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Meta-analyses

Efficacy of branched chain amino acids supplementation in liver cirrhosis: A systematic review and meta-analysis

Georgios Konstantis [a], Chryssa Pourzitaki [a, *], Michail Chourdakis [b], Elisavet Kitsikidou [a], Georgios Germanidis [c]

[a] Clinical Pharmacology, Faculty of Medicine, School of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece
[b] Laboratory of Hygiene, Social & Preventive Medicine and Medical Statistics, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece
[c] Division of Gastroenterology and Hepatology, 1st Department of Internal Medicine, AHEPA University Hospital, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece

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SUMMARY

Background: Branched chain amino acids' (BCAAs) beneficial role in the management of hepatic encephalopathy is already well established, whereas a number of randomized clinical trials (RCTs) have showed promising results examining BCAA supplementation in the management of other aspects of liver cirrhosis. Current results in the light of BCAAs' biochemical properties make them an attractive supplementation option, in addition to standard pharmaceutical treatment of cirrhosis.
Aim: The aim of this systematic review is to summarize the current literature and assess the efficacy of BCAA supplementation in patients with liver cirrhosis.
Methods: Major electronic databases and grey literature sources were searched up to October 4th, 2021 for RCTs assessing the supplementation of BCAA against an active comparator, diet or placebo in patients with liver cirrhosis.
Results: Twenty RCTs fulfilled selection criteria. Relative to other interventions BCAAs showed beneficial effect regarding muscle mass (SMD 0.21, 95% CI 0.01 to 0.4, I^2 0%), but no effect regarding fat mass. Furthermore, BCAAs were associated with significant increase in plasma albumin concentration (SMD 0.52, CI 95% 0.18 to 0.86, I^2 84.99%), reduction in occurrence of serious cirrhotic complications (logOR −046, CI 95% −0.78 to −0.13, I^2 0%) and increase in body mass index (WMD 0.24, CI 95% 0.08 to 0.40, I^2 0%). On the other hand, no significant effect was noted concerning the incidence of mortality.
Conclusion: Supplementation with BCAA seems to improve significant prognostic factors for patients with cirrhosis, with potential positive impact in mortality. Heterogeneity of study findings attributed to many factors limit overall conclusion and results require further assessment.

1. Introduction

Cirrhosis is a late stage of chronic liver disease, characterized by replacement of normal hepatic parenchyma by scarring tissue, due to progressive fibrosis, and formation of regenerative nodules. Despite the fact that effective treatments are now available for some of the previous leading causes of cirrhosis, such as hepatitis C virus (HCV), the individual and public health burden remains high, especially in lower income countries [1].

Many of the serious complications characterizing cirrhosis, are considered a result of interactions between several mediators, such as ammonia, decreased hormones [testosterone, insulin-like growth factor-1(IGF-1)], and endotoxemia [2]. Deterioration of liver function and portosystemic shunting, accompanied by insufficient ammonia removal through urea cycle, are thought to be pivotal events for the establishment of cirrhosis [3].

Several randomized clinical trials (RCTs) have showed a strong correlation between cirrhotic malnutrition and development of serious complication of cirrhosis, such as hepatorenal syndrome, hepatic encephalopathy, and fatal infections [4], suggesting overlapping pathophysiological pathways. Moreover, taking into account the lower survival rates in malnourished cirrhotic patients, malnutrition is indubitably considered an independent prognostic

* Corresponding author. School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Greece University, University Campus, 54124, Thessaloniki, Greece.
E-mail address: chpour@gmail.com (C. Pourzitaki).

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Abbreviations

a-KG	a-Ketoglutarate
AAA	Aromatic Amino Acids
AMA	Arm Muscle Area
AMC	Arm Muscle Circumference
BCAA	Branched Chain Amino Acids
BCKA	Branched Chain Keto Acids
BIA	Bioelectrical Impedance Analysis
BMI	Body Mass Index
CI	Confidence Interval
EASL	European Association for the Study of the Liver
ESPEN	European Society for Clinical Nutrition and Metabolism
g.	Grams
GLN	Glutamine
HAIC	Hepatic Artery Infusion Chemotherapy
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C virus
IGF-1	Insulin like growth factor-1
L-ALB	Lacto-albumin
M-DXT	Maltodextrin
MAFA	Midarm Fat Area
MAMC	Midarm Muscle Circumference
mTORC1	Mammalian target of rapamycin complex 1
N/A	Not Available
OR	Odds Ratio
RCT	Randomized Clinical Trial
RFA	Radio-frequency Ablation
RoB	Risk of Bias
SMD	Standardized mean difference
TACC	Treatment Arm Continuity Correction
TACE	Transarterial chemoembolization
TCA	Tricarboxylic acid
TSF	Tricep Skin Fold
vs	Versus
WMD	Weighted mean difference

factor [5]. It is advised for cirrhotic patients that a thorough nutritional assessment is being made at regular basis using a vast array of clinical, imaging, and biochemical methods [6]. Among them, simple bedside anthropometric measurements, such as mid-arm muscular area (MAMC) and triceps skin fold (TSF), although not as accurate as more advanced methods (e.g., dual-energy X-ray absorptiometry and cross-sectional computed tomographic image analysis), provide a reasonable and adequate quantification of skeletal muscle mass [7]. In addition according to recent data [8] a strong agreement exists between MAMC measurements and newer methods regarding muscle mass evaluation in patients with cirrhosis. Serum albumin concentration and body mass index (BMI), provide valuable clues regarding the nutritional state, despite the fact that their values may be affected from events, such as edema, ascites formation, and decreased synthetic ability due to cirrhosis [9,10].

Various interventions have been implemented in the clinical setting for the reversal and prevention of cirrhotic malnutrition, ranging from simple remedies, such as prohibition of meat intake, to hormone replacement therapy, with testosterone or growth hormone [11]. Moreover, supplementation with branched chain amino acids (BCAAs) (namely Valine-Leucine-Isoleucine, a type of essential amino acids with a aliphatic side branch chain) has been characterized as a potential treatment for many of the metabolic alterations and resultant complications accompanying cirrhosis [12].

The favorable effects of BCAAs in hepatic encephalopathy are already well established [13]. Although recent recommendation by EASL [6], suggests supplementation with BCAA in patients with chronic liver disease, an extended synopsis of the available evidence is needed, due to mixed results from previous analyses and lack of high level of evidence.

Therefore, we conducted a systematic review and meta-analysis of RCTs comparing BCAAs with placebo or other interventions in adult patients with liver cirrhosis to analyze evidence on their efficacy, with a special interest in malnutrition parameters.

2. Materials and methods

This systematic review and meta-analysis has been conducted according to the PRISMA statement [14]. Extensive research of literature was performed searching electronic databases Medline, Scopus and Cochrane including the following terms "*cirrhosis*," "*liver*," "*branched chain*," "*amino acids*" in combination up to 4th October 2021. Search strategy is presented in detail in Supplementary File 1. Grey literature sources and the archives of European Association for the Study of the Liver (EASL) and the European Society of Clinical Nutrition and Metabolism (ESPEN) were also searched for. No language restrictions were placed on the search so as to reduce systematic publishing error. Cirrhosis was defined by pathological, imaging, and clinical criteria. In order to increase the possible search results and the number of articles under evaluation, synonymous phrases or a combination of words with the use of the terms "*and*," "*or*" were used.

