

# The Adverse Impact of Sarcopenia and Visceral Fat Deposition on the Course of Hepatocellular Carcinoma and the Role of Nutritional Interventions

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## Abstract

There is mounting evidence to support the impact of sarcopenia on the prognosis of a wide range of clinical conditions. This review examines the literature on the effect of body composition measures, including sarcopenia, on outcomes in patients with hepatocellular carcinoma (HCC). Available studies support the adverse impact that sarcopenia has on overall survival, response to different treatment modalities, and tumour recurrence. Some studies have identified visceral fat deposition as a negative prognostic sign, and the incorporation of body composition measures into current HCC staging schemes have been shown to improve prognostic accuracy. On the other hand, there is a paucity of studies assessing nutritional interventions in HCC and further trials are needed to inform evidence-based practice.

## INTRODUCTION

Hepatocellular carcinoma (HCC) is the third most common cause of solid tumour mortality worldwide, with over half a million new cases diagnosed annually around the world.<sup>1</sup> In Europe, HCC accounts for around 47,000 deaths a year, with mortality rates expected to rise over the next decade.<sup>2</sup> The prognosis in HCC is poor, with a 5-year survival rate of approximately 10%.<sup>3</sup> In >90% of cases, HCC develops in patients with liver cirrhosis, most commonly due to infection with hepatitis B or C virus.<sup>4</sup> Other aetiological

factors for the development of HCC include chronic alcohol consumption and nonalcoholic fatty liver disease (NAFLD).<sup>4</sup>

The Barcelona Clinic Liver Cancer (BCLC) staging system incorporates information on tumour burden, underlying liver function, and clinical features (e.g., performance status) to guide therapeutic decision-making and prognostication in HCC.<sup>5</sup> Treatment for HCC comprises both surgical and nonsurgical techniques. Hepatic resection or liver transplantation is reserved for early stage disease.<sup>5</sup> More advanced cases of HCC

are considered for nonsurgical treatment modalities, including radiofrequency ablation (RFA), transarterial chemoembolisation (TACE), and sorafenib.<sup>5</sup>

Although it remains one of the best HCC staging systems, BCLC has some shortcomings, particularly with regard to prognostication in the highly heterogeneous patient population with intermediate-stage HCC (Stage B).<sup>6</sup> There is increasing research interest into the pathological, genetic, and clinical factors that may improve HCC prognostication and guide appropriate treatment choice.<sup>7</sup> In particular, the addition of clinical factors, such as sarcopenia and visceral fat deposition derived from computed tomography (CT) scanning, have been shown to improve prognostic accuracy compared with the BCLC staging system alone.<sup>8</sup> Therefore, it is important that the effect of body composition variables on outcome in HCC is delineated and the role of clinical nutrition in influencing response to surgical and medical treatments is adequately explored.

This review describes the existing knowledge on the effect of sarcopenia on outcomes in HCC and will also present the role of other body composition changes. Finally, the available studies evaluating nutritional interventions will be summarised to guide practical recommendations for optimisation of nutritional status in patients with HCC.

## METHODS

Relevant studies were identified by searching the medical databases Embase and Medline (January 1996–March 2018). Additional searches were carried out using Google Scholar and Clinical Key® (Elsevier, Amsterdam, Netherlands) to identify other published data on the subject. Two separate searches were conducted; the first included the following search terms: “Hepatocellular carcinoma” AND (“Sarcopenia” OR “Body composition”). The second search included the following terms: “Hepatocellular carcinoma” AND (“Nutrition support” OR “Dietary supplements” OR “Enteral nutrition” OR “Nutrition intervention”). A total of 139 and 209 studies were generated from the two searches, respectively, and relevant articles were selected following screening of titles, keywords, and abstracts.

