Nutritional therapy for hepatocellular carcinoma

Astrid Ruiz-Margáin, Berenice M Román-Calleja, Paulina Moreno-Guillén, José A González-Regueiro, Deyanira Kúsulas-Delint, Alejandro Campos-Murguía, Nayelli C Flores-García, Ricardo Ulises Macías-Rodríguez

Abstract
Hepatocellular carcinoma (HCC) is the most frequent primary liver cancer and presents together with cirrhosis in most cases. In addition to commonly recognized risk factors for HCC development, such as hepatitis B virus/hepatitis C virus infection, age and alcohol/tobacco consumption, there are nutritional risk factors also related to HCC development including high intake of saturated fats derived from red meat, type of cooking (generation of heterocyclic amines) and contamination of foods with aflatoxins. On the contrary, protective nutritional factors include diets rich in fiber, fruits and vegetables, n-3 polyunsaturated fatty acids and coffee. While the patient is being evaluated for staging and treatment of HCC, special attention should be paid to nutritional support, including proper nutritional assessment and therapy by a multidisciplinary team. It must be considered that these patients usually develop HCC on top of long-lasting cirrhosis, and therefore they could present with severe malnutrition. Cirrhosis-related complications should be properly addressed and considered for nutritional care. In addition to traditional methods, functional testing, phase angle and computed tomography scan derived skeletal muscle index-L3 are among the most useful tools for nutritional assessment. Nutritional therapy should be centered on providing enough energy and protein to manage the increased requirements of both cirrhosis and cancer. Supplementation with branched-chain amino acids is also recommended as it improves response to treatment, nutritional status and survival, and finally physical exercise must be encouraged.
human immunodeficiency virus coinfection, in males and in the elderly. In the latter, HBV, exposure to aflatoxin is associated with a risk of HCC up to 30 times greater than exposure alone. In most cases, HCC arises in the setting of cirrhosis; in fact, the annual incidence of HCC arising from cirrhosis ranges from 2% to 5%[4].

INTRODUCTION
Liver cancer is the sixth most common cancer and the second leading cause of cancer-related deaths globally; hepatocellular carcinoma (HCC) represents about 70%-90% of primary liver cancers and constitutes a major public health problem worldwide[1-3]. HCC is an especially challenging clinical scenario for people involved with its care; this is particularly difficult for dietitians and specialists involved in the nutritional care of these patients due to two factors: the accompanying cirrhosis in most of the cases (and therefore the cirrhosis-specific needs) and the nutritional requirements derived from cancer itself.

The first part of this review includes general information related to HCC, aimed to provide the basic knowledge of the disease to screen patients and recognize them in clinical practice. The second part of the review includes the nutritional approach, clinical relevance of nutritional status and the best options for nutritional treatment.

Epidemiology and Risk Factors
Liver cancer constitutes the fifth most frequent cancer in men and the seventh most frequent in women, according to age-standardized incidence rates[3]. It is more common in men than in women, with a ratio of 2.4:1. Incidence of HCC varies between geographic regions and ethnic groups depending on the prevalence of risk factors, although it increases progressively with age in all populations, reaching a peak during the seventh decade of life[4].

Emerging evidence indicates that the etiology in many cases of HCC is multifactorial, involving infections, comorbid conditions, and environmental exposure. In most cases, HCC arises in the setting of cirrhosis; in fact, the annual incidence of HCC arising from cirrhosis ranges from 2% to 5%[5]. The most common risk factors for HCC worldwide include hepatitis B virus (HBV), hepatitis C virus (HCV) and aflatoxin B1 exposure[6-8].

From a public health perspective, active HCV and HBV infections continue to drive most of the global burden of cirrhosis and subsequent HCC[9]. HCV carriers have 15 to 20 times higher risk of developing HCC than non-carriers. In people infected with HBV, exposure to aflatoxin is associated with a risk of HCC up to 30 times greater than in those exposed to aflatoxin alone[10]. In addition, the risk increases in patients with HBV/human immunodeficiency virus coinfection, in males and in the elderly. In the same way, the time of infection also seems to increase the risk of developing cancer, as...
does excessive alcohol consumption and active smoking[6].

It is likely that in the next few years, HCV/HBV as the primary cause of HCC will decrease significantly due to the availability of HCV curative treatment and HBV vaccines, whereas metabolic-associated fatty liver disease will become the major contributor to the global burden of HCC. Regarding this, up to 70% of patients with type 2 diabetes mellitus have metabolic-associated fatty liver disease, and in this context the probability of developing HCC doubles in patients with both diseases[2]. Additionally, there is a higher predisposition to cancer among carriers of the PNPLA3 rs378409 risk allele and the LEP rs7799039 polymorphism[11].

**DIETARY INVOLVEMENT IN HCC DEVELOPMENT**

Although there are many factors involved in HCC development, there is a role of dietary factors that can help prevent its development or increase its risk. Figure 1 summarizes this data.

**Nutritional risk factors**

Many studies have pointed to the possibility that specific components or nutrients in the diet are associated with an increased risk of different types of cancer, including HCC.

The main dietary risk factor for the development of HCC is the contamination of food with aflatoxins. Aflatoxins are a group of mycotoxins produced by the fungi *Aspergillus flavus* and *Aspergillus parasiticus* that are produced by improper storage of certain foods and constitute a risk factor that plays a causal role in 4.6%-28.2% of all worldwide HCC cases.

Aflatoxins can be found in products such as corn, wheat, peanuts, rice, sesame, sunflower seed, cottonseed and many spices; the presence of aflatoxins in these foods can be due to aspergillus infection during crop growth or due to an improper transport or storage where they are exposed to warm and humid conditions. Even animals fed with contaminated foods can pass aflatoxins into eggs and dairy products.

Another dietary factor associated with the development of HCC is excessive consumption of saturated fats especially those derived from red meat. The mechanisms are believed to be the generation of reactive oxygen species when iron is reduced in the diet (Fenton reaction) and through the generation of heterocyclic amines when meat is cooked at high temperatures. A prospective cohort study found that red meat intake was associated with an increased risk of mortality from liver disease and the incidence of HCC (hazard ratio: 1.74, 95% confidence interval: 1.16-2.61, 14.9 vs 5.7 cases/100000 person-years)[12]. Diets rich in red meat also correlate with circulating markers of inflammation and endothelial dysfunction, potentially having a negative influence in patients with both cirrhosis and HCC[13].

