Systematic Review and Meta-Analysis

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The efficacy of parenteral nutrition (PN) and enteral nutrition (EN) supports in cirrhosis

A systematic review and network meta-analysis

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Abstract

Importance: Multiple nutritional therapies are currently available for patients with liver cirrhosis, yet many interventions have not been compared head-to-head within randomized clinical trials.

Objective: To evaluate the improvement of nutritional indicators and liver function indexes of liver cirrhosis treated with different nutrition intervention.

Data source: We searched PubMed, Embase. com and Cochrane Library database from construction to April 3, 2020. After eliminating the duplicated or overlapping reports, 6 studies were included. We performed a Bayesian network meta-analysis by Stata 12.0 and GeMTC 0.14.3 in order to compare different nutritional interventions with consistency model.

Study selection: Randomized clinical trials comparing 2 or more therapies in patients with cirrhosis were evaluated. Six randomized clinical trials met the selection criteria.

Data extraction and synthesis: Two investigators independently reviewed the full manuscripts of eligible studies and extracted information into an electronic database: patients' characteristics study design, interventions, the number of events of interest in each group.

Main outcomes and measures: Body mass index, Child-Pugh score, model for end-stage liver disease score, total bilirubin, alanine transaminase, aspartate transaminase, total protein, Triceps skinfold, Midarm Muscle Circumference, Fischer ratio, overall survival.

Results: There are 6 studies enrolling a total of 1148 patients who received different nutrition supports including parenteral nutrition (PN), enteral nutrition (EN), EN (without branched-chain amino acids), EN + intestinal probiotics, PN + EN, late evening snacks (LES), EN + LES, noLES. The direct comparisons showed that the effect of EN was better than EN (without branched-chain amino acids); EN + intestinal probiotics was better than EN and PN; PN + EN was better than them alone; EN + LES was better than LES and EN; LES was better than noLES. Although the difference of indirect comparisons between the included regimens was not statistically significant, the results showed that EN + intestinal probiotics appeared to be superior to PN + EN. While LES and EN + LES seemed to rank behind them and the difference between them was extremely small.

Conclusion and relevance: Available evidence suggests that EN + intestinal probiotics appear to be the most effective strategy for patients with cirrhosis compared with other interventions.

Abbreviations: ALT = alanine transaminase, AST = aspartate transaminase, BCAAs = branched-chain amino acids, BMI = body mass index, CIs = confidence intervals, EN = enteral nutrition, LES = late evening snacks, MAMC = Midarm Muscle Circumference, MELD score = Model for End-Stage Liver Disease Score, PN = parenteral nutrition, RCTs = randomized clinical trials, TBIL = total bilirubin, TP = total protein.

Keywords: cirrhosis, enteral nutrition, parenteral nutrition

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The datasets presented in this study can be found in online repositories. The names of the repository/repositories can be found below: Embase, MEDLINE/Ovid, Epistemonikos and Cochrane.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are publicly available.

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1. Introduction

The liver is the central organ for the metabolism of sugar, fat, and protein. While the cirrhosis caused by all kinds of reasons such as virus, drugs, and alcoholic can lead to the reduction of metabolic function.[1] It is reported that over 1 million people die from cirrhosis worldwide each year and malnutrition accounts for as high as 75% to 90% of patients with cirrhosis.[2,3] Meanwhile, malnutrition is associated with complication of cirrhosis.[4] The tight connection between cirrhosis and malnutrition suggests that it is critical to assess the nutritional status and start the appropriate intervention to minimize morbidity and mortality as early as possible.[5,6]

It is well-known that early screening for nutritional status and interventions in patients with chronic liver disease reduces the risk of complications,[7] so how to define malnutrition and choose interventions become quite important. In population with cirrhosis, malnutrition is most commonly defined as a loss in skeletal muscle mass and/or strength as well as decreased subcutaneous and visceral fat mass. These structural changes often occur in the case of protein reduction and total energy consumption.[8,9] The optimal nutritional approaches in cirrhosis include sufficient energy intake to surpass the daily requirements and overcome the catabolism, the intake of high-quality protein and micro-element.[10] In patients with cirrhosis, acid supply to the muscle is impaired through different mechanisms. Branched-chain amino acids (BCAAs) either together or as individual components, have been proven to be effective as a nutritional supplement in cirrhosis.[11] Furthermore, BCAAs also show an improvement in hepatic encephalopathy, general status, and quality of life.[12] On the other hand, intestinal probiotics can promote the growth of beneficial bacteria, limit the growth of harmful bacteria and the production of their harmful metabolites, increase intestinal transport, which are helpful for cirrhotic patients with hepatic encephalopathy.[13,14] In order to achieve the above-mentioned methods, plenty of inventions were created, including parenteral nutrition (PN) with BCAAs, human serum albumin, fat milk, vitamin, micro-element; enteral nutrition (EN) with BCAAs, Intestinal probiotics, Ensure (American Abbott), homemade homogenized food; the late evening snacks (LES) with BCAAs. Different combinations of the above measures can have different effects, and the direct and indirect comparison between them through network meta analysis may bring some new references for clinical practice.

