

# World Journal of *Clinical Cases*

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## Branched-chain amino acids supplementation has beneficial effects on the progression of liver cirrhosis: A meta-analysis

Jia-Yu Du, Liu Shu, Yu-Tian Zhou, Li Zhang

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### Abstract

#### BACKGROUND

Liver cirrhosis (LC) is currently the 11<sup>th</sup> most common cause of death and 15<sup>th</sup> cause of morbidity globally. The treatment of LC is mainly aimed at etiological intervention, lifestyle intervention, prevention and treatment of complications and nutritional treatment. Nutritional treatment of LC mainly includes increasing dietary intake, food intake time and branched-chain amino acids (BCAAs). Despite the recommendation of BCAAs in some guidelines, adverse effects have been reported in studies so the efficacy and safety of BCAAs remain controversial. Currently, BCAAs have been widely used in chronic liver disease, while the summary of the effect of BCAAs on long-term prognosis is rare.

#### AIM

To determine the effects of BCAAs in patients with LC.

#### METHODS

The PubMed, Cochrane Library, Embase and Web of Science databases were searched. The retrieval deadline was 1 October 2021 and there were no language restrictions set in the retrieval. The study was performed in strict accordance with the inclusion and exclusion criteria. Nine studies were finally included. The primary outcome was complications of LC. The secondary outcomes were nutritional status and liver function. This meta-analysis used the Review Manager, version 5 statistical package (Cochrane Collaboration, Oxford, England) for

analysis.

## RESULTS

The analysis included nine studies that consisted of 1080 patients (554 in the BCAA groups and 526 in the control groups). The nine studies were randomized control trials (RCTs). The quality of the studies was assessed using the risk of bias method recommended by the Cochrane Collaboration. BCAAs reduced the rate of complications in LC patients [Risk ratio: 0.70, 95% confidence interval (CI): 0.56-0.88,  $P = 0.002$ ] and improved patients' albumin levels [std mean difference SMD: 0.26, 95%CI: 0.12-0.40,  $P = 0.0002$ ]. Meanwhile, BCAAs significantly ameliorated the levels of alanine transaminase (SMD: -2.03, 95%CI: -2.52 to -1.53,  $P < 0.00001$ ) and aspartate aminotransferase (SMD: -1.8, 95%CI: -2.14 to -1.46,  $P < 0.00001$ ). Meanwhile, glucose in the LC was significantly increased in BCAA-treated patients (MD: 13.04, 95%CI: 6.81-19.89,  $P = 0.0002$ ).

## CONCLUSION

BCAAs reduce the incidence of complications in patients with LC and ameliorate nutritional status.

**Key Words:** Liver cirrhosis; Branched-chain amino acids; Complications; Nutrition; Liver function; Glucose

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**Core Tip:** Liver cirrhosis (LC) is currently the 11<sup>th</sup> most common cause of death and the 15<sup>th</sup> cause of morbidity globally. Nutritional treatment of LC mainly includes increasing dietary intake, food intake time and branched chain amino acids (BCAAs). The efficacy and safety of BCAAs remain controversial. We performed a meta-analysis and nine studies were finally included. The primary outcome was complications of LC. The secondary outcomes were nutritional status and liver function. The conclusion is that branched-chain amino acids reduce the incidence of complications in patients with liver cirrhosis and ameliorate nutritional status.

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## INTRODUCTION

As the 11<sup>th</sup> leading cause of death and 15<sup>th</sup> leading cause of morbidity worldwide, liver cirrhosis (LC) is the end stage of liver diseases[1]. It is the top 20 causes of disability-adjusted life years and years of life lost and accounts for 1.6% and 2.1% of the worldwide burden. Asrani *et al*[2] summarized that LC causes two million deaths, one million deaths from cirrhosis complications and one million deaths from viral hepatitis and hepatocellular carcinoma annually.

For the high mortality and poor prognosis, much research has reported the following indicators of poor prognosis of LC[3-6]. Although liver biopsy and hepatic venous pressure gradient are currently recommended invasive indicators to predict the prognosis of LC[3,4], noninvasive prediction tools are commonly used in clinical work. Child Pugh and the model for end-stage liver disease (MELD), including creatinine, International Normalized Ratio and bilirubin are two of the most recommended forecasting tools in recent years[7]. Child Pugh scores included encephalopathy, ascites, urine volume, bilirubin, albumin and prothrombin time[5]. MELD scores included creatinine, international normalized ratio and bilirubin[6]. In our study, nutritional status (serum albumin), the occurrence of complications, and liver functions [aspartate aminotransferase (AST), alanine transaminase (ALT), bilirubin] were chosen as indicators to evaluate and predict the prognosis of LC. The disease progresses to decompensation, and complications follow, such as the development of ascites, portal hypertensive gastrointestinal bleeding, encephalopathy and jaundice[8]. Similarly, as mentioned above, malnutrition also means a poor prognosis. Protein calorie malnutrition is not only the most common symptom in patients with LC[9] but also an independent risk factor for death[10,11], leading to more severe complications[12,13]. A clinical trial reported that 51% of patients with LC showed some clinical evidence of protein caloric malnutrition[14].