Finally, obesity, particularly abdominal obesity, also confers an increased risk of developing HCC according to various epidemiological studies. This risk seems to be related to the adipose tissue production of adipokines (leptin, adiponectin and resistin)[14]. Interestingly, the serum levels of leptin are elevated in patients with HCC, which points to the role of this adipokine as a promoter of HCC in obese patients.

**Nutritional protective factors**

In contrast with other types of cancer, relatively few studies have investigated the protective effect of diet on HCC.

It has been found that the consumption of fish rich in n-3 polyunsaturated fatty acids or supplementation with n-3 polyunsaturated fatty acids seems to protect against the development of HCC, even among subjects with HBV and/or HCV infection[15]. Fatty acids could exert anticancer effects through their ability to induce apoptosis of cells, regulate cell cycle and manipulate the production of eicosanoids[16].

Similarly, evidence indicates that polyphenols, found mainly in fresh fruits and vegetables, target angiogenesis and metastasis in HCC through regulation of multiple intracellular signals and finally reducing the risk of HCC[17,18].

Another important source of polyphenols is coffee, and in fact, the protective role of coffee in liver diseases has been well documented. Coffee is a complex mix of different chemicals including antioxidants and mutagenic and antimutagenic compounds; the mechanisms of action are unclear but may involve modification of cysteine residues in proteins that play important roles in liver carcinogenesis[19]. Interestingly, increased consumption of more than two cups of caffeinated coffee, and to a lesser extent decaffeinated coffee, is associated with a reduced risk of HCC, even in pre-existing...
Dietary factors associated with risk and protection for the development of hepatocellular carcinoma. HCC: Hepatocellular carcinoma.

On the other hand, diets with a high fiber content could reduce the risk of HCC by reducing subjective appetite and energy intake, contributing to the maintenance of healthy body weight in addition to exerting a beneficial effect on postprandial glucose levels and lipid profile[21,22]. Other protective mechanisms include binding to bile acids, with inhibition of their transformation to secondary bile acids, increasing hydration of the fecal bolus, diluting possible carcinogens, modification of the colonic flora with inhibition of bacterial enzymes responsible for the formation of carcinogens and decrease in intestinal transit time with less contact time between carcinogens and the intestinal wall[22].

CLINICAL MANIFESTATIONS AND DIAGNOSIS

HCC usually manifests with nonspecific symptoms. Some patients are asymptomatic at the time of diagnosis, but in advanced stages, clinical findings may include right upper quadrant abdominal pain and symptoms of malignant disease such as nausea, anorexia, malaise, fatigue and weight loss. Patients with unrecognized cirrhosis or known compensated cirrhosis may also present with liver decompensation including ascites, jaundice, variceal bleeding, portal vein invasion and thrombosis[1,23].

The diagnosis of HCC is mainly based on imaging studies and laboratory tests. In most cases, assuming tumor meets imaging criteria in patient at increased risk, biopsy is rarely needed. Triple-phase contrast enhanced computerized tomography (CT) is a sensitive and specific tool for identifying liver lesions larger than 1 cm[24,25]. The classic radiological finding is arterial enhancement with early washout in the portal phase. Other diagnostic options are gadolinium or liver-specific contrast agents for enhanced magnetic resonance imaging and contrast ultrasound (higher diagnostic performance than conventional ultrasound). In 2011, the Liver Imaging Reporting and Data System was introduced to standardize the reporting and collection of CT and magnetic resonance imaging findings for HCC[26]. The Liver Imaging Reporting and Data System classifies liver lesions into five categories based on size, threshold growth and enhancement patterns (enhancing capsule and washout). It is important to consider liver biopsy in those patients without cirrhosis, small lesions and probably malignant lesions (Liver Imaging Reporting and Data System 4).

Alpha-fetoprotein is elevated above 20 ng/mL in more than 70% of patients with HCC. However, its specificity is quite poor since high levels are associated with inflammatory states, such as viral hepatitis and tobacco use, although levels > 200 ng/mL have a high positive predictive value of HCC in patients with cirrhosis[1].

STAGING AND TREATMENT

Staging

Staging assessment is crucial to establish prognosis and treatment of patients with HCC. This evaluation should include tumor stage, severity of the underlying liver disease and performance status. Several staging systems have been developed for prognosis; the most widely used is the Barcelona Clinic Liver Cancer (BCLC) staging system is recommended both for prognostic prediction and treatment allocation and remains as the most validated and reliable system used widely. It is endorsed in several international clinical practice guidelines[27]. BCLC staging system classify patients in five stages. This classification categorizes patients into early HCC (stage 0 and A), intermediate HCC (stage B), advanced HCC (stage C) and end-stage HCC.
(stage D) [27].

**Treatment**

The goal of treatment in patients with HCC is to increase survival with the best possible quality of life, and therefore treatment decisions revolve around what is worth doing and should be agreed upon by a multidisciplinary team.

Surgical resection should be offered to patients with a single lesion and a non-cirrhotic liver or with cirrhosis and a hepatic venous pressure gradient lower than 10 mmHg without evidence of hepatic decompensation [28].

There are different therapeutic tools that are tumor-directed. One of these is transarterial chemoembolization, which uses injection of a chemotherapeutic agents into the tumor-feeding hepatic artery, followed by obstruction of this artery, reducing tumor burden and delaying progression. Also, it is particularly useful in patients on the transplant list if the waiting time is expected to be more than 6 months [29]. TACE is the first-line non-curative therapy for patients with multifocal HCC or lesions greater than 5 cm that does not have vascular invasion or extrahepatic spread. On the other hand, percutaneous ethanol injection is minimally invasive, safe, and associated with a low cost. Radiofrequency ablation is another tumor-directed treatment that uses a percutaneous or in situ heat-generating probe to destroy tumor cells and has a more predictable effect in tumors larger than 2 cm [1].

In patients with advanced HCC, monotherapy with sorafenib, a tyrosine kinase inhibitor, has a small but significant survival benefit compared to supportive care [30]. Phase III randomized controlled trials with lenvatinib as first-line therapy and regorafenib, cabozantinib and ramucirumab as second-line therapy, after disease progression with sorafenib, have shown good results. Regorafenib is now approved by the Food and Drug Administration in this setting. Immunotherapy with the programmed cell death protein 1 checkpoint inhibitor, nivolumab, is in phase II trials with accelerated Food and Drug Administration approval, while other kinase inhibitors (sunitinib, brivanib and erlotinib) showed no benefit in mortality in unresectable HCC [31].

