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Comparison of Effectiveness Between Protein and BCAA in Late Evening Snack on Vietnamese Liver Cirrhotic Outpatients: a Randomized Clinical Trial

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ABSTRACT

Background & Aims: Late-evening snacks bring multiple benefits to liver cirrhosis patients. However, a consensus on the nutrient composition of the snack is still not clear. This study showed a direct comparison between a protein snack and a a branched-chained amino acid (BCAA) snack.

Methods: A randomized clinical trial with 32 Vietnamese liver cirrhosis outpatients (61.0, 57-63 years), allocated into two groups: Protein group (n=16) and BCAA group (n=16) took place. Both groups received a snack providing 270-300 kcal, 50g carbohydrates, <5g lipid, and 13g of protein with 8g being protein powder in Protein group and 4g protein powder and 4g BCAA powder in BCAA group. Serum biochemical parameters, anthropometric data, and Chronic Liver Disease Questionnaire scores were examined in both groups before and after the 3-week intervention.

Results: After receiving the snacks for 3 weeks, albumin was significantly increased in the Protein group ($p<0.01$) while it was not in the BCAA group. Only the ALT liver enzyme was statistically decreased in the Protein group ($p<0.01$). After the intervention, the handgrip strength of the Protein group increased from 24.3kg (±9.1 SD) to 25.7kg (±9.2 SD) ($p=0.012$); while, in BCAA group, the mean also changed from 24.7kg (±6.6 SD) to 25.6kg (±7.4 SD) ($p=0.237$). The overall Chronic Liver Disease Questionnaire score was significantly increased from 6.0 to 6.7 and 6.6 in the Protein group and the BCAA group, respectively.

Conclusions: A protein snack is an effective dietary intervention in improving albumin, biochemical parameters, and nutritional status for compensated liver cirrhosis outpatients. Considering cost, availability, and taste, a BCAA snack might be unnecessary for liver cirrhosis outpatients.

Key words: liver cirrhosis – late-evening snack – protein – branch-chained amino acid.

Abbreviations: AC: activity; ALT: alanine aminotransferase; AS: abdominal symptoms; AST: aspartate aminotransferase; BCAA: branch-chained amino acid; BMI: body mass index; CHO: carbohydrates; CLDQ: Chronic Liver Disease Questionnaire; CTP: Child-Turcotte-Pugh; EF: emotional function; FA: fatigue; INR: international normalized ratio; LES: late-evening snack; LC: liver cirrhosis; PT: prothrombin time; SS: systemic symptoms.

INTRODUCTION

Since 1990, liver cirrhosis (LC) has been a threat to worldwide health being the 10th cause of death [1]. Though, with the help of hepatitis vaccination, it descended to the 12th spot in 2021 according to Global Burden of Diseases, it remains one of the biggest health issues in low-income countries such as Vietnam, being the 6th leading cause of death [1]. In liver cirrhosis without proper nutrition aid, patients more than often become malnourished, increasing from 20% in patients with the well-compensated stage to more than 60% in patients with advanced cirrhosis [2]. During the progression of the disease, patients experience rapid starvation, with an early shift from glucose to lipid use for energy during the postabsorptive stage. After an overnight fast, lipids contribute 75% of the total calories used in cirrhotic patients, indicating higher rates of ketogenesis and gluconeogenesis. This metabolic profile means that the rate of gluconeogenesis increases and amino acids are consumed more as a source of energy (protein catabolism) [3]. A late evening snack (LES) has been recommended as a first-liner nutritional therapy for LC to prevent this anabolic state by multiple guidelines [2, 4, 5]. Not only can LES improve

nocturnal starvation but it can also be beneficial to hepatic biochemical parameters such as albumin, liver enzymes, and quality of life [6].

While LES has been widely recommended by both Clinical Guidelines on Nutrition in chronic liver disease by the European Association for the Study of the Liver [4] and the European Society for Clinical Nutrition and Metabolism (ESPEN) [2], the nutritional composition is not specified. However, recent reviews and meta-analyses showed that an LES comprising complex carbohydrates and proteins could improve the respiration quotient and enhance nutritional status, nitrogen balance, liver function, and overall quality of life in patients with cirrhosis [7, 8]. The use of 50g of carbohydrates (CHO) was most commonly mentioned in the official guidelines; on the other hand, the source of nitrogen/protein was not clarified [2, 8]. In one of the network meta-analysis comparing different LES compositions based on their effectiveness on hepatic biochemical indexes such as albumin, alanine aminotransferase (ALT), aspartate transferase (AST), LES containing the complex of CHO and conventional protein was found to be the most effective compared to others, including a snack with a mixture of CHO and branch-chained amino acid (BCAA), a high CHO snack, and a snack using coconut milk [7].

