



Perioperative management of patients with liver cancer complicated with sarcopenia

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Primary liver cancer is one of the most common digestive system malignancies worldwide, with hepatocellular carcinomas accounting for about 90% of cases. It has a concealed onset, rapid progression, high degree of malignancy, and is difficult to treat, which presents a serious threat to people's life and health (1). At present, the primary treatment methods for liver cancer include hepatectomy, liver transplantation, transcatheter arterial chemoembolization, systematic treatment, and combined therapy, among which surgical resection is the most important (2,3).

The previously reported prognostic variables affecting liver cancer resection included age, performance status, tumor number, body mass index (BMI), and other factors, which significantly improved the incidence of postoperative complications and the long-term survival rate of liver cancer patients. However, sarcopenia is being gradually explored and studied as a new prognostic factor. Sarcopenia refers to a degenerative loss of muscle mass, strength, and function, with a prevalence of between 11% and 30% in patients undergoing surgery for digestive system cancers (4).

At present, numerous studies have shown that sarcopenia is an independent risk factor for poor short- and long-term prognosis after hepatectomy for liver cancer. Berardi *et al.* (5) recently reported on 234 patients undergoing hepatectomy for liver cancer in the *JAMA Surgery* and analyzed the relationship between sarcopenia and short-term prognosis after hepatectomy. Their study pointed out that sarcopenia was associated with poor short-term prognosis following malignant liver tumor resection, especially in terms of 90-

day mortality, hospital stay, and rehospitalization rate. As for the long-term prognosis, Harimoto *et al.* (6) reported on the prognosis of patients with sarcopenia and liver cancer after hepatectomy for the first time in 2013. They analyzed the data of 186 patients with liver cancer and found that the 5-year overall survival rate and 5-year relapse-free survival rate in the sarcopenia group were significantly lower than those in the non-sarcopenia group. The Chinese scholars, Cao *et al.* (7), analyzed the clinical data of 139 patients with liver cancer who underwent hepatectomy, and observed that the incidence of severe postoperative complications (Clavien-Dindo grade III and above) (19.6% *vs.* 6.0%) and total complications (35.7% *vs.* 13.3%) were significantly higher than non-sarcopenia patients ($P < 0.05$). In additional radical surgery, Omiya *et al.* (8) demonstrated that sarcopenia was a poor prognostic factor of survival after reductive hepatectomy in advanced hepatocellular carcinoma patients ($P = 0.049$).

The development mechanism of poor prognosis in liver cancer patients combined with sarcopenia is more complex and may involve factors such as reduced functional liver volume. One previous study proved that sarcopenia negatively affected the preoperative total functional liver volume in patients undergoing liver resection (9). The preoperative hepatic physiologic reserve may therefore be smaller in sarcopenic patients; however, the reasons beyond this phenomenon remain unclear. In addition, there is a significant correlation between sarcopenia and the nutritional status of the patients; the nutritional status of patients with sarcopenia is generally poor, and

their immunity and recovery ability are also diminished postoperatively.

The occurrence mechanism of liver cancer patients complicated by sarcopenia involves a variety of molecular processes, including autophagy, abnormal hormone metabolism, intestinal microecology, and so on. At present, insulin-like growth factor-1 (IGF-1) and mammalian target of rapamycin complex 1 (mTORC1) have been identified as two important molecules involved in sarcopenia. Chew *et al.* (10) found that IGF-1 can be used as a specific serological marker of low muscle mass in the elderly. In hepatocellular carcinoma, a large number of damaged hepatocytes produce less IGF-1 and normal hepatocytes rarely express IGF-1 receptors. Meanwhile, the expression of IGF-1 receptors increases in patients with hepatocellular carcinoma, resulting in low levels of IGF-16 in the blood circulation, which is one of the causes of sarcopenia in hepatocellular carcinoma patients. On the other hand, mTORC1 is a regulator of skeletal muscle tissue regeneration. Knockout of mammalian target of rapamycin (mTOR) in muscle satellite cells can effectively inhibit its activation, proliferation, and differentiation, thereby damaging skeletal muscle regeneration. In addition, IGF-1 promotes muscle protein synthesis in skeletal muscle by binding to receptors in skeletal muscle cells and induces insulin receptor substrate 1 (IRS-1) phosphorylation to activate the phosphatidylinositol 3-kinases (PI3K)/serine threonine kinase (AKT)/mTORC1 pathway. In patients with liver cancer, low and medium levels of IGF-1 will affect the mTORC1 muscle protein synthesis pathway.

Autophagy has different effects on the regulation of skeletal muscle cells. Jones *et al.* (11) found that excessive autophagy of skeletal muscle mediates increased muscle protein hydrolysis in patients with liver cirrhosis. They also reported that the markers of protein synthesis in the skeletal muscle of liver cirrhosis patients are decreased, resulting in the continuous loss of skeletal muscle in these patients. Increased autophagy of skeletal muscle is the main cause of sarcopenia, especially in alcoholic liver cirrhosis.

The level of serum testosterone is also associated with sarcopenia. Testosterone can improve muscle mass and protein synthesis by increasing IGF-1 levels and activating mTORC1. Studies have found that more than 90% of patients with advanced liver disease have decreased testosterone levels. Sinclair *et al.* (12) showed that the muscle quality of cirrhotic men with low serum testosterone levels improved significantly following the intramuscular injection of testosterone.

The metabolites of intestinal flora, such as folic acid and vitamin B12 tryptophan, act as nutrients or metabolic regulators in muscle. The possible effects of intestinal flora on sarcopenia include the synthesis of amino acids, the prevention of oxidative stress, and the promotion of IGF-1 secretion to stimulate muscle synthesis and metabolism or cell proliferation (13).

Given these mechanisms, combined with the sarcopenia evaluation index, perioperative management is critical for the treatment of liver cancer patients complicated by sarcopenia. At present, the treatment of sarcopenia is mainly focused on nutritional support, exercise, and drug therapy.

Nutritional therapy is one of the main interventions for sarcopenia. Branched-chain amino acids, such as leucine isoleucine and valine, are not metabolized by the liver and are often used as sources of amino acids in patients with advanced liver cancer. In a prospective study, Uojima *et al.* (14) found that supplementation of branched-chain amino acids could effectively improve the muscle strength of patients with advanced liver disease.

Exercise intervention is one of the effective means of obtaining and maintaining the quality and strength of skeletal muscle, and is also the optimal method of sarcopenia treatment. Oliveira *et al.* (15) conducted a meta-analysis to study the effects of exercise on skeletal muscle area, strength, and physical activity in elderly patients aged 65 years and over. The results showed that exercise effectively prevented muscle loss and atrophy.

At present, there are no drugs indicated for sarcopenia. Some drugs used in the clinical treatment of other diseases, including angiotensin-converting enzyme inhibitors, androgens, selective androgen receptor regulators, growth hormones, myostatin inhibitors, etc., may benefit muscles, and could then be extended to sarcopenia. Patients with sarcopenia may exhibit increased expression of myostatin and impaired mTOR signal transduction pathway.

In the future, clinical workers should establish a set of optimal diagnostic and treatment systems for the early identification of patients with sarcopenia and individualized treatment, which is crucial to improving the prognosis of patients with liver cancer. At the same time, further in-depth research on the mechanism of sarcopenia is expected to provide new clinical treatment targets.

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