Liver transplantation is a highly effective therapeutic option for unresectable early-stage HCC, especially in patients with underlying liver cirrhosis; it offers the best treatment of both the chronic liver disease and the tumor and is associated with excellent long-term survival rates for HCC within certain criteria [31, 32]. In order to achieve an optimal distribution of the limited number of available liver allografts for the patients on the waiting list, it is important to identify the patients who benefit most from liver transplantation with an acceptably good prognosis [33].

Thus, in 1996, a prospective cohort study defined restrictive selection criteria that led to superior survival for transplant patients with HCC. In this study, transplant eligibility criteria included: a single lesion ≤ 5 cm or 3 or fewer lesions all < 3 cm and no evidence of macrovascular invasion, lymph node involvement or extrahepatic metastasis [33]. Since then, these selection criteria are known as the Milan criteria and represent the criterion standard in transplant programs to select and list patients with HCC for liver transplantation in many centers [34].

Expanded criteria beyond the Milan criteria (e.g., UCSF criteria and up-to-7 criteria) and the use of downstaging therapies to meet Milan criteria have resulted in similar post-transplant outcomes. Of note, these criteria focus mainly on tumor volume, and do not factor in tumor biology [35].

It is important that specialists in nutrition involved in the care of HCC patients know these modalities of treatment because they will add even more “nutritional stress” into a patient with two conditions (both cirrhosis and cancer) with a high risk of malnutrition. Therefore, additional nutritional care should be provided after surgery, either liver transplantation or resection, given the increase in metabolic demand. On the other hand, side effects such as nausea, hyporexia and pain can be present during the use of some of the above-mentioned therapies (systemic therapy, TACE, radiofrequency ablation), limiting usual nutritional support.

**NUTRITIONAL APPROACH IN PATIENTS WITH CIRRHOSIS AND HCC**

**Nutritional assessment**

Nutritional assessment is of great importance in patients with cirrhosis and HCC, the goal is to establish a baseline body composition assessment and continue with frequent follow-ups to monitor the response to nutritional therapy. It is important to consider the fact that patients with previous liver disease have many complications...
that make nutritional assessment very complex. First, the decrease of hepatocyte synthesis of proteins such as albumin, make these common biomarkers unreliable for nutritional diagnosis. Second, the presence of complications such as ascites/edema and hepatic encephalopathy also limit the use of other methods. Traditional markers, such as body weight, body mass index and even bioelectrical impedance (for prediction of fat mass, fat free mass and skeletal muscle mass) are directly influenced by fluid overload; while hepatic encephalopathy hampers the use of functional testing such as handgrip-strength, six-minute walk test and frailty assessment. All these issues must be acknowledged in order to select the best and most reliable tool for nutritional assessment[35].

There are simple anthropometric methods, such as mid-arm muscle circumference, mid-arm area and triceps skinfold thickness measurement, that reflect muscle and fat content. They have been widely used and validated and are easy to implement in clinical practice[36].

In terms of functional testing, it can be applied when hepatic encephalopathy is not present. Handgrip strength is a widely used method that measures muscle strength typically with a hand-held dynamometer[37]. Recently, liver frailty index was developed and has been validated in patients with cirrhosis. It also includes handgrip strength and adds two more tests: time to complete five chair stands and time in three balance positions. These tests are inexpensive and easy to perform and can be used in outpatient clinics[38].

Another useful nutritional marker is phase angle (PhA) derived from bioelectrical impedance. It reflects the integrity of cell membranes and tissue homeostasis as well as muscle integrity[39]. Several studies have reported PhA as a clinically useful nutritional marker, predicting complications and mortality both in elderly people and in cirrhosis, where a PhA value < 4.9 is associated with higher risk of hepatic encephalopathy and decreased survival[40-42]. Furthermore, PhA has been widely used and validated as a nutritional marker associated to survival in different types of cancer [43]. Therefore, it is reasonable to use PhA in patients with cirrhosis and HCC, as has been shown in a small study including 51 patients with HCC, where a PhA < 4.8 was associated with higher mortality[44]. PhA has been recently validated against CT scan as a marker of sarcopenia in cirrhosis, where values of PhA < 5.4 in females and < 5.6 in males are diagnostic of sarcopenia[45]; this is a marker derived from a portable device and can be used in all settings, outpatients, hospitalized patients and even critically ill patients as it does not require active participation. Thus, this is a reliable tool for the sequential assessment of patients with cirrhosis requiring multiple evaluations to monitor response to nutritional treatment.

Finally, skeletal muscle index-L3 derived from CT scan is considered the gold standard for body composition assessment. It quantifies the total muscle area at the third lumbar vertebra, and it is normalized for the patient’s height. It is a very accurate method, although it remains difficult to include in daily clinical practice; however, patients with HCC require several imaging studies, including CT and/or magnetic resonance imaging for diagnosis and monitoring response to treatment. Thus, these already available images can also be used to evaluate body composition. The additional advantage of this method is allowing the detection of ascites and even the presence of myosteatosis[46]. For practical reasons, including costs, patient comfort and availability, these methods are not suitable for serial monitoring.

Regardless of the method of choice (based on expertise with the method, costs, and availability) for nutritional assessment, decreased skeletal muscle mass is associated with a worse prognosis, including lower response to treatment and lower survival; a summary of the studies addressing this topic is found in Table 1. All patients with HCC should be evaluated and monitored by nutrition specialists specialized in liver disease due to the enormous impact that nutritional status has on the prognosis of patients. It is important that these patients are referred early to avoid the progression of malnutrition.

**NUTRITIONAL THERAPY**

After thorough nutritional assessment, dietary advice and tailored nutritional therapy must be indicated. Figure 2 includes a summary of dietary recommendations depending on the BCLC stage.

Nutritional interventions must be individualized, considering many aspects such as the presence and etiology of cirrhosis, the stage of the underlying liver disease and the stage HCC, the presence of malnutrition and its degree, comorbidities as well as the
physical activity level of the patient. It is also important to consider surgical or radiological treatments to which the patient is subjected and to consider this level of physical stress in the calculation of the total energy expenditure.

