



Hepatocellular carcinoma and sarcopenia: a narrative review[✳]

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Background and Objective: Hepatocellular carcinoma (HCC) affects millions of people each year and is associated with high mortality and morbidity. Sarcopenia, a condition of muscle wasting, and decreased muscle performance is common among aging adults, and is associated with poor clinical outcomes. Individuals with HCC and chronic liver disease (CLD) are at high risk of sarcopenia because of the adverse effects of chronic inflammation, endocrine dysfunction, and hyperammonemia on muscle metabolism and adequate nutrition. Our aim is to review the clinical relationship between HCC and sarcopenia, and the assessment and management of these patients.

Methods: A narrative review based on a literature search using PubMed. Keywords related to HCC and sarcopenia were used to identify relevant articles, primarily those published 2018–2023. The information was synthesized to provide a narrative review focused on the most recent literature.

Key Content and Findings: Sarcopenia frequently co-exists with HCC and increases risk for adverse clinical outcomes such as symptom burden, quality of life (QoL), survival, and side effects of antineoplastic therapy. Tools are available to screen, assess and manage patients with HCC, and although there is no specific pharmacologic agent approved for sarcopenia in the United States, multimodal therapy is feasible in daily practice. Comprehensive management by an interdisciplinary team should include nutritional counseling, an exercise regimen and control of symptoms affecting nutrition and function.

Conclusions: Sarcopenia has adverse effects on prognosis and tolerability of surgical and medical therapy in HCC. Patients with CLD and/or HCC would benefit from early identification, assessment, and therapeutic intervention. Management should be comprehensive, interdisciplinary, and include both pharmacologic and non-pharmacologic treatments. Further research is needed to identify individual agents that may mitigate muscle wasting and trials are needed to evaluate the benefit of multimodal therapy in HCC.

Keywords: Sarcopenia; malnutrition; hepatocellular carcinoma (HCC); chronic liver disease (CLD)

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Introduction

Background

In 2020, an estimated 905,700 people globally were diagnosed with hepatocellular carcinoma (HCC) and 830,200 individuals died (1) from the illness. As the third most common cause of cancer death worldwide, several risk factors account for HCC prevalence, including chronic infections such as hepatitis B virus (HBV) or hepatitis C virus (HCV), toxins such as alcohol and nonalcoholic fatty liver disease (NAFLD). Most individuals diagnosed with HCC have some evidence of cirrhosis, caused by exposure to risk factors (2). NAFLD, cirrhosis and HCC are associated with a higher prevalence of sarcopenia, a condition characterized by loss of muscle mass and diminished physical performance.

Rationale and knowledge gap

By identifying sarcopenia early and modifying exacerbating factors, clinicians could improve symptom burden, quality of life (QoL) and patients' ability to tolerate anti-neoplastic therapy in HCC. We believe a review of the literature is necessary given the high prevalence of sarcopenia in HCC and CLD and the potential for improving clinical outcomes.

Both HCC and sarcopenia are associated with a chronic pro-inflammatory response that plays a prominent role in disease progression. The pro-inflammatory response typically found in patients with solid tumors is thought to drive a variable combination of anorexia, fatigue, and muscle wasting.

A meta-analysis of 57 studies involving 9,790 HCC patients (3) reported a sarcopenia pooled prevalence of 41.7% (range, 11.1% to 78.3%). Another meta-analysis revealed significant differences in the pooled prevalence depending on the methods for sarcopenia assessment and geographic location (Asia, Europe, or North America) (4). Differences in prevalence also depend on the illness trajectory. Overall, for solid tumors the prevalence of sarcopenia was 39.6% in the curative, compared to 49.2% in the palliative setting ($P < 0.001$). In HCC the difference in prevalence between curative and palliative settings was narrower (35.4% vs. 38.2%) (5).

The objective of this narrative review is to provide clinicians with updated information to better identify, assess, and manage patients with HCC and sarcopenia. Given there is no Food and Drug Administration (FDA) approved agent for sarcopenia in cancer, an interdisciplinary multimodal