All studies, either interventional or observational, that evaluated body composition measures or nutritional interventions in HCC were included. Studies evaluating sarcopenia were required to quantify skeletal muscle mass by CT or magnetic resonance imaging (MRI) scanning, which are considered the gold standard techniques for estimating muscle mass.<sup>9</sup> These methods overcome the difficulties associated with accurate nutritional assessment in patients with ascites and oedema related to underlying liver disease. Eighteen papers were selected for inclusion in this review; [Tables 1, 2, and 3](#) summarise the chosen studies, including study design, participants, and findings. Excluded articles were those with no relevance to the topic, general review articles, and conference abstracts.

## RESULTS

### The Effect of Sarcopenia on Hepatocellular Carcinoma

Sarcopenia is associated with ageing and chronic illness and is defined by the European Working Group on Sarcopenia in Older People (EWGSOP) as the loss of muscle mass and strength.<sup>9</sup> Most of the available studies on sarcopenia and HCC, however, are retrospective and did not include measurements for muscle strength at the data collection stage. Therefore, for the purposes of this review, sarcopenia is used interchangeably with the skeletal muscle index or the cross-sectional area of muscles at the third lumbar vertebral level on CT scanning, measured in cm<sup>2</sup>/m<sup>2</sup>.

Meza-Junco et al.<sup>10</sup> found that sarcopenia was an independent risk factor for mortality in 116 patients with HCC undergoing evaluation for liver transplantation (hazard ratio [HR]: 2.04; p=0.02). Later, Iritani et al.<sup>11</sup> evaluated 217 treatment-naïve HCC patients of any stage and found that those with sarcopenia had a significantly reduced overall survival (p=0.0043). In 2017, two further retrospective analyses<sup>12,13</sup> identified sarcopenia as a significant risk factor for overall survival in 92 and 178 newly diagnosed HCC patients, respectively. A further study in 2017<sup>14</sup> showed that patients with sarcopenia died significantly earlier than nonsarcopenic patients (p=0.007); however, this difference was

not measured following adjustment for age, sex, tumour size, tumour number, and the degree of portal vein invasion.

Two recent meta-analyses<sup>15,16</sup> corroborated the above findings. Zhang et al.<sup>15</sup> evaluated eight retrospective studies that included 1,161 patients undergoing mostly surgical interventions or curative RFA. They showed that HCC patients with sarcopenia had a poorer prognosis with respect to the 1-year and 3-year overall survival, 5-year disease-free survival, incidence of recurrence, and post-treatment overall complications. Chang et al.<sup>16</sup> investigated

13 studies comprising 3,111 patients with HCC of varying stages. A significant association between sarcopenia and all-cause mortality was demonstrated (HR: 1.95; 95% confidence interval: 1.60–2.37). Similarly, loss of skeletal muscle mass was associated with tumour recurrence (adjusted HR: 1.76; 95% confidence interval: 1.27–2.45). In both analyses, the researchers cited the limitations of the included studies, including the absence of a consistent definition for sarcopenia in terms of cm<sup>2</sup>/m<sup>2</sup>, low patient numbers, and a lack of any measures for muscle function.