2.1. Eligibility criteria

RCTs comparing BCAA, administered orally or intravenously vs placebo or any other intervention in adult patients with liver cirrhosis, which reported data for at least one of the foreordained outcomes of interest were included in the meta-analysis. Studies comparing BCAA supplementations with other formulas containing BCAA were excluded. Considering the already important body of data that justifies the use of BCAA in patients with over hepatic encephalopathy and the increased mortality rate accompanying these patients, such studies were also excluded. When a trial examined BCAA supplementation in cross-over fashion, data from the first period only were taken into account, due to potential carry-over effect.

2.2. Data collection and extraction

Suitable records were imported in Endnote 19 and duplicates were removed. Two independent reviewers (GK, EK) examined records retrieved from the aforementioned sources, at title and abstract level and afterward eligible studies in full text level. Any discords occurred during study selection were solved by a third reviewer (CP). Data of the included studies, concerning year of publication, follow-up period, dosage, and ratio of administered BCAAs, baseline characteristics, number of participants and type of comparator in each study, were extracted to a prespecified form by two independent reviewers (GK, EK).

2.3. Quality assessment

Cochrane risk of bias tool (ROB) 2.0 [15] was employed for the assessment of risk of bias for the primary outcomes, by two

independent reviewers (GK, EK), with any disagreement at this state being resolved by a third reviewer (CP). ROB 2.0 incorporates data regarding randomization process, deviations from intended interventions, missing outcome data, selection of the reported results, and measurement of the outcome. According to ROB 2.0 any study fulfilling all individual domains as low risk, was categorized as low risk and in contrast if any eligible study was found to fulfill any domain as high risk, was considered high risk. In all other circumstances RoB was appraised as with some concerns. For the existence of publication bias funnel plot and Egger's test were mustered for some outcomes. We conducted sensitivity analysis to validate the robustness of our results.

2.4. Outcome measurements

Primary outcomes were considered the effect of BCAA supplementation in relation to body composition, i.e., anthropometric characteristics, changes in serum albumin concentration and all-cause mortality in patients with liver cirrhosis. Secondary outcomes were considered the incidence of liver cirrhosis-associated serious complications and changes in body mass index (BMI). If a study included more than one active comparator, it was preferred to include data from the study arm that involved a placebo or no other intervention, when evaluating continuous outcomes. If a trial studied multiple BCAA supplementation methods in different groups, their data were combined to a single measurement. Data on BCAA dosage, ratio, time of administration, severity of liver cirrhosis, and details about interventions apart from nutritional supplementation used in some studies were also gathered. We chose to evaluate data referring only to the period of BCAA supplementation for biochemical data and malnutrition parameters regardless of the follow up period of each study. Regarding cirrhotic complications and death from all causes we evaluated data from the maximum available follow up period. When studies with zero events in one treatment groups were included in analyses of dichotomous data, the treatment arm continuity correction was implemented to each cell [16].

2.5. Statistical analysis

Data for continuous outcomes were extracted and weighted mean difference with 95% confidence intervals (CIs) was calculated using DerSimonian-Laird estimation method [17], when the same outcome measure was used among treatment and comparator arm of the study. In contrast standardized mean difference with 95%CIs was calculated using Hedges' g [18] estimation method was used when different measures for the same outcome were reported. We chose to address change in serum albumin and BMI, as change from baseline, because previous analyses with ANCOVA have showed strong relationship between final value and value at entry. In cases where a study was lacking any means of dispersion useful for calculation standard deviations, the method described in Cochrane Textbook was used [19]. For dichotomous data odds ratio alongside 95% CIs were calculated using restricted maximum likelihood method. Cochran's Q was used for exploration of the between study heterogeneity, and I^2 statistic was used for quantification of heterogeneity with a cutoff of 60% or more indicating high heterogeneity.

Due to great variability between studies due to differences in methodology and participant characteristics, a random effect formula was used, aside from between study heterogeneity. In an attempt to investigate clinical heterogeneity, sensitivity analyses were performed, taking into account severity of cirrhosis, whether or not trial participants received any other intervention apart from nutritional supplementation and frequency of administration of BCAA supplements. Because many studies were conducted in Japan, a post-hoc subgroup analysis examining the results in relation to country of origin of each study was performed. Dosage of BCAAs and duration of each study were also examined with the assistance of meta-regression when possible.

From a statistical point of view sensitivity analyses for primary outcomes based on the risk of bias and different estimation methodologies were also performed. All statistical analyses were made using STATA SE, version 16.1 (Stata Corp) and Review manager (RevMan 5.3, Nordic Cohrane Center, Copenhagen, Denmark). Our analyses included data on available cases and participants excluded from primary analysis due to protocol indiscipline, lost to follow up or other reasons were ignored under the assumption that they were missing at random.

3. Results

3.1. Search results

Twenty studies [20–39], all of which had BCAAs administered orally, were included in our systematic review. Basic characteristics of the studies and participants are summarized in Table 1. The study selection process and the reasons for exclusion are explicitly presented in Fig. 1.

3.2. Baseline characteristics

Twenty studies with a total number of 1297 cirrhotic patients at different stages of disease, were included. Participants' age ranged between 47.8 and 73.5 years. BCAA supplementations were compared with standard diet in 11 studies [20,22,24,26,27,32–34,36,37,39], with casein in 1 study [31], with maltodextrin (M-DXT) in 3 studies [23,29,30], with liquid nutrient snacks in 2 studies [25,37], and with L-albumin (L-ALB) in 1 study [30]. Two studies used multiple arms comparisons [30,32]. Dosage ranged from 5.25 to 30 g per day and ratio of administered BCAAs presented diversity, with all the studies, though, using supplements containing mainly isoleucine.

The duration of follow-up ranged between 1 and 168 weeks, whereas 12 studies examined the effects of BCAA supplementation for a period greater than 12 weeks [20,21,23,26,27,29–34,36]. Variance was also encountered concerning morbidity of cirrhosis, with child Pugh scores ranging from A to C, and number of participants. Seven studies [20,22,25,28,32,37,38] examined the effect of BCAA supplementation as concurrent intervention in cirrhotic patients undergoing treatments for complication of cirrhosis. Elaborately, four studies [22,28,32,38] examined BCAA supplementation in cirrhosis parallel with interventions for hepatocellular carcinoma (HCC) such as transarterial chemoembolization (TACE), radiofrequency ablation (RFA) while three [20,25,37] studies examined endoscopic treatment for varices.

In all studies, participants continued to take their standard therapy for cirrhosis which mostly consisted of lactulose, if a history of hepatic encephalopathy was present, b-blocker, furosemide, and Aldactone.

3.3. Risk of bias in the included studies

Regarding within study bias, 20 studies were assessed by two independent reviewers using the ROB 2.0, for the change from baseline in albumin concentrations body composition changes and mortality. Results are presented in Supplementary Tables 1-4. Publication bias, with usage of funnel plot and Egger's test, due to small study effect, was estimated only for albumin, due to inadequate number of studies for other endpoints. Analyses showed no small-study effect and thus low publication bias ($P = 0.957$) (Supplementary Figure 1).

Table 1
Basic characteristics and summary of trials.