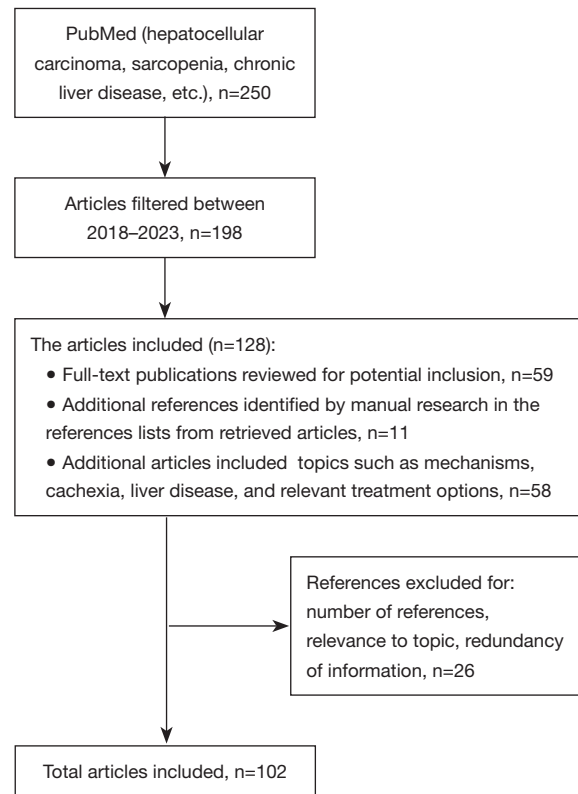


Figure 1 Schema of literature review.

approach that includes a combination of pharmacologic and non-pharmacologic therapies is emphasized. We present this article in accordance with the Narrative Review reporting checklist (available at <https://apm.amegroups.com/article/view/10.21037/apm-23-332/rc>).

Methods (Figure 1)

A literature search used PubMed as the primary database. Keywords included ‘hepatocellular carcinoma’, ‘chronic liver disease’, ‘liver cirrhosis’, ‘hepatitis’, ‘fatty liver disease’, ‘sarcopenia’, ‘cachexia’, ‘anorexia’ in various combinations (Table 1). PubMed searches were filtered to yield articles published between 2018 and 2023. Additional articles were included after reviewing the citations of articles identified by the primary search. Older articles were included if the authors were of the opinion they were particularly important to the field.

Definitions and diagnosis

Muscle wasting is common in patients with cancer and is a

Table 1 The search strategy summary

Items	Specification
Date of search	January 25th 2023
Databases and other sources searched	PubMed
Search terms used	'Hepatocellular carcinoma', 'chronic liver disease', 'liver cirrhosis', 'hepatitis', 'fatty liver disease', sarcopenia', 'cachexia', 'anorexia'
Timeframe	2018–2023
Inclusion criteria	Studies in English or with English translations
Selection process	Revoredo S and Del Fabbro E conducted the selection
Any additional considerations, if applicable	Additional articles were obtained after reviewing references of primarily obtained articles

key component of several conditions sometimes found in the same individual, particularly in older patients. These conditions include sarcopenia, cachexia, and frailty (6). The detrimental role of excess adipose tissue in combination with muscle wasting [sarcopenic obesity (SO)] and the infiltration of fat into muscle (myosteatosis) needs to be considered in patients with muscle loss.

Sarcopenia: dual X-ray absorptiometry (DXA) or computerized tomography (CT) scan with cut-offs depending on variables such as race and sex, is a clinical diagnosis that includes loss of muscle mass (measured by imaging) and function typically occurring due to aging but may also occur because of another illness such as cancer (secondary sarcopenia).

In 2018, the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) updated the consensus definition of sarcopenia (7) to include low muscle strength as the key characteristic of sarcopenia, with low muscle quantity and quality confirming the diagnosis, and poor physical performance indicating severe sarcopenia. The EWGSOP updated their clinical algorithm for sarcopenia (Find-Assess-Confirm-Severity or F-A-C-S) and provided clinically relevant cut-off points for the variables that characterize sarcopenia, including cut-offs for physical performance. The EWGSOP2 recommends the SARC-F, a 5-item self-reported questionnaire as a screen for sarcopenia risk (8) and finding appropriate patients. The SARC-F is validated and reports on strength, walking, ability to rise from a chair, climb stairs, and frequency of falls. In a study of 256 oncology patients one third screened positive for sarcopenia using the SARC-F (9). Those with sarcopenia had higher rates of impairment, lower QoL, and increased

mortality.

Thereafter, assessment of muscle strength is recommended either by hand grip strength (HGS) (using a dynamometer) or the chair stand test (time needed to rise five times from a seated position without a patient using their arms). HGS is relatively easy to measure and correlates moderately well with other muscle compartments (10). The Foundations for the National Institutes of Health (FNIH) Biomarkers Consortium has estimated cut-off points for weakness (grip strength <26 kg for men and <16 kg for women) that are similar to EWGSOP2 (11). The importance of HGS and decreased muscle mass was underscored in a study of 234 patients undergoing liver resection for malignant tumors. Compared with patients in the other groups, those with both decreased HGS and lower muscle mass experienced a longer hospital stay ($P<0.001$), and more frequent readmission to hospital ($P=0.02$) (12).