**Table 1: Summary of studies assessing the impact of sarcopenia on hepatocellular carcinoma.**

Study	Study design	Participants	Study focus	Significant findings
Meza-Junco et al., <sup>10</sup> 2013	Retrospective cohort study.	116 patients with HCC being evaluated for liver transplant.	To determine the link between sarcopenia and mortality.	Sarcopenia was a strong and independent risk factor for mortality (HR: 2.04; p=0.02).
Iritani et al., <sup>11</sup> 2015	Retrospective cohort study.	217 treatment-naïve patients with HCC.	To determine whether skeletal muscle depletion is a significant prognostic factor for HCC.	Sarcopenic patients showed significantly lower overall survival than those without sarcopenia (p=0.0043).
Begini et al., <sup>12</sup> 2017	Retrospective cohort study.	92 consecutive HCC patients.	To assess the influence of sarcopenia on overall survival in cirrhotic patients with HCC.	Mean OS reduced in sarcopenic patients: 66 weeks versus 123 weeks (p=0.003).
Ha et al., <sup>13</sup> 2017	Retrospective cohort study.	178 patients with newly diagnosed HCC.	To demonstrate the prognostic significance of changes in body composition in patients with newly diagnosed HCC.	The presence of sarcopenia at HCC diagnosis was independently associated with survival (p=0.04).
Imai et al., <sup>14</sup> 2017	Retrospective cohort study.	351 patients with HCC.	To identify factors that contribute to skeletal muscle depletion in HCC patients.	Sarcopenia patients died significantly earlier than non-sarcopenia patients (p=0.007).
Zhang et al., <sup>15</sup> 2017	Systematic review and meta-analysis.	1,161 patients undergoing surgical resection or curative ablation.	To evaluate the clinical significance of sarcopenia in the treatment of patients with primary liver tumours.	There was a significant difference between patients with or without sarcopenia in 1-year and 3-year OS (p=0.0004; p=0.03, respectively). There was no significant difference in 5-year OS (p=0.08). Sarcopenia had a significant impact on recurrence (p=0.002).
Chang et al., <sup>16</sup> 2018	Systematic review and meta-analysis.	3,111 HCC patients at varying stages.	To assess the link between sarcopenia and outcomes.	A significant association between sarcopenia and all-cause mortality was demonstrated (HR: 1.95; 95% CI: 1.60–2.37). Loss of skeletal muscle mass associated with tumour recurrence (adjusted HR: 1.76; 95% CI: 1.27–2.45).

CI: confidence interval; HCC: hepatocellular carcinoma; HR: hazard ratio; OS: overall survival.

**Table 2: Summary of studies evaluating the effect of adipose tissue distribution on hepatocellular carcinoma.**

Study	Study design	Participants	Study focus	Significant findings
Fujiwara et al., <sup>19</sup> 2015	Retrospective cohort study.	1,257 patients with HCC.	To analyse the impact of body composition (BMI, skeletal muscle mass, intramuscular fat deposition, IMF, VSR) on prognosis in HCC.	Sarcopenia, IMF, and VSR were significant predictors of mortality in HCC (HR: 1.52, 1.34, 1.35, respectively). BMI was not.
Montano-Loza et al., <sup>20</sup> 2018	Prospective cohort.	247 patients who underwent liver transplantation, 96 of whom had HCC.	To determine whether VATI was associated with HCC recurrence following liver transplantation.	In male patients with HCC who underwent liver transplant, a VATI of $\geq 65$ cm <sup>2</sup> /m <sup>2</sup> was independently associated with higher risk of HCC recurrence (HR: 5.34; 95% CI: 1.19–23.97; p=0.03).
Saito et al., <sup>21</sup> 2015	Retrospective cohort study.	96 consecutive HCC patients who underwent TACE.	To identify independent factors to predict overall survival of HCC patients after TACE.	Multivariate analyses showed visceral fat accumulation was an independent factor associated with 1-year mortality after TACE (p=0.033).
Parikh et al., <sup>22</sup> 2018	Retrospective cohort study.	165 patients in total; 75 patients in derivation cohort; 90 patients in validation cohort.	To determine if body composition could predict survival among patients undergoing TACE.	Visceral fat density was the only factor predictive of overall and 1-year survival (p<0.001). Patients with higher visceral fat density were more likely to experience hepatic decompensation.

CI: confidence interval; HCC: hepatocellular carcinoma; HR: hazard ratio; IMF: intramuscular fat deposition; TACE: transarterial chemoembolisation; VATI: visceral adipose tissue index; VSR: visceral-to-subcutaneous adipose tissue area ratio.

Overall, the available studies demonstrate the adverse impact that sarcopenia has on the prognosis of HCC of varying stages, both prior to and following medical and surgical treatments. Sarcopenia also increases the risk of tumour recurrence following curative treatment. However, the studies are hampered by their mainly retrospective designs, and further prospective studies incorporating measurements of muscle strength and physical function are needed to determine whether these better predict the outcome than use of muscle mass alone. Finally, the available research does not address the underlying mechanisms by which sarcopenia worsens outcomes in HCC. An increased understanding of these mechanisms of muscle depletion would engender improved interventions and treatment strategies.