Total energy expenditure mainly depends on the presence or absence of cirrhosis and malnutrition and can be calculated by indirect calorimetry or estimated by standardized formulas. Also rapid weight based formulas are available and suggested by the European Society for Clinical Nutrition and Metabolism guidelines[47].

Energy needs and protein requirements increase as the disease progresses. General recommendations from the European Society for Clinical Nutrition and Metabolism for liver disease and for cancer patients suggest 1.2-1.5g/kg/d of protein, and given recommendations from the European Society for Clinical Nutrition and Metabolism guidelines physical stress in the calculation of the total energy expenditure.

Energy needs and protein requirements increase as the disease progresses. General recommendations from the European Society for Clinical Nutrition and Metabolism for liver disease and for cancer patients suggest 1.2-1.5g/kg/d of protein, and given recommendations from the European Society for Clinical Nutrition and Metabolism guidelines physical stress in the calculation of the total energy expenditure.
It is estimated that carbohydrates should contribute 45%-60% of the total daily energy expenditure, and complex carbohydrates must be included to get >30 g of fiber. Once the protein and carbohydrate intake has been established, the rest of the total energy expenditure must be covered by lipids, paying special attention to meeting the needs for polyunsaturated fatty acids.

Finally, in patients with cirrhosis and HCC, supplementation with branched-chain amino acids (BCAAs), which include leucine, isoleucine and valine, is always recommended. BCAAs are the most widely studied type of supplement in HCC, and when given to these patients it has a beneficial effect in all stages of HCC, mainly in HCC stages 0 to C.

Preservation of liver function in patients with HCC is of great relevance, and in this context, there is evidence of the potential beneficial effect of BCAAs. On the one hand, they increase the efficiency of the treatment in HCC, by improving liver function and also increasing albumin when used from early stages, in addition to increasing the BCAA/L-tyrosine molar ratio.

Thus, early administration of BCAAs can improve outcomes after cancer therapy, even in the absence of encephalopathy and hypoproteinemia. Mainly, BCAA intake greater than 3 mo anticipates various benefits including prevention of a reduction in residual liver function caused by HCC treatment and prevention of recurrence after HCC treatment. Even BCAA granules have been reported to be effective in inhibiting early relapse after hepatectomy.

For unresectable HCC, it is common to perform TACE repeatedly, but it is necessary to pay attention to the liver function after this procedure. In this respect, the administration of BCAA granules prior to TACE inhibited reduction of serum albumin levels measured 3 mo and 6 mo after TACE and helped maintain residual liver function in patients with cirrhosis. A summary of the evidence on BCAAs supplementation in HCC is found in Table 2.

It is important to consider that although BCLC D patients have a poor prognosis, and nutritional support does not improve survival, enough energy and protein as well as micronutrients must still be provided in order to improve quality of life. Standard polymeric formulas can be suggested for these patients, without strict dietary advice.

**Exercise prescription**

Physical deconditioning is a frequent complication in patients with cirrhosis and end-stage liver disease, so in combination with nutritional treatment, a recommendation of physical exercise should be prescribed according to the characteristics of each patient.
Although there are no specific recommendations for patients with cirrhosis and HCC, based on available evidence for cirrhosis some recommendations can be made. Generally, in extremely frail or malnourished patients, it is recommended to start with balance training to strengthen postural muscles and improve range of motion. Subsequently, to improve the condition of malnutrition and frailty, it is suggested to start with resistance exercises with light weight. In addition, at this point it is appropriate to start with aerobic exercise to improve cardiopulmonary endurance and overall fitness[35,53]. An easy and effective strategy to start physical training is to count the number of steps that a patient performs routinely during a week using pedometer-based bracelets to monitor exercise and to increase > 2500 per day above the number of basal steps, aiming to reach at least 5000 steps per day; this physical program has been carried out in patients with cirrhosis, finding beneficial results in body composition and nutritional status[54,55]. In addition to these effects, exercise improves quality of life and general wellness that are extremely important in patients with cirrhosis and HCC.

### Table 2 Branched-chain supplementation in patients with hepatocellular carcinoma

| Ref. | Type of study | Population | Intervention (BCAA amount, time of supplementation) | Outcomes |
|------|---------------|------------|-----------------------------------------------------|----------|
| Tada et al [63], 2019 | Clinical trial (78 patients) | BCAA group: 27 patients | 5.712 g of L-leucine, 2.856 g of L-isoleucine, 3.432 g of L-valine. 18 mo | BCAA therapy was independently associated with good prognosis in patients with HCC (HR: 0.317, 95%CI = 0.123–0.813, P = 0.017). Multivariate analysis using competing risks methods indicated that BCAA therapy is independently associated with reduction of disease-specific mortality (HR: 0.216, 95%CI = 0.068–0.689, P = 0.001) |
| Nojiri et al [64], 2016 | Randomized clinical trial (51 patients) | Control: 26 patients. Diet: Energy: 30–35 kcal/kg; Protein: 1:1.3 g/kg per day. Intervention: 25 patients. Diet + BCAA | 420 kcal. 26.6 g of protein. 4.074 g of L-leucine. 3.845 g of L-isoleucine. 3.204 g of L-valine. 3 mo | Event-free survival was significantly higher in the BCAA group, whereas the intrahepatic recurrence rate was significantly lower (P = 0.04 and 0.056, respectively). A significant improvement in the SF-8 mental component score was observed in the BCAA group only (P < 0.01) |
| Ichikawa et al[65], 2013 | Randomized clinical trial (56 patients) | Control: 30 patients. Standard diet. Intervention: 26 patients. Standard diet + BCAA | 1.144 g of L-isoleucine, 1.904 g of L-leucine, 0.952 g of L-valine. 2 wk before hepatic resection and 6 mo after. | There was no significant difference in the overall survival rate between the two patients groups. Recurrence rate at 30 mo after surgery was significantly better in the BCAA group in comparison to the control group. Tumor markers such as AFP and PIVKA-II, significantly decreased at 36 mo after liver resection in the BCAA group in comparison to the control group |
| Saito et al [66], 2011 | Prospective cohort study (40 patients) | Control: 13 patients. Standard diet. Intervention: 27 patients. Standard diet + BCAA | 2.856 g of L-isoleucine, 5.712 g of L-leucine, 3.432 g of L-valine. > 3 mo | Supplementation with BCAA granules improves energy metabolism after RFA. BCAA granules improve the liver function after RFA. Improvements in the residual liver function may result in consistently adequate treatment for HCC recurrence after RFA |
| Nishikawa et al[67], 2012 | Retrospective cohort study (99 patients) | Control = 59 patients. Regular diet. Intervention: 40 patients. BCAA treatment | 2.856 g L-isoleucine, 5.712 g L-leucine, 3.432 g L-valine. > 3 mo | Serum albumin level and Child-Pugh score improved significantly in the BCAA group as compared with the control 3 and 6 mo after TACE (P < 0.05) |
| Hayaishi et al[68], 2011 | Randomized clinical trial (211 patients) | Control: 155 patients. Standard diet. Intervention: 56 patients. Standard diet + BCAA | Intervention: 12 g/d BCAA (LIVACT Granules; Ajinomoto Co., Inc., Tokyo, Japan). > 6 mo | The incidence of HCC was significantly lower in the BCAA group than in the control group (HR: 0.416, 95%CI: 0.216–0.860, P = 0.0085). Oral BCAA supplementation also seems to be effective in the prevention of liver-related complications in patients with Child-Pugh A cirrhosis |
| Hachiya et al[69], 2020 | Randomized clinical trial (156 patients) | Control: 81 patients. Standard diet. Intervention: 75 patients. Standard diet + BCAA | Intervention: 12 g/d BCAA (LIVACT Granules; Ajinomoto Co., Inc., Tokyo, Japan). 4 yr | BCAA supplementation may reduce tumor recurrence in low-risk patients. BCAA may not reduce the risk of tumor recurrence after hepatic resection in HCC in high-risk patients |