In the last decade, the use of BCAA has become more and more popularized, especially among chronic liver disease patients with evidence of having a beneficial effect on symptoms and signs of hepatic encephalopathy (HE) [9]. A decreased serum ratio of BCAA to aromatic amino acids has been associated with a poor prognosis so BCAA has been advocated to be prescribed to decompensated LC and HE patients [2, 4]. BCAA has also been provided for mild or moderate cases of LC as a BCAA enrichment-LES in many recent trials [10-12]. In these studies, a BCAA-enriched LES was usually compared with a control group or a CHO-only LES but not with another nitrogen source. In the aforementioned network meta-analysis, it is believed that a conventional protein source might be preferable to BCAA in a late-evening snack for compensated LC patients [7]. Nonetheless, the results of the network meta-analysis were pooled from a network of indirect comparison and there was no direct comparison between a CHO-Protein snack and a CHO-BCAA snack. Therefore, this study was conducted with the aim of confirming these findings and determining the effectiveness of a protein LES composition and a BCAA-containing snack in a direct comparison for LC outpatients.

METHODS

Population and Research Design

This randomized clinical trial was carried out at Dong Da General Hospital (800 beds) in Hanoi, Vietnam from February 2023 to August 2023. This research received ethical approval from the Institutional Review Board for Ethics in Biomedical Research – Hanoi Medical University (number 596/HMUIRB) on February 10, 2023. All participants were informed about the aims and procedures of the study before the data collection period.

The inclusion criteria were: age ≥ 18 years old, previously diagnosed by documented laboratory data and/or histology with any etiology, Child-Pugh class A-B, did not have LES before the study; do not change medicine during the intervention; and abstain from drinking alcohol for at least 3 months before and during the study. The criteria for non-inclusion were: patients who had hepatic encephalopathy, jaundice, severe ascites, and variceal hemorrhage, who were in the acute phase, acute inflammation, diabetes, renal dysfunction, and cancer at the time of recruitment, or they had albumin administration before or during the study. For this study, a sample size of 16 patients/group was calculated using a power of 80% and a significance level of 5%. This sample size was calculated based on a previous study with a standard deviation of 0.4 [13] to detect a difference of 0.3g/L in albumin. In the beginning, 34 patients were included in the study; however, 1 patient dropped out of the study due to personal reasons and 1 patient was excluded from the study because of alcohol relapse. Therefore, 32 outpatients who completed the research intervention were included in the analysis (Fig. 1).

Before randomization, patients were match-paired by gender, age, and albumin then one participant from each pair was randomly assigned to the Protein group or BCAA group, and the other was automatically assigned to the other group. A researcher who was not directly involved in the sample selection was responsible for the computer block randomization. At baseline, the outpatients were evaluated for all the outcome parameters in the first week after recruitment. Both groups were followed up in individual counseling, by the same dietitian during the 3 weeks trial. After the intervention period, the groups were submitted to the same evaluations (Fig. 1).

Demographic Data

Personal data such as name, age, gender as well as medical history were collected. Liver cirrhosis etiology, Child-Turcotte-Pugh (CTP) score, and some dietary habits (drinking, number of meals per day) were also recorded for recruiting purposes.

Biochemical Evaluation

After 12h of fasting, venous samples were taken for analysis of liver biochemistry: albumin, ALT, AST, total bilirubin and fasting blood glucose. The blood was separated by centrifugation and immediately analyzed in the laboratory department of Dong Da General Hospital. Albumin, AST, ALT, total bilirubin, prothrombin time (PT) to calculate the international normalized ratio (INR), and fasting blood glucose were analyzed by a biochemical analyzer (Beckman Coulter AU680).

Anthropometric Data and Nutritional Status

Bodyweight and height were measured in light clothing and without shoes. Body mass index (BMI) was computed as the ratio of weight (kg) per height squared (m^2). A BMI <18.5 kg/m^2 was considered underweight. For nutritional assessment, Handgrip strength is a non-invasive, straightforward, and rapid approach to assessing nutritional status, particularly among malnourished individuals who have lean mass depletion and poor muscular strength. Low handgrip strength is suggested as <26 kg for men and <18 kg for women [14].