## The Effect of Adipose Tissue Distribution on Hepatocellular Carcinoma

NAFLD has more recently been recognised as another important aetiological factor for the development of liver cirrhosis and HCC.<sup>17</sup> Liver cirrhosis in this context can lead to further skeletal muscle loss and gain of adipose tissue, culminating in sarcopenic obesity.<sup>18</sup> NAFLD is also one of the main risk factors for HCC development in the absence of established liver cirrhosis.<sup>17</sup>

A handful of studies have demonstrated the importance of adipose tissue distribution on outcomes in HCC. Fujiwara et al.<sup>19</sup> examined the CT scans of 1,257 patients with HCC of differing stages and with differing treatment plans. Multivariate analysis revealed that, in addition to low skeletal muscle index, both high visceral-

to-subcutaneous adiposity ratio and low mean muscle attenuation (increased intramuscular fat deposition) were significantly associated with mortality (HR: 1.52,  $p=0.001$ ; HR: 1.35,  $p=0.005$ ; and HR: 1.34,  $p=0.02$ , respectively). In liver transplantation, one study found that male patients with cirrhosis and increased visceral adiposity had higher rates of HCC

recurrence.<sup>20</sup> Similarly, two studies<sup>21,22</sup> evaluating body composition measures in HCC patients undergoing TACE found that patients with higher visceral fat density and area were at an increased risk of death at 1 year. Moreover, patients with higher visceral fat density were more likely to experience hepatic decompensation after TACE ( $p<0.001$ ).

**Table 3: Summary of studies evaluating nutritional or exercise interventions in hepatocellular carcinoma.**

Study	Study design	Participants	Study focus	Significant findings
Fan et al., <sup>27</sup> 1994	Prospective study.	124 patients undergoing resection of HCC; 64 patients in intervention group; 60 patients in control group.	To investigate whether perioperative nutritional support could improve outcomes in patients undergoing hepatectomy for HCC.	Reduction in the overall postoperative morbidity rate in the perioperative-nutrition group.
Ziegler, <sup>28</sup> 1996	Prospective, randomised, controlled trial.	150 consecutive patients with resectable HCC were randomly assigned to receive either perioperative PN in addition to a usual oral diet, or to no additional therapy.	To evaluate the efficacy of perioperative PN in patients requiring hepatectomy for primary HCC.	No significant difference in postoperative hospital mortality occurred between groups (PN 8% versus control 15%; $p=0.30$ ). Perioperative PN use was associated with a significant reduction in overall postoperative morbidity rate (PN 34% versus control 55%; $p=0.02$ ).
Bothe and Steele, <sup>29</sup> 1997	Prospective study.	124 patients undergoing resection of HCC. 64 patients were randomly assigned to receive perioperative IV nutritional support in addition to an oral diet, and 60 patients were randomly assigned to a control group.	To investigate whether perioperative nutritional support could improve outcome in patients undergoing hepatectomy for HCC.	Reduction in the overall postoperative morbidity rate in the perioperative-nutrition group as compared with the control group.
Yao et al., <sup>30</sup> 2015	Prospective cohort study.	43 patients with and 36 patients without preoperative nutrition.	To compare short-term outcomes between HCC patients with and without preoperative nutrition.	Preoperative enteral nutrition group had shorter lengths of postoperative hospital stays ( $p=0.007$ ), less exogenous albumin infusion ( $p=0.030$ ), earlier first exhaust time ( $p=0.043$ ), and first defecation time ( $p=0.001$ ) observed. No significant differences observed in incidence of overall complications, infectious complications, or major complications.
Nishikawa et al., <sup>33</sup> 2012	Prospective cohort study.	99 patients who underwent TACE for HCC.	To examine the significance of BCAA treatment before TACE for HCC.	Serum albumin level and Child-Pugh score improved significantly in the BCAA group as compared with the control group after TACE ( $p<0.05$ ).