**Abbreviations:** AFP: Alpha-fetoprotein; BCAA: Branched-chain amino acid; CI: Confidence interval; HCC: Carcinoma hepatocellular; HR: Hazard ratio; PIVKA-II; Protein induced by vitamin K absence-II; RFA: Radiofrequency ablation; SF-8: School Form 8 Learner’s Basic Health and Nutrition Report; TACE: Transcatheter arterial chemoembolization.
REFERENCES

1 Yang JD, Hainaut P, Gores GJ, Amadou A, Plymouth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention and management. Nat Rev Gastroenterol Hepatol 2019; 16: 589-604 [PMID: 31493937 DOI: 10.1038/s41575-019-01869-y]
2 Sayiner M, Golabi P, Younossi ZM. Disease Burden of Hepatocellular Carcinoma: A Global Perspective. Dig Dis Sci 2019; 64: 910-917 [PMID: 30835028 DOI: 10.1007/s10620-019-05537-2]
3 Ziouzuio I, Shirat SF, Ajidi F, Khabbal Y. Association of Processed Meats and Alcohol Consumption with Renal Cell Carcinoma: A Worldwide Population-Based Study. Nutr Cancer 2020; 1-6 [PMID: 33283531 DOI: 10.1080/01635581.2020.1856388]
4 White DL, Thrift AP, Kanwal F, Davila J, El-Serag HB. Incidence of Hepatocellular Carcinoma in All 50 United States, From 2000 Through 2012. Gastroenterology 2017; 152: 812-820.e5 [PMID: 27889576 DOI: 10.1053/j.gastro.2016.11.020]
5 Golabi P, Rhea L, Henry L, Younossi ZM. Hepatocellular carcinoma and non-alcoholic fatty liver disease. Hepatol Int 2019; 13: 688-694 [PMID: 31701393 DOI: 10.1007/s12072-019-09995-8]
6 El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology 2012; 142: 1264-1273.e1 [PMID: 22537432 DOI: 10.1053/j.gastro.2011.12.061]
7 Kew MC. Aflatoxins as a cause of hepatocellular carcinoma. J Gastrointestin Liver Dis 2013; 22: 305-310 [PMID: 24079898]
8 Wild CP, Gong YY. Mycotoxins and human disease: a largely ignored global health issue. Carcinogenesis 2010; 31: 71-82 [PMID: 19875698 DOI: 10.1093/carcin/bgp264]
9 Kulik L, El-Serag HB. Epidemiology and Management of Hepatocellular Carcinoma. Gastroenterology 2019; 156: 477-491.e1 [PMID: 30637835 DOI: 10.1053/j.gastro.2018.08.065]
10 Baecker A, Liu X, La Vecchia C, Zhang ZF. Worldwide incidence of hepatocellular carcinoma cases attributable to major risk factors. Eur J Cancer Prev 2018; 27: 205-212 [PMID: 29489473 DOI: 10.1097/CEJ.0000000000000428]
11 Zhou YJ, Zheng KJ, Wang XB, Yan HD, Sun OF, Pan KH, Wang TY, Ma HL, Chen YP, George J, Zheng MH. Younger patients with MAFLD are at increased risk of severe COVID-19 illness: A multicenter preliminary analysis. J Hepatol 2020; 73: 719-721 [PMID: 32348790 DOI: 10.1016/j.jhep.2020.04.027]
12 Freedman ND, Cross AJ, McGlynn KA, Abnet CC, Park Y, Holdenbeck AR, Schatzkin A, Everhart JE, Sinha R. Association of meat and fat intake with liver disease and hepatocellular carcinoma in the NIH-AARP cohort. J Natl Cancer Inst 2010; 102: 1354-1365 [PMID: 20729477 DOI: 10.1093/jnci/djq301]
13 Defagó MD, Elorriaga N, Irázola VE, Rubinstein AL. Influence of food patterns on endothelial biomarkers: a systematic review. J Clin Hypertens (Greenwich) 2014; 16: 907-913 [PMID: 25376124 DOI: 10.1111/jch.12431]
14 Andrighetto LV, Poziomyck AK. Serum leptin levels and hepatocellular carcinoma: review article. Arq Bras Cir Dig 2016; 29: 276-278 [PMID: 26076486 DOI: 10.1590/0102-6722201600040015]
15 Sawada N, Inoue M, Iwaski M, Sasazuki S, Shimazu T, Yamaji T, Takachi R, Tanaka Y, Mizokami M, Tsugane S; Japan Public Health Center-Based Prospective Study Group. Consumption of n-3 fatty acids and fish reduces risk of hepatocellular carcinoma. Gastroenterology 2012; 142: 1468-1475 [PMID: 22342990 DOI: 10.1053/j.gastro.2012.02.018]
16 Fauser JK, Prisciandaro LD, Cummings AG, Howarth GS. Fatty acids as potential adjunctive colorectal chemotherapeutic agents. Cancer Biol Ther 2011; 11: 724-731 [PMID: 21430438 DOI: 10.1016/j.cbt.2011.8.15281]
17 Cazaroli LH, Zanatta L, Alberton EH, Figueiredo MS, Folador P, Damazio RG, Pizzolatti MG, Silva FR. Flavonoids: prospective drug candidates. Mini Rev Med Chem 2008; 8: 1429-1440 [PMID: 18991758 DOI: 10.2174/138955708786369564]
18 Kuruthiga C, Devi KP, Nabavi SM, Bishayee A. Autophagy: A Potential Therapeutic Target of Polyphenols in Hepatocellular Carcinoma. Cancers (Basel) 2020; 12 [PMID: 32121322 DOI: 10.3390/cancers12030562]

