatment of inflammatory conditions that lead to cirrhosis, such as HCV, insulin resistance, obesity, and alcohol use disorder, is recommended to manage malnutrition, frailty, and sarcopenia.

Identification and management of cirrhosis-specific complications (e.g., HE, ascites) is recommended in all patients with cirrhosis to manage malnutrition, frailty, and sarcopenia.

TIPS placement for standard indications (e.g., ascites, acute variceal bleeding) may offer an indirect benefit of improving muscle mass.

In the absence of specific data on which patients will experience improvement in frailty and sarcopenia posttransplant, liver transplantation cannot be recommended specifically for the treatment of frailty or sarcopenia.

We do not recommend using frailty or sarcopenia as an absolute contraindication against liver transplantation.

All patients with cirrhosis (regardless of a diagnosis of malnutrition) should receive educational resources and counseling regarding the association between nutritional status and outcomes and to

optimize nutritional status.

Patients with cirrhosis who screen positive for malnutrition risk, frailty, or sarcopenia should receive a personalized intake “prescription” that is tailored to actual needs and incorporates individual habits around nutrition.

Calorie needs should be personalized to the patient. 20a When possible, indirect calorimetry should be used to measure the patient’s REE in order to provide a personalized intake prescription.

20b In the absence of indirect calorimetry, data, although limited, support the use of the following: Traditional predictive equations, such as the Harris-Benedict equation

Weight-based equations (using ideal body weight)

Nonobese—target of at least 35 kcal/kg body weight/day

Obese (nonhospitalized, clinically stable)—use of caloric targets stratified by BMI: 25-35 kcal/kg/day for individuals with BMI 30-40 kg/m² and 20-25 kcal/kg/day for individuals with BMI $\geq$ 40 kg/m²

20c In patients who screen positive for frailty or sarcopenia and cannot meet nutritional targets on a sodium-restricted diet, liberalization of sodium restriction should be considered to facilitate adequate oral intake.

Recommended protein intake for adults with cirrhosis is 1.2-1.5 g/kg ideal body weight per day. 21a For adults with cirrhosis who are critically ill, a target of 1.2-2.0 g/kg ideal body weight per day is recommended.

21b A diverse range of protein sources, including vegetable and dairy products, should be encouraged.

21c BCAA supplementation is not recommended beyond emphasizing the importance of meeting daily overall protein targets from a diverse range of protein sources.

For children with chronic liver disease, recommended protein intake should be up to 4 g/kg ideal body weight per day.

Protein intake should not be restricted in patients with HE.

Fasting time should be minimized, with a maximum interval of 3-4 hours between nutritional intake while awake.

To minimize nocturnal fasting time, an early breakfast and/or late-evening snack should be recommended.

In ambulatory patients with cirrhosis and children with cirrhosis/end-stage liver disease who do not meet dietary intake requirements with oral intake, enteral nutritional supplementation may be considered to achieve targets.

Percutaneous gastrostomy tubes should not be placed in patients with cirrhosis and ascites.

If medically required, weight loss should be undertaken under the supervision of a multidisciplinary team. 28a Particular caution should be applied to prescribing weight loss in a patient with decompensated cirrhosis.

28b Intake of target protein and physical activity are required to reduce the loss of muscle contractile function and muscle mass that can occur with weight loss.

All hospitalized patients with cirrhosis should receive formal consultation with a registered dietitian within 24 hours of admission or, if not available, then assessment for malnutrition using the RFH-NPT.

Strategies to minimize this fasting period or frequency of NPO orders (e.g., prebedtime snack, early-morning snack if the procedure will be in the late afternoon, consider advancing diet rapidly when there is no indication for NPO status) should be implemented.

Oral nutritional supplementation is the first-line therapy for hospitalized patients with cirrhosis who are unable to meet energy needs through volitional intake alone.

In hospitalized patients with cirrhosis who are unable to meet energy needs with volitional intake and oral nutritional supplementation, enteral nutritional supplementation should be considered to achieve targets. 32a Precautions should be taken to reduce risk of aspiration and development of hyperglycemia.

32b The presence of esophageal varices is not an absolute contraindication to placement of an enteric feeding tube, but close monitoring is warranted for signs of rebleeding if an enteric tube is required after recent banding of esophageal varices.

32c Parenteral nutritional should be reserved for patients with cirrhosis who are intolerant of enteral nutrition and unable meet dietary intake requirements through oral intake alone.

In patients who are critically ill with cirrhosis, a higher protein target of 1.2-2.0 g/kg ideal body weight/day is recommended.

In hospitalized patients with decompensated cirrhosis, parenteral nutritional support should be considered in those who are unable to meet nutritional requirements through oral intake alone and are unable to receive enteral nutritional support.

Micronutrient deficiencies should be assessed at least annually, repleted if deficient, and reassessed after repletion.

Physical activity–based interventions are recommended to improve muscle contractile function and muscle mass in patients with cirrhosis.

The three components to activity-based interventions in patients with cirrhosis should include (1) assessing and reassessing frailty and/or sarcopenia using standardized tools, (2) recommending a combination of aerobic and resistance exercises, and (3) tailoring recommendations based on assessments.

In men with cirrhosis who may be candidates for testosterone therapy, testosterone levels should be checked at baseline.

Testosterone replacement may be considered in select men with low testosterone to improve muscle mass. 39a Relative contraindications to use of testosterone include a history of HCC, other malignancy, or thrombosis.