To date, there are no large randomized controlled trials assessing the potential effects of nutritional interventions in cirrhotic patients, thus defining effective strategies among PN, EN, EN (without BCAAs), EN + intestinal probiotics, PN + EN, LES, EN + LES, noLES are quite necessary. To attain a better understanding on this issue, the available observation studies are estimated by updated Bayesian network meta analysis in order to investigate the efficacy between use of different nutritional interventions in patients with cirrhosis. The results are expected to provide reference for clinical practice.

2. Method

2.1. Literature search

An electronic search was performed by using PubMed, Embase, and Cochrane Library until February 2020, of which the search strings contained: PN, EN, cirrhosis, nutritional interventions, meta, network meta. These words were used in different combinations. The ethics committee of Southwest Medical University approved the study (PROSPERO Registration number: CRD42020188815).

2.2. Eligibility criteria

All the studies met the following eligibility criteria: study: we included randomized clinical trials (RCTs) that compared different nutritional interventions for cirrhosis; The study period of all studies was at least 1 months; patients: adults (age >18 years) with cirrhosis, with male and female, with comprehensive treatment of hepatology, with different nutritional interventions; comparators: any of the above mentioned treatment strategy; outcome: body mass index (BMI), Child-Pugh score, model for end-stage liver disease score (MELD score), total bilirubin (TBIL), alanine transaminase (ALT), aspartate transaminase (AST), total protein (TP), Triceps skinfold, Midarm Muscle Circumference (MAMC), Fischer ratio, overall survival. The study with multiple arms was preferred as much as possible so as to build comparative loops in network meta-analysis.

2.3. Outcome measures and data extraction

The outcomes were BMI, Child-Pugh score, MELD score, TBIL, ALT, AST, TP, Triceps skinfold, MAMC, Fischer ratio, overall survival. Two investigators independently reviewed the full manuscripts of eligible studies and extracted information into an electronic database: patients' characteristics study design, interventions, the number of events of interest in each group. Any discrepancies regarding the extraction of data were resolved by an additional investigator. When relevant information on design or outcomes was unclear, or when some needed data was unavailable directly from the study, the original authors were sought for eligible data by email.

2.4. Risk of bias and quality assessment

The Cochrane risk of bias assessment tool was used to assess the methodological quality of individual studies, based on the following aspects: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome and assessment; incomplete outcome data; selective reporting; and other bias. Each item was answered with high, low, or unclear risk of bias and disagreements were resolved through open discussion or a third reviewer.

2.5. Statistical analysis

We conducted the traditional pairwise meta-analysis, and summarized the available data for efficacy indexes from the results of all studies. Summary measures were calculated as weighted mean difference, together with 95% confidence intervals (CIs), which was pooled using Stata 12.0 software (TX, USA). The chi-square statistic was used to assess the heterogeneity between trials, and I^2 values over 50% indicated substantial heterogeneity. A Bayesian network meta-analysis was performed to simultaneously compare all interventions in the network. The network meta-analysis can be considered to be an extension of the traditional pair-wise meta-analysis, as it incorporates both direct and indirect information through a common comparator to obtain estimates of the relative interventional effects on the multiple interventions comparisons,

which was performed by using the automated software Gemtc (Groningen, USA). The rank accumulate probability plot produced by the network meta analysis was to find out which administered intervention is the best. Node-splitting models were conducted to assess whether direct and indirect effect is in agreement. The random effect variance and inconsistency random effect variance were also used to analyse the consistency.

3. Results

3.1. Study selection

The PRISMA flowchart of electronic searching processes is shown in Figure 1. The combined electronic and reference searches recovered 3373 potential relevant articles and after the initial screening, 3196 publications were excluded according to title and abstract. After detailed assessment of the full text, a further 171 were excluded because they were not case control, without available date, or were animal or basic research studies or review articles. Overall, 6 observational studies from different countries enrolling a total of 1154 patients who received different nutritional strategies were included in this analysis (Table 1).[7,15–19]

3.2. Study characteristics

The details of the nutritional interventions, baseline characteristics of the populations, study period, efficacy Index and other characteristics of 6 eligible trials were shown in Table 1. Six nutritional intervention were included according to these eligible studies: PN, EN, EN (without BCAAs), EN + intestinal probiotics, EN + LES, PN + EN, LES, noLES. In terms of study sample sizes, the number of patients involved in the studies ranged from 10 to 523. The primary outcomes were BMI, Child-Pugh score, MELD score, TBIL, ALT, AST, TP, Triceps skinfold, MAMC, Fischer ratio, overall survival, the category and quantity of effective indicators were different from trail to trial. The studies included were multiple-arm trials, patients were treated with at least 2 studies.

3.3. Risk of bias

Figure 2 summarizes the quality assessment of included studies, which showed that the quality of included studies were reliable. There were 6 studies with low risk of bias in random sequence generation; 4 studies with unclear risk of bias in allocation concealment, blinding of participants and personnel, blinding of outcome assessment; 5 studies with low risk of bias in incomplete outcome data; 6 studies with low risk of bias in selective reporting. Overall, 4 studies were free of high risk for bias in all above-mentioned domains. Egger test showed $t = -1.62$, $P = .135$ ($P > .05$), suggesting the absence of any small study effects or publication bias.

