Review

The Best Compositions of Late Evening Snack for Liver Cirrhosis Patients Using Systematic Review and Network Meta-Analysis

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ABSTRACT

Background and purpose. Liver Cirrhosis (LC) is ranked the 11th in the world and the 10th in Vietnam among common causes of death. Malnutrition frequently imposes a burden on patients with LC, and it is an independent predictor of lower survival. However, in Vietnam, the nutrition management in LC patients is insufficient. Moreover, glycogen storage is decreased in LC patients so if they do not have a late evening snack (LES), they will feel a lack of energy when they wake up the next day. However, a nutrient composition for LES has not been unified yet, there is a lack of evidence in comparing LES compositions with each other. ***Method.*** Network meta-analysis (NMA) was conducted to compare the effectiveness of different compositions of LES from direct and indirect evidence. The evidence was the published articles with intervention trials using different types of LES. All the papers searched from 5 databases (PubMed, Cochrane library, Google Scholar, ScienceDirect, Medical Online) until March 1st, 2022 that met the inclusion criteria were selected. The outcome parameters were albumin, pre-albumin, nitrogen balance, respiratory quotient, AST, ALT, total bilirubin, ammonia, cholinesterase, and BCAA/Tyr. ***Results***. After screening and full-text assessing 270 papers, 15 final papers with 4 types of LES (high CHO, Protein-CHO, BCAA-CHO, and coconut milk-CHO) were included in the meta-analysis. One of the most important parameters is albumin, an effective indicator in the management of cirrhosis and its complications. And according to the meta-analysis, Protein-CHO has the highest probability of improving it, followed by high CHO, coconut milk-CHO, and then BCAA-CHO. Other parameters (such as Pre-Alb, nitrogen balance, ALT, AST…) also indicated the same results. On the other hand, BCAA-CHO was not effective on most of the parameters but only on BCAA/Tyr. There was no direct comparison between BCAA and protein. ***Conclusion***. The recommendable LES compositions should provide at least 200kcal with 50g of carbohydrate. About the nitrogen source, protein is maybe more effective than BCAA in terms of improving protein synthesis and energy metabolism as well as liver parenchyma damage. However, since there is no direct comparison between protein and BCAA as LES, a future study is needed to confirm this finding.

Key Words*:* Cirrhosis, late evening snack, protein, network meta-analysis.

INTRODUCTION

Liver cirrhosis (LC) is one of the leading causes of mortality worldwide, it was the 11th most common cause of death each year in the world with 2.1% of total deaths (1). According to Institute for Health Metrics and Evaluation (IHME), in 2019, LC ranked 7th among the top 10 most common causes of death in Vietnam with a 47.3% increment from 2009 to 2019 (2). The etiologies of LC are most commonly alcohol, hepatitis B, hepatitis C, and non-alcoholic fatty liver disease or sometimes autoimmune hepatitis. Alcoholic liver disease and hepatitis B are the most common causes in most parts of Asia (3). Cirrhosis is defined as the histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury, which leads to portal hypertension and end-stage liver disease. In the asymptomatic phase of the disease, usually referred to as compensated cirrhosis, patients may have a good quality of life, and the disease may progress undetected for several years. The decompensation phase is regularly marked by ascites, gastrointestinal bleeding due to esophageal varices, hepatic encephalopathy (HE), and jaundice (4).

Malnutrition is frequently a burden in patients with LC; it is usually related to the clinical stage of chronic liver disease, increasing from 20% in patients with well-compensated disease to more than 60% in patients with advanced cirrhosis (5). Malnutrition and muscle mass loss (sarcopenia) are associated with a higher rate of complications such as susceptibility to infections, hepatic encephalopathy (HE), and ascites, as well as being independent predictors of lower survival in cirrhosis and in patients undergoing liver transplantation (6). Various mechanisms are considered to contribute to malnutrition in cirrhosis such as poor oral intake, increased intestinal protein loss, decrease protein synthesis, disturbances in substrate utilization, hyper-metabolism, and malabsorption (7). According to Trang Thu Nguyen et al. study in 2020, the prevalence of malnutrition in LC patients was 60% by subjective global assessment (SGA), an international questionnaire for nutrition assessment (8). According to ESPEN's clinical nutrition practice guideline for LC patients in 2019, cirrhotic patients should ingest an increased amount of energy (30-35 kcal/kg/d of energy and 1.2-1.5 g/kg/d of protein) (5).

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Nonetheless, in Vietnam's clinical setting, a restricted protein diet is still recommended for LC patients (9). As a result, the energy intake and protein intake of Vietnamese LC patients were lower than their recommendation, 1445.9 ± 727.7kcal/day and 1.0 ± 0.5g/IBWkg/day, respectively (8).

In addition, several guidelines have recommended short periods of starvation with 4 - 6 meals a day, especially a late evening snack (LES) is highly recommended as LC is characterized by a state of accelerated starvation, with an early shift from glucose to lipid and amino acids utilization for energy during the postabsorptive state (fasting), which can also lead to a decrement in respiratory quotients of LC patients (10). Some systematic reviews and meta-analyses have proved that LES intervention helped to improve liver biochemical parameters for albumin, ammonia, respiratory quotients, and liver enzymes including aspartate aminotransferase (AST) and alanine aminotransferase (ALT) (11, 12). Moreover, increasing the number of meals can also help to increase the amount of dietary intake in LC patients. However, 77.5% of Vietnamese LC patients did not have LES and only 22.5% had the snack but the compositions of the snacks were inconsistent (8).

Having said that, it is also necessary to find the most suitable compositions of LES for Vietnamese patients from taste-wise to economically. In a systematic review, Tsien et al. recommended a 200kcal with 50g carbohydrate (CHO) late evening snack to minimize gluconeogenesis and preserve muscle mass (12). However, there has been a trend of using branched-chain amino acids (BCAA) in LES and some studies suggested it was more effective than CHO-LES (13-14). In addition, there were a number of studies that used a snack including both protein and carbohydrates, which showed improvement in LC patients as well (15-17). It seems that there have been a variety of compositions of LES used across different studies and to date, there is no trial comparing the potential effects of different LES in cirrhotic patients, thus defining effective compositions among CHO, BCAA, protein, no LES…are necessary.

To attain a better understanding on this issue, the available published trials are estimated by updated Bayesian network meta-analysis in order to investigate the efficacy of improving various parameters of liver cirrhosis patients between the use of different LES compositions. The results are expected to provide a reference for clinical practice.

METHODS

The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for reporting network meta-analyses of health care interventions (18).