Table 3 continued.

Study	Study design	Participants	Study focus	Significant findings
Moriyama et al., <sup>34</sup> 2012	Prospective study.	30 patients who had RFA for HCC randomly assigned to a standard diet group (control), a morning BCAA administration group, or a LES with BCAA administration group.	To examine whether BCAA-enriched nutrient mixture as a LES helps maintain and/or improve liver functioning in liver cancer patients who have undergone RFA for HCC.	Compared to the control and morning BCAA groups, the LES with BCAA group experienced a rapid and significant improvement in albumin and total serum bilirubin levels.
Chen et al., <sup>35</sup> 2015	Meta-analysis.	11 eligible studies (974 patients in total) were evaluated and included in the analysis.	To assess supplementation effects of oral BCAA in HCC patients undergoing interventions.	Oral BCAA supplementation helped maintain liver reserve with higher serum albumin (p=0.022) and lower rates of ascites (p=0.029) and oedema (p=0.035) than the control group.

BCAA: branched-chain amino acid; HCC: hepatocellular carcinoma; IV: intravenous; LES: late evening snack; PN: parenteral nutrition; RFA: radiofrequency ablation; TACE: transarterial chemoembolisation.

The reasons for the negative impact of visceral and intramuscular adipose tissue deposition on HCC outcomes are not fully understood. In sarcopenic obesity, muscle depletion is characterised by both a reduction in muscle size and an increased proportion of inter and intramuscular fat deposition, named myosteatorsis.<sup>23</sup> Myosteatorsis is associated with increasing insulin resistance and decreased strength and mobility.<sup>24</sup> Visceral fat accumulation increases the levels of proinflammatory adipokines, such as tumour necrosis factor- $\alpha$ , interleukin-6, and monocyte chemoattractant protein-1, and decreases the level of the anti-inflammatory adipokine adiponectin.<sup>25</sup> Excess visceral fat may also contribute to portal hypertension because free fatty acids and adipokines released from visceral fat flow directly into the liver via the portal vein.<sup>26</sup> It is clear the exact mechanisms underlying the interaction of visceral adiposity, liver function, and prognosis in HCC are highly complex and require further investigation.

### Nutritional Interventions to Improve Outcome in Hepatocellular Carcinoma

Interventional studies addressing the effect of nutritional therapy in HCC patients are few. The benefits of perioperative nutrition support

on outcomes were evaluated in a series of studies in the mid-1990s.<sup>27-29</sup> These demonstrated that perioperative nutrition support for 14 days with a parenteral nutrition (PN) solution rich in branched-chain amino acids (BCAA) resulted in a reduction of morbidity, diuretic use for ascites control, weight loss post-hepatectomy, and liver function, as measured by indocyanine green clearance. A more recent cohort study<sup>30</sup> compared patients who had received enteral nutrition 3 days prior to hepatic resection with a medium-chain triglyceride-rich formula with those who had not. They found a shorter length of hospital stay and less exogenous albumin use in the group that had received enteral nutrition. There were no significant differences seen in the incidence of overall complications, infectious complications, or major complications. Additional data are needed to delineate further the relationship between pre and postoperative nutrition support and outcomes following HCC resection.

The benefits of BCAA supplementation and a late evening snack in patients with liver cirrhosis alone have been explored recently, with studies suggesting that these strategies hold promise in reversing anabolic resistance and sarcopenia, improving quality of life.<sup>31,32</sup> In HCC, one study<sup>33</sup> evaluated the effects of

BCAA supplementation in 40 patients 1 month prior to TACE and compared these to 59 control patients on a normal diet. They found that the BCAA group had significantly improved albumin levels and Child-Pugh scores at 3 and 6 months post-TACE ( $p < 0.05$ ). Similarly, the benefits that a late evening snack containing BCAA had in improving Child-Pugh scores were demonstrated by Morihara et al.<sup>34</sup> Results from a meta-analysis of 11 studies<sup>35</sup> showed that BCAA supplementation conferred a 3-year mortality benefit, higher serum albumin levels, and lower rates of ascites. The 1-year mortality and HCC recurrence rates were not improved by BCAA supplementation, however, and many of the included studies were retrospective and had small sample sizes. All participants in this study had liver cirrhosis and therefore the benefit of BCAA supplements in HCC patients without cirrhosis is unknown.