19 Tao KS, Wang W, Wang L, Cao DY, Li YQ, Wu SX, Dou KF. The multifaceted mechanisms for coffee's anti-tumorigenic effect on liver. Med Hypotheses 2008; 71: 730-736 [PMID: 18701223 DOI: 10.1016/j.mehy.2008.06.026]

20 Kennedy OJ, Roderick P, Buchanan R, Fallowfield JA, Hayes PC, Parkes J. Coffee, including caffeinated and decaffeinated coffee, and the risk of hepatocellular carcinoma: a systematic review and dose-response meta-analysis. BMJ Open 2017; 7: e013739 [PMID: 28490552 DOI: 10.1136/bmjopen-2016-013739]

21 Wanders AJ, van den Borne JJ, de Graaf C, Huls Hof T, Jonathan MC, Kristensen M, Mars M, Schols HA, Feskens EJ. Effects of dietary fibre on subjective appetite, energy intake and body weight: a systematic review of randomized controlled trials. Obes Rev 2011; 12: 724-739 [PMID: 21676152 DOI: 10.1111/j.1467-789X.2011.00895.x]

22 Babio N, Balanza R, Basulto J, Bulló M, Salas-Salvadó J. Dietary fibre: influence on body weight, glycemic control and plasma cholesterol profile. Nutr Hosp 2010; 25: 327-340 [PMID: 20593113]

23 Bruix J, Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. Hepatology 2005; 42: 1208-1236 [PMID: 16250051 DOI: 10.1002/hep.20933]

24 Marrero JA, Kalik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, Roberts LR, Heimbach JK. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2018; 68: 723-750 [PMID: 29624699 DOI: 10.1002/hep.29913]

25 European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018; 69: 182-236 [PMID: 29628281 DOI: 10.1016/j.jhep.2018.03.019]

26 Mitchell DG, Bruix J, Sherman M, Sirlin CB. LI-RADS (Liver Imaging Reporting and Data System): summary, discussion, and consensus of the LI-RADS Management Working Group and future directions. Hepatology 2015; 61: 1056-1065 [PMID: 25041904 DOI: 10.1002/hep.27304]

27 Sala M, Forner A, Varela M, Bruix J. Prognostic prediction in patients with hepatocellular carcinoma. Semin Liver Dis 2005; 25: 171-180 [PMID: 15918146 DOI: 10.1055/s-2005-871197]

28 Serper M, Taddei TH, Mehta R, D’Adddeo K, Dai F, Aytaçman A, Baytarian M, Fox R, Hunt K, Goldberg DS, Valderrama A, Kaplan DE; VOCAL Study Group. Association of Provider Specialty and Multidisciplinary Care With Hepatocellular Carcinoma Treatment and Mortality. Gastroenterology 2017; 152: 1954-1964 [PMID: 28283421 DOI: 10.1016/j.gastro.2017.02.040]

29 Lencioni R, de Baere T, Soulen MC, Rilling WS, Geschwind JF. Lipiodol transarterial chemoembolization for hepatocellular carcinoma: A systematic review of efficacy and safety data. Hepatology 2016; 64: 106-116 [PMID: 26765068 DOI: 10.1002/hep.28453]

30 Llovet JM, Montal R, Sia D, Finn RS. Molecular therapies and precision medicine for hepatocellular carcinoma. Nat Rev Clin Oncol 2018; 15: 599-616 [PMID: 30061739 DOI: 10.1038/s41571-018-0073-4]

31 Morgul MH, Felgendreff P, Kienlein A, Gauger U, Semmling K, Hau HM, Tautenhahn HM, Bartels M. Milan criteria in the MELD era-is it justifiable to extend the limits for orthotopic liver transplantation? World J Surg Oncol 2020; 18: 158 [PMID: 32635931 DOI: 10.1186/s12957-020-01932-6]

32 Samuel D, Colombo M, El-Serag H, Sobesky R, Heaton N. Toward optimizing the indications for orthotopic liver transplantation in hepatocellular carcinoma. Liver Transpl 2011; 17 Suppl 2: S6-13 [PMID: 21858912 DOI: 10.1002/lt.22423]

33 Saberi B, Garonzik-Wang J, Ma M, Ajayi T, Kim A, Luu H, Jakhete N, Pustavoitau A, Anders RA, Georgiades C, Kanel I, Ottmann S, Philosophe B, Cameron AM, Gurakar A. Accuracy of Milan, University of California San Francisco, and Up-To-7 Criteria in Predicting Tumor Recurrence Following Deceased-Donor Liver Transplant in Patients With Hepatocellular Carcinoma. Exp Clin Transplant 2020; 18: 463-469 [PMID: 30084757 DOI: 10.6002/ect.2017.0288]

34 Mazzaferro V, Bhoori S, Sposito C, Bongini M, Langer M, Miceli R, Marianni L. Milan criteria in liver transplantation for hepatocellular carcinoma: an evidence-based analysis of 15 years of experience. Liver Transpl 2011; 17 Suppl 2: S44-S57 [PMID: 21695773 DOI: 10.1002/lt.22365]

35 Duarte-Rojo A, Ruiz-Margáin A, Montaño-Loza AJ, Macias-Rodríguez RU, Ferrando A, Kim WR. Exercise and physical activity for patients with end-stage liver disease: Improving functional status and sarcopenia while on the transplant waiting list. Liver Transpl 2018; 24: 122-139 [PMID: 29024353 DOI: 10.1002/lt.24958]