Eligibility criteria. The eligibility criteria are detailed below following the participants, intervention, controls, outcomes, and study design (PICOS) framework: (i) Participants: adults (age >18 years) with cirrhosis, male and female; (ii) Interventions: any types of late evening snack (LES) that provides about 200kcal; (iii) Comparisons: studies that compared 1 or more LES compositions; (iv) Outcomes: At least one of these parameters: albumin (Alb), pre-albumin, nitrogen balance (NB), respiratory quotient (npRQ), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB), ammonia (NH3), cholinesterase (Che), and BCAA/Tyr (BTR); (v) Studies lasting ≥ 1week. All the published articles with original data (except conference abstract and case report) in any language up to 01 March 2022 met the listed criteria were included.

Studies including patients in acute phase or hepatic encephalopathy and/or a specific health condition such as diabetes, stroke, chronic obstructive pulmonary disease, chronic kidney disease, other critical illnesses, and recent transplants were excluded. Studies using other nutritional interventions other than LES or patients who took other nutritional supplements before the study were also excluded.

Search strategy. The following five electronic databases were searched until March 2022: (i) PubMed, (ii) Cochrane Library, (iii) Google Scholar, (iv) ScienceDirect, and (v) Medical Online using the following terms: ("Liver Cirrhos*"[Mesh] OR "Cirrhos*" OR "Hepatic cirrhos*" OR "Liver Fibros*" OR "Hepatic Fibros*" OR "end-stage liver disease" OR "Advanced liver disease") AND ("Snacks"[Mesh] OR "Late evening snack" OR "nocturnal nutritional supplementation" OR "nocturnal snack" OR "evening snack" OR "nocturnal meal" OR "bedtime snack" OR "late night snack" OR "midnight snack" OR "late evening meal"). In addition to electronic database searches, cross-referencing was conducted by examining the reference lists of previous review articles as well as each included study for potential articles that met the inclusion criteria.

Study selection. All retrieved articles were combined in Endnote20 and Microsoft Excel (V.2016; Microsoft Corporation; 2016) to remove duplicates. After screening the titles and abstracts according to the prespecified criteria, the full texts of articles that potentially met the eligibility criteria were reviewed. Reasons for excluded studies were recorded using the following categories: (i) inappropriate population, (ii) inappropriate intervention, (iii) inappropriate comparison(s), (iv) inappropriate outcome(s), (v) inappropriate study design and (vi) other.

Data extraction. Microsoft Excel (V.2016; Microsoft Corporation; 2016) was used to develop comprehensive electronic codebooks. The major categories of variables coded included (i) study characteristics (author, journal, year of publication, design, etc.), (ii) participant characteristics (age, gender, liver cirrhosis etiology, LC severity, etc.), (iii) intervention characteristics (type, length, frequency, nutrients compositions, duration, etc.) and (iv) data for outcomes (sample sizes, baseline and post LES means and SD, etc.). When relevant information on design or outcomes was unclear, or when some needed data was unavailable directly from the study, the original authors sought eligible data by email.

Risk of bias and quality assessment. The Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) [19] was used to assess the methodological quality of the randomized controlled trials (RCTs), and the Quality Assessment Tool for Quantitative Studies (19) assessed the quality of controlled pre-post studies and nonrandomized experimental studies (non-RCTs). In both quality assessment tools, each domain will be

considered as strong, moderate, or weak and studies will be classified as high, moderate, and low risk of bias.

Statistical analysis. Network meta-analysis (NMA) was conducted to estimate the effectiveness of different types of LES compositions on various parameters. The results of the comparative effects are presented as the mean differences (MDs) or standardized mean differences (SMDs) and 95% confidence intervals (CIs). We also estimated the ranking probabilities of the intervention effect using the surface under the cumulative ranking curve (SUCRA) (20). The larger the SUCRA value, the better the ranking of the intervention effect. The consistency between the direct and indirect evidence was evaluated using inconsistency tests to assess the validity of the transitivity assumption. Publication biases or small sample effects were examined using a comparison-adjusted funnel plot.

In addition, a pairwise meta-analysis using the random-effects model was performed when the data was not sufficient for a NMA (Pre-albumin and Nitrogen balance), and the I2 statistic and p values were calculated as a measure of the statistical heterogeneity (21), with I2 ≥ 50% indicating substantial heterogeneity.

Stata version 17 was used to conduct the analyses. The "metan" package was used for the pairwise meta-analysis, and the "network" package was used to conduct the NMA. Statistical significance was set as a P value < 0.05 in all analyses.

RESULTS

Study selection

A total of 267 articles were retrieved by following the pre-designed literature retrieval strategy. By further searching the references included in the articles, 3 additional articles were obtained. After reading the titles and abstracts, 43 studies were selected for further review. Finally, 15 studies met the inclusion criteria (13-17, 22-31). The detailed process of the search strategy is described in Figure 1.