3.4. Results from direct comparisons

The MELD score improved in the EN group compared to the EN without BCAA group. BMI of EN group was higher than EN without BCAA group (Fig. 3).[7]

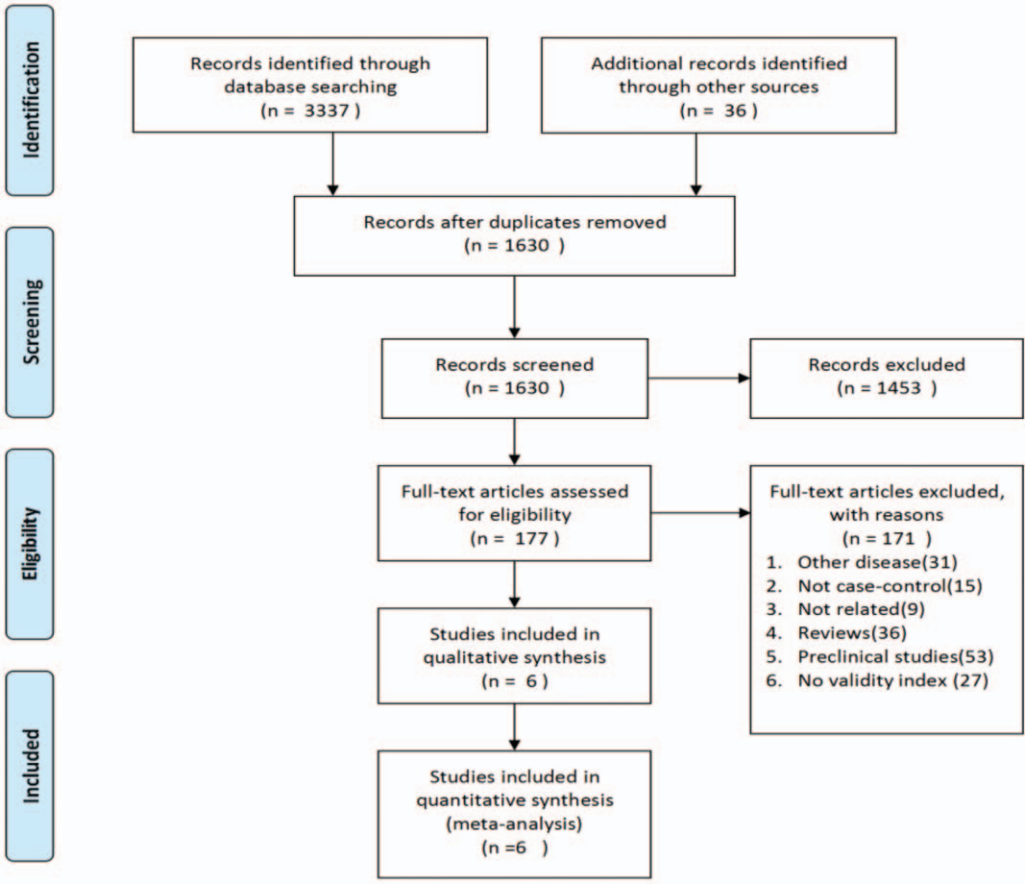


Figure 1. Flow chart of studies evaluating nutritional interventions for cirrhosis through selection process.

Table 1

Characteristics of the included study.

Study	Location	Intervention	n	Year	Study period	Efficacy index
Park et al,[7]	South Korea	EN vs EN (without BCAAs)	307	59.5±9.9	6 mo	BMI, Child-Pugh score, MELD, TBIL, CP score
Ruiz-Margáin et al,[15]	Mexico City	EN vs EN (without BCAA)	72	51.4±12.9	6 mo	BMI, Child-Pugh score, MELD, TBIL, Triceps skinfold, MAMC
Wang et al,[16]	China	EN+PN vs EN vs PN	148	50.1±13.5	1 mo	ALT, AST, TP, TBIL
Tang et al,[17]	China	PN vs EN vs EN+intestinal probiotics	64	46.7±11.6	1 mo	ALT, AST, BMI, TBIL
Maki et al,[18]	Japan	EN+LES vs EN vs LES	10	73.1±8.9	1 mo	ALT, AST, BMI, TBIL, Fischer ratio
Hanai et al,[19]	Japan	LES vs noLES	523	66.5±4.7	3 mo	BMI, ALT, Child-Pugh score, MELD, TBIL, overall survival

ALT = alanine transaminase, AST = aspartate transaminase, BMI = body mass index, BCAAs = branched-chain amino acids, EN = enteral nutrition, LES = late evening snacks, MAMC = Midarm Muscle Circumference, MELD score = model for end-stage liver disease score, PN = parenteral nutrition, TBIL = total bilirubin, TP = total protein.

Between the EN group and EN without BCAA group, there was an increase in muscle mass and a decrease in fat mass in the EN with BCAA group through triceps skinfold thickness and mid-arm muscle circumference measurements, but not in the EN without BCAA group (Fig. 3).[15]

Compared with PN group and EN group, PN+EN group did a best job in the decline range of ALT, AST and also in the upward trend of TP (Fig. 3).[16]

AST, ALT, TBIL of EN+intestinal probiotics group is significantly lower when compared with PN and EN group. BMI of EN and EN+intestinal probiotics were significantly higher than PN group ($P < .05$) (Fig. 3).[17]

The Fischer ratio was significantly higher in the LES (2.2±0.8) and EN+LES (2.3±0.8) groups than in the control group (1.8±0.6). Furthermore, the Fischer ratio was significantly lower in the EN group (1.8±0.7) than in the LES and EN+LES groups (Fig. 3).[18]