First author, year, country	Patients randomized	Male (%)	Mean age (M ± SD)	Duration (weeks)	BCAA Dosage (g/day)	Interventions	Child-pugh score	Ratio Of BCAAs (Isol:Leu:Val)
Furuichi 2016, Japan	61	66%	66.8 ± 11.3	12	5.5	BCAA	A-B	N/A
		70%	64.3 ± 9.7			Diet		
Habu 2003, Japan	40	35%	66.9 ± 8.9	104	14.3	BCAA	A	N/A
		36%	64.1 ± 7.0			Control		
Harima 2010, Japan	26	84%	64.5 1 9.5	5	5.5	BCAA	A-B	35:36:29
		80%	66.4 1 12.8			Diet		
Hernádez-Conde 2021, Spain	44	88.2%	61.0 ± 9.4	12	5.25	BCAA	A-C	20:50:30
		86.7%	69.0 ± 9.7			M-DXT		
Ichikawa 2013, Japan	21	53%	66.2 ± 8.2	8	N/A	BCAA	A-B	N/A
		44%	67.4 ± 9.8			Diet		
Katsumi 2005, Japan	19	66%	61.6 ± 9.4	1	11	BCAA	A-C	N/A
		40%	62.4 ± 9.2			Snack (liquid nutrient)		
Kawamura 2009, Japan	56	48%	62.7 ± 10.0	Mean 166	12.45	BCAA	A	23:45:27
		52%	62.3 ± 7.3			Diet		
Kobayashi 2008, Japan	39	N/A	62.9 ± 5.7	168	12	BCAA	A	24:48:28
		N/A	59.5 ± 7.2			Diet		
Lee 2011, South Korea	50	95%	54.0 ± 11.2	6	12	BCAA	A	24:48:28
		88%	55.6 ± 10.3			Placebo		
Les 2011, Spain	116	77%	64.1 ± 10.4	56	30	BCAA	B–C	30:45:25
		74%	62.5 ± 10.4			M-DXT		
Marchesini 1990, Italy	64	80%	60(44–70)	24	Circa 16.5	BCAA	N/A	25:50:25
		79%	60(43–70)			Casein		
Marchesini 2003, Italy	174	61%	59.0 ± 1.0	52	14.4	BCAA	B–C	25:50:25
		66%	59.0 ± 1.0			M-DXT		
		62%	60.0 ± 1.0			L-ALB		
Mathias-Plauth 1993, Germany	17	66%	52.0 ± 10	8	Circa 12.5	BCAA	A-C	28.5:43:28.5
		62%	49.0 ± 14			Placebo		
Morihara 2012, Japan	31	80%	66.9 ± 9.7	12	5.5	BCAA-M	A-B	35:36:29
		80%	73.5 ± 8.5			BCAA-LES		
		70%	69.3 ± 8.0			Diet		
Muto 2005, Japan	625	46%	62.0 ± 8.0	104	12	BCAA	A-C	24:48:28
		47%	61.0 ± 9.0			Diet		
Nakaya 2007, Japan	47	68%	67.0 ± 9.0	12	6.1	BCAA	A-C	34:37:29
		36%	67.0 ± 8.0			Diet		
Ruiz-Margain 2017, Mexico	72	82.9%	54.9 ± 10.3	24	8.6	BCAA	A-B	30:45:25
		78.4%	47.8 ± 14.6			Diet		
Sakai 2015, Japan	44	68%	59.1 ± 12.0	1	12	BCAA	A-B	N/A
		60%	64.4 ± 9.2			Snack (liquid nutrient)		
		69%	64.3 ± 15.2			Diet		
Takeshita 2009, Japan	56	67%	69.1 ± 8.2	2	N/A	BCAA	A-B	N/A
		75%	70.6 ± 9.7			Diet		
Tangkijvanich 2000, Thailand	30	66%	53.0 ± 10.5	4	16.5	BCAA	A-C	N/A
		80%	53.2 ± 12.7			Diet		

N/A: not available, BCAA: branched chain amino acids, M: morning, LES: late evening snack, M-DXT: maltodextrins, L-ALB: lactoalbumin, SD: standard deviation.

3.4. Analysis of primary outcomes

3.4.1. Body composition

Data for the effect of BCAA supplementation in body composition were available in eight studies [20,23,25,29,34–36,39] and five studies [20,23,25,34,36] in relation to muscle mass and body fat, respectively.

3.4.2. Muscle mass

Two studies [20,25] reported MAMC percentage changes, four studies [29,34,36,39] reported change in centimeters for MAMC, while one study [23] used muscle mass index and another used arm muscle area (AMA) [35] as tools. BCAAs showed a beneficial effect compared with all other interventions (SMD 0.21, CI 95% 0.01 to 0.4, I^2 0%) (Fig. 2).

3.5. Sensitivity analyses

Analyzing data reporting changes in centimeter [29,34,36,39], results showed a trend for BCAAs in increasing muscle mass without statistical significance (WMD 0.32 cm, CI 95% −0.6 to 1.23, I^2 0%). Excluding a trial where muscle mass was assessed using AMA [35], a measure which takes into account TSF, results suggested a less noteworthy effect (SMD 0.16, CI 95% −0.05 to 0.37, I^2 0%). Results taking into consideration overall RoB 2.0, was not feasible due to lack of low bias studies.

In subgroup analyses, according to whether participants underwent additional interventions for cirrhotic complications (with concomitant interventions [20,25] SMD 0.25, CI 95% −0.18 to 0.68, I^2 0%, without concomitant interventions [23,29,34–36,39] SMD 0.20, CI 95% −0.03 to 0.43, I^2 0%) (Fig. 3), stage of liver cirrhosis (SMD 0.36, CI 95% −0.11 to 0.83, I^2 0%, for patients with decompensated cirrhosis [20,25,29,35], SMD 0.11, CI 95% −0.27 to 0.50, I^2 0%, for studies with a combination of cases [23,34,39], SMD 0.26, CI 95% −0.2 to 0.72, I^2 0%, for the only study [36] with exclusively compensated cirrhosis patients) (Fig. 4), frequency of BCAA administration (SMD 0.20, CI 95% −0.14 to 0.53, I^2 0%, for trials administrating BCAA once per day, SMD 0.08, CI 95% −0.27 to 0.44, I^2 0%, for trials administrating BCAA twice per day) (Fig. 5) and country of each study (SMD 0.16, CI 95% −0.19 to 0.52, I^2 0%, for studies conducted in Japan and SMD 0.24, CI 95% −0.01 to 0.49, I^2 0%, for studies conducted in other countries) (Fig. 6) results were also inconsistent with the main analysis, showing only a trend in muscle mass gain, without statistical significance.