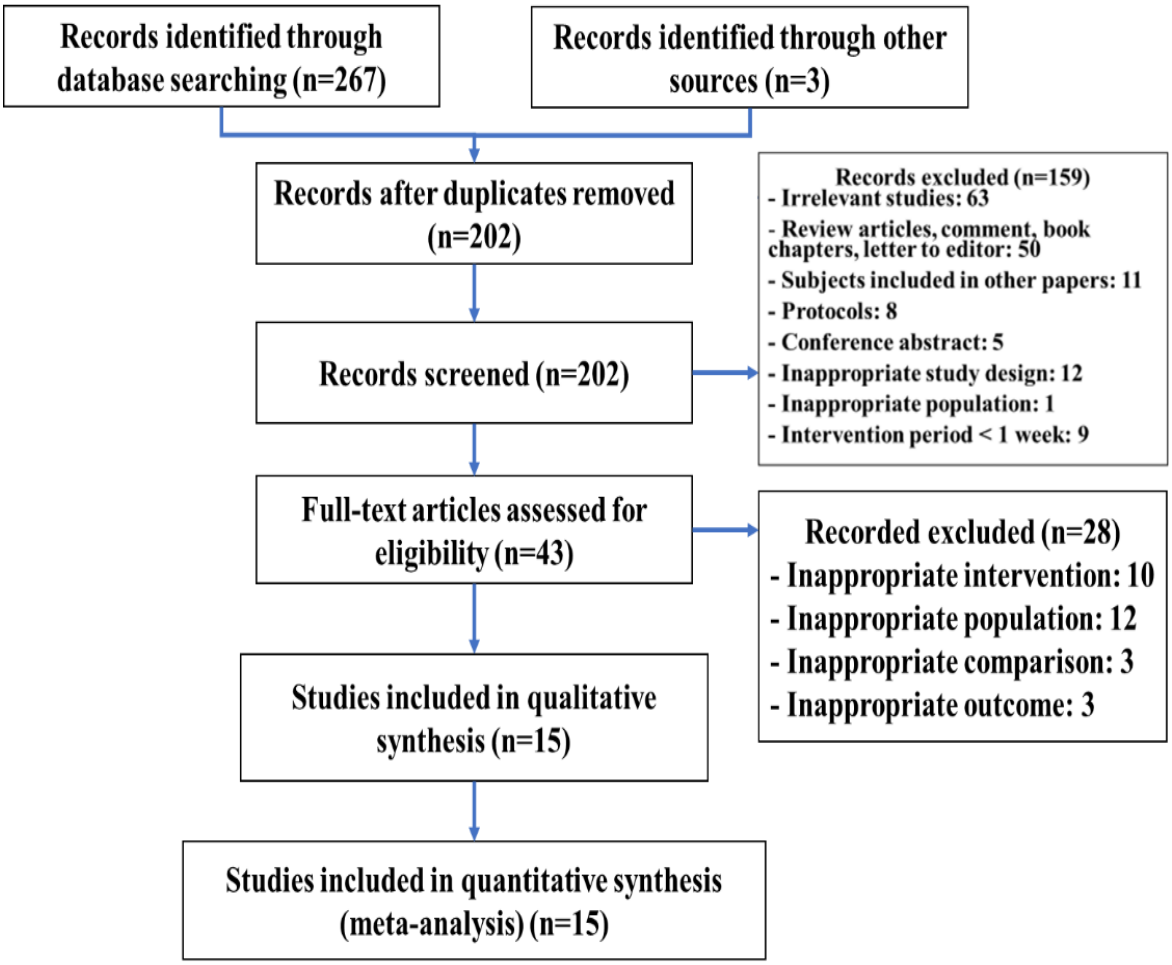

Figure 1. Flow chart of studies evaluating LES for cirrhosis through the selection process

Table 1 summarizes the basic characteristics of the included studies. There were 5 LES compositions according to these eligible studies: (i) CHO (CHO provides >80% energy); (ii) BCAA-CHO (Protein 14%, BCAA 12%, CHO 59%, Lipid 15%); (iii) Protein-CHO (Protein 20-45%, CHO 50%?, Lipid ?); (iv) Coconut milk-CHO (CHO 70%, Protein 2.5%, Lipid 27.5%), and (v) No LES. The included studies were published between 2006 to 2021, most of the studies were from Japan (7 studies) and China (6 studies), while Egypt and Indonesia each had 1 study. A total of 695 participants were included in this review and the average age of the participants was 59.6 years. The mean duration of the intervention was 8.6 weeks.

Six studies compared CHO and no LES with 347 participants. Three studies compared BCAA-CHO and no LES with 89 subjects. Three studies compared Protein-CHO and no LES with 138 patients. Two studies compared BCAA-CHO and CHO with 59 subjects. One study with 35 participants compared Coconut milk and CHO.

The primary outcomes were albumin (Alb), pre-albumin, nitrogen balance (NB), respiratory quotient (RQ), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB), ammonia (NH3), cholinesterase (Che), and BCAA/Tyr (BTR). The risk of bias assessments showed that most of these studies were of moderate quality. No publication biases or small sample effects were found.

Table 1. Characteristics of the 15 included study

Comparison	Study	Location	n	Gender (M/F)	Age	Duration	Outcome
(i) CHO (CHO >80%) Vs (v) No LES	Hou W. 2021(22)	China	86	68/18	51.5 ± 11.8	6 months	ALT, AST, TB, Alb, Pre-Alb, Che, NH3, BTR
	Yamanaka-Okumura H. 2010 (23)	Japan	39	28/11	68.1± 9.7	6 months	BMI, AST, ALT, TB, NH3, Alb
	Li P. 2021(25)	China	86	62/24	55.4±4.9	3 months	Alb, Pre-Alb
	Yamanaka-Okumura H. 2006 (29)	Japan	21	47/0	63 ± 10	1 week	AST, ALT, TP, Alb, TB, Che, RQ
	Dong J. 2016 (30)	China	105	-	50.8±8.5	3 months	RQ, TP, Alb, Pre-Alb, Che
	Yu HW. 2012 (31)	China	10	-	42.6±9.7	2 weeks	RQ
(ii) BCAA-CHO (P: 14% P, BCAA 12%; CHO 59%; L 15%) Vs (v) No LES	Takeshita S. 2009 (26)	Japan	56	40/16	69.1±8.2	2 weeks	Alb, AST, ALT, TB, BRT, NH3, Che
	Y. Harima. 2010 (27)	Japan	23	19/4	64.5±9.5	5 weeks	RQ, BRT, Alb, Pre-Alb, ALT, TB, Che, NH3
	Maki H. 2019 (28)	Japan	10	5/5	73.1 ± 8.9	1 month	Alb, AST, ALT, Che, NH3, TB
(iii) Protein-CHO (P: 20-45%) Vs (v) No LES	Ferial. 2014 (15)	Egypt	30	19/11	-	15 days	NH3, NB, TB, ALT, AST. Alb
	Xu J. 2015 (17)	China	83	28/11	68.1± 9.7	4 weeks	AST, ALT, TB, NH3, Alb
	Chen T.2014 (16)	China	25	14/11	49.4±12.7	6 weeks	Alb, Pre-Alb
(ii) BCAA-CHO (P: 14% P, BCAA 12%; CHO 59%; L 15%) Vs (i) CHO (CHO>80%)	Nakaya Y. 2007 (14)	Japan	38	20/18	67±8	3 months	Alb, AST, TB, NB, RQ
	Tatsuki I. 2010 (13)	Japan	21	11/10	66.2±8.2	8 weeks	Alb, AST, ALT, TB, BTR, NH3, Che
(iv) Coconut milk - CHO (CHO 70%, P 2.5%, L 27.5%) vs (i) CHO (CHO 100%)	Suwito Indra. 2015 (24)	Indonesia	35	8/27	54.3±10.6	1 month	Pre-Alb, Alb

Results from network meta-analysis

Albumin

Human serum albumin is a critical plasma protein produced by the liver. Advanced cirrhosis is characterized by reduced albumin concentration as well as impaired albumin function (32).

Data from 13 studies with all five LES compositions were included in the Alb analysis (13-17, 22-29). The network map for Alb in is shown in figure 2. The most common group was the no LES group followed by the CHO group. The most common comparison was CHO versus no LES. The inconsistency test exhibited no inconsistencies in the global analysis, indicating that the direct comparison and indirect comparison results were consistent ($\chi 2 = 0.85$; $p = 0.3556$).