Muscle quantity or mass is confirmed by a variety of techniques, each with their advantages and limitations. DXA or CT scan with cut-offs depending on variables such as race and sex, are used most often. Magnetic resonance imaging (MRI) is also able to accurately assess sarcopenia in chronic liver disease including an abbreviated MRI protocol without the need for contrast injection (13). DXA rapidly measures appendicular muscle mass with low radiation. In imaging studies with DXA, sarcopenia refers to appendicular skeletal muscle mass divided by body height squared in meters (skeletal muscle mass index) two standard deviations or more below reference values from young, healthy individuals. Cut-offs for appendicular lean mass by DXA adjusted for body mass index (BMI) (<0.789

for men and <0.512 for women) are similar for FNIH and EWGSOP2. Regional analysis of fat and fat-free tissue at the 3rd lumbar vertebra with CT strongly predicts whole-body fat and fat-free mass. This allows for the opportunistic, accurate evaluation of body composition when patients undergo CT scans for diagnosis or re-staging (14). Although most studies analyze body composition at the 3rd lumbar vertebra, a preliminary report in patients with HCC showed CT measurements of the psoas muscle were significant prognostic factors for overall survival (OS) and progression-free survival (PFS) (15).

Other methods for evaluation of body composition such as electrical bioimpedance (BIA) are less accurate but have no radiation risk and are inexpensive by comparison. In a systematic review of BIA, 24 studies were selected for inclusion in the review (total number of 3,607 patients). In five studies, BIA was rated comparable to axial CT scan, calf circumference, or grip strength for sarcopenia screening, while in 14 studies, BIA-identified sarcopenia was associated with adverse clinical outcomes (16). Furthermore, the measurement of phase angle by BIA is a predictive marker for hospitalization, falls and mortality in outpatients with cirrhosis (17).

A review found ultrasound (US) to be a simple and reliable non-invasive diagnostic tool for sarcopenia in liver disease. Most of the 10 studies used large muscles of the upper and lower limbs as anatomical landmarks, half included patients with HCC (18), and the majority showed a correlation between muscle measurements and clinical outcomes. One study of HCC patients showed a significant correlation between skeletal muscle index (SMI) and the subcutaneous fat of lower limbs, using US (19). The absence of an ideal reference standard, not allowing a clear comparison among the studies, was the main limitation identified.

The EWGSOP2 suggests calf circumference measures may be used as a diagnostic proxy for older adults in settings where no other muscle mass diagnostic methods are available.

Once sarcopenia is confirmed by one of the methods outlined above, physical performance tests are needed to evaluate the severity of sarcopenia.

A recent meta-analysis reported a prevalence for severe sarcopenia ranging from 2–9% depending on region and classification system used (20). Tests of severity included but were not limited to gait speed, the Short Physical Performance Battery (SPPB), and the Timed-Up and Go (TUG) test. Tests such as HGS and SPPB

are used extensively in the aging population, and their use in oncology research is growing (21). A systematic review found physical performance tests show a significant correlation with survival and could be used as a prognostic tool, particularly for older adult patients. As an example, the SPPB, a composite test that includes assessment of gait speed, a balance test, and a chair stand test is predictive of important clinical outcomes including mortality and health care utilization (22). A SPPB score <10 is predictive of decreased OS in older patients with Leukemia (23), increased post-operative complications (24), and adverse events with lower chemo completion in non-small cell lung cancer (NSCLC) (25).

A study of inpatients with liver cirrhosis found the SPPB was better at assessing function than the handgrip test and a low SPPB score was associated with adverse outcomes such as re-admission and mortality (26).

A single diagnostic for sarcopenia and adherence to published guidelines should be a future priority in order to lessen the heterogeneity between studies.

SO is a combination of reduced lean body mass (LBM) and excess adiposity. The risk and prevalence for SO increases with age (27) and varies with definitions, and cut-offs (28). Myosteatosis, the infiltration of muscle by fat, is an indicator of diminished muscle quality and is associated with decreased strength and shorter survival in cancer. Specifically in HCC, a retrospective analysis of patients with advanced HCC on immunotherapy, found sarcopenia and myosteatosis were independent poor prognostic factors (29).