Propensity score matching analysis showed that the overall survival was significantly higher in LES-treated patients than in untreated patients (hazard ratio [HR], 0.57; 95% CI, 0.34-0.93). The survival benefit of LES therapy was most prominent in patients with Child–Pugh C cirrhosis (HR, 0.40; 95% CI, 0.20-0.81). Inverse probability of treatment weighting analysis also revealed that LES significantly improved the prognosis of patients with cirrhosis (HR, 0.57; 95% CI, 0.33-0.99).[19]

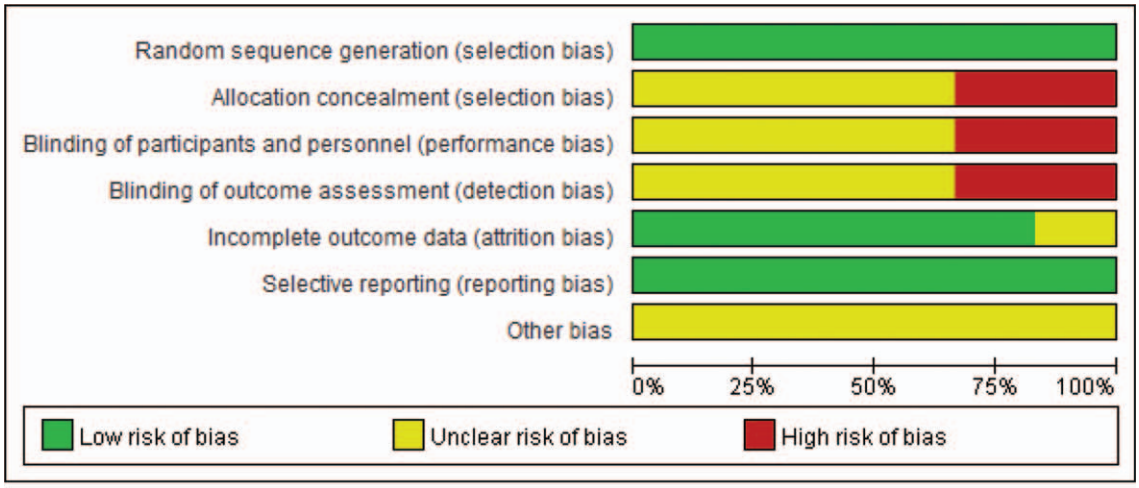
3.5. Results from the network meta-analysis

From the direct comparison, we can conclude that EN, PN+EN, EN+intestinal probiotics, LES, EN+LES groups had unique advantages in their own comparison groups, while the comparison between these advantage groups depends on the indirect comparison through network meta-analysis. We summarized the result of random-effects network meta-analysis for cirrhosis nutritional interventions in Figure 4. The network meta-analysis results for 6 kinds of interventional therapies (a=PN; b=EN; c=PN+EN; d=EN+intestinal probiotics; e=EN (without BCAAS); f=LES; g=EN+LES; h=noLES), which illustrated ALT, AST, TBIL, BMI with 95% CI were in Figure 5. The rank probability was in Table 2. From the indirect comparison, EN+Intestinal probiotics more likely ranked lowest in ALT, AST, TBIL and more likely ranked highest in BMI, which suggest that EN+intestinal may be the most effective nutritional intervention for cirrhosis. The results of traditional pairwise and network meta-analyses showed small differences, the CI from traditional pairwise meta-analyses and the Bayesian network meta analyses in general overlapped. Besides, the random effect variance and inconsistency variance were roughly equal, suggesting the data are consistent.

4. Discussion

Malnutrition is a frequent complication in cirrhosis population.[20] Reduced dietary intake contributes to malnutrition,[21] insufficient dietary intake increases the risk of morbidity and mortality, whereas sufficient dietary intake can improve clinical outcomes,[22] which suggests that patients with malnutrition frequently require the relatively most effective nutritional intervention to improve their clinical outcomes. Currently, several interventional therapies have been applied in cirrhosis, which were PN, EN, EN+intestinal probiotics, PN+EN, EN (without BCAAs), LES, EN+LES, noLES. PN, EN and PN+EN are routine therapies for cirrhosis while EN+intestinal probiotics, LES, EN+LES are novel therapies in recent years. The comparison between old ones and new ones can find a relatively most effective therapy and also means much for the development of nutritional intervention for patients with cirrhosis.

From the results of meta and network meta-analysis, we found that EN+intestinal probiotics may be the relatively most valid intervention among the studies included, which means conventional EN with BCAAs, ensure (American Abbott) or homemade homogenized food plus intestinal probiotics can improve clinical outcomes effectively. The efficacy of EN alone is normal, but the efficacy improves obviously after adding intestinal probiotic. The reason is that Patients with cirrhosis often need a lot of antibiotics during the treatment, which will lead to the imbalance of intestinal flora and the increase of pathogenic flora, and then produce a large number of enterotoxins and metabolic waste. When the intestinal mucosal barrier function is damaged, these enterotoxins and metabolic waste will easily penetrate the intestinal wall and invade the lymphatic system, causing body infection, especially lung infection.[23–25] Probiotics can improve the intestinal micro ecological environment, enhance the intestinal barrier function, prevent the invasion of foreign bacteria, stimulate the immune response of the body, inhibit the production of endotoxin, repair the intestinal mucosal barrier, reduce inflammatory factors and promote the absorption of enteral nutrition.[26] These advantages show that EN combined with intestinal probiotics has a good effect in the treatment of cirrhosis, and has a positive effect on the rehabilitation of patients' diseases, which can be used as a routine clinical treatment.