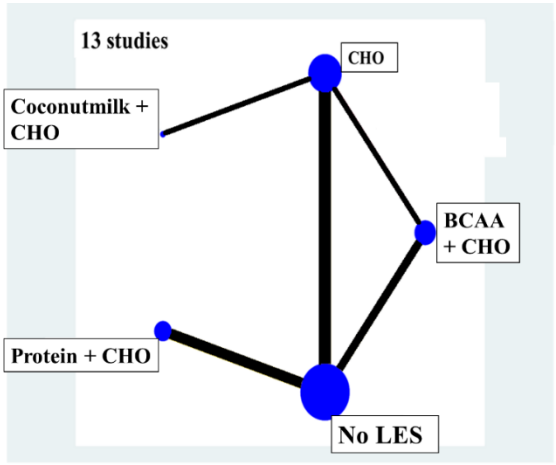

Figure 2. Network map for Albumin.
The nodes (circles) represent the different LES compositions while the edges (lines) represent the available direct comparisons between pairs of LES. Both nodes and edges are weighted by the number of studies involved in each treatment and comparison, respectively.

Figure 3 shows the results of the effects of the LES on Alb. Compared with no LES, Protein-CHO (0.62 g/dL, 95% CI: 0.05 to 1.18) resulted in a significant increment in Alb. There were no significant differences between the other compositions in terms of the effectiveness in increasing Alb.

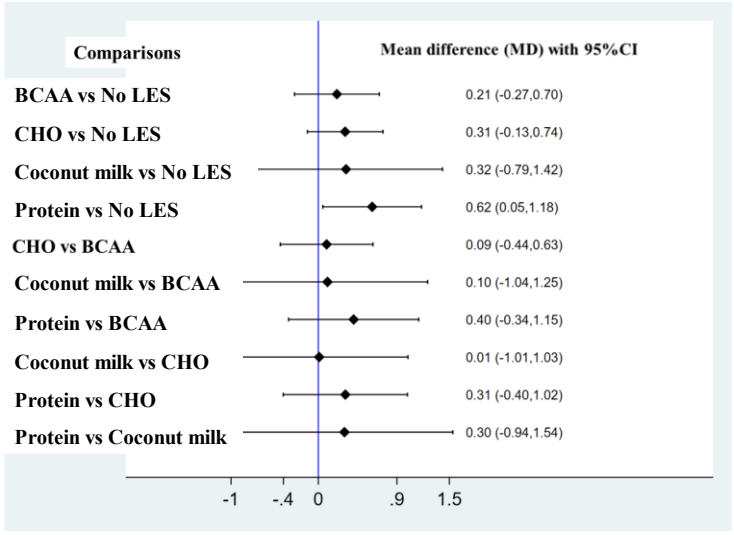

Figure 3. Interval plot for mean difference in Albumin (g/dL) from NMA
**BCAA=BCAA-CHO; Protein=Protein-CHO; Coconut milk=Coconut milk-CHO*

The ranking of treatments for Albumin is shown in table 2. As can be seen, Protein-CHO had the highest probability of being ranked as the best LES composition with 77% of the surface under the cumulative ranking curve (SUCRA). This was followed by CHO and Coconut milk-CHO and then BCAA-CHO.

Table 2. The surface under the cumulative ranking curve (SUCRA) of different LES compositions in various parameters

LES	SUCRA							
	Alb	RQ	AST	ALT	TB	NH_3	BTR	Che
Protein + CHO (P 20-45%, CHO 50%?, L 10%?)	77%		80%	70%	100%	30%		100%
CHO (CHO>80%)	60%	90%	40%	60%	30%	90%	50%	30%
BCAA + CHO (P 14% P, BCAA 12%; CHO 59%; L 15%)	46%	60%	40%	40%	40%	60%	90%	40%
Coconut milk + CHO (CHO 70%, P 2.5%, L 27.5%)	55%							
No LES	10%	0%	30%	30%	30%	20%	0%	30%

Respiratory quotient (RQ)

In patients with liver cirrhosis, glycogen storage in the liver is reduced. Therefore, glucose supply is impaired from nighttime to the early morning fasting state. In this situation, low RQ has been frequently reported.

According to the network map (figure 4), there were 3 LES compositions (CHO, BCAA-CHO, and no LES) from 5 studies (14, 27, 29-31). The overall test for inconsistency was not statistically significant ($\chi2$=3.05, p=0.08).

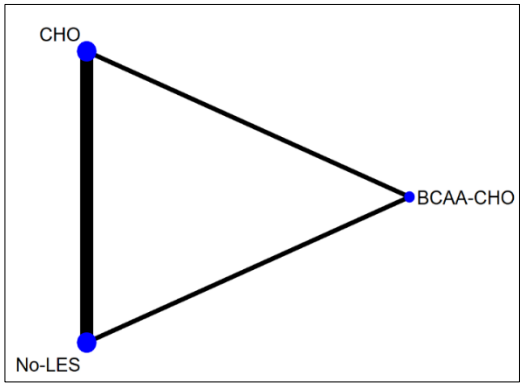

Figure 4. Network map for RQ

From the results of mean difference from NMA, when compared to no LES, CHO and, BCAA-CHO both significantly increased RQ, 0.06, 95%CI: 0.01-0.11; 0.04, 95%CI: 0.02-0.06, respectively.

From SUCRA, CHO (90% area) had a higher probability of improving RQ of liver cirrhosis patients than BCAA-CHO (60% area).

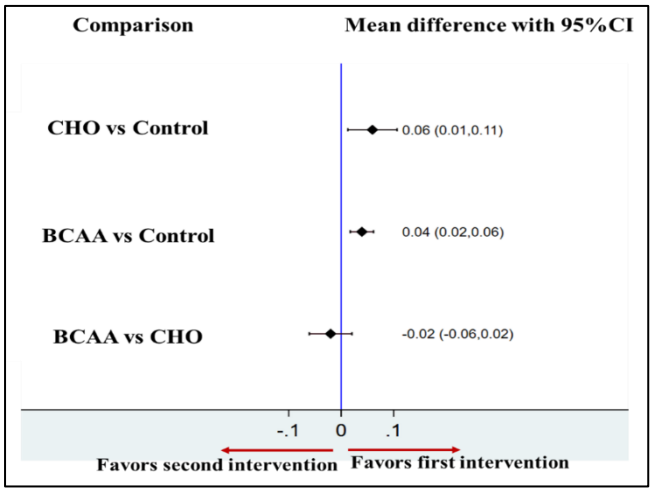

Figure 5. Interval plot for mean difference in RQ from NMA

Alanine Aminotransferase (ALT)

ALT is an enzyme that is concentrated primarily in the liver. In liver cirrhosis, liver cells are damaged which can lead to the leak of this enzyme into the bloodstream and cause an abnormal increment of ALT.