Mechanisms contributing to sarcopenia (Figure 2)

Primary sarcopenia is a result of adverse muscle changes that accumulate over a lifetime. In addition to the effects of aging, many older individuals have comorbidities or lifestyles that contribute to low muscle mass, termed ‘secondary sarcopenia’. Examples include malignancy, chronic inflammatory disease, organ dysfunction, poor nutrition, and decreased activity such as bed rest. In general, sarcopenia mechanisms can be viewed as disordered protein catabolism and anabolism, resulting in decreased protein synthesis and increased protein degradation. Potential therapeutic targets are noted in this section on mechanisms, however, these mechanisms should not be viewed in isolation since they are inter-related, e.g., inflammation may contribute to hormone resistance and autonomic dysfunction.



Figure 2 Contributors to sarcopenia. IL-6, interleukin 6; TNF-alpha, tumor necrosis factor alpha; IFN-gamma, interferon gamma; GDF-15, growth differentiation factor 15; NIS, nutrition impact symptoms; COPD, chronic obstructive pulmonary disease; RA, rheumatoid arthritis.

CLD may accompany or precede HCC and share similar mechanisms contributing to sarcopenia. The relationship between CLD and sarcopenia is complex. For example, sarcopenia is associated with non-alcoholic steatohepatitis and significant fibrosis, independent of obesity, inflammation, and insulin resistance (30). However, it is unclear whether sarcopenia is a risk factor for disease progression of NAFLD, or a complication of NAFLD due to worsening liver disease. There is also evidence that NAFLD and sarcopenia share a pathophysiological pathway along the muscle-liver-adipose axis and that a bidirectional relationship may exist whereby NAFLD contributes to sarcopenia development (31).

Muscle loss stimulates a pathophysiological pathway, along the:

- (I) *Muscle-liver-adipose tissue axis*, producing insulin-resistance, decreased glycogenesis, increased lipolysis, and decreased protein synthesis. Accumulation of adipose tissue within the liver is

associated with chronic low-grade inflammation mediated by adipokines and proinflammatory cytokines. In addition, altered myokine levels from decreased skeletal muscle mass promote hepatic fat accumulation and disease progression. Although muscle mass is a key determinant of whole-body insulin-mediated glucose metabolism and impacts fatty liver oxidation and energy homeostasis, the accumulation of ectopic fat in the liver and in the muscle (32) (myosteatorosis) seems to be more closely associated with liver injury than loss of muscle mass.

Several mechanisms contribute to sarcopenia along the muscle-liver-adipose tissue axis, including pro-inflammatory cytokine activation, endocrine dysfunction, hyperammonemia, and autonomic nervous system dysfunction.

- (II) *Hyperammonemia* may be a key mediator of sarcopenia in both NAFLD and cirrhosis through

mitochondrial dysfunction, increased myostatin expression and cognitive dysfunction (33). In addition, hyperammonemia is associated with elevated reactive oxygen species (34) and increased proteolysis (35) via autophagy.

- (III) *Aging* is also associated with increased muscle denervation and alterations in neuromuscular junctions (36), atrophy of type IIa muscle fibers, decreased mitochondrial content and increased lipid content of type I fibers (37). Additionally, aging is associated with decreased circulating anabolic steroids including testosterone (38) and growth hormone (GH) (39) and increased activation of the myostatin-activin A pathway (40), which modulates muscle catabolism and insulin resistance.
- (IV) *Ghrelin*, an endogenous brain-gut peptide is predominantly secreted by the stomach, distributed in many other tissues, and has a key role in appetite regulation (41). The administration of Ghrelin to animal models of NAFLD has beneficial effects, including amelioration of liver injury by modulating mechanisms such as dysregulated hepatic lipid metabolism, oxidative stress, apoptosis, and inflammation (42). Anamorelin, a ghrelin receptor agonist, stimulates appetite while also decreasing pro-inflammatory cytokines thought to mediate cachexia and sarcopenia (43). A post hoc analysis of a randomized controlled trial (RCT) leading to anamorelin's approval for cancer cachexia in Japan, found LBM improved from baseline to week 12 significantly with anamorelin compared to placebo (44).
- (V) *Pro-inflammatory cytokines* such as interleukin-6 (IL-6), tumor necrosis factor alpha (TNF- α) and interferon (IFN) gamma are associated with the pathogenesis of sarcopenia. IL-6 increases the production of ubiquitin and E3 ubiquitin ligase proteins leading to increased, possibly preferential ubiquitination of the myosin heavy chain, with dissociation of myosin from the contractile apparatus and subsequent degradation into peptides by the proteasomes. The combination of TNF- α and IFN gamma is thought to suppress the nuclear transcription factor MyoD thereby decreasing transcription of the myosin heavy chain (45). In addition, cytokines involved in the

pathogenesis of sarcopenia such as adiponectin, leptin, IL-6, IL-8, IL-10, TNF, soluble receptor of TNF (sTNFr)-1 and sTNFr-2 may serve as potential biomarkers to diagnose and determine the severity of sarcopenia (46).