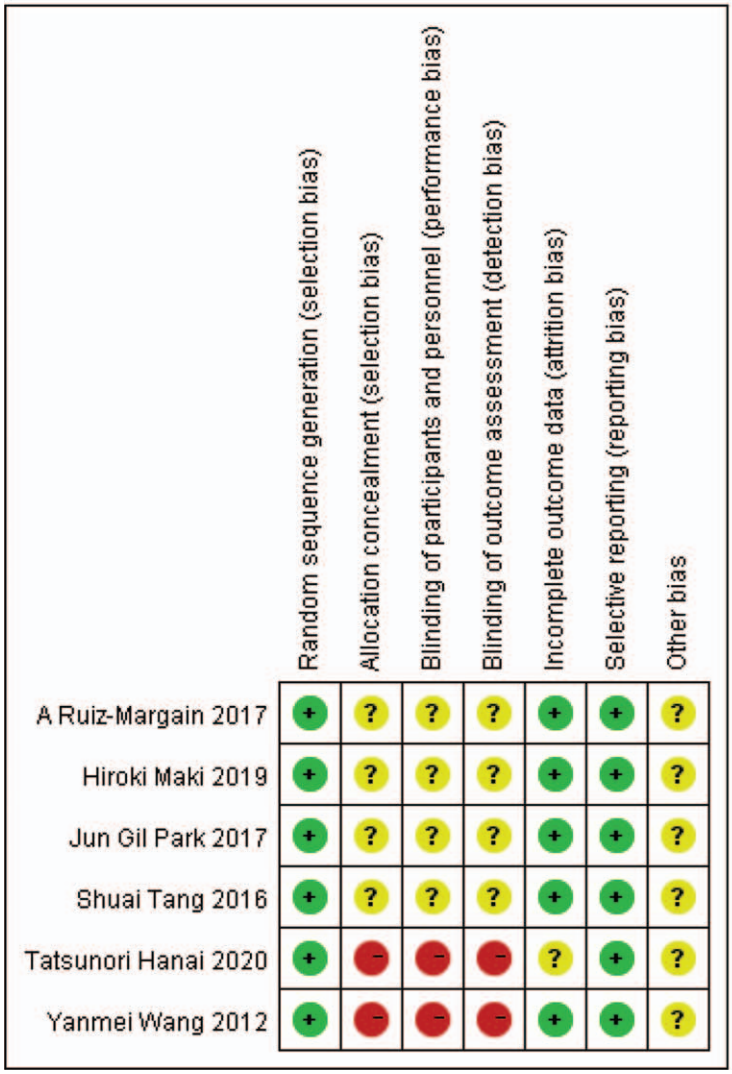


Figure 2. Quality assessment of included studies.