The network map (Figure 6) demonstrates that ALT data was formed by 8 studies with four compositions (CHO, BCAA-CHO, Protein-CHO, and no LES) (13, 15, 22-23, 26-29). The overall test for inconsistency was not statistically significant ($\chi2$=0.3, p=0.586).

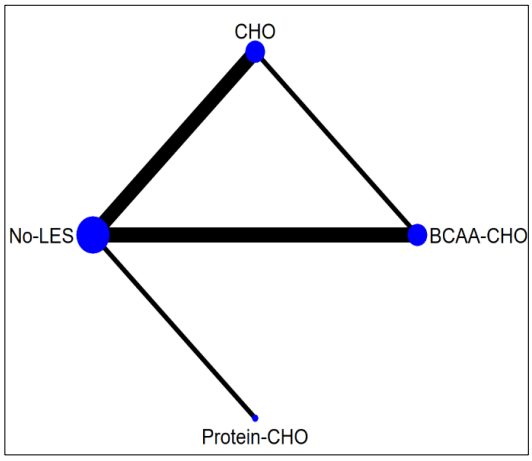

Figure 6. Network map for ALT

The interval plot (Figure 7) indicates that in comparison with no LES, all the compositions tended to decrease ALT; however, there was no statistical significance in any of the comparing pairs.

According to the ranking of SUCRA (table 2), Protein-CHO had the highest probability of being the best in improving ALT, followed by CHO and BCAA-CHO.

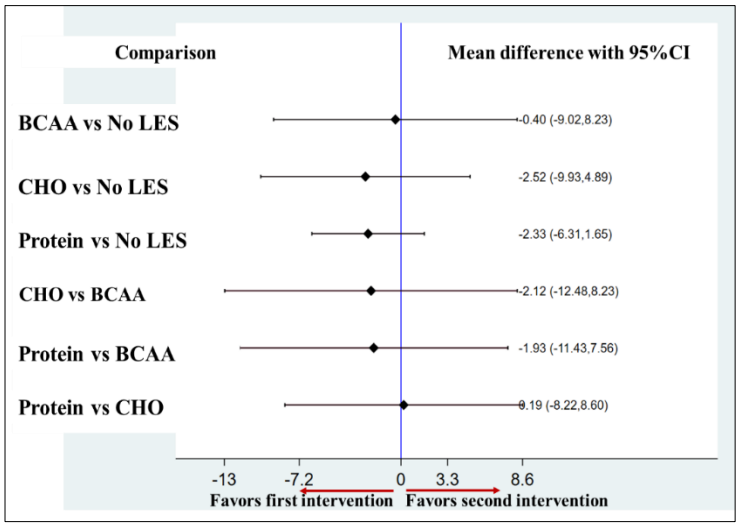

Figure 7. Interval plot for mean difference in ALT (U/L) from NMA

Aspartate transaminase (AST)

Similar to ALT, AST is also an enzyme that is concentrated primarily in the liver and usually elevates in liver diseases.

There were also 8 studies and four compositions (CHO, BCAA-CHO, Protein-CHO, and no LES) that contributed to forming the network map for AST (Figure 8) (13-15, 22-23, 26, 28-29). The inconsistency test showed no inconsistencies in the global analysis ($\chi 2$=0.72, p=0.3951).

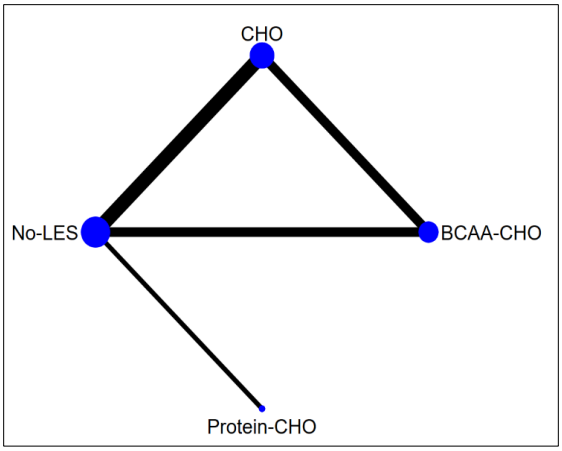

Figure 8 Network map for AST

While there was a decrement in AST, no significant difference was found in the mean difference of AST in all of the comparisons (Figure 9).

Table 2 indicates that Protein-CHO also had the highest probability of being the best in improving AST as well with 80% SUCRA, followed by CHO and BCAA-CHO with both having 40% of the area.

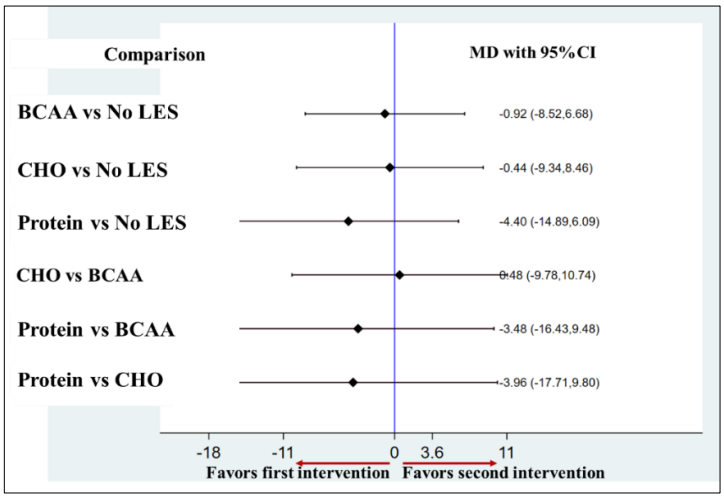

Figure 9. Interval plot for mean difference in AST (U/L) from NMA

Total bilirubin (TB)

The liver normally removes bilirubin from the blood and disposes of it in the stool. But in liver cirrhosis, bilirubin builds up in the blood and can cause jaundice.

The network map was formed from the data of 10 studies including four compositions (CHO, BCAA-CHO, Protein-CHO, and no LES) (Figure 10) (13-15, 17, 22-23, 26-29). There were no inconsistencies in the inconsistencies analysis ($\chi 2$=0.00, p=0.9742).

Figure 11 demonstrates that when comparing to no LES (-1.39mg/dL, 95% CI: -2.32 to -0.46), to BCAA-CHO (-1.32mg/dL, 95% CI: -2.45 to -0.2), and to CHO (-1.38mg/dL, 95% CI: -2.5 to -0.26), Protein-CHO showed great decrement in TB. There was no significant difference in other comparisons.