- (VI) *Growth differentiation factor-15* (GDF-15), a member of the TGF- β superfamily has emerged as a mediator of weight loss and appetite suppression. In the context of cancer related sarcopenia, GDF-15 is believed to induce muscle apoptosis via the Bcl2-/caspase 3 pathway (47). Overexpression of GDF-15 following activation of the mTOR1 signaling is also associated with aging and sarcopenia (48), supporting findings that GDF-15 tends to increase with age and with decreased muscle mass. GDF-15 administration in animal models enhances energy expenditure, inducing weight loss (49) and decreases NAFLD. Plasma GDF15 levels are associated with intrahepatic fat content, increased in youth with NAFLD and therefore have potential as a biomarker for NAFLD (50). A phase II clinical trial using GDF-15 as both marker and therapeutic target for the GDF-15 inhibitor, Ponssegromab is underway in cachectic patients with advanced lung, pancreatic and colon cancer (51) (HCC patients are ineligible). While it is anticipated that participants may gain weight, the effect on muscle mass and function is uncertain.
- (VII) *Autonomic dysfunction* and activation of the sympathetic nervous system is common in patients with advanced cancer, leading to symptoms such as gastroparesis and hypermetabolism. The therapeutic role of beta-adrenergic receptor blockers has long been of interest in modulating sarcopenia (52). In a phase II clinical trial, espidolol, a nonselective beta-receptor antagonist, partial beta-2 receptor agonist, and 5-HT1A receptor antagonist, promoted weight gain, and improved HGS in patients with NSCLC and colorectal cancer (53).
- (VIII) *Alteration of the gut microbiome* is an emerging mechanism identified in cirrhosis, promoting sarcopenia and increased protein and amino acid metabolism (54). Excess alcohol use, a common cause of liver cirrhosis (55) is also associated with alterations of the gut microbiome and overall decreased protein synthesis.

(IX) *Anti-neoplastic therapies* may also contribute to sarcopenia. Tyrosine kinase inhibitors (TKIs) have a proven role in treating HCC, however, they may exacerbate muscle loss. In one study, 54 out of 67 patients had decreased muscle mass 1–3 months after receiving either sorafenib or lenvatinib therapy for HCC, regardless of tumor progression (56). A meta-analysis that included four studies of TKI therapy for HCC, reported poorer prognosis with sarcopenia *vs.* non-sarcopenia patients (57). In addition, based on a meta-analysis of 48 studies with a variety of malignancies, the association between treatment toxicity and low skeletal muscle mass, is stronger in kinase inhibitors than conventional chemotherapy or check point inhibitors (58). A multicenter Japanese group has developed ‘the management of sorafenib score (MS score)’ to stratify patients’ survival according to three parameters (skeletal muscle mass, disease control of sorafenib, and post-sorafenib therapy). Patients with an MS score ≥ 2 showed longer survival than those with an MS score ≤ 1 (16.4 *vs.* 8.4 months; $P < 0.001$) (59).

Sarcopenia and prognosis in HCC

Several prognostic scoring systems exist for patients with HCC; however, sarcopenia provides additional independent prognostic information.

Cirrhosis and HCC are associated with poorer clinical outcomes when sarcopenia is present, and interestingly, sarcopenia may increase the risk of cirrhosis transitioning to HCC. In a study of 492 patients with cirrhosis and no evidence of HCC at baseline, male patients with sarcopenia had a significantly higher risk of developing HCC (60).

A meta-analysis found sarcopenia was highly associated with risk of mortality in patients with cirrhosis (61). Sarcopenia also increases risk for complications in cirrhosis, such as hepatic encephalopathy and sepsis, and is associated with worse outcomes after liver transplantation, including increased length of stay, dependence on mechanical ventilation, organ injury, and post-operative mortality (62). Sarcopenia assessed radiologically by musculature at the level of the third lumbar vertebra can be combined with the Model for End-Stage Liver Disease score (MELD) to improve the prognostic model in patients with HCC awaiting transplantation (63). Furthermore, the combination of sarcopenia and obesity (as measured by visceral obesity

on CT scan) is associated with increased post-transplant mortality in acutely ill patients with cirrhosis, and remains significant even after adjusting for age, sex, diabetes, encephalopathy, HCC, and MELD (64).