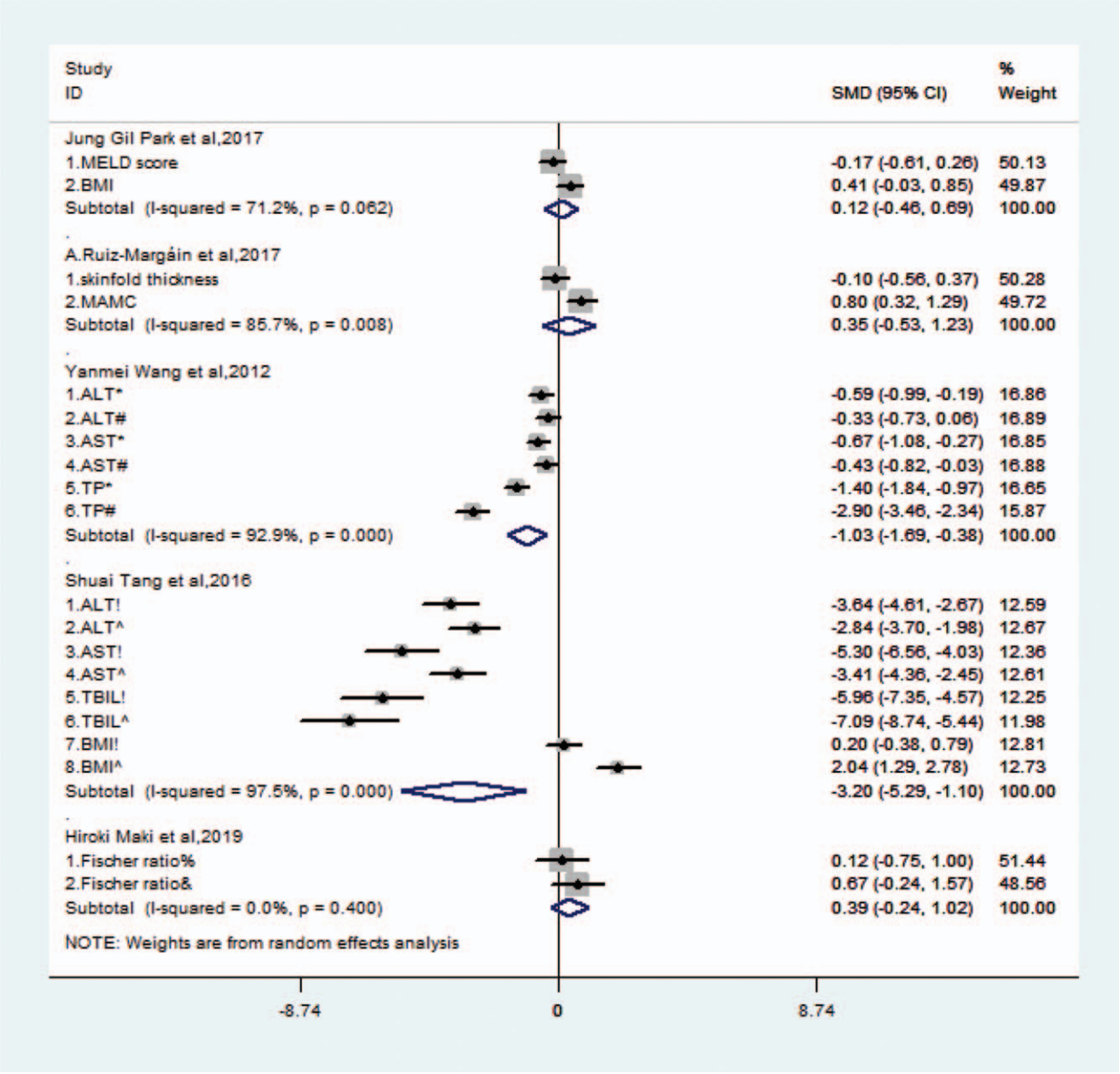


Figure 3. The result of direct meta-analysis. * = PN + EN vs EN; # = PN + EN vs PN; ! = EN + intestinal probiotics vs EN; ^ = EN + intestinal probiotics vs PN; % = EN + LES vs LES; & = EN + LES vs EN. ALT = alanine transaminase, AST = aspartate transaminase, BMI = body mass index, EN = enteral nutrition, MAMC = Midarm Muscle Circumference, MELD score = model for end-stage liver disease score, PN = parenteral nutrition, TBIL = total bilirubin, TP = total protein.

4.1. Strengths and limitations of this review

This study has limitations. We conducted a comprehensive literature search with a sensitive search algorithm and an extensive manual search of reference lists and conference proceedings. However, we could not obtain additional unpublished data and are aware that a substantial amount of information is not available to the public. Thus, we cannot rule out publication bias.

First, meta analyses are based on the assumption of directness, in which populations, therapies and outcomes of included studies are aligned with population, therapies and outcomes targeted by the meta-analysis. Our meta-analysis targeted all available therapies and included only several statistically significant indicators of effectiveness. Both factors ensured a certain degree of directness.

Second, network meta-analyses are also based on the assumption of transitivity, in which the included studies are similar enough to build a network. In this study, the well-defined populations and outcomes resulted in a network with high overall transitivity. Although we found out that EN + intestinal appear to be the most effective way for cirrhosis, the indirectness result was not statistically significant, which means that more relevant studies and more comprehensive outcome indicators were demanded.