Protein-CHO with 100% of SUCRA had the highest probability of being the best in decreasing TB compared to others, followed by BCAA-CHO and CHO.

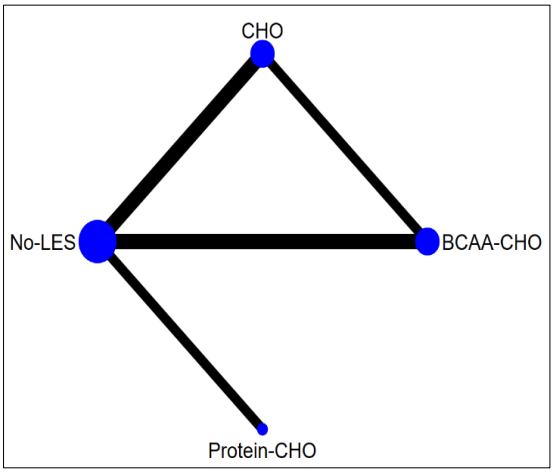

Figure 10. Network map for TB

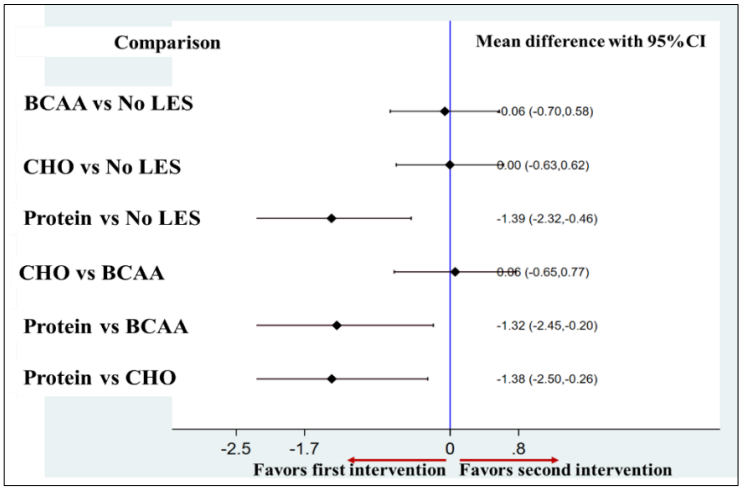

Figure 11. Interval plot for mean difference in TB (mg/dL) from NMA

Ammonia (NH3)

Ammonia (NH3) is a waste product of the digestion of protein. In normal people, ammonia is processed into urea in the liver. In liver cirrhosis, it builds up in the bloodstream which leads to an increased serum NH3.

Data from 4 studies including 4 compositions (CHO, BCAA-CHO, Protein-CHO, and no LES) was presented as the network map for NH3 in figure 12 (13, 26-28). According to the global inconsistencies test, there were no inconsistencies ($\chi 2=0.15$, $p=0.7009$).

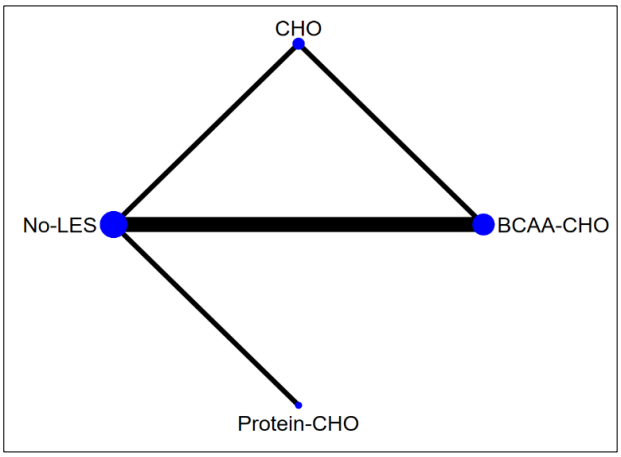

Figure 12. Network map for NH_3

Branched-chain amino acids to Tyrosine ratio (BTR)

It has been reported that BCAA decreases in severe cases of liver cirrhosis patients so BTR (BCAA/Tyrosine) is decreased[6].

Six studies with 3 compositions (CHO, BCAA-CHO, and no LES) provided the data to create a network map for the BTR parameter (Figure 14) (13-14, 22, 28-28). There were no inconsistencies in the inconsistencies global analysis ($\chi 2=2.6$, $p=0.107$).

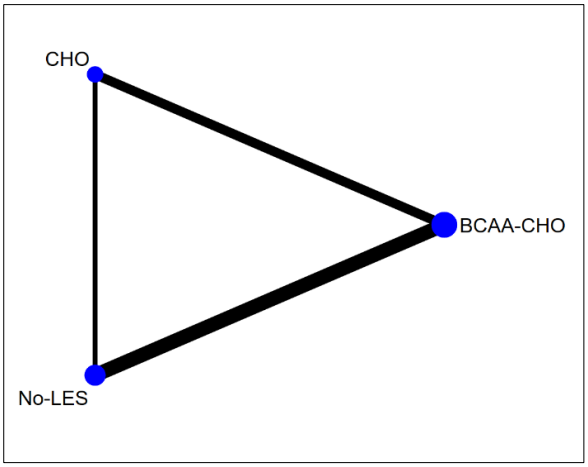

Figure 14. Network map for BTR

The interval plot for the standardized mean difference in NH3 (Figure 13) shows that only the comparison between CHO and no LES had a considerable decrease in NH3 (-0.72, 95% CI: -1.41 to -0.03). CHO also ranks the best in having the most effective area of improving the NH3 status in LC patients (90% SUCRA).

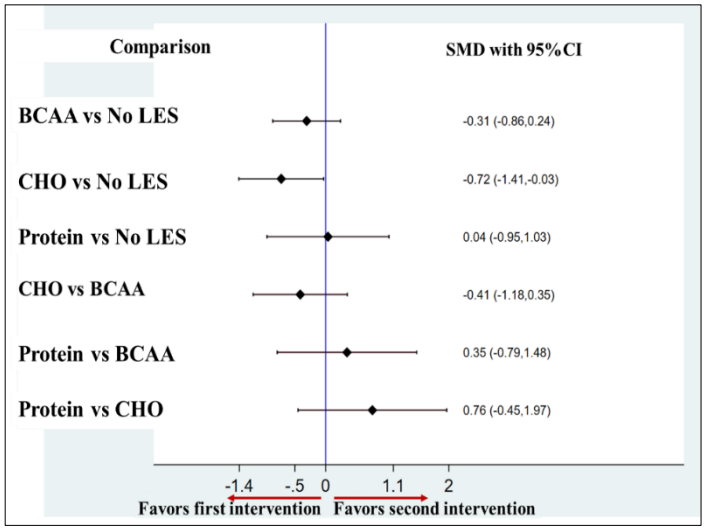

Figure 13. Interval plot for mean difference in NH3 from NMA

From the results of the mean difference of BTR, BCAA-CHO significantly increased BTR compared to no LES (0.63, 95%CI: 0.19 to 1.07) (Figure 15). In addition, the results from table 2 also indicate that BCAA-CHO had a higher probability of increasing BTR than CHO (SUCRA 90%, 50%, respectively).