Treatment modalities for HCC are also adversely affected by sarcopenia. A systematic review and meta-analysis of 57 studies and 9,790 patients with HCC found 41.7% of patients had sarcopenia (defined using CT/MRI with various cut-off values). Those with sarcopenia had decreased OS, increased rates of tumor recurrence following hepatectomy or living donor liver transplant, decreased tumor response, and increased rates of drug-related severe adverse events. The study evaluated several treatments including radiofrequency ablation, hepatectomy, intra-arterial therapy, radiotherapy, sorafenib, levatinib, and immune checkpoint inhibitors. Most forms of therapy demonstrated decreased survival with the presence of sarcopenia. The presence of cirrhosis and Child Pugh class B increased the hazard of mortality from sarcopenia, suggesting an additive or synergistic effect of HCC and cirrhosis in patients with sarcopenia (3).

A multi-center study of more than 1172 patients undergoing hepatic resection for HCC, compared ‘Textbook Outcomes’ (TO) between patients with sarcopenia (29%) and non-sarcopenia (43%). TO were defined as no 30-day mortality, no 30-day readmission, negative margins, no prolonged hospital stay, and no major complications. Sarcopenia was an independent predictor of TO ($P < 0.001$). These positive short term post-operative outcomes were in turn, independent predictors of OS and recurrence-free survival ($P < 0.001$) (65). A prospective study in 171 non-cirrhosis liver cancer patients determined the relationship between the combined measures of muscle mass (measured by pre-operative CT scan) and muscle strength (measured by handgrip) and clinical outcomes (major complications and 90-d readmission rate). Patients with both low muscle mass and decreased strength had significantly higher postoperative complications, 90-day readmission rate (21.7%, $P = 0.037$) and hospitalization costs than other groups (66).

In HCC treated with a programmed death receptor-1 (PD-1) inhibitor, higher levels of inflammation, lower albumin and a shorter PFS are found in patients with sarcopenia than those without sarcopenia (67). In 138 patients with advanced HCC (>80% with extra-hepatic metastasis) patients with sarcopenia had poorer PFS and OS ($P = 0.002$) than those without sarcopenia. In addition, patients with myosteatosis exhibited poorer PFS and OS

($P < 0.001$) than those without myosteatorsis (29). The value of measuring myosteatorsis is supported by another study of 611 patients undergoing transarterial chemoembolization (TACE) at a tertiary care center. Although there was no difference in TACE response between sarcopenia and non-sarcopenia patients, myosteatorsis was associated with poor TACE response and reduced survival (15.9 *vs.* 27.1 months, $P < 0.001$) (68).

Sarcopenia combined with markers of inflammation/nutrition

Several markers of nutrition status and inflammation have been combined with sarcopenia in attempts to improve prognostication for CLD and HCC. Caution is required in attributing poor clinical outcomes directly to the combination of inflammation and sarcopenia because inflammatory markers such as C-reactive protein (CRP) may also reflect HCC growth and invasiveness. The lymphocyte-monocyte ratio (LMR) is reported to be an independent risk factor for OS and recurrence free survival in HCC patients after hepatectomy (69). The prognostic nutritional index (PNI), a marker of nutritional status and inflammation, is calculated using albumin and lymphocyte count. When combined, PNI and sarcopenia are stronger prognostic factors for postoperative complications in patients with HCC than either alone (70).

Treatment

Given the multifactorial nature of sarcopenia, therapeutic interventions should be individualized and address the many underlying causes pertinent to each patient. Most professional organizations endorse a multimodal approach. For example, the Clinical Oncology Society of Australia (COSA) recommends management of sarcopenia include nutritional therapy, exercise and physical activity, plus physical and psychological symptom management. The European Society for Parenteral and Enteral Nutrition (ESPEN) recommend exercise and nutritional counseling. No pharmacological intervention has been approved, although replacement therapy (testosterone and vitamin D) may be helpful.

Pharmacologic therapy

While there is no single agent approved for sarcopenia or cancer cachexia, several promising therapies reported

improved outcomes in clinical trials.