36 Alberino F, Gatta A, Amadio P, Merkel C, Di Pascoli L, Boffo G, Caregaro L. Nutrition and survival in patients with liver cirrhosis. Nutrition 2001; 17: 445-450 [PMID: 11399401 DOI: 10.1053/s0899-9007(01)00521-4]

37 Figueiredo F, Dickson ER, Pasha T, Kasparova P, Thorneau T, Malinchoc M, DiCecco S, Francisco-Ziller N, Charlton M. Impact of nutritional status on outcomes after liver transplantation. Transplantation 2000; 70: 1347-1352 [PMID: 11087151 DOI: 10.1097/00007890-200011150-00014]

38 Lai JC, Covinsky KE, Dodge JL, Boscardin WJ, Segov JP, Feng S. Development of a novel frailty index to predict mortality in patients with end-stage liver disease. Hepatology 2017; 66: 564-574 [PMID: 28422306 DOI: 10.1002/hep.29219]
Ruiz-Margáin A, Macias-Rodríguez RU, Duarte-Rojo A, Rios-Torres SL, Espinosa-Cuevas Á, Torre A. Malnutrition assessed through phase angle and its relation to prognosis in patients with compensated liver cirrhosis: a prospective cohort study. *Dig Liver Dis* 2015; 47: 309-314 [PMID: 25618555 DOI: 10.1016/j.dld.2014.12.015]

Ruiz-Margáin A, Macias-Rodríguez RU, Ampuero J, Cubero FJ, Chi-Cervera L, Rios-Torres SL, Duarte-Rojo A, Espinosa-Cuevas Á, Romero-Gómez M, Torre A. Low phase angle is associated with the development of hepatic encephalopathy in patients with cirrhosis. *World J Gastroenterol* 2016; 22: 10064-10070 [PMID: 28018114 DOI: 10.3748/wjg.v22.i45.10064]

Wirth R, Volkert D, Rösler A, Sieber CC, Bauer JM. Bioelectric impedance phase angle is associated with hospital mortality of geriatric patients. *Arch Gerontol Geriatr* 2010; 51: 290-294 [PMID: 20044156 DOI: 10.1016/j.archger.2009.12.002]

Peres WA, Lento DF, Baluz K, Ramalho A. Phase angle as a nutritional evaluation tool in all stages of chronic liver disease. *Nutr Hosp* 2012; 27: 2072-2078 [PMID: 23588459 DOI: 10.3305/nh.2012.27.6.6015]

Barbosa-Silva MC, Barros AJ, Wang J, Heymsfield SB, Pierson RN Jr. Bioelectrical impedance analysis: population reference values for phase angle by age and sex. *Am J Clin Nutr* 2005; 82: 49-52 [PMID: 16002799 DOI: 10.1093/ajcn.82.1.49]

Schütte K, Tippelt B, Schulz C, Röhl FW, Feneberg A, Seidensticker R, Arend J, Malfertheiner P. Malnutrition is a prognostic factor in patients with hepatocellular carcinoma (HCC). *Clin Nutr* 2015; 34: 1122-1127 [PMID: 25434576 DOI: 10.1016/j.clun.2014.11.007]

Ruiz-Margáin A, Xie JJ, Román-Calleja BM, Pauly M, White MG, Chapa-Ibarungi-Gómez M, Campos-Murguia A, González-Regueiro JA, Macías-Rodríguez RU, Duarte-Rojo A. Phase angle from bioelectrical impedance for the assessment of sarcopenia in cirrhosis with or without ascites. *Clin Gastroenterol Hepatol* 2020 [DOI: 10.1016/j.cgh.2020.08.066]

Montano-Loza AJ, Meza-Junco J, Prado CM, Liefers JF, Barcos VE, Bain VG, Sawyer MB. Muscle wasting is associated with mortality in patients with cirrhosis. *Clin Gastroenterol Hepatol* 2012; 10: 166-173, 173.e1 [PMID: 21893129 DOI: 10.1016/j.cgh.2011.08.028]

Plaut M, Bernal W, Dasarathy S, Merli M, Plank LD, Schütz T, Bischoff SC. ESPEN guideline on clinical nutrition in liver disease. *Clin Nutr* 2019; 38: 485-521 [PMID: 30712783 DOI: 10.1016/j.clnu.2018.12.022]

Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, Fearon K, Hüterer E, Oldervoll L, Ravasco P, Solheim T, Strasser F, de van der Schueren M, Preiser JC. ESPEN guidelines on nutrition in cancer patients. *Clin Nutr* 2017; 36: 11-48 [PMID: 27637382 DOI: 10.1016/j.clnu.2016.07.015]

Ruiz-Margáin A, Méndez-Guerrero O, Román-Calleja BM, González-Rodríguez S, Fernández-Del-Rivero G, Rodríguez-Córdova PA, Torre A, Macias-Rodríguez RU. Dietary management and supplementation with branched-chain amino acids in cirrhosis of the liver. *Rev Gastroenterol Mex (Engl Ed)* 2018; 83: 424-433 [PMID: 30292383 DOI: 10.1016/j.rgmx.2018.05.006]

Tajiri K, Shimizu Y. Branched-chain amino acids in liver diseases. *Transl Gastroenterol Hepatol* 2018; 3: 47 [PMID: 30148232 DOI: 10.21037/tgh.2018.07.06]

Takami T, Yamasaki T, Saeki I, Matsumoto T, Suehiro Y, Sakaida I. Supportive therapies for prevention of hepatocellular carcinoma recurrence and preservation of liver function. *World J Gastroenterol* 2016; 22: 7252-7263 [PMID: 27621572 DOI: 10.3748/wjg.v22.i32.7252]

Nishikawa H, Osaki Y, Inuzuka T, Takeda H, Nakajima J, Matsuda F, Henni S, Sakamoto A, Ishikawa T, Saito S, Kita R, Kimura T. Branched-chain amino acid treatment before transcatheter arterial chemoembolization for hepatocellular carcinoma. *World J Gastroenterol* 2012; 18: 1379-1384 [PMID: 22493552 DOI: 10.3748/wjg.v18.i12.1379]