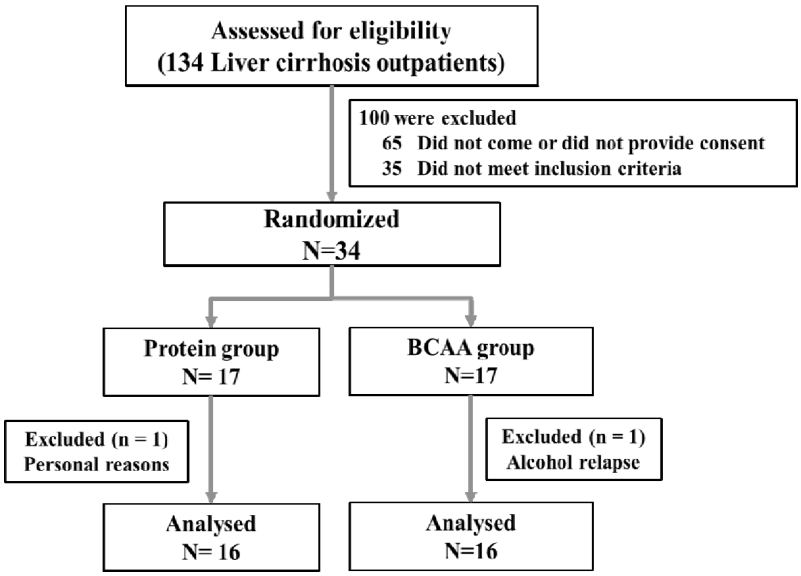

Fig. 1. Recruitment flow chart.

Quality of Life

The Chronic Liver Disease Questionnaire (CLDQ) was developed by Yonossi et al. in 1999 to assess the quality of life of patients with liver diseases [15]. The CLDQ is the only approved tool for assessing the various etiologies and severity of liver disease. It consists of 29 questions in six domains: abdominal symptoms (AS), fatigue (FA), systemic symptoms (SS), activity (AC), emotional function (EF), and worry (WO). Each item is graded on a seven-point Likert scale. A higher score on the questionnaire suggests fewer symptoms, whereas a lower score indicates more severe symptoms. The questionnaire was translated into Vietnamese and tested and re-tested with a Cronbach's alpha of 0.93.

Dietary Intervention

Before the trial, both groups were given nutritional counseling for a standard diet for LC patients with 30-35 kcal/kg/day and 1.2-1.5 g/kg/day in compliance with ESPEN guidelines for 1 week [2]. Starting from the second week, both groups still followed the standard diet plus a late-evening snack that was prepared by the researchers for 21 days. The snacks in both groups contained two components with one providing carbohydrates such as Pho (Vietnamese noodles), cupcakes and a sachet of 8g white powder. The powder was either 8 g of whey protein corresponding to the Protein group or a mixture of 4 g whey protein and 4 g BCAA (2 g leucine, 1 g isoleucine, 1 g valine) in the BCAA group. The characteristics of the LES prescribed to each group are described in Table I.

Table I. Characteristics of the provided late evening snaks

	Protein group	BCAA group
Energy	270-300kcal	
Carbohydrates	≈50g	
Lipid	≤5g	
Nitrogen source(protein)	13g (5g from food, 8g from whey protein)	13g (5g from food, 4g whey protein,4g BCAA)

Statistical Analysis

Statistical analysis was performed using Stata software (version 17.0, StataCorp). Parametric and non-parametric tests were used according to the Skewness-Kurtosis All test and histograms graphic. A significance level of 5% was adopted ($p<0.05$). Continuous variables were represented by median and interquartile range or mean and standard deviation. Categorical variables were expressed as absolute (n) and relative (%) frequencies. The t-test was used for independent samples or Mann-Whitney U test for comparing continuous variables at baseline and after intervention between groups. Changes in quantitative variables during treatment were assessed using the Student's t-test for paired data or the Wilcoxon's test. Categorical variables were compared by the chi-square test ($\chi 2$), Fisher's Exact test, and McNemar test.

RESULTS

The median age of the finalized 32 outpatients was 61.0 years old with an interquartile range of 6.0, in which 43.8% (n=14) were males and 84.4% were CTP grade A. At baseline, both Protein and BCAA groups had a ratio of male and female 7/9 and more than 80% of the members with CTP grade A. The etiology of LC in both groups was mainly hepatitis virus B with only one case of alcohol-induced cirrhosis in each group. There was also one case of mild ascites in each group. They were also similar in concerning laboratory parameters, BMI, and quality of life score (Table II), confirming the randomization process's appropriateness.