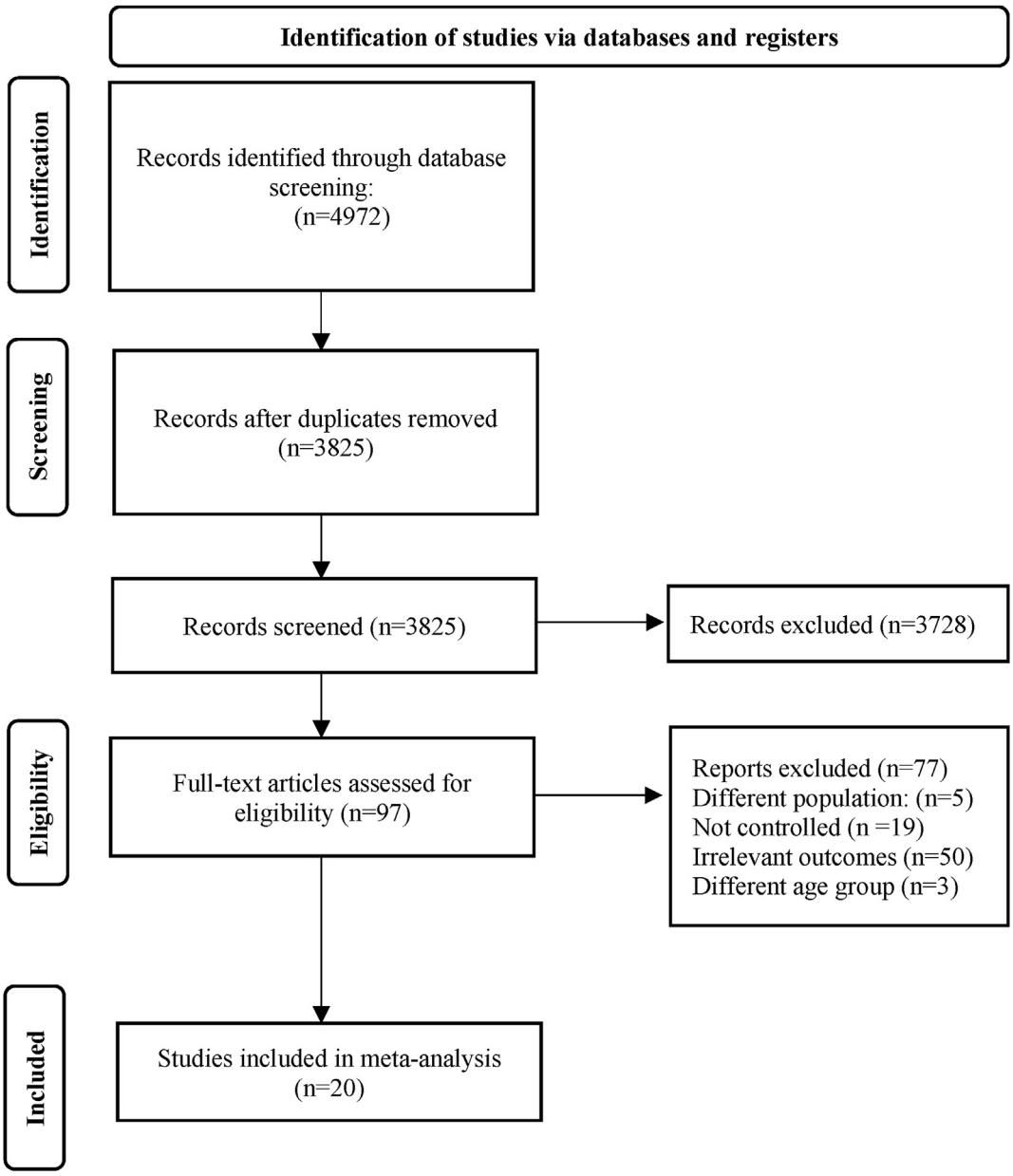

Fig. 1. Flow diagram for literature search.

3.6. Meta-regression

We also explored the relationship between muscle mass improvement and duration of each study as well as dosage, by performing meta regression. Regression coefficients were −0.03 and −0.03 respectively, and did not show significant correlation between the magnitudes of effect and duration or dosage as covariates. During cumulative analysis using duration as a covariate, as the number of weeks increased, *P*-value increased, and mean difference remained relatively unchanged.

3.6.1. Fat mass

Among the five studies that examined the effect of BCAAs in fat mass, four trials employed TSF [20,25,34,36] while one trial used CT measurements [23]. Three trials [20,23,25] assessed percentage changes while the other two reported results in millimeter [34,36]. BCAA supplementation had no effect in regard to TSF, compared with all other interventions (SMD −0.11, CI 95% −0.37 to 0.15, I^2 0%) (Fig. 7).

3.7. Sensitivity analyses

Results remained unchanged when concomitant interventions (Fig. 8), method of evaluating adipose tissue (Fig. 9), stage of cirrhosis (Fig. 10), and country of each study (Fig. 11) were taken into account.

3.8. Meta-regression

Regression coefficients were 0.06 for dosage and −0.01 for duration and dosage, without any statistical significance.

3.8.1. Change from baseline albumin concentration

Data from overall 1297 cirrhotic patients across 17 studies [20–28,30–34,37–39] were available to evaluate the efficacy of BCAA supplementation regarding changes in serum albumin concentration. Serum albumin concentration was significantly increased in patients randomized to BCAA supplementation (SMD 0.52, CI 95% 0.18 to 0.86, I^2 84.99%) (Fig. 12).

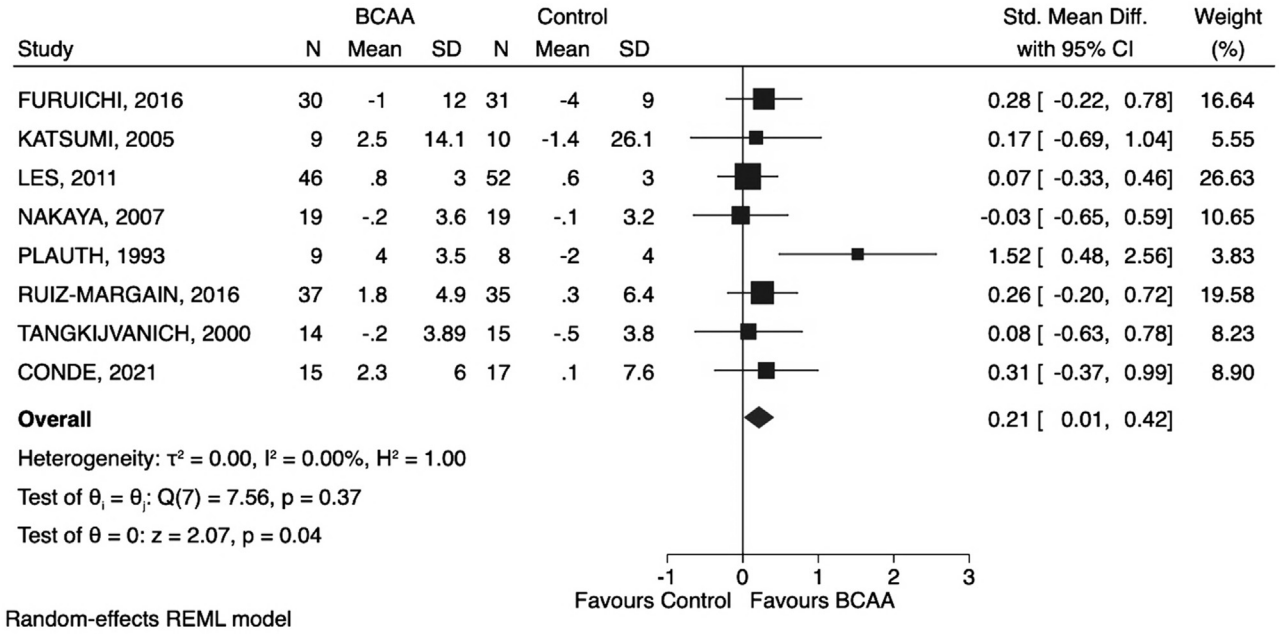

Fig. 2. Effect of BCAAs on muscle mass, main analysis SMD.