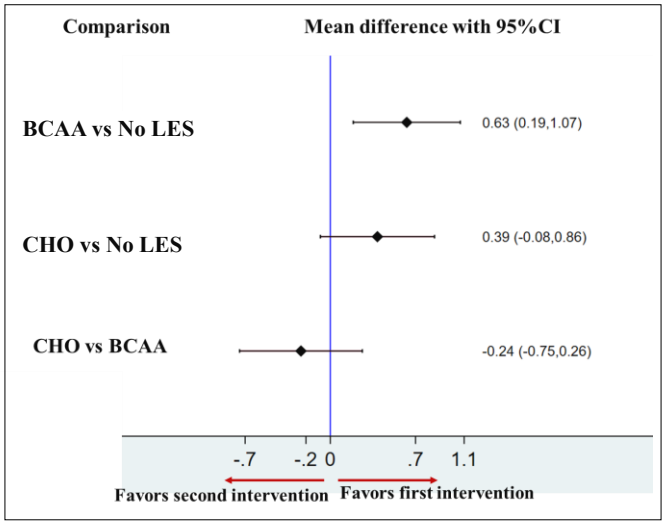

Figure 15. Interval plot for mean difference in BTR

Cholinesterase (Che)

Serum cholinesterase (ChE) is an enzyme synthesized by hepatocytes and its serum levels reflect the synthetic function of the liver. In liver cirrhosis, the Che level is decreased.

9 studies reported on Che involving 4 compositions (CHO, BCAA-CHO, Protein-CHO, and no LES). The data was used to make the network of data for Che (Figure 16) (13, 17, 22-23, 26-30). No inconsistencies were found by inconsistencies global analysis ($\chi 2=0.25$, p=0.6179).

Figure 17 illustrates that when comparing to no LES (3.72, 95% CI: 2.8 to 3.74), to BCAA-CHO (2.98, 95% CI: 2.38 to 3.57), and to CHO (3.22, 95% CI: 2.71 to 3.73), Protein-CHO was more effective in increasing Che. There was no significant difference in other comparisons.

According to table 2, Protein-CHO had the highest probability of increasing Che with 100% SUCRA. BCAA-CHO was ranked second with 40% area and CHO was third with 30% area.

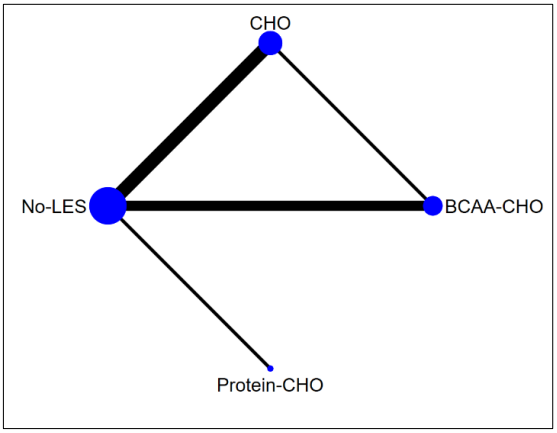

Figure 16. Network map for Che

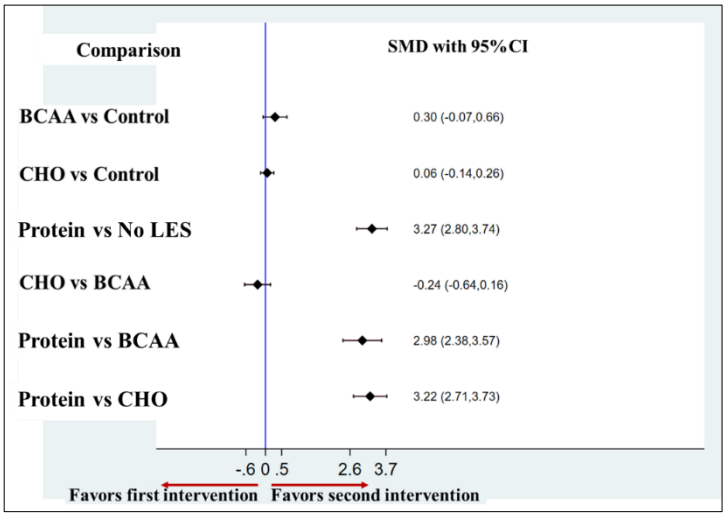

Figure 17. Interval plot for mean difference in Che from NMA

Results from the pairwise meta-analysis

Table 3. Results of the pairwise meta-analysis

	Studies	n	MD (95%CI)	p	I^2
Pre-Albumin					
CHO vs. No LES	4	245	5.45 (-2.5, 13.4)	0.18	96.6%
Protein-CHO vs. No LES	2	108	11.6 (6.37, 16.82)	0.00	96.7%
BCAA-CHO vs. No LES	1	23	-1.26 (-5.35, 2.83)	0.55	-
Coconut milk-CHO vs. No LES	1	17	-0.4 (-12.16, 11.36)	0.95	-
Nitrogen Balance					
CHO vs. No LES	1	19	-0.04 (-2.2, 2.12)	0.97	-
Protein-CHO vs. No LES	1	15	5.47 (1.95, 8.99)	0.00	-
BCAA-CHO vs. No LES	1	19	1.56 (0.02, 3.1)	0.05	-

Pre-albumin (Pre-Alb)

Pre-albumin is the precursor to albumin. It is also made by the liver. So in liver cirrhosis, the level of pre-Alb also decreases.

Pre-Alb was reported in eight out of the 15 studies. Four studies reported comparison between CHO and no LES (22, 24-25, 30); two studies reported comparison between Protein-Cho and no LES (16-17); comparisons between Coconut milk-CHO with no LES and BCAA-CHO with no LES each had 1 study (24, 27).

There was statistical heterogeneity among these trials (I2 = 97%). Using the random-effects model, results indicate that only Protein-CHO had a significant increase in Pre-Alb from baseline (MD = 11.6, 95% CI: 6.37 to 16.82, p = 0.00) (Table 3).