There were no significant differences between the two intervention groups at baseline for all indices. Albumin in both groups increased after 3 weeks of intervention, but only a significant difference was found in the Protein group (increasing from 42.6 g/L to 44.4 g/L). A similar trend was also seen in ALT, both groups showed a decrease, with the Protein group going from 27.7U/L to 27.2U/L with a statistical significance and the BCAA group going from

Table II. Baseline demographic and clinical characteristics of liver cirrhosis outpatients

	Protein group (N=16)	BCAA group (N=16)	p
Male/female, n (%)	7/9 (43.8/56.2)	7/9 (43.8/56.2)	1.00‡
Age, Median (IQR) (y)	61.0 (7.0)	61.5 (7.0)	0.48†
Child-Pugh class A/B, n (%)	14/2 (87.5/12.5)	13/3 (81.2/18.8)	0.63‡
Etiology of cirrhosis, n (%)			
Hepatitis virus B	15 (93.8)	15 (93.8)	1.00‡
Alcohol	1 (6.2)	1 (6.2)	
Presence of mild ascites, n (%)	1 (6.2)	1 (6.2)	1.00‡
BMI, Mean ± SD (kg/m^2)	21.4±3.2	22.8±2.8	0.21*
	Median (IQR)		
ALB (g/L)	42.6 (3.5)	42.6 (3.1)	0.48†
AST (U/L)	39.9 (18.7)	37.0 (9.2)	1.00†
ALT (U/L)	27.7 (16.1)	36.7 (19.2)	0.35†
TB (μmol/L)	12.2 (7.1)	14.2 (10.6)	0.34†
FBG (mmol/L)	5.3 (0.6)	5.2 (0.8)	0.70†
INR	1.5 (0.4)	1.6 (0.6)	0.53†

ALB: albumin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; FBG: fasting blood glucose; INR: international normalized ratio; TB:total bilirubin. p-value: between-group comparisons at the base line by *Student T-test; †Wilcoxon rank sum test; ‡Chi-square test.

36.7U/L to 39.4U/L with no statistical significance. For AST, total bilirubin, fasting blood glucose, INR, and CPT score, there were no changes in the Protein group or the BCAA group between baseline and final (Table III).

The mean handgrip strength in the Protein group increased from 24.3 kg (±9.1 SD) to 25.7 kg (±9.2 SD) (p=0.012) showing a significant difference (Fig. 2). In the BCAA group, the mean also changed from 24.7kg (±6.6 SD) to 25.6kg (±7.4 SD) (p=0.237). The comparison between the means of the two groups before and after the snack gave statistically insignificant results. The mean BMI of protein group and BCAA group were 21.5 kg/m^2 (±3.2 SD) and 22.7 kg/m^2 (±2.8 SD), respectively. There was no difference within and between the two groups (p=0.27) after the intervention period.

There were no differences between the protein group and the BCAA group at baseline and final in relation to quality of life by CLDQ assessment.

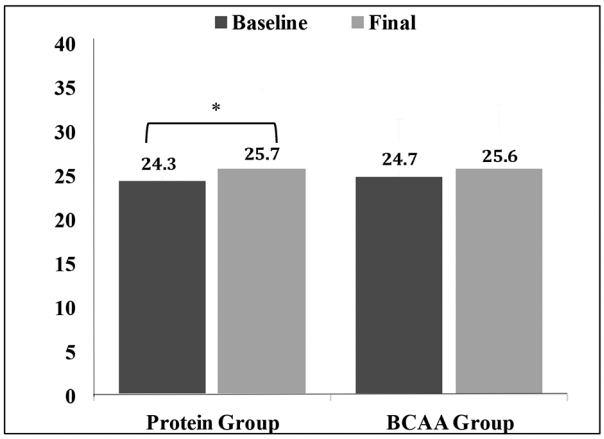

Fig. 2. Comparison of the effectiveness of protein LES and BCAA LES on handgrip strength in LC outpatients. *Significant difference between baseline and final (p=0.01) in the Protein group, using *t*-test.