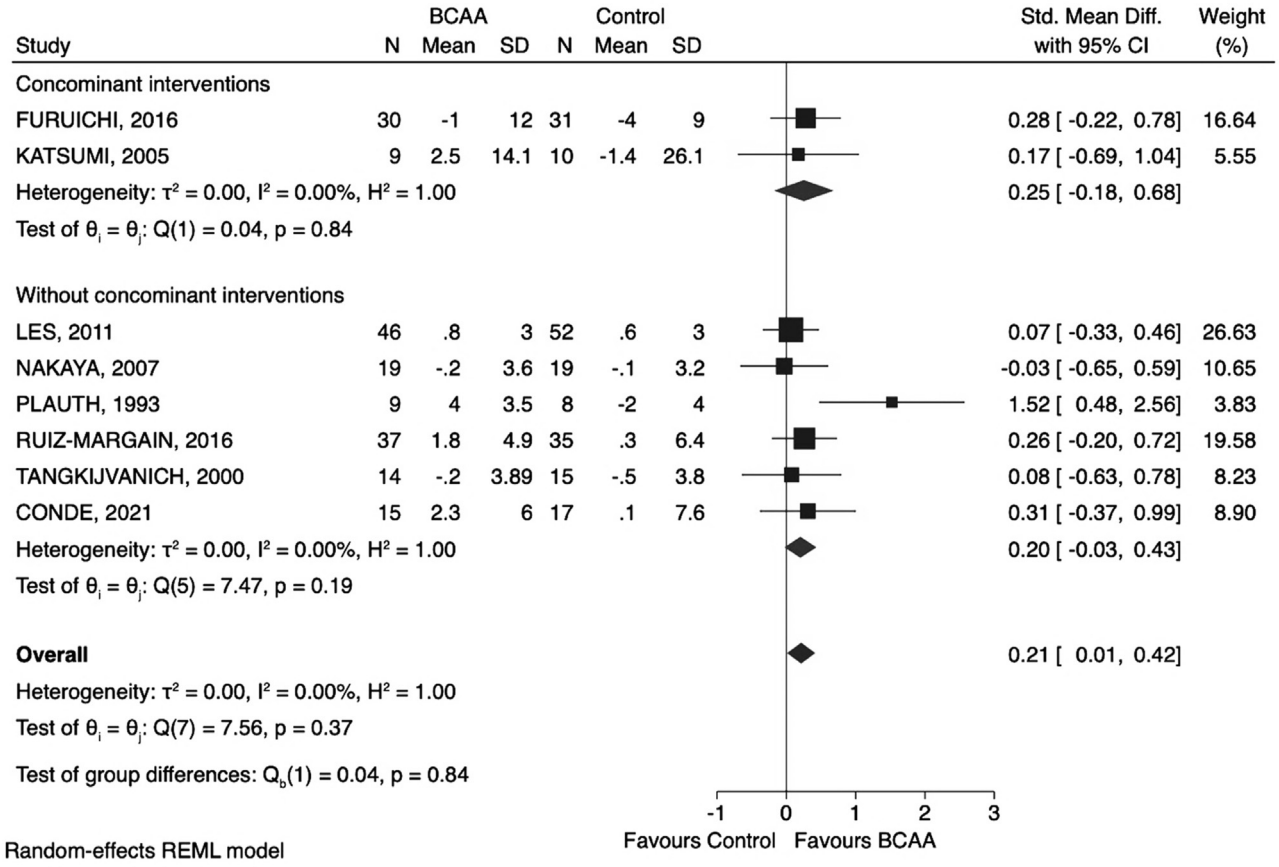

Fig. 3. Effect of BCAAs on muscle mass, subgroup analysis additional interventions for cirrhotic complications.

3.9. Sensitivity analyses

In subgroup analysis BCAA supplementation did not show favorable results in maintaining serum albumin concentration, with adjuvant treatments [20,22,25,28,30,32,37,38] for cirrhotic complications such as endoscopic therapy of varices or chemoembolization for HCC (WMD 0.38, CI 95% −0.02 to 0.78, I^2 58.8%) (Fig. 12). In a prespecified sensitivity analysis, where studies with

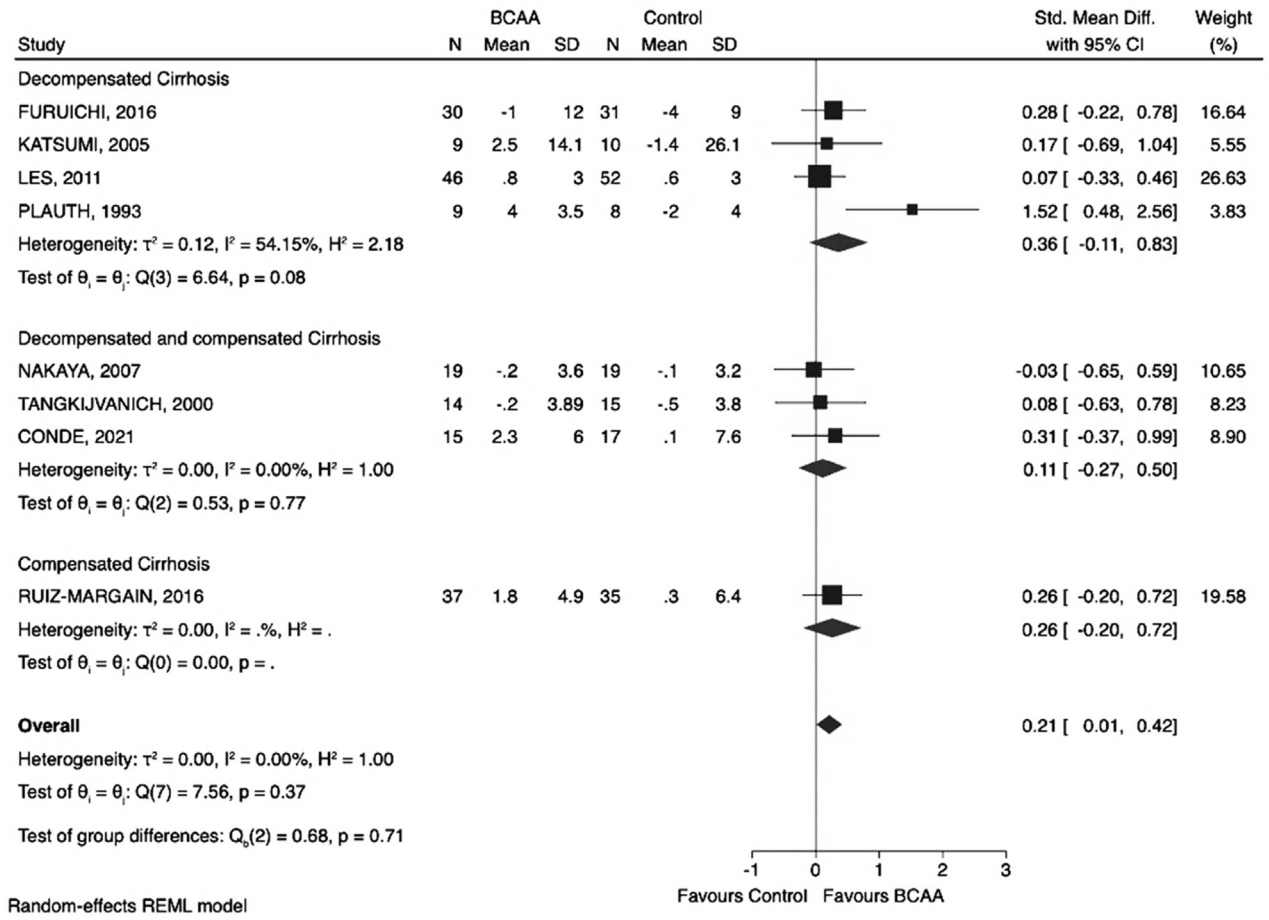

Fig. 4. Effect of BCAAs on muscle mass, subgroup stage of cirrhosis.

high risk of bias [4,21–23,25,26,34,37,39] were excluded, BCAAs did not showed significance in studies characterized as low risk of bias (WMD 0.32, CI 95% −0.27 to 0.92, I^2 92.1%) (Fig. 13). Duration of supplementation longer than 12 weeks, also showed greater improvement (SMD 0.72, CI 95% 0.2 to 1.25, I^2 91.4%). BCAA administration once per day showed better results in increasing serum albumin (SMD 0.73, CI 95% 0.23 to 1.22, I^2 72.34%) in contrast to twice and thrice per day, where no statistical significance was proved (Fig. 14). In an attempt to explain between-study heterogeneity, we conducted re-analysis, excluding the only study [37] presenting data as percentage changes through box plot and using weighted mean difference as an effect size. BCAAs showed WMD 0.13 g/dL, CI 95% 0.05 to 0.25, I^2 80%) (Supplementary Figure 2), increase in serum albumin. A secondary analysis, using data only extracted from text and not taking into account data presented in graphs or plots [20,28,30,32,33,37], agreed with our main analysis (WMD 0.55, CI 95% 0.09 to 1.01, I^2 80%) (Fig. 15). All the other analyses were in agreement with the main results.