The purported mechanisms for modulating muscle mass in oncology patients by drugs such as anamorelin, espidolol and a GDF-15 inhibitor, were discussed earlier in this review. Since anamorelin is approved for cancer cachexia in Japan and increases weight LBM and appetite, this oral medication has the greatest potential to be available more widely for wasting conditions. However, as regards its potential therapeutic benefit for sarcopenia specifically, caution should be exercised because anamorelin did not improve HGS in a large international RCT, despite significant improvement in LBM (71).

A recent review focused on pharmacologic interventions for sarcopenia included testosterone, selective androgen receptor modulators (SARMs), estrogen, dehydroepiandrosterone (DHEA), insulin-like growth factor-1 (IGF-1), GH, GH secretagogue (GHS), drugs targeting myostatin and activin receptor pathway, vitamin D, angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs), or β -blockers. The review concluded that some drugs have been effective in improving muscle mass, but unfortunately this was not accompanied by clinically relevant improvements in physical performance (72).

Other promising drugs noted in pre-clinical development include metformin, exerkines (73) (IL-6, TNF- α , IL-15, fibroblast growth factor 21, irisin, apelin) or senolytics (dasatinib and quercetin, ruxolitinib). Agents currently available to clinicians and shown to be safe include testosterone and vitamin D.

Androgens

An umbrella review of meta-analyses concluded testosterone replacement can be justified in daily practice for older men with muscle weakness (74). Another meta-analysis reported anabolic androgens combined with exercise may enhance outcomes (75). Although no trials have specifically evaluated the effect of androgens on sarcopenia in patients with HCC, there is evidence testosterone replacement therapy improves outcomes in men with cirrhosis and in men with advanced solid tumors. A 12-month double blind placebo-controlled trial of intramuscular testosterone increased muscle mass, bone mass and hemoglobin with no increase in adverse effects (76). A preliminary double blind placebo-controlled trial in men with advanced solid tumors found intramuscular testosterone improved fatigue scores and performance status compared to placebo injections, by week 10 (77).

Vitamin D

Given the low risk of side-effects or harm, and meta-analyses showing sarcopenic adults have lower blood 25(OH) D concentrations (78), vitamin D supplementation is a reasonable recommendation for older people with low serum levels. Based on meta-analyses vitamin D has a significant effect on muscle strength and physical performance, especially in women with low baseline values (<25 nmol/L). Vitamin D deficiency is common in CLD, associated with increased risk of sarcopenia (79) and poorer prognosis when sarcopenia and severe vitamin D deficiency co-exist (80). The results of clinical trials using vitamin D are inconsistent, in part because vitamin D is often combined with interventions such as exercise or protein supplementation, making it difficult to determine the benefit of vitamin D alone (81). A meta-analysis of vitamin D in combination with whey protein and exercise found benefit for lean muscle mass and physical function (82) while another reported combination therapy with vitamin D supplementation, protein supplementation and exercise significantly increased grip strength and trended toward increasing muscle mass (83). The form of supplementation may also play a role; for example, calcifediol may have a positive effect on muscle strength parameters (with less evidence on physical performance) (84).

Non-pharmacologic therapy

Non-pharmacologic interventions such as exercise (85) and nutrition are key components of multimodal therapy and may be most effectively delivered in combination, and by an interdisciplinary team.

Nutrition

In patients with cancer, many older individuals may be consuming insufficient calories and protein. Dieticians should provide individualized counseling with a focus on maintaining adequate calorie and protein intake in patients with HCC or CLD. A study of 320 Canadian patients with advanced cancer and weight loss found the majority consumed diets insufficient to maintain weight even in healthy individuals (86). The study also found higher consumption of protein and energy correlated with greater weight gain. When considering the relationship between nutrition and sarcopenia, macronutrient content may be especially important. A scoping review reported energy dense 'fat and fish' diets, are associated with reduced risk of low muscle mass in patients with cancer (87).

While there are no specific recommendations for HCC, ESPEN has practical guidelines for clinical nutrition in liver disease (88). For patients with malnutrition and muscle depletion, ESPEN recommends 30–35 kcal/kg/d and 1.5 g/kg/d of protein and 0.25 g/kg/d of branched chain amino acids (BCAAs) for those who are protein intolerant (i.e., develop encephalopathy). Furthermore, a meta-analysis concluded that a late-evening snack high in protein or carbohydrates improved nitrogen balance and decreased protein and fat catabolism (89).