At present, the treatment of LC is mainly for the cause of intervention, lifestyle intervention, and the prevention and treatment of complications[15]. Toshikuni *et al*[16] mentioned that nutritional therapy for LC mainly included increasing dietary intake, the timing of food intake and branched-chain amino

acids (BCAAs). In recent years, BCAAs have been found to have a unique effect on LC[17-24]. BCAAs are a set of essential amino acids including leucine, isoleucine and valine. It was considered that the end stage of liver disease is characterized by a low concentration of BCAAs and a high concentration of aromatic amino acids (phenylalanine, tyrosine and tryptophan)[21]. Suzuki *et al*[25] found that in patients with compensated cirrhosis, amino acid imbalance also occurs. Hyperinsulinemia and hyperammonemia are thought to lead to changes in the amino acid ratio in patients with LC[26,27]. The decrease in BCAA levels is considered to be a crucial pathogenic factor in LC[28]. Consequently, studies have reported that oral BCAAs can ameliorate patients' nutritional status[17,19-21,23,24], reduce the incidence of complications[17,19] and ameliorate liver function[20,22,23]. Although BCAAs have been recommended in some guidelines[29,30], adverse reactions have been reported in recent studies and the effectiveness and safety of BCAAs are still controversial[31,32]. Kobayashi *et al*[31] considered that BCAAs have no inhibitory effect on the progression from compensatory cirrhosis to decompensated cirrhosis. In addition, the effect of BCAAs on the overall condition of cirrhosis is less well studied. Therefore, we conducted a meta-analysis of these studies to evaluate the effect of its application in LC.

## MATERIALS AND METHODS

### Objective

This analysis's ultimate goal was to demonstrate the patients' treatment effect with LC using BCAAs.

### Selection of studies

Studies that conformed to the following criteria were included in our meta-analysis: (1) Randomized controlled studies; (2) the patient was diagnosed with cirrhosis; and (3) the intervention factor was BCAAs.

Studies were excluded if they met at least one of the following exclusion criteria: (1) The patient used BCAAs or other nutritional agents; (2) the patient had a high suspicion of liver neoplasms or had developed liver neoplasms; and (3) the patient had other major non-hepatic diseases.

In addition, filtering studies, abstracts, letters, reviews without original data, expert opinions, editorials, case reports and studies lacking control groups were excluded.

### Search strategy

We selected articles from PubMed, Cochrane Library, Embase and Web of Science. The retrieval deadline was 1 October 2021, and there were no language restrictions set in the retrieval. Search terms were utilized in the title, abstract, mesh fields, and the following keywords and their combinations were applied: (((liver cirrhosis[MeSH Terms])) OR (((hepatic[All Fields])) OR (liver)) AND ((cirrhosis[All Fields])) OR (fibrosis)) AND ((Amino Acids, Branched-Chain [MeSH Terms])) OR (((((((Acids, Branched-Chain Amino[All Fields])) OR (Branched-Chain Amino Acids)) OR (Amino Acids, Branched Chain)) OR (Branched-Chain Amino Acid)) OR (Acid, Branched-Chain Amino)) OR (Amino Acid, Branched-Chain)) OR (Branched Chain Amino Acid).

The outcomes of the meta-analyses were the occurrence of complications, nutritional status and liver function. These data included albumin, alanine transaminase, aspartate aminotransferase, bilirubin, glucose and the occurrence of ascites, hepatic encephalopathy or esophagogastric varices.

### Data extraction

Reviewers independently reviewed the quality and qualification of these studies according to the inclusion and exclusion criteria and the second reviewer (corresponding author) was allowed to intervene.

### Statistical analysis

This meta-analysis used the Review Manager, version 5 statistical package (Cochrane Collaboration, Oxford, England) for analysis. A risk ratio (RR) value with a 95% confidence interval (CI) was used for binary variables. Mean difference (MD) or Std MD (SMD) values with a 95%CI are used for continuous variables. The overall effects were measured using a z score with a significance set at  $P < 0.05$ . If  $P \geq 0.05$ , there was no significant difference in the results. In contrast, the results are significantly different. Statistical heterogeneity was evaluated using chi-square and I-square ( $I^2$ ) tests with significance set at  $P \leq 0.1$ . Values of  $P \leq 0.1$  and  $I^2 > 50\%$  were considered to be significantly heterogeneous. For the articles with  $I^2 > 0$ , we used the random effect model and sensitivity analysis or subgroup analysis, and for the articles with  $I^2 = 0$ , we used the fixed-effect model.

## RESULTS

### Study selection and characteristics of included studies

The analysis included nine studies that consisted of 1080 patients (554 in the BCAA groups and 526 in the control groups)[17,19-24,31,32]. The nine studies were randomized control trials (RCTs) (Figure 1). The characteristics of the studies included in the meta-analysis are shown in Table 1. The patient baseline characteristics of the studies included in the meta-analysis are shown in Table 2.

### Risk of bias assessment

The quality of the studies was assessed using the risk of bias method recommended by the Cochrane Collaboration. Some trials had a high risk of bias (Figure 2)[22]. The main reason is that blind methods are not adopted and the inevitable loss of visits is inevitable.

### Outcome

**Complications rate:** Statistical heterogeneity was low across the studies for the complication rate ( $Tau^2 = 0.00$ ;  $\chi^2 = 2.00$ ,  $df = 4$  ( $P = 0.74$ );  $I^2 = 0\%$ ) by fitting a fixed-effects model. The complication rate of LC was significantly reduced in BCAA-treated patients (RR: 0.70, 95%CI: 0.56-0.88,  $P = 0.002$ , Figure 3).

**Nutritional status:** Statistical heterogeneity was high across the studies for nutritional status [ $Tau^2 = 0.29$ ;  $\chi^2 = 36.72$ ,  $df = 6$  ( $P < 0.00001$ );  $I^2 = 84\%$ ] by fitting a random-effects model. The albumin level of LC was significantly ameliorated in BCAA-treated patients (SMD: 0.63, 95%CI: 0.17-1.09,  $P = 0.007$ , Figure 4A). Nevertheless, they have slight heterogeneity.