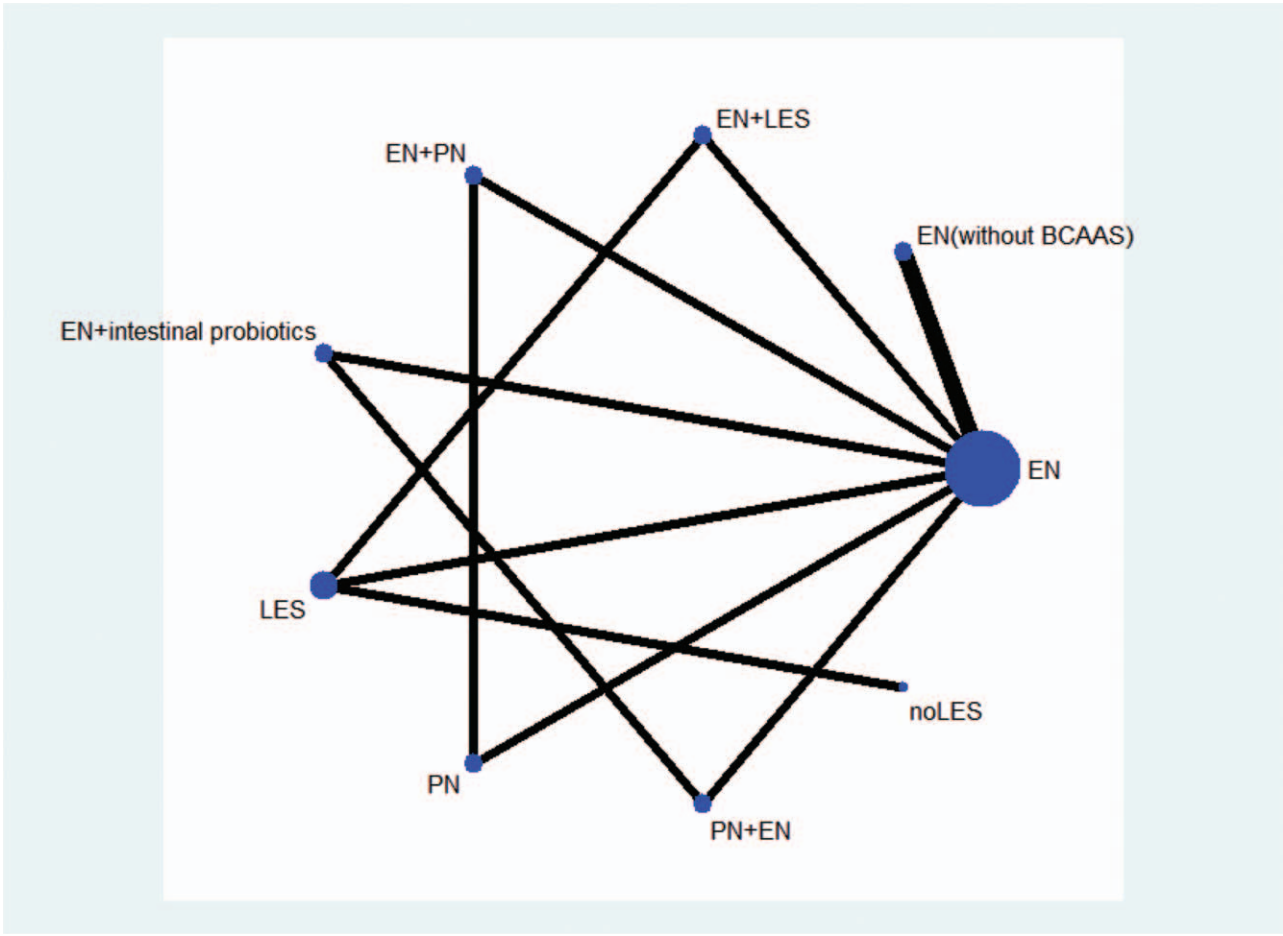


Figure 4. Comparison network of the included studies. BCAAs = branched-chain amino acids, EN = enteral nutrition, LES = late evening snacks, PN = parenteral nutrition.

Third, 2 RCTs had a high risk of bias due to absent blinding of participants and personnel and blinding of outcome assessment. Absent blinding has been shown to be associated with an average exaggeration of estimated therapeutic effects of approximately 9%, so the extent of superiority needs to be interpreted with caution.

4.2. Implication

The combination of meta and network meta analysis can provide comprehensive and objective result. So our results have implications for clinicians, guideline committees, and researchers. Firstly, malnutrition affect the morbidity, survival rate, mortality and prognosis of cirrhosis. This kind of tiny connection request clinicians choose a suitable intervention for patients. Secondly, more data will come out when clinicians use the intervention recommended by us, which can support the adaption of clinical guidelines. Although there is no requirement to incorporate all evidence from RCTs into clinical guidelines, this systematic review presents an overview of the existing evidence from which guideline makers can choose. Thirdly, with the development and innovation of nutritional intervention for cirrhosis population, more and more studies will constantly come out by researcher, the present results may guide future research by highlighting necessary head-to-head comparisons and facilitating their trial design. Specifically, EN + intestinal probiotics vs PN + intestinal probiotics or EN + intestinal probiotics vs PN + EN + intestinal probiotics can be researched in the future. Furthermore, we find that EN (without BCAAs) has the lowest efficacy, which means comparisons with placebo as a reference are discouraged for the future. Moreover, the quality assessment of currently available RCTs revealed that further studies should incorporate blinding to avoid overestimation of effects and improve the overall quality of evidence in the field.

5. Conclusions

Above all, the direct and indirect comparison suggest that EN + intestinal probiotics appear to be the most effective strategy for patients with cirrhosis compared with other interventions.

Author contributions

Data curation: Jiting Wang.
Formal analysis: Jiting Wang.
Software: Bin Yu.
Writing – review & editing: Bin Yu.