## DISCUSSION

There is much evidence to support the deleterious effects of sarcopenia on a wide range of clinical conditions. This is no different in HCC and the available studies demonstrate the adverse impact of sarcopenia on overall survival, response to different treatment modalities, and tumour recurrence following curative resection. In addition to sarcopenia, some studies have identified visceral fat deposition as a negative prognostic sign and the development of sarcopenic obesity appears to drive poorer responses to treatment and reduces survival rates.

Nonetheless, the available body composition data in HCC are limited to mainly retrospective studies, making conclusions on causality difficult. For example, it is unclear whether sarcopenia is driven by the catabolic effects of liver cirrhosis, neoplasia, or a combination of the two. Increasingly, HCC in NAFLD<sup>23</sup> occurs in the absence of cirrhosis, and the mechanisms by which intrahepatic, visceral, and intramuscular fat deposition causes neoplastic effects are yet to be established. An increased understanding of these mechanisms would help inform practical evidence-based guidance on nutrition support in HCC, and this review has highlighted the distinct paucity of nutrition intervention studies in this field. Inferences on the optimum

nutrition management from guidance on liver cirrhosis and cancers may not be applicable to HCC patients given the unique cell biology of the condition and complex interplay with liver function and gut microbiota.

Future studies, therefore, should focus on the mechanisms by which sarcopenia and adipose tissue distribution effect HCC prognosis. Whether these measures adversely impact survival by undermining liver function or promoting tumour invasion and metastasis is unknown. An improved understanding of the relationship between body composition, response to therapy, and prognosis will enable the formulation of a tailored management strategy. Nutritional intervention studies in HCC are warranted to investigate the effect of manipulating body composition on outcomes. Although notoriously limited due to the complexity of modulating dietary intake, such studies should prospectively evaluate optimum dietary composition, the effect of BCAA supplementation, enteral tube feeding, vitamin D repletion, and the impact of exercise and physiotherapy.

In terms of current practical recommendations, clinicians should identify HCC patients at risk of sarcopenia at an early stage in their pathway and during follow-up appointments. Full anthropometric measures should be taken at regular intervals, including subjective global assessment and grip strength. BMI should not be used as a marker of malnutrition in such patients.<sup>12,13,36</sup> Where available, the analysis of psoas muscle cross-sectional area at the initial staging CT scan would more accurately identify those with sarcopenia. Alternatively, the bioelectrical impedance measure phase angle has been shown to correlate with survival in HCC and can be measured at the bedside.<sup>36</sup> Patients with underlying liver cirrhosis should receive adequate calorific intake as dictated by well-recognised international guidelines (for example, the European Society for Parenteral and Enteral Nutrition [ESPEN] guidance<sup>37</sup>). Patients with cirrhosis should also be considered for BCAA supplementation and the importance of a late evening snack should be re-enforced. Nutritional support in the form of oral nutritional supplements or nasogastric feeding should be administered if the patient is unable to meet their nutritional requirements. Patients being

considered for hepatectomy should receive intensive preoperative dietary input and have a low threshold for preoperative enteral feeding. Finally, it goes without saying that all patients should receive regular dietary follow-up and have their nutritional statuses re-evaluated when a change in medical or surgical therapy is being considered.

## CONCLUSION

To conclude, the available literature supports the adverse impact of sarcopenia and visceral fat deposition on overall survival, response to different treatment modalities, and tumour recurrence in HCC. There is a lack of studies investigating the optimum nutritional support for this condition and it is imperative that this field grows to complement future advances in medical therapy.

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