Nitrogen balance (NB)

As mentioned before, with the alternative metabolism of LC patients, especially at night, the protein was used as a source of energy instead of glucose, which increases nitrogen loss. Thus, a negative nitrogen balance was reported in LC patients (32).

Two out of 15 papers investigated the effect of LES on improving NB in LC patients with three different comparisons (CHO vs. no LES, Protein-CHO vs. no LES, and BCAA-CHO vs. no LES) (14-15).

Using the random-effects model, both Protein-CHO and BCAA-CHO showed an increment in NB but only Protein-CHO had a statistical significant (MD = 5.47, 95% CI: 1.95 to 8.99, p = 0.00) (Table 3).

DISCUSSION

Cirrhosis is characterized by a state of accelerated starvation, with an early shift from glucose to lipid utilization for energy during the postabsorptive state. After an overnight fast, lipids account for 75% of the total calories utilized in cirrhotic patients, reflecting increased rates of ketogenesis and gluconeogenesis. In addition, there is an increased consumption of amino acids as a source of energy (protein catabolism) (33). Therefore, many international guidelines have suggested a late evening snack for LC patients (6-7). However, according to a previous study, 77.5% of Vietnamese LC patients did not have the LES and 22.5% of them had LES but with inappropriate nutrient compositions (8). Thus, it is an urgent matter to give Vietnamese LC patients nutrition education regarding LES and know the most appropriate and suitable nutrient compositions concerning acceptability, taste, and finance.

In the previous systematic review conducted by Tsien et al, the formula and dosages of LES were suggested to provide at least 200kcal with 50g of carbohydrates; however, there was no suggestion for the nitrogen source whether it is protein or BCAA (12). LC patients are encouraged to have a high protein diet to prevent a negative nitrogen balance, malnutrition, and sarcopenia. Adequate protein intake has been defined as 1.2 to 1.5 g/kg body weight daily by the ESPEN guidelines (6). In recent years, instead of protein, there has been a surge of interest in the clinical utility of BCAA, mostly in supplemental forms to be included in LES. Some studies have suggested a BCAA-LES over CHO and other compositions (13-14). However, the methodology of these studies is usually a comparison between BCAA, regardless of doses and timing, with control or with CHO and there are no studies directly comparing BCAA with protein as the nitrogen source for LES.

This is the first systematic review and network meta-analysis to examine the effects of different types of LES compositions with the purpose to find the most effective composition. The results revealed that the combination of CHO and protein seems to have the highest probability of improving the nutritional status and liver function of LC patients. Protein-CHO has a higher probability of improving Alb, Pre-Alb, nitrogen balance, ALT, AST, TB, and Che of LC patients than other LES compositions. While late evening snack with predominately CHO has the highest probability of improving RQ and NH3. Lastly, BCAA-CHO contained LES has a higher probability of improving BTR of LC patients than other LES compositions.

In this systematic review, serum albumin, pre-albumin, and nitrogen balance were all significantly increased by Protein-CHO. These biomarkers reflect the synthetic metabolism of liver cells. It is reported that albumin has an important clinical significance in estimating the prognosis of patients with cirrhosis and a better assessment of malnutrition (32). The results of SUCRA of Alb from NMA showed that Protein combined with CHO and CHO alone had been more effective than Coconut milk-CHO and BCAA-CHO. It is worth noting that in the BCAA contained LES, there was 59% of energy from CHO and 14% from Protein as well (Aminoleban EN; Otsuka Pharmaceutical, Tokyo, Japan). It raises the question of whether BCAA is necessary to be provided in LES or not. In the advanced stage of cirrhosis (decompensated liver cirrhosis), a decline in serum BCAA was seen but not in the mild cases (compensated liver cirrhosis) (31). Therefore, the ESPEN guidelines recommend a supplement of BCAA for severe cases of LC (6). Nevertheless, in the studies that used BCAA, all level severity of LC was included and only a few of them offered an iso-nitrogenous regime in comparison (34). Of note, there was a large withdrawal rate (15%) across studies, due to poor palatability, difficulties with compliance with multiple-dose per day, and adverse gastrointestinal symptoms including diarrhea and abdominal distension (34-36). In addition, in many countries like Vietnam, oral BCAA supplements are not available because of the high cost (about 4$/snack). It may be feasible to derive benefits of BCAA from dietary sources rich in BCAA such as chicken breast, beef, salmon, and red bean… (37).

Regarding respiratory quotient (RQ) and BCAA/Tyr ratio (BTR), both of the parameters only included CHO and BCAA-CHO in the comparison as no Protein-CHO studies reported them. The results of RQ indicated that LES helps increase RQ and CHO is maybe more effective than BCAA-CHO. Masahiro et al. reported that survival rate was significantly lower in patients with low non-protein RQ (<0.85) than in patients with scores above 0.85 where 0.85 is the point at which substrate for thermogenesis turns from carbohydrate dominant to lipid dominant (38). This confirms the importance of carbohydrates as the main source of energy for LES and it should be at least 50g as the previous recommendations (6, 12). As for the BTR, BCAA-CHO showed advanced effectiveness in increasing serum BCAA than CHO. However, as there is a lack of evidence from other sources of protein, we could not confirm whether the protein can be as effective as BCAA supplements or not.

The levels of ALT and AST were not significantly different from the baseline when supplying LES in cirrhotic patients. This finding was similar to the systematic review of Guo YJ et al (2018), which suggested that bedtime snacks may not contribute to liver parenchyma damage in patients with cirrhosis in a short time (39). However, in this review, total bilirubin and cholinesterase were significantly improved after the Protein-CHO snack administration. Moreover, ammonia was also successfully decreased by CHO snacks. Thus, with the appropriate compositions of LES which includes both CHO and protein, not only protein synthesis and

energy metabolism can be improved but liver damage can also be managed.

Several limitations in this meta-analysis and network meta-analysis should be considered. First, most studies included in the meta-analysis were single-center studies; furthermore, the sample size in some of the studies was small. Second, the subjects in all searched studies were Asian (most were Japanese). Final, there was no direct comparison between some of the compositions, especially between Protein-CHO and BCAA-CHO. Therefore, I would like to conduct a large, multicenter RCT to confirm the effects of Protein-CHO LES on patients with liver cirrhosis in comparison to an iso-nitrogenous and iso-caloric BCAA contained LES.

CONCLUSION

With the results from the systematic review and network meta-analysis, the recommendable LES compositions should provide at least 200kcal with 50g of carbohydrate. About the nitrogen source, protein is maybe more effective than BCAA in terms of improving protein synthesis and energy metabolism as well as liver parenchyma damage. However, since there is no direct comparison between protein and BCAA as LES, a future study is needed to confirm this finding.

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