3.10. Meta-regression

Due to existence of relatively high variation in regards of dosage and duration, meta-regression analyses taking into account the aforementioned parameters were performed. Regression coefficient were −0.02 and −0.02, respectively. Neither of these parameters explained the heterogeneity and neither of them bared any statistical significance. Excluding data from Kobayashi et al. [27], results were also in agreement with our main analysis.

3.11. Post-hoc analysis

In addition, BCAAs showed a stronger effect in increasing albumin concentration in post-hoc analysis considering studies recruiting patients with more severe hypoalbuminemia, using mean 3.5 g/dL albumin at baseline as a cutoff (SMD 0.73, CI 95% 0.26 to 1.2, I^2 81%) (Supplementary Figure 3) and studies that were conducted outside of Japan (SMD 0.78, CI 95% 0.21 to 1.34, I^2 76.9%) (Supplementary Figure 4).

We also performed cumulative analysis regarding duration and dosage (Supplementary Figures 5 and 6). Concerning duration, as the number of weeks increases, the overall standardized mean difference and its significance (*P*-value) also increases.

3.11.1. Mortality

Data from eight studies [22,23,28–31,33,34] were included in the evaluation of BCAA supplementation efficacy against mortality from all causes. Using a treatment arm continuity correction (TACC) approach to account for studies with zero event in one arm, BCAA supplementation showed a trend in improving survival, without achieving statistical significance (LogOR −0.34, CI 95% −0.91 to 0.23, I^2 0%) (Fig. 16).

3.12. Sensitivity analyses

Results were substantiated when data from two studies [22,28] that evaluated cirrhotic patients with concomitant hepatocellular carcinoma and from a study [34] that the only case of death was

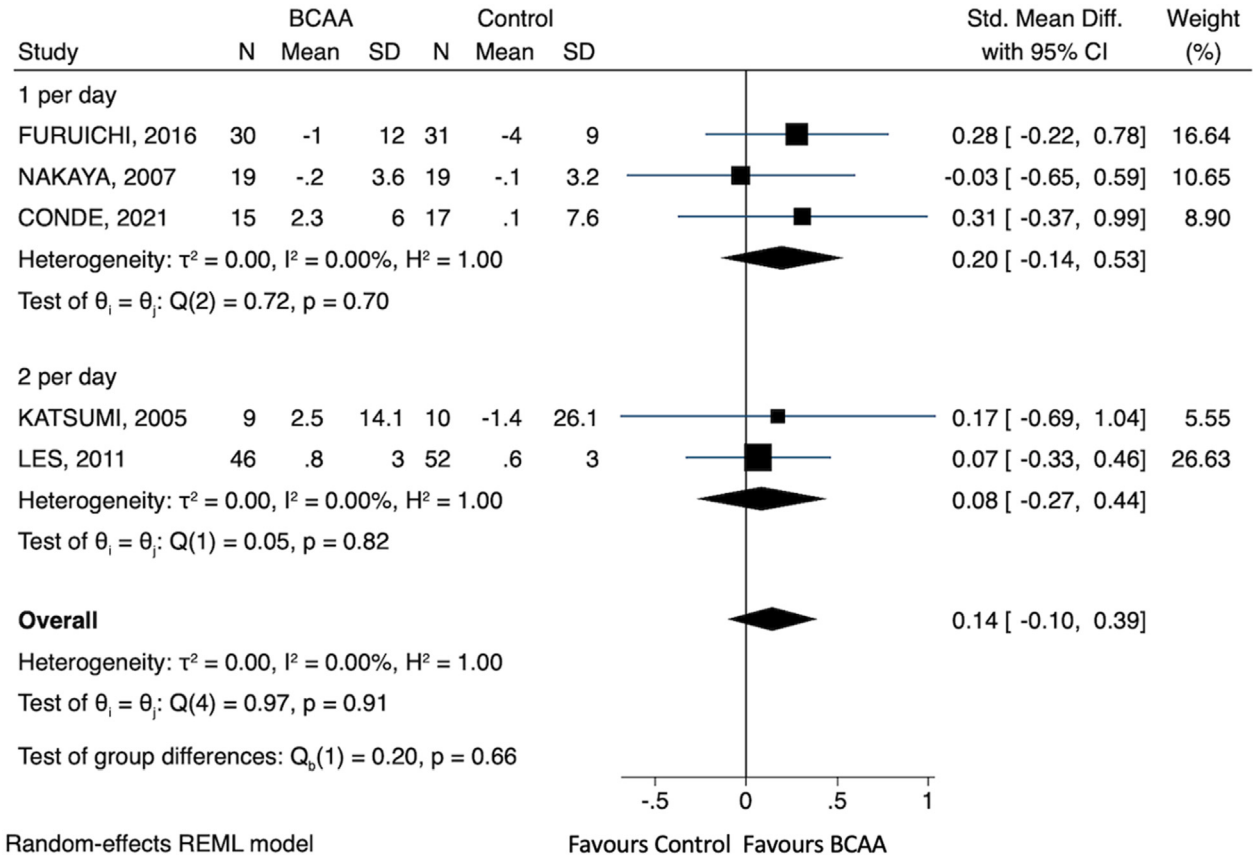

Fig. 5. Effect of BCAAs on muscle mass, subgroup frequency of administration.

accounted to cerebral bleeding were excluded (logOR −0.33, CI 95% −0.93 to 0.27, I^2 0% and logOR −0.38, CI 95% −0.99 to 0.23, I^2 0%, respectively). Results were also supported excluding studies [22,23,29,34] with high RoB (logOR −0.55, CI 95% −1.26 to 0.17, I^2 0%) (Fig. 17).

Subgroup analysis showed similar results for both short term (LogOR −0.68, CI 95% −2.01 to 0.64) and long term (LogOR −0.26, CI 95% −0.89 to 0.37, I^2 0%) BCAA supplementation (Supplementary Figure 7) as well as for administration of BCAAs once (LogOR −0.26, CI 95% −2.03 to 1.51, I^2 0%) or thrice (LogOR −0.55, CI 95% −1.26 to 0.17, I^2 0%) (Supplementary Figure 8) per day. Finally, results were not altered when an analysis with drop-rate 20% as a threshold was performed (logOR −0.48, CI 95% −1.17 to 0.22, I^2 0) (Fig. 18). Post hoc analysis for studies conducted outside of Japan showed a trend in improving survival (LogOR −0.57, CI 95% −1.30 to 0.16, I^2 0%) in contrast to studies conducted in Japan where control showed more favorable effect (LogOR 0.12, CI 95% −0.89 to 1.13, I^2 0%) (Supplementary Figure 9).

3.13. Meta-regression

Regression coefficients, using duration and dosage as covariates, were 0.07 and 0.02 respectively, without statistical significance.

3.14. Analysis of secondary outcomes

3.14.1. Body mass index

Seven studies [20,23–25,37–39] reported data, in respect to changes in body mass index. Against all other interventions BCAAs significantly increased BMI, in patients with liver cirrhosis (WMD 0.24, CI 95% 0.08 to 0.40, I^2 0%) (Fig. 19).