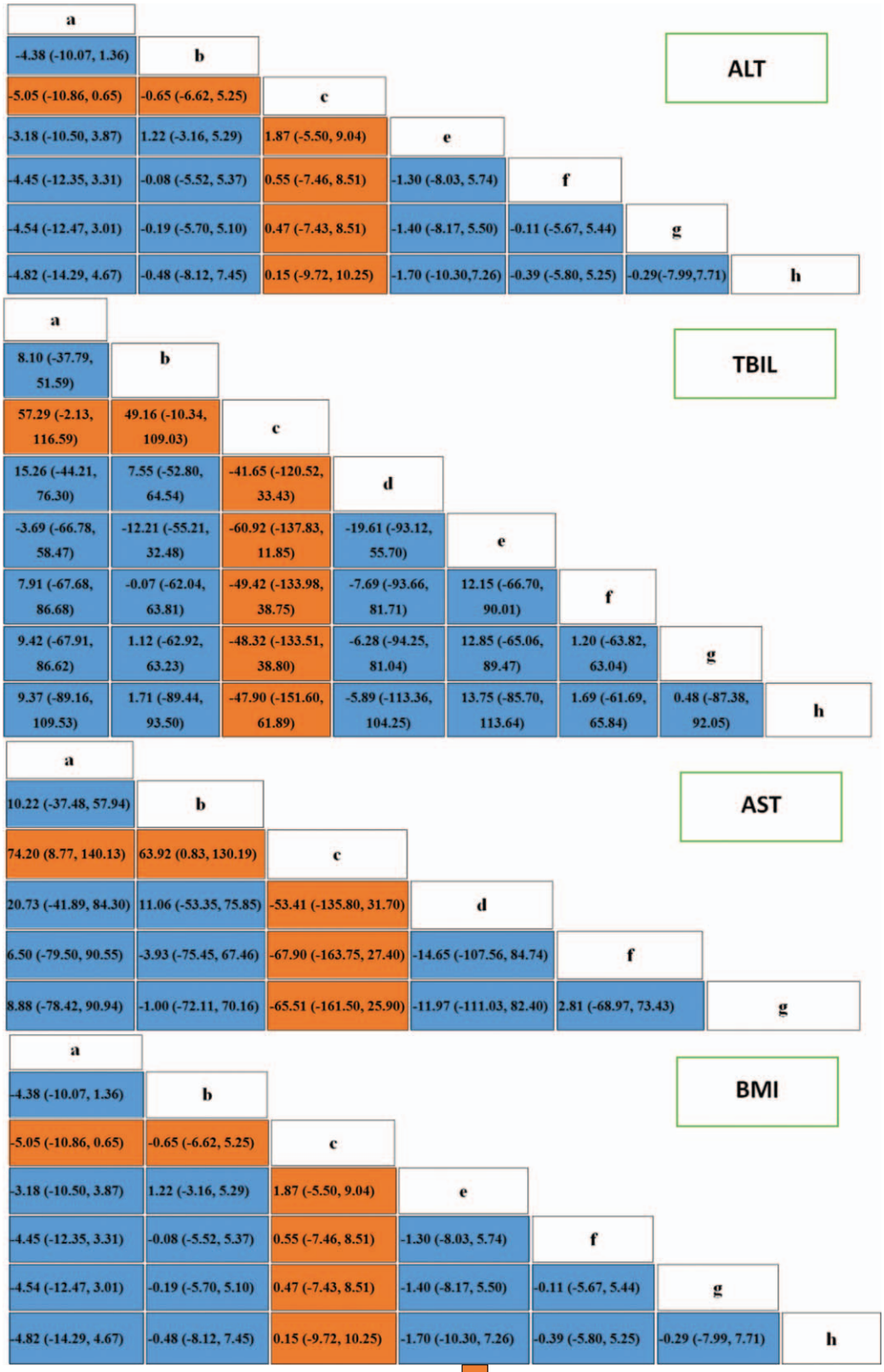


Figure 5. The network meta-analysis results for 6 kinds of interventional therapies. The result of intervention c; a = PN; b = EN; c = PN + EN; d = EN + intestinal probiotics; e = EN (without BCAAS); f = LES; g = EN + LES; h = noLES. ALT = alanine transaminase, AST = aspartate transaminase, BMI = body mass index, BCAAs = branched-chain amino acids, EN = enteral nutrition, LES = late evening snacks, PN = parenteral nutrition, TBIL = total bilirubin.

Table 2

Results of rank test for different interventional therapies.

Intervention	Rank1	Rank2	Rank3	Rank4	Rank5	Rank6	Rank7	Rank8
ALT								
a	0.45	0.22	0.13	0.10	0.06	0.02	0.00	
b	0.02	0.13	0.21	0.26	0.24	0.11	0.02	
c	0.03	0.07	0.08	0.10	0.13	0.22	0.37	
d	0.04	0.08	0.09	0.11	0.14	0.24	0.29	
f	0.07	0.18	0.19	0.18	0.17	0.15	0.12	
g	0.10	0.14	0.16	0.16	0.16	0.15	0.12	
h	0.28	0.18	0.12	0.10	0.10	0.10	0.12	
AST								
a	0.47	0.20	0.15	0.12	0.05	0.00		
b	0.05	0.19	0.33	0.33	0.08	0.00		
c	0.00	0.01	0.01	0.03	0.07	0.88		
d	0.07	0.10	0.11	0.15	0.53	0.05		
f	0.24	0.29	0.18	0.15	0.11	0.03		
g	0.17	0.21	0.21	0.22	0.15	0.03		
TBIL								
a	0.20	0.21	0.17	0.15	0.12	0.10	0.05	0.00
b	0.02	0.09	0.19	0.25	0.23	0.16	0.06	0.00
c	0.00	0.01	0.01	0.02	0.03	0.06	0.12	0.75
d	0.08	0.09	0.10	0.11	0.12	0.15	0.28	0.06
e	0.30	0.20	0.16	0.12	0.09	0.07	0.05	0.01
f	0.09	0.16	0.14	0.14	0.16	0.17	0.11	0.02
g	0.11	0.13	0.13	0.13	0.15	0.15	0.15	0.05
h	0.19	0.12	0.10	0.09	0.09	0.14	0.18	0.10
BMI								
a	0.00	0.02	0.02	0.03	0.05	0.11	0.77	
b	0.05	0.16	0.23	0.27	0.22	0.05	0.00	
c	0.36	0.14	0.11	0.11	0.14	0.12	0.02	
e	0.05	0.08	0.09	0.11	0.15	0.43	0.08	
f	0.08	0.21	0.21	0.20	0.18	0.10	0.03	
g	0.16	0.18	0.21	0.16	0.15	0.10	0.03	
h	0.29	0.21	0.12	0.11	0.11	0.10	0.06	

a = PN; b = EN; c = PN + EN; d = EN + intestinal probiotics; e = EN (without BCAAS); f = LES; g = EN + LES; h = noLES.
ALT = alanine transaminase, AST = aspartate transaminase, BMI = body mass index, TBIL = total bilirubin.

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