Macías-Rodríguez RU, Ruiz-Margáin A, Román-Calleja BM, Moreno-Tavarez E, Weber-Sangri L, González-Arellano MF, Fernández-Del-Rivero G, Ramírez-Soto K. Exercise prescription in patients with cirrhosis: Recommendations for clinical practice. *Rev Gastroenterol Mex (Engl Ed)* 2019; 84: 326-343 [PMID: 31262552 DOI: 10.1016/j.rgmx.2019.02.011]

Macías-Rodríguez RU, Ruiz-Margáin A, Román-Calleja BM, Espin-Nasser ME, Flores-García NC, Torre A, Galicia-Hernández G, Rios-Torres SL, Fernández-Del-Rivero G, Orea-Tejeda A, Lozano-Cruz OA. Effect of non-alcoholic beer, diet and exercise on endothelial function, nutrition and quality of life in patients with cirrhosis. *World J Hepatol* 2020; 12: 1299-1313 [PMID: 33442456 DOI: 10.4255/wjg.v12.i12.1290]

Chen HW, Ferrando A, White MG, Dennis RA, Xie J, Pauly M, Park S, Bartter T, Dunn MA, Ruiz-Margáin A, Kim WR, Duarte-Rojo A. 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 [PMID: 31907774 DOI: 10.1007/s10620-019-06034-2]

Faron A, Sprinkart AM, Pieper CC, Kuetting DLR, Fimmers R, Block W, Meyer C, Thomas D, Attenerberger U, Luetkens JA. Yttrium-90 radioembolization for hepatocellular carcinoma: Outcome prediction with MRI derived fat-free muscle area. *Eur J Radiol* 2020; 125: 108889 [PMID: 32087468 DOI: 10.1016/j.ejrad.2020.108889]

Fujita M, Takahashi A, Hayashi M, Okai K, Abe K, Ohira H. Skeletal muscle volume loss during transarterial chemoembolization predicts poor prognosis in patients with hepatocellular carcinoma. *Hepatol Res* 2019; 49: 778-786 [PMID: 30884044 DOI: 10.1111/hepr.13331]

Kobayashi T, Kawai H, Nakano O, Abe S, Kamimura H, Sakamaki A, Kamimura K, Tsuchiya A,
Takamura M, Yamagiwa S, Terai S. Rapidly declining skeletal muscle mass predicts poor prognosis of hepatocellular carcinoma treated with transcatheter intra-arterial therapies. *BMC Cancer* 2018; 18: 756 [PMID: 30041616 DOI: 10.1186/s12885-018-4673-2]

Nishikawa H, Nishijima N, Enomoto H, Sakamoto A, Nasu A, Komekado H, Nishimura T, Kita R, Kimura T, Iijima H, Nishiguchi S, Osaki Y. Prognostic significance of sarcopenia in patients with hepatocellular carcinoma undergoing sorafenib therapy. *OncoL Lett* 2017; 14: 1637-1647 [PMID: 28739390 DOI: 10.3892/ol.2017.6287]

Levogel S, van Vletter MG, Muslem R, Koek M, Niessen WJ, de Man RA, de Bruin RW, Ijzermans JN. Sarcopenia impairs survival in patients with potentially curable hepatocellular carcinoma. *J Surg Oncol* 2015; 112: 208-213 [PMID: 26266324 DOI: 10.1002/jso.23976]

Iritani S, Imai K, Takai K, Hanai T, Ieda T, Miyazaki T, Suetsugu A, Shiraki M, Shimizu M, Moriwaki H. Skeletal muscle depletion is an independent prognostic factor for hepatocellular carcinoma. *J Gastroenterol* 2015; 50: 323-332 [PMID: 24817668 DOI: 10.1007/s00535-014-0964-9]

Harimoto N, Shirabe K, Yamashita YI, Ikegami T, Yoshizumi T, Soejima Y, Ikeda T, Maehara Y, Nishie A, Yamakata T. Sarcopenia as a predictor of prognosis in patients following hepatectomy for hepatocellular carcinoma. *Br J Surg* 2013; 100: 1523-1530 [PMID: 24037576 DOI: 10.1002/bjs.9258]

Tada T, Kumada T, Toyoda H, Yasuda S, Koyabu T, Nakashima M. Impact of Branched-Chain Amino Acid Granule Therapy in Patients with Hepatocellular Carcinoma Who Have Normal Albumin Levels and Low Branched-Chain Amino Acid to Tyrosine Ratios. *Nutr Cancer* 2019; 71: 1132-1141 [PMID: 30955354 DOI: 10.1080/01635581.2019.1597905]

Nojiri S, Fujiwara K, Shinkai N, Iio E, Joh T. Effects of branched-chain amino acid supplementation after radiofrequency ablation for hepatocellular carcinoma: A randomized trial. *Nutrition* 2017; 33: 20-27 [PMID: 27908546 DOI: 10.1016/j.nut.2016.07.013]

Ichikawa K, Okabayashi T, Maeda H, Namikawa T, Iiyama T, Sugimoto T, Kobayashi M, Mimura T, Hanazaki K. Oral supplementation of branched-chain amino acids reduces early recurrence after hepatic resection with hepatocellular carcinoma: a prospective study. *Surg Today* 2013; 43: 720-726 [PMID: 22890582 DOI: 10.1007/s00595-012-0288-4]

Saito M, Yano Y, Minami A, Hirano H, Monose K, Sugimoto M, Yoshida M, Azuma T. Branched-chain amino acid granules improve the non-protein respiratory quotient after radiofrequency ablation. *Intern Med* 2014; 53: 1469-1475 [PMID: 25303556 DOI: 10.2169/internalmedicine.53.2115]

Hayashi S, Chung H, Kudo M, Ishikawa E, Takita M, Ueda T, Kitai S, Inoue T, Yada N, Hagiwara S, Minami Y, Ueshima K. Oral branched-chain amino acid granules reduce the incidence of hepatocellular carcinoma and improve event-free survival in patients with liver cirrhosis. *Dig Dis* 2011; 29: 326-332 [PMID: 21829025 DOI: 10.1159/000327571]

Hachiya H, Aoki T, Iso Y, Shimizu T, Tago K, Park KH, Sakaura Y, Shiraki T, Mori S, Kubota K. Effects of branched-chain amino acids on postoperative tumor recurrence in patients undergoing curative resection for hepatocellular carcinoma: A randomized clinical trial. *J Hepatobiliary Pancreat Sci* 2020; 27: 819-829 [PMID: 32949091 DOI: 10.1002/jhbp.830]