Subgroup analysis was therefore performed according to the number of included patients and studies with a total number of patients less than 50 were excluded. Statistical heterogeneity was low across the studies for nutritional status [ $Tau^2 = 0.00$ ;  $\chi^2 = 2.78$ ,  $df = 3$  ( $P = 0.43$ );  $I^2 = 0\%$ ] by fitting a fixed-effects model. The SMD of the fixed effect model analysis was 0.26 (95%CI: 0.12-0.40,  $P = 0.0002$ , Figure 4B).

Additional subgroup analysis included studies with treatment durations greater than 3 mo. Statistical heterogeneity was low across the studies for nutritional status [ $Tau^2 = 0.00$ ;  $\chi^2 = 2.06$ ,  $df = 3$  ( $P = 0.56$ );  $I^2 = 0\%$ ] by fitting a fixed-effects model. The SMD of the fixed effect model analysis was 0.27 (95%CI: 0.13-0.42,  $P = 0.0002$ , Figure 4C).

The last subgroup analysis included studies in which the majority of patients had Child grade A or B and treatment duration was greater than 3 mo. Statistical heterogeneity was low across the studies for nutritional status [ $Tau^2 = 0.00$ ;  $\chi^2 = 1.67$ ,  $df = 2$  ( $P = 0.43$ );  $I^2 = 0\%$ ] by fitting a fixed-effects model. The SMD of the fixed effect model analysis was 0.26 (95%CI: 0.11-0.41,  $P = 0.0005$ , Figure 4D).

These results further confirmed that BCAAs significantly ameliorate nutritional status in these patients.

### Liver function

**Aspartate aminotransferase (AST):** Statistical heterogeneity was low across the studies for AST [ $Tau^2 = 0.00$ ;  $\chi^2 = 3.03$ ,  $df = 3$  ( $P = 0.39$ );  $I^2 = 1\%$ ] by fitting a random-effects model. AST of LC was significantly ameliorated in BCAA treatment patients (SMD: -1.8, 95%CI: -2.14 to -1.46,  $P < 0.00001$ , Figure 5).

**Alanine transaminase (ALT):** Statistical heterogeneity was high across the studies for ALT ( $Tau^2 = 1.33$ ;  $\chi^2 = 24.94$ ,  $df = 2$  ( $P < 0.00001$ );  $I^2 = 92\%$ ) by fitting a random-effects model. The ALT level in the LC was significantly ameliorated in BCAA-treated patients (SMD: -1.43, 95%CI: -2.80 to -0.06,  $P = 0.04$ , Figure 6A). Nevertheless, they have slight heterogeneity.

In the sensitivity analysis, the study by Kawamura *et al*[19] was excluded because the disease cause of most patients in this study was found to be a virus. However, the antiviral drugs available in 2009 temporarily failed to achieve good control of viremia, resulting in persistently high serum AST/ALT levels. Statistical heterogeneity was low across the studies for ALT [ $\chi^2 = 0.43$ ,  $df = 1$  ( $P = 0.51$ );  $I^2 = 0\%$ ] by fitting a fixed-effects model. The ALT of LC was significantly ameliorated in BCAA-treated patients (SMD: -2.03, 95%CI: -2.52 to -1.53,  $P < 0.00001$ , Figure 6B).

**Bilirubin:** Statistical heterogeneity was high across the studies for bilirubin [ $Tau^2 = 0.40$ ;  $\chi^2 = 15.44$ ,  $df = 3$  ( $P = 0.001$ );  $I^2 = 81\%$ ] by fitting a random-effects model. The results showed that the effect of BCAAs on bilirubin in patients with LC was not statistically significant (SMD: -0.37, 95%CI: -1.06-0.32,  $P = 0.29$ , Figure 7).

### Glucose

Statistical heterogeneity was high across the studies for glucose [ $Tau^2 = 57.47$ ;  $\chi^2 = 8.54$ ,  $df = 2$  ( $P = 0.01$ );  $I^2 = 77\%$ ] by fitting a random-effects model. The results showed that the effect of BCAAs on glucose in patients with LC was not statistically significant (MD: 8.10, 95%CI: -1.76-17.95,  $P = 0.11$ , Figure 8A). Nevertheless, they have slight heterogeneity.

In the sensitivity analysis, the study by Marchesini *et al*[23] was excluded because the Child grade of patients included in the other two studies was graded A or B. Statistical heterogeneity was low across the studies for glucose [ $\chi^2 = 0.26$ ,  $df = 1$  ( $P = 0.61$ );  $I^2 = 0\%$ ] by fitting a fixed-effects model. The Glucose

**Table 1 Characteristics of studies included in the meta-analysis, n = 1080**

Trail	Country	Group	n	Treatment time	Child grade	Mean age	M/F	Study type
Etsushi Kawamura, 2009	Japan	BCAA	27	12 mo	A	62.70 ± 10.08	13/14	RCT
		Control	23			62.30 ± 7.30	12/11	
Muto Y, 2005	Japan	BCAA	314	> 5 mo	A/B/C	62 ± 8	147/167	RCT
		Control	308			61 ± 9	147/161	
Yutaka Nakaya, 2007	Japan	BCAA	19	3 mo	A/B	67 ± 9	13/6	RCT
		Control	19			67 ± 8	7/12	
Les, 2011	Spain	BCAA	58	56 wk	A/B	64.1 ± 10.4	45/13	RCT
		Control	58			62.5 ± 10.4	43/15	
Tangkijvanich P, 2000	Thailand	BCAA	15	4 wk	-	53.07 ± 10.58	10/5	RCT
		Control	15			53.20 ± 12.74	12/3	
Marchesini G, 1990	Italy	BCAA	29	12 mo	-	60	24/6	RCT
		Control	32			60	27/7	
Michel H, 1985	France	BCAA	36	5 d	A/B/C	60.5 ± 11.5	25/11	RCT
		Control	34			59.3 ± 12.8	24/10	
Ruiz-Margain, A, 2017	Mexico	BCAA	37	6 mo	A/B	54.9 ± 10.3	6/31	RCT
		Control	35			47.8 ± 14.6	8/27	
Masahiro Kobayashi, 2008	Japan	BCAA	19	168 wk	A/B	62.9 ± 5.7	19/0	RCT
		Control	20			59.5 ± 7.2	20/0	

BCAA: Branched-chain amino acid; N: Number; M: Male; F: Female; RCT: Randomized controlled trial.

of the LC was significantly increased in BCAA-treated patients (MD: 13.04, 95%CI: 6.81-19.89,  $P = 0.0002$ , [Figure 8B](#)).