3.15. Sensitivity analyses

Subgroup analysis including patients undergoing endoscopic therapy due to cirrhotic varices [20,25,37], resulted also in substantial increase of BMI (WMD 0.25, CI 95% 0.05 to 0.44, I^2 0%) (Supplementary Figure 10). Results were endorsed by excluding the only study [37] publishing data with through box plot (WMD 0.26, CI 95% 0.07 to 0.46, I^2 0%). Administration of BCAAs once per day showed better results in increasing BMI (WMD 0.25, CI 95% 0.03 to 0.48, I^2 0%) compared to twice per day (WMD 0.32, CI 95% −0.04 to 0.67, I^2 0%) (Supplementary Figure 11). Post-hoc analysis also showed that BMI was significantly increased only in studies conducted in Japan (WMD 0.24, CI 95% 0.07 to 0.41, I^2 0%) (Supplementary Figure 12).

3.15.1. Cirrhotic complications

Six studies [23,26,27,30,33,34] evaluated the effectiveness of BCAA supplementation on the basis of incidence of serious cirrhotic complications, such as development of ascites, hepatocellular carcinoma, varices rupture, hepatic encephalopathy, and serious infections. Compared to control, BCAAs reduced the incidence of cirrhotic implications (logOR −0.46, CI 95% −0.78 to −0.13, I^2 0%) (Fig. 20).

3.16. Sensitivity analyses

Due to great variation in follow up period of each study we conducted subgroup analysis according to duration of each study, setting 6 months as threshold. Long-term BCAA supplementation [27,30,33] showed significant reduction in incidence of serious

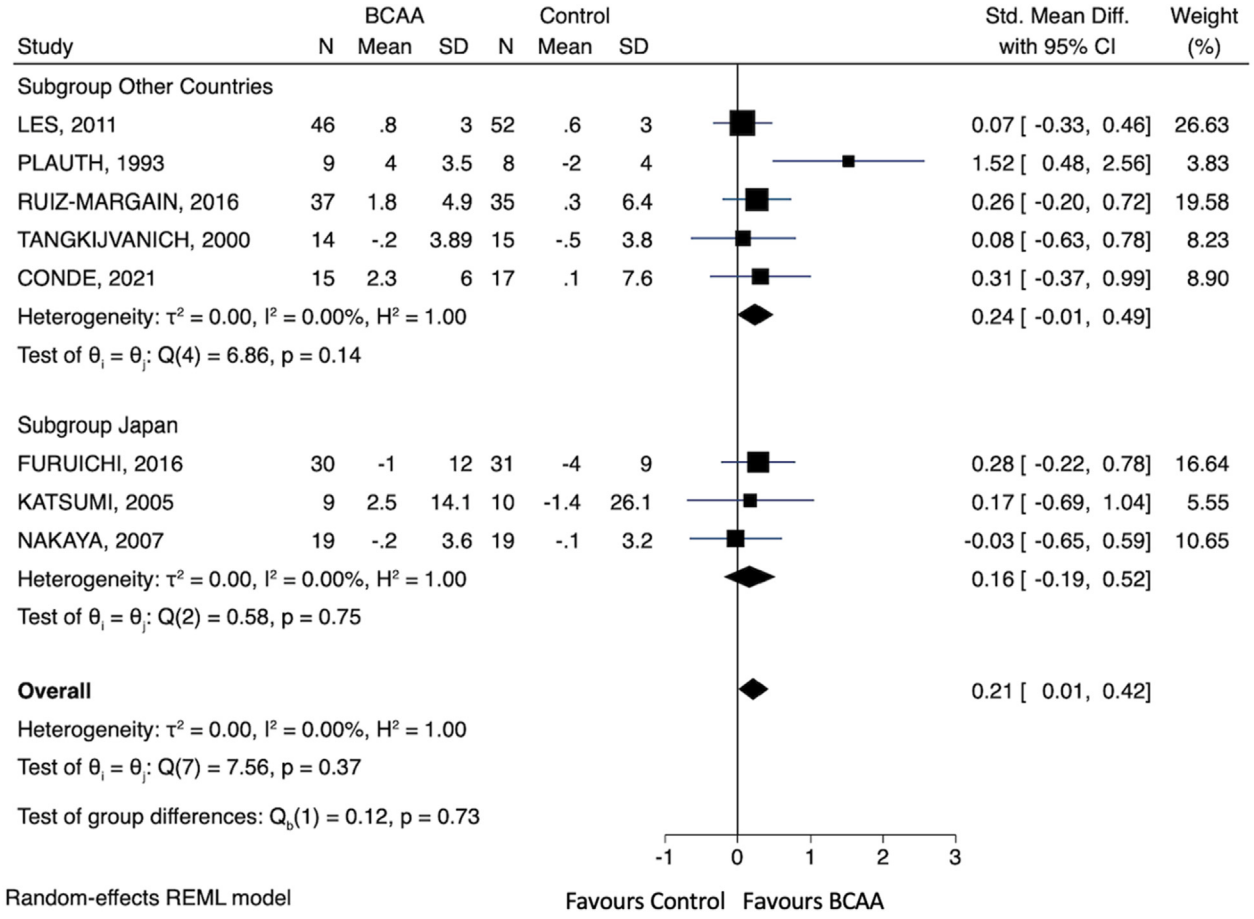

Fig. 6. Effect of BCAAs on muscle mass, subgroup country.

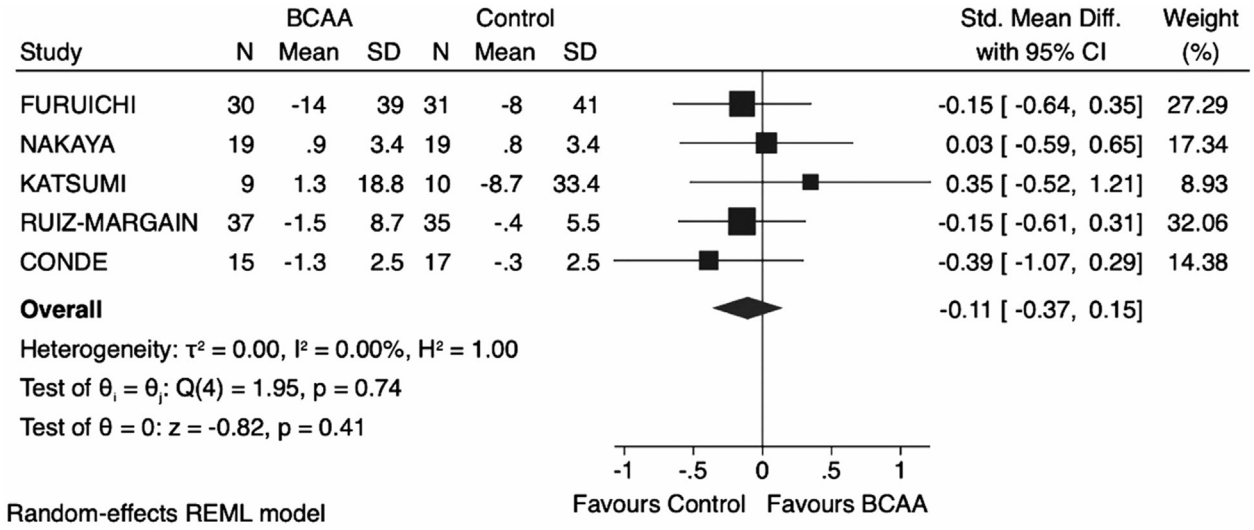

Fig. 7. Effect of BCAAs on fat mass, main analysis SMD.

cirrhotic complication (LogOR −0.46, CI 95% −0.81 to −0.12, I^2 0%) (Fig. 20). Post-hoc subgroup analysis showed that complications were significantly reduced only in studies conducted in Japan (logOR −0.45, CI 95% −0.80 to −0.10, I^2 0%) (Supplementary Figure 13).