Exercise

Some professional organizations include exercise in their guidelines for managing cancer-associated sarcopenia, while others such as the American Society for Clinical Oncology (ASCO) have found insufficient evidence for recommendations (90). COSA, ESPEN, and the European Society for Clinical Oncology (ESMO) recommend individualized prescriptions, including resistance exercise in addition to aerobic exercise for maintaining muscle strength and mass (91).

Although there are no direct comparisons between aerobic and resistance exercise in HCC, studies in other solid tumors and hematological malignancies have demonstrated the value of resistance exercise. A meta-analysis of 34 resistance-training trials in patients with cancer or survivors, showed greater LBM increase compared to controls ($P=0.004$). In prostate cancer (92) younger men and those with lower baseline levels of physical function, derived greater benefits regarding muscle strength and physical function. Although most exercise interventions are aerobic based in patients with liver cirrhosis, a 12-week resistance training program improved muscle size and physical performance with significantly increased 6-minute walk distances (93).

A combination of exercise interventions may be optimal for improving outcomes in HCC. A prospective observational study of patients with HCC and CLD evaluated the effect of rehabilitation on skeletal muscle mass using a combination of stretching, strength, balance, and endurance training. Patients instructed by physical therapists on exercise had increased SMI and improved survival compared to patients not exercising (94). Similarly, individuals undergoing TACE treatment for HCC had increased muscle mass when they completed in-hospital combination exercises for 20–40 min/day (95).

Aerobic exercise is important for outcomes related to sarcopenia and in the elderly, may be indistinguishable from

resistance exercise in the ability to prevent sarcopenia (96). Also, perioperative cardiopulmonary function and change in anaerobic threshold (the point during exercise at which oxygen demand outstrips oxygen delivery and metabolism starts to become anaerobic) were found to be more important than muscle mass for long-term survival in patients undergoing first hepatectomy for HCC (97). Perioperative exercise (stretching and walking) was prescribed based on individual patients' anaerobic threshold. The authors concluded that exercise involving >5,000 steps per day is necessary for postoperative walking.

Overall, a recent systematic review of diet and/or exercise interventions in cirrhosis of 22 controlled trials and 5 single arm trials showed improvement in body composition, with the largest improvements occurring when diet and exercise interventions were combined (98).

Symptoms

High symptom burden may impact therapy for nutrition and physical performance. Nutrition impact symptoms (NIS) limit an individual's ability to consume food, exacerbating weight loss. Symptoms such as nausea, depression, and pain are often identified in oncology patients because of their disease or anti-neoplastic treatment side-effects (99). The opportunity for improving NIS and thereby increasing protein and caloric intake is likely present in patients with HCC, although there are no studies specifically addressing NIS in HCC. Specific medications for NIS are often inexpensive and readily available, but beyond the scope of this review.

Furthermore, addressing symptom burden is an essential component for optimizing physical function. For example, a relationship between symptoms and sarcopenia related outcome measures such as SPPB was reported in 359 older oncology patients from two tertiary medical centers. Each unit increase in a composite symptom score was associated with greater instrumental activity of daily living (IADL) impairment (4.8%), physical activity limitations (4.4%), falls (2.9%), and SPPB ≤ 9 (2.5%) ($P < 0.05$) (100).

Psychological

Patients with sarcopenia and cancer experience stressors that affect their mental health, including decreased cognitive function, psychological and spiritual distress, increased dependency, and changes in body image. In patients with HCC, health-related quality of life (HRQoL) decreases over time, with a particular emphasis on the mental health component (101). In patients with incurable gastrointestinal or lung cancer, sarcopenia diagnosed by

CT imaging was associated with worse QoL and greater depression symptoms (102). These findings underscore the need to adopt a comprehensive approach to managing patients with sarcopenia, addressing their symptom burden, including mood.

Conclusions

The association of sarcopenia with adverse clinic outcomes such as decreased OS, increased side-effects of anti-neoplastic therapy and decreased physical performance suggests that sarcopenia should be a priority for clinicians managing patients with HCC. Sarcopenia is present in almost half of patients with HCC and given its prevalence in cirrhosis, may be frequently present at the initial cancer diagnosis. Clinical trials are required to determine whether therapeutic interventions targeting sarcopenia can improve clinical outcomes such as survival, treatment side-effects and QoL. This review highlights current guidelines regarding screening, assessing, and managing patients with sarcopenia and how this may apply specifically to patients with HCC. Although no single agent is approved, the multifactorial nature of sarcopenia suggests a multimodal combination of pharmacological and non-pharmacological therapies may be most effective.

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