Table III. Biochemical parameters of liver cirrhosis outpatients in protein group and BCAA group at baseline and final

	Protein group (n=16)		BCAA group (n=16)		p1	p2	p
	Baseline	Final	Baseline	Final			
ALB (g/L)	42.6 (3.5)	44.4 (4.2)	42.6 (3.1)	43.7 (3.5)	0.00	0.31	0.47
AST (U/L)	39.9 (18.7)	33.5 (14.2)	37.0 (9.2)	38.3 (16.6)	0.09	0.85	0.39
ALT (U/L)	27.7 (16.1)	27.2 (11.6)	36.7 (19.2)	30.4 (12.2)	0.00	0.06	0.20
TB (μmol/L)	12.2 (7.1)	12.7 (6.7)	14.2 (10.6)	13.4 (8.3)	0.73	0.18	0.73
FBG (mmol/L)	5.3 (0.6)	5.1 (0.5)	5.2 (0.8)	5.0 (0.8)	0.11	0.38	0.54
INR	1.5 (0.4)	1.5 (0.6)	1.6 (0.6)	1.6 (0.6)	0.36	0.60	0.32
Child-Pugh score	6.0 (1.0)	5.0 (0.5)	5.0 (1.0)	5.0 (0.5)	0.06	0.25	0.82

Data are represented as median and interquartile range. p1, p2 values are within-group comparisons at the baseline and 3 weeks after intervention by the Wilcoxon sign rank test. p-value is between-group comparisons after intervention by the Wilcoxon rank sum test. (For abbreviations see Table II).

The overall CLDQ score was significantly increased from 6.0 to 6.7 and 6.6 in the Protein group and the BCAA group, respectively. Scores in 3 domains (FA, AC, EF) were statistically enhanced in the Protein group after the intervention. On the other hand, BCAA group demonstrated a significant increment in 4 other domains (AS, FA, SS, AC). There was no change in the WO domain in all groups.

DISCUSSION

To reduce rapid starvation and glucogenesis, a primary dietary approach entails eating every 4 to 6 hours and minimizing fasting periods between meals. Though the effectiveness of a LES has been thoroughly studied in preventing deterioration during the longest interval at night, its composition in literature is still varied. In the review of Leoni et al. [8], a LES including 40 g (25-55g) of complex carbohydrates, 15 g (11.5-18g) of protein, and 550 mg of sodium, providing about 250 kcal was recommended. However, it is still unclear the source of nitrogen (protein) in these LES. While there are several papers advocating the usefulness of BCAA, it is important to consider patients' severity and accessibility.

In this study, 2 types of LES containing whey protein or BCAA mixture were compared with each other to examine their feasibility and effectiveness as a LES for LC outpatients with mild or moderate conditions. The result indicates that both of the LES improved the biochemical parameters of LC patients, especially significantly increased albumin and decreased ALT enzyme after 3-week administration. These findings were also reported by Nakaya et al. [11], El-Kara et al. [16], and Chen et al. [17]. Patients with cirrhosis have an impaired hepatocellular function and reduced albumin synthesis. Subtle abnormalities in serum albumin were reported to predict both clinical decompensation and death in patients with compensated cirrhosis with a cutoff of 4.0 g/dL [18, 19]. Thus, it is essential to maintain or improve the albumin status of not only advanced LC patients but also compensated patients. This study showed the opposite result to Nakaya's study with a significant increment in protein snacks but not the BCAA group. It is worth noting that in Nakaya's, the protein content in the BCAA group and normal snacks group was not equal (13.5 g vs 9 g, respectively) [11]. On the other hand, the results of the current study aligned with those of El-Kara et al. [16] and Chen et al. [17], LC patients' albumin rose when given a 15 g protein–containing LES. BCAA has been accounted for promoting albumin synthesis in the liver and is recommended for decompensated and hepatic encephalopathy patients, but this might not be necessary for mild cases as their albumin can increase by a protein compound snack. There was a decrement in ALT and AST, which was only statistically significant in the ALT of the Protein group. This result once more emphasized the findings of previous studies and reviews on administering LES substantially improved albumin and reduced ALT and AST in patients with liver diseases [6].