## DISCUSSION

In our meta-analysis, we demonstrated that BCAAs reduce the occurrence of complications in patients with LC. Moreover, nutritional status was improved by BCAA treatment. There was no significant publication bias in the main outcome indicators ([Figure 9](#)).

The occurrence of LC complications indicates the decompensated stage of LC, and the prognosis is inferior. It is essential to delay the progression of LC. Most of the complications of LC were hepatic encephalopathy, ascites and esophageal varices in our analysis. Our study showed that BCAAs can significantly reduce the occurrence of complications. In our opinion, the mechanism by which BCAAs ameliorate hepatic encephalopathy mainly includes the following aspects. First, BCAAs can promote the metabolism of ammonia in muscle and reduce the level of blood ammonia in patients with hepatic encephalopathy[33]. Second, BCAAs can ameliorate albumin levels in patients with hepatic encephalopathy[34,35] thus increasing skeletal muscle weight. The increased muscle mass may increase extrahepatic ammonia detoxification[36]. Third, BCAAs may further enhance the detoxification of ammonia in skeletal muscle through the amidation process of glutamine synthesis[37]. Last, the addition of BCAAs reduces the brain efflux of aromatic amino acids across the blood brain barrier and the imbalance of dopamine, norepinephrine and serotonin synthesis[38]. There is a lack of detailed research on the mechanism by which BCAAs prevent other complications. Although many studies have shown that BCAAs are helpful for delaying LC[17,19], Michel *et al*[32] and Kobayashi *et al*[31] showed that BCAAs have no pronounced effect on the progression of LC. However, the subgroup analysis showed that BCAAs could inhibit the occurrence of hepatocellular carcinoma (HCC) in patients with compensated cirrhosis whose serum albumin level was less than 4 g/gL[31].

We also showed that BCAAs increased the nutritional status in patients with LC. The albumin level is an important indicator to evaluate the nutritional status of patients with LC. However, there is no further discussion on the correlation between albumin level and BCAA treatment. Some studies have shown that BCAAs can significantly improve the level of albumin[17,19,20]. In addition, many studies used mid-arm muscle circumference (MAMC) and skinfold thickness to determine patients' nutritional

Table 2 Patient baseline characteristics of studies included in the meta-analysis, *n* = 1080

Trail	Group	Albumin in g/dL	Etiology as viral hepatitis/alcoholic/others	Ascites as absent/presence	Hepatic encephalopathy as absent/presence	Esophagogastric varices as absence/presence
Etsushi Kawamura, 2009	BCAA	3.70 ± 0.38	25/2/0	27/0	27/0	27/0
	Control	3.81 ± 0.32	21/2/0	23/0	23/0	23/0
Muto, Y, 2005	BCAA	3.3 ± 0.3	266/20/28	240/74	287/27	144/170
	Control	3.3 ± 0.3	237/32/39	241/66	295/12	121/187
Yutaka Nakaya, 2007	BCAA	3.0 ± 0.4	-	16/3	-	-
	Control	3.0 ± 0.3	-	15/4	-	-
Les, 2011	BCAA	2.9 ± 0.6	24/17/17	-	-	-
	Control	2.9 ± 0.5	18/25/15	-	-	-
Tangkijvanich P, 2000	BCAA	3.81 ± 0.86	6/6/2	-	-	-
	Control	3.66 ± 0.75	7/6/2	-	-	-
Marchesini, G, 1990	BCAA	3.41 ± 0.45	9/20/1	-	-	-
	Control	3.39 ± 0.43	7/16/1	-	-	-
Michel, H, 1985	BCAA	2.61 ± 0.10	4/28/4	10/26	0/36	-
	Control	2.76 ± 0.08	4/29/1	11/23	0/34	-
Ruiz-Margain, A, 2017	BCAA	3.2 ± 0.6	-	-	-	-
	Control	3.2 ± 0.7	-	-	-	-
Masahiro Kobayashi, 2008	BCAA	3.86 ± 0.26	-	19/0	19/0	9/10
	Control	3.90 ± 0.33	-	20/0	20/0	10/10

BCAA: Branched-chain amino acid.

level with LC[24]. These indexes are essential for evaluating the nutritional level of patients with LC. However, there is no meta-analysis on these indexes in this paper due to the lack of several homogeneous studies. Meanwhile, sarcopenia is a complication of LC and an independent risk factor for the disease[39,40]. Qiu *et al*[41] confirmed that hyperammonemia-induced autophagy is a potential cause of skeletal muscle loss in cirrhosis. The incidence of sarcopenia is increasing year by year. Kitajima *et al*[42] confirmed that BCAAs could prevent muscle loss. A large number of experiments are needed to explore the effect of BCAAs on patients with LC and sarcopenia.

Meanwhile, the decreases in AST and ALT were investigated after BCAA treatment. ALT and AST are enzymes of hepatic gluconeogenesis. When hepatocytes are damaged, they are released from the cells. The increase in AST and ALT levels can be used as a reference index of liver function damage, but other diseases may increase AST and ALT levels which need to be excluded[43]. The included studies did not adequately report data on INR, creatinine, resolution of ascites or remission of encephalopathy. Therefore, as a meta-analysis, the relationship between BCAAs and liver function could not be determined at this time. Additionally, with regard to bilirubin, the meta-analysis related to bilirubin was not statistically significant due to the heterogeneity of the included studies and inadequate sample size, and it is hoped that more studies with sufficient data size will be discussed further in the future.

The meta-analysis of the two studies included in this paper demonstrated that BCAAs might increase the glucose level of patients. BCAAs have a specific effect on blood glucose, which has been confirmed in many studies. A review has shown that BCAAs may increase insulin resistance. Elevated BCAAs stimulate mTORC1, a nutrient sensing complex, and IRS-1 serine phosphorylation results in insulin resistance and other metabolic disorders[44]. Simultaneously, it has been widely confirmed that BCAAs upregulate glucose transporters and activate insulin secretion[45-47]. Some studies have shown that BCAAs may induce insulin resistance by inhibiting insulin signaling[48,49]. Recently, a clinical trial showed that BCAAs can induce insulin resistance through mTOR activation[50]. In contrast, it is still reported that BCAAs can decrease insulin resistance[51,52]. Despite the controversy, we recommend, based on our results, that we still need to adhere to monitoring the changes in blood glucose and be alert to endocrine disorders when taking BCAAs. In addition, it has been reported that supplementation with BCAAs may lead to an increase in ammonia produced by glutamine decomposition in the intestine and kidney due to the stimulating effect of BCAAs on glutamine synthesis, which may harm the

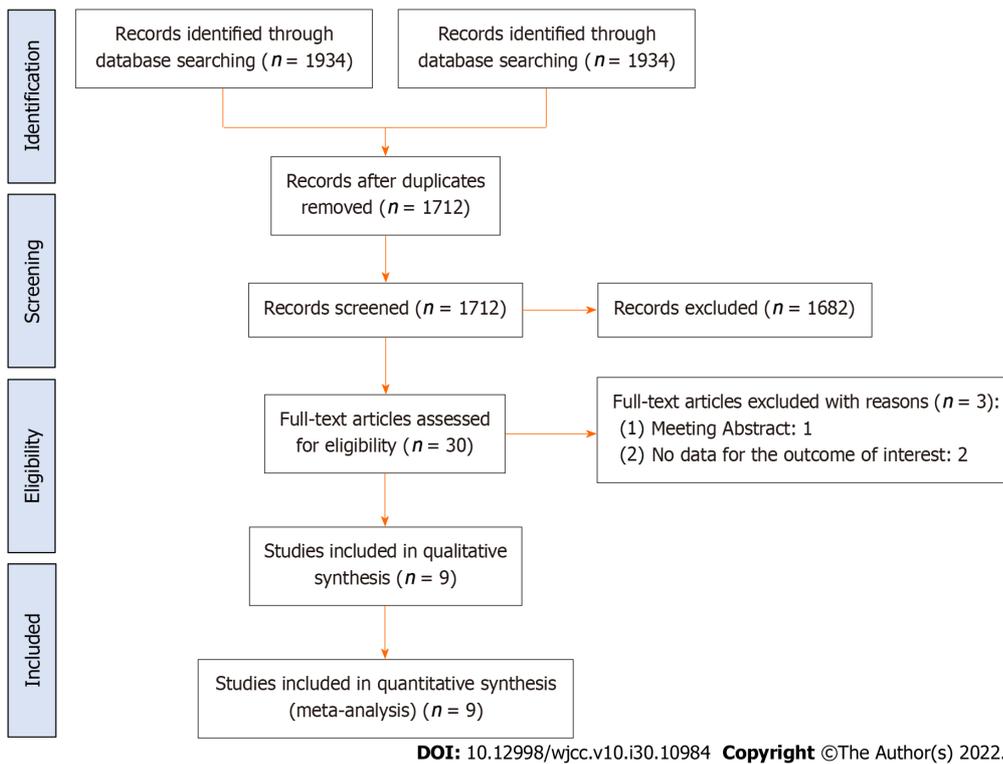


Figure 1 Flow chart of the literature search and study selection.

Author (Year)	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Esusshi Kawamura, 2009	+	+	+	+	+	+	+
Les, 2011	+	+	+	+	+	+	+
Marchesini, G., 1990	+	+	+	+	+	+	+
Masahiro Kobayashi, 2008	+	?	?	?	+	+	+
Michel, H., 1985	+	?	?	?	+	+	+
Muto, Y., 2005	+	+	+	+	+	+	+
Ruiz-Margain, A., 2017	+	+	+	+	+	+	+
Tangkiyanich, P., 2000	+	?	?	?	+	+	+
Yutaka Nakaya, 2007	+	+	+	+	+	+	+

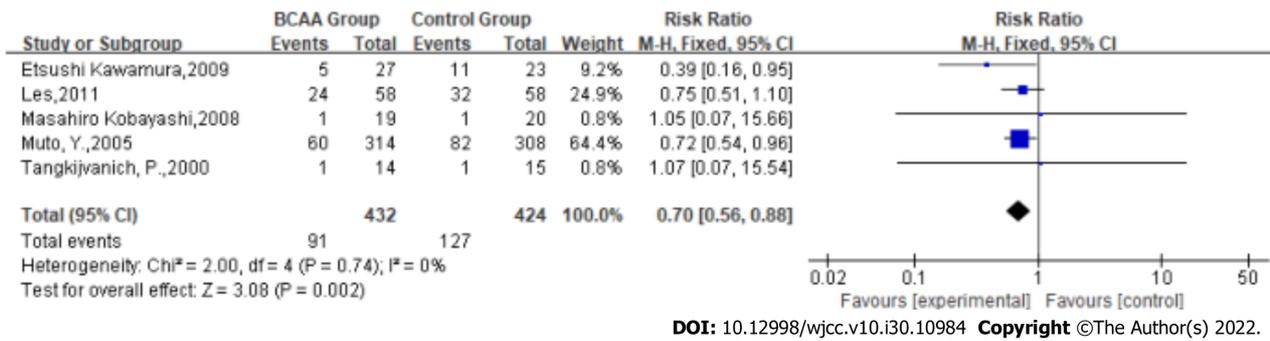
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Figure 2 Risk of bias summary of all studies.

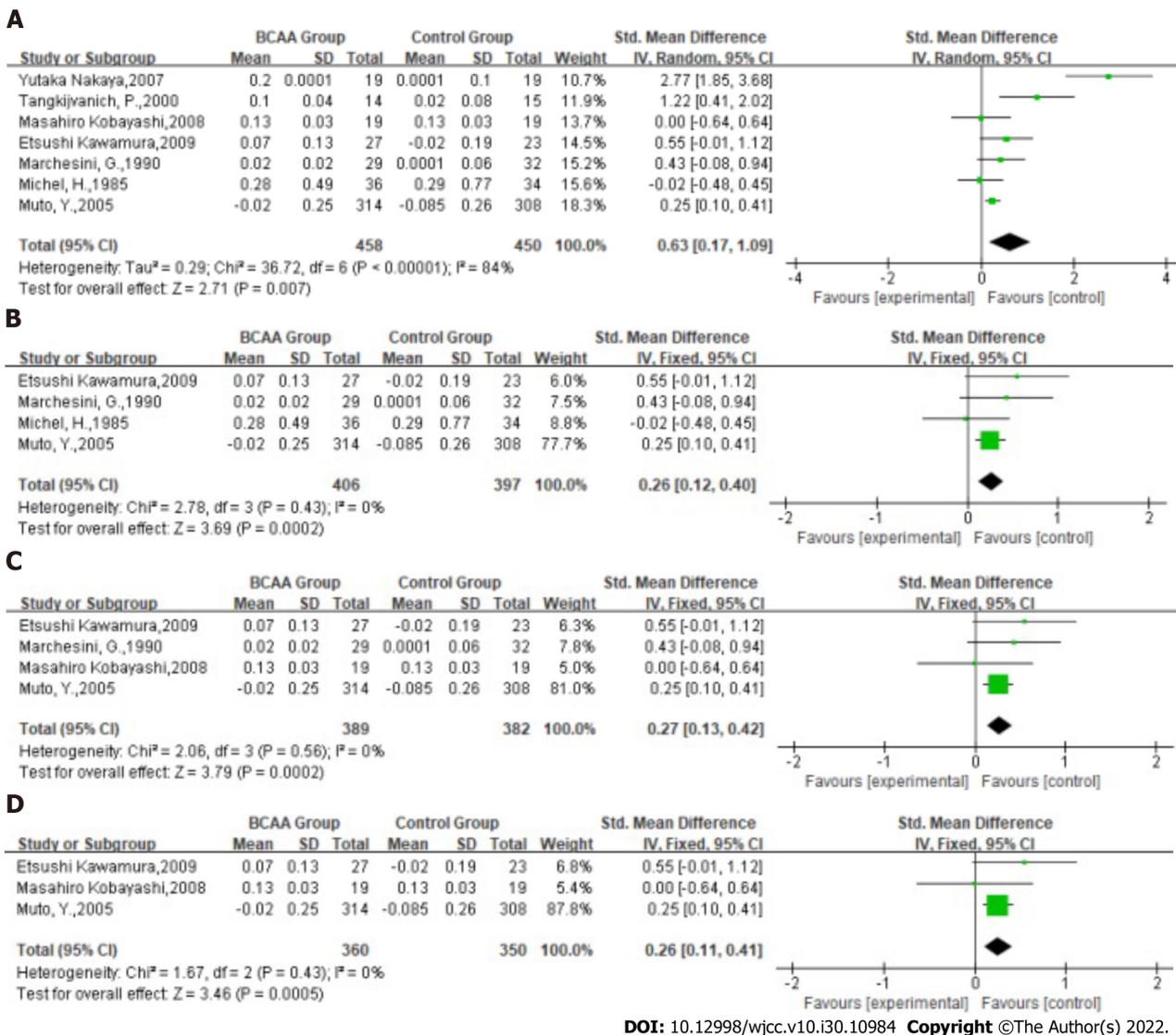
development of hepatic encephalopathy. Therefore, BCAAs and  $\alpha$ -ketoglutarate or phenyl butyric acid should be used simultaneously to treat hepatic encephalopathy[53].

Our study has some limitations. First, the article only included RCT research, excluding non-RCT research. Second, the article aims to uneven the population areas and lacks targeted research for a specific area. There may be deviations in treatment. Third, because of the lack of high-quality literature in this area, we only selected the articles that met the requirements after excluding the quality problems and needed large-scale experiments to confirm our ideas further.

Finally, our results provide a reference for the nutritional treatment of patients with LC which is helpful for clinical and nursing applications. We hope that there will be better nutritional support treatment plans for LC patients in the future.



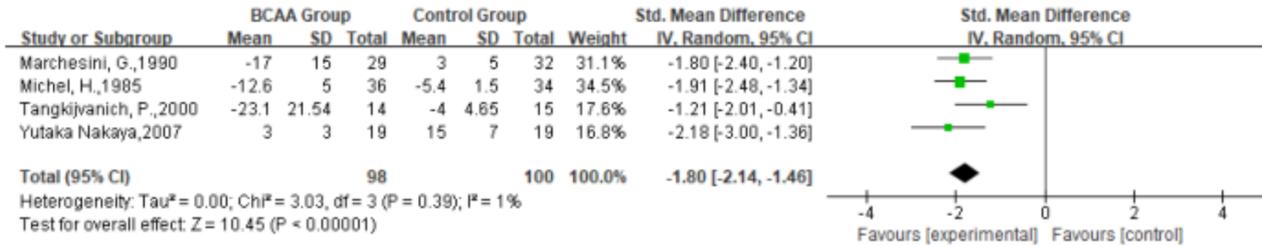
**Figure 3** Forest plots of the meta-analysis of the complication rate. BCAA: Branched-chain amino acids; N: Number; CI: Confidence interval; I<sup>2</sup>: I-square.



**Figure 4** Forest plots. A: Forest plots of the meta-analysis of the albumin level; B: Forest plots of subgroup analysis of the albumin level (studies with a total number of patients less than 50 were excluded); C: Forest plots of subgroup analysis of the albumin level (studies with treatment duration greater than 3 mo were excluded); D: Forest plots of subgroup analysis of the albumin level (among the included studies, the majority of patients had Child grade A or B and treatment duration was greater than 3 mo). BCAA: Branched-chain amino acids; N: Number; CI: Confidence interval; SMD: Standard mean difference; I<sup>2</sup>: I-square.

## CONCLUSION

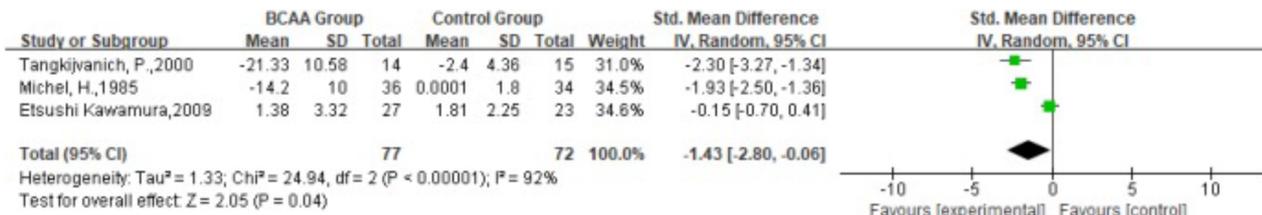
Branched-chain amino acids could reduce the incidence of complications in patients with liver cirrhosis and ameliorate nutritional status.



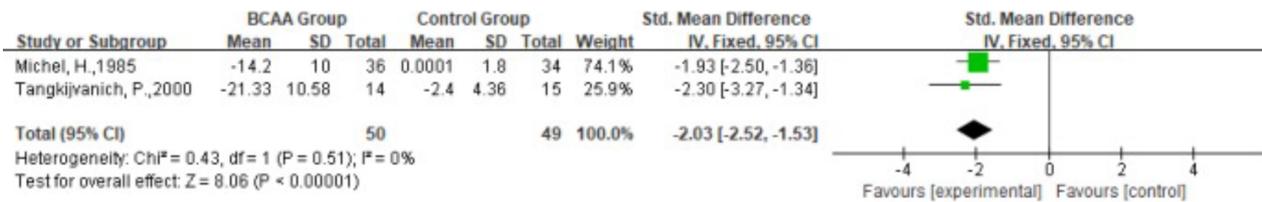
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**Figure 5** Forest plots of the meta-analysis of the aspartate aminotransferase level. BCAA: Branched-chain amino acids; N: Number; CI: Confidence interval; SMD: Standard mean difference; I<sup>2</sup>: I-square.

**A**

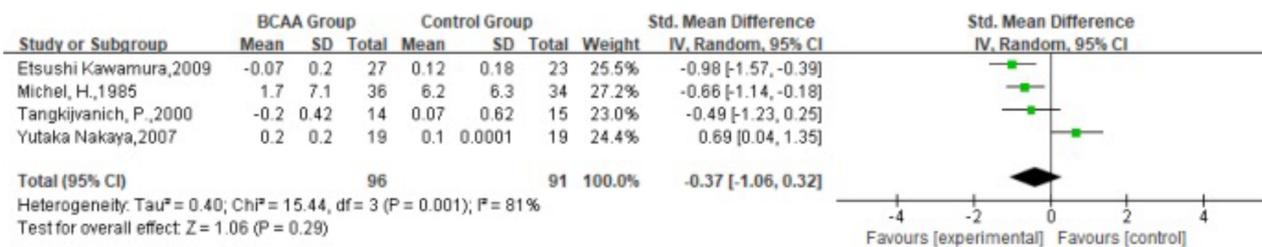


**B**



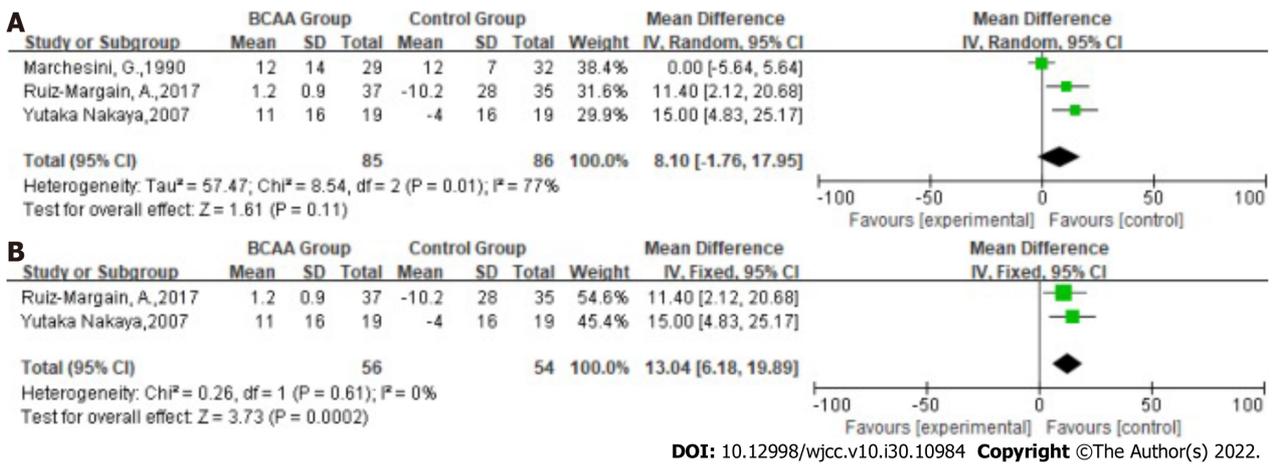
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**Figure 6** Forest plots. A: Forest plots of the meta-analysis of the alanine transaminase (ALT) level; B: Forest plots of subgroup analysis of the ALT level (Kawamura *et al*[19]'s study was excluded). BCAA: Branched-chain amino acids; N: Number; CI: Confidence interval; SMD: Standard mean difference; I<sup>2</sup>: I-square.

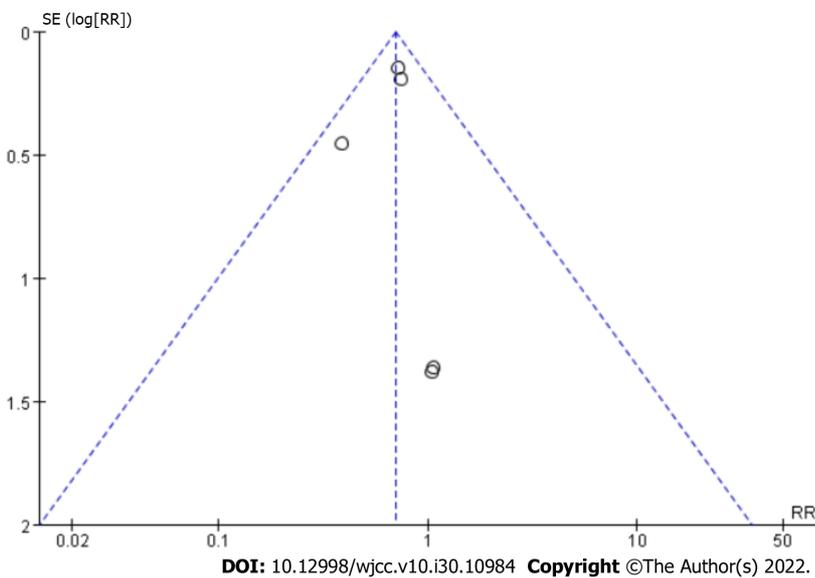


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**Figure 7** Forest plots of the meta-analysis of the bilirubin level. BCAA: Branched-chain amino acids; N: Number; CI: Confidence interval; SMD: Standard mean difference; I<sup>2</sup>: I-square.



**Figure 8 Forest plots.** A: Forest plots of the meta-analysis of the glucose level; B: Forest plots of subgroup analysis of the glucose level (the Child grade of the patients in the included studies was A or B). BCAA: Branched-chain amino acids; N: Number; CI: Confidence interval; SMD: Standard mean difference; I<sup>2</sup>: I-square.



**Figure 9 Publication bias.**

## ARTICLE HIGHLIGHTS

### Research background

Liver cirrhosis (LC) mainly includes increasing dietary intake, food intake time and branched-chain amino acids ( BCAAs). Despite the recommendation of BCAAs in some guidelines, adverse effects have been reported in studies so the efficacy and safety of BCAAs remain controversial.

### Research motivation

We performed a meta-analysis to determine the effects of BCAAs in patients with LC.

### Research objectives

To determine the effects of BCAAs in patients with LC.

### Research methods

Nine studies were finally included. The primary outcome was complications of LC. The secondary outcomes were nutritional status and liver function. This meta-analysis used the Review Manager, version 5 statistical package (Cochrane Collaboration, Oxford, England) for analysis.

### Research results

BCAAs reduced the rate of complications in LC patients (Risk ratio: 0.70, 95% confidence interval (CI):

0.56-0.88,  $P = 0.002$ ) and improved patients' albumin levels [std mean difference SMD: 0.26, 95%CI: 0.12-0.40,  $P = 0.0002$ ]. Meanwhile, BCAAs significantly ameliorated the levels of alanine transaminase (SMD: -2.03, 95%CI: -2.52 to -1.53,  $P < 0.00001$ ) and aspartate aminotransferase (SMD: -1.8, 95%CI: -2.14 to -1.46,  $P < 0.00001$ ). Meanwhile, glucose in the LC was significantly increased in BCAA-treated patients (MD: 13.04, 95%CI: 6.81-19.89,  $P = 0.0002$ ).

### Research conclusions

Branched-chain amino acids could reduce the incidence of complications in patients with liver cirrhosis and ameliorate nutritional status.

### Research perspectives

Our results provide a reference for the nutritional treatment of patients with LC which is helpful for clinical and nursing applications. We hope that there will be better nutritional support treatment plans for LC patients in the future.

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## FOOTNOTES

**Author contributions:** Du JY contributed to conception and design; Zhang L contributed to administrative support; Du JY, Liu S, and Zhou YT contributed to data collection, assembly, analysis and interpretation; all authors contributed to manuscript writing and final approval of the manuscript.

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**P-Editor:** Zhang XD

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