4. Discussion

The objective of this systematic review and meta-analysis was to examine the efficacy of BCAA supplementation in patients with cirrhosis. Twenty studies with a total number of 1297 cirrhotic

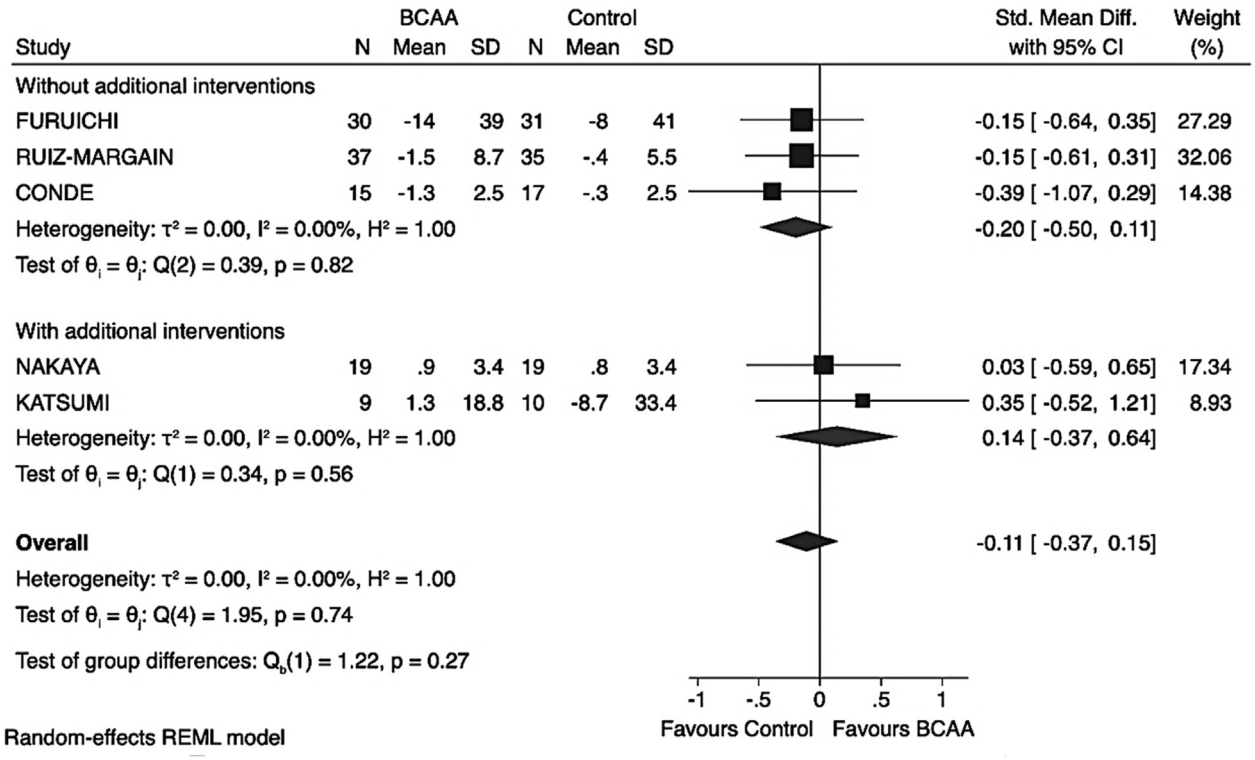

Fig. 8. Effect of BCAAs on fat mass, subgroup additional interventions for cirrhotic complications.

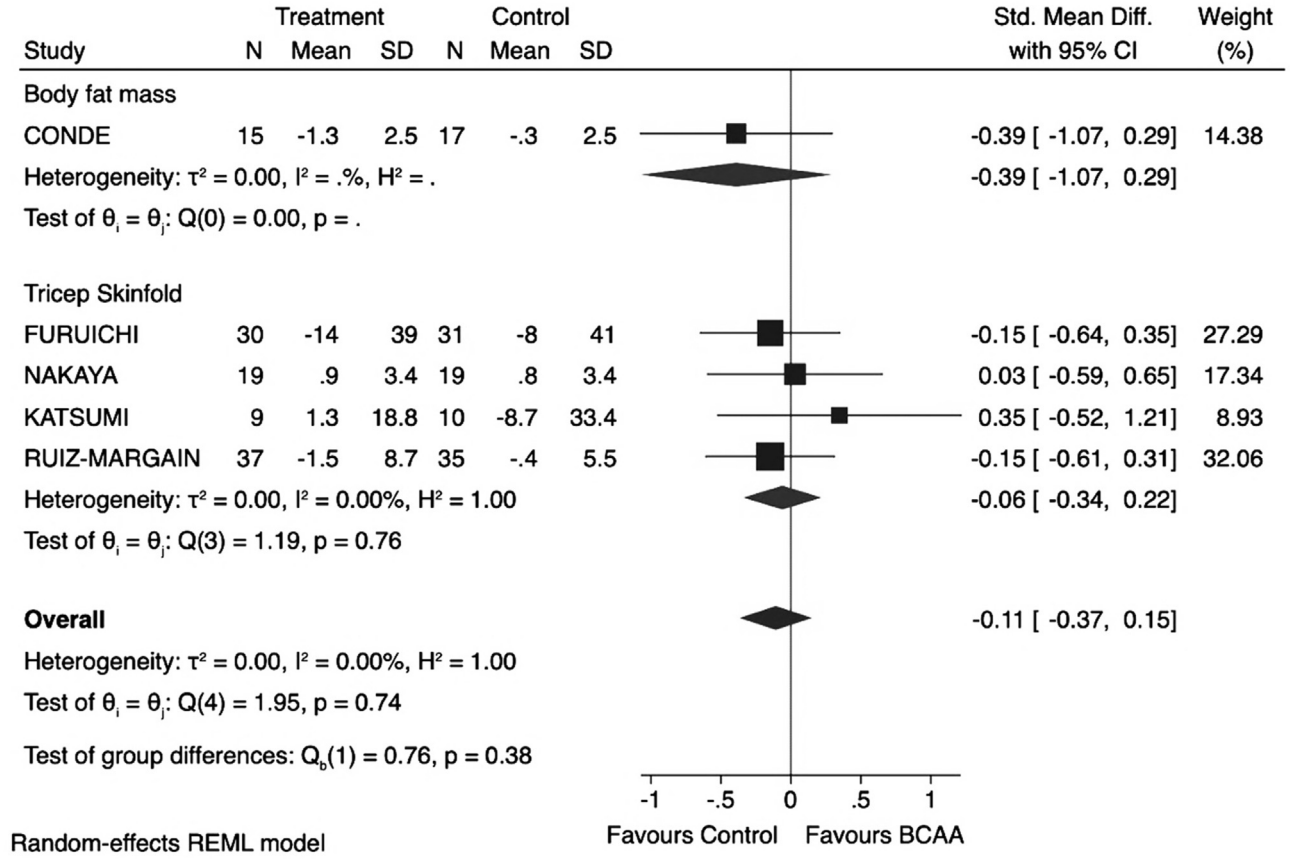

Fig. 9. Effect of BCAAs on fat mass, subgroup method of choice.