In addition, the fasting blood glucose remained unchanged after the consumption of LES in both groups. This illustrates the safety of taking LES in cirrhotic patients, which was also found in the Nakaya et al. [11] and Fukushima et al. [20] rresearch which reported the same result after both short-term and long-term studies. It is rather suggested that LES has helped maintain the balance of glucose homeostasis preventing hypoglycemic symptoms and enhancing patients' energy metabolism when blood glucose levels declined during late-night fasting. A recent review study has demonstrated that LES significantly reduced fasting plasma glucose levels in patients with hepatogenic diabetes but not with patients without diabetes such as the patients in the present study as they might not have dysglycemia yet [21]. There was no change in the participants' INR (i.e. prothrombin time) and their overall Child-Pugh score or classification. This result is similar to the results of longer-term studies such as Zhao et al. [12] after 6 months or Yu et al. [22] after 3 months. It is worth noting that the INR of the patient was within the normal range from the beginning in all the above studies and the present study's subjects were all compensated patients without hepatic encephalopathy or hepatocellular carcinoma.

During fasting in LC patients, the metabolism of essential amino acids catabolizes skeletal muscle to create energy sources. This causes skeletal muscular atrophy and, eventually, protein energy malnutrition (PEM) or sarcopenia. Sarcopenia is a disorder characterized by a slow and pervasive decrease in skeletal muscle mass, strength, and function (performance), with a significant risk of complications. Sarcopenia in cirrhosis is classified as secondary sarcopenia, which is caused by sickness (cirrhosis), inactivity (e.g., disuse), or inadequate nutrition (e.g., protein deficit) [23]. Sarcopenia in cirrhosis can be diagnosed based on muscle mass and strength loss, as well as function. In previous attempts to counter sarcopenia in cirrhotic patients, Nakaya et al. [11] and Sorrentino et al. [24] failed to show improvement in the anthropometric measurement such as mid-upper arm circumference and triceps skin fold thickness, following LES with BCAA supplementation. In another study in 2024, Yu et al. [22] supplied patients with nocturnal snacks for 3 months and was not able to show the enhancement of skeletal muscle mass. However, none of these studies has measured handgrip strength, which has been suggested that to have the highest diagnostic accuracy for malnutrition compared to other anthropometric tests [25, 26]. Handgrip strength seems to be a simple, affordable, and effective approach to both the diagnosis of sarcopenia as well as the monitoring of muscle function in liver disease patients as well [27]. In this study, after 3 weeks of consuming 13 g protein in snacks, the mean handgrip strength in the Protein group increased from 24.3 kg (±9.1 SD) to 25.7 kg (±9.2 SD) ($p=0.012$) showing a significant difference. Interestingly, the mean in the BCAA group also changed from 24.7 kg (±6.6 SD) to 25.6 kg (±7.4 SD) but there was no statistical difference. Normal protein diets have been shown to be safe for persons suffering from hepatic encephalopathy. Thus, it is essential to ensure the sufficient protein intake of cirrhosis patients adheres to international guidelines (1.2-1.5g/kg body weight/day) [2].

There have been numerous reports on how patients with chronic liver diseases tend to have an impaired health-related quality of life compared to a healthy population [28, 29]. Health-related quality of life is becoming a key component in the evaluation of some therapeutic intervention methods. Evaluating the HRQoL for LC patients is especially crucial, given the limited availability of treatments that significantly

enhance their life expectancy. In this study, the total CLDQ scores along with other domains of both groups were successfully increased. As both groups showed improvements in total score, fatigue, and activity domains, each snack group has different advantages in certain aspects. A rise in emotional function was found in the Protein group while the BCAA group showed more effect on alleviating abdominal and systematic symptoms in cirrhosis patients. In previous studies, Yamanaka-Okumura et al. [13], Okuda et al. [30], and Dong et al. [31] have also concluded that LES administration helped maintain higher HRQoL in LC patients.

CONCLUSIONS

A protein snack is an effective dietary intervention in improving albumin, biochemical parameters, and the nutritional status for compensated LC outpatients. Considering cost, availability, and taste, a BCAA snack might be unnecessary for LC outpatients. Both types of snacks were able to meliorate the quality of life of the patients. BCAA may not be suitable for everyday intake over the long term. It is more cost-effective to use normal meals rather than costly nutritional supplements. When opposed to specific supplements, the recommended ordinary meals with protein are far less expensive and more tailored to individual tastes.

Conflicts of interest: None to declare.

Authors' contributions: T.T.N. designed the concept of the study, and all authors participated in the literature search and review. T.T.N. and L.T.N. wrote the manuscript. T.M.T.N., H.M.T.N., and T.C.T.B. collected the data. T.T.N. performed statistical analysis. S.Y. was involved in editing the manuscript. All authors read and approved the final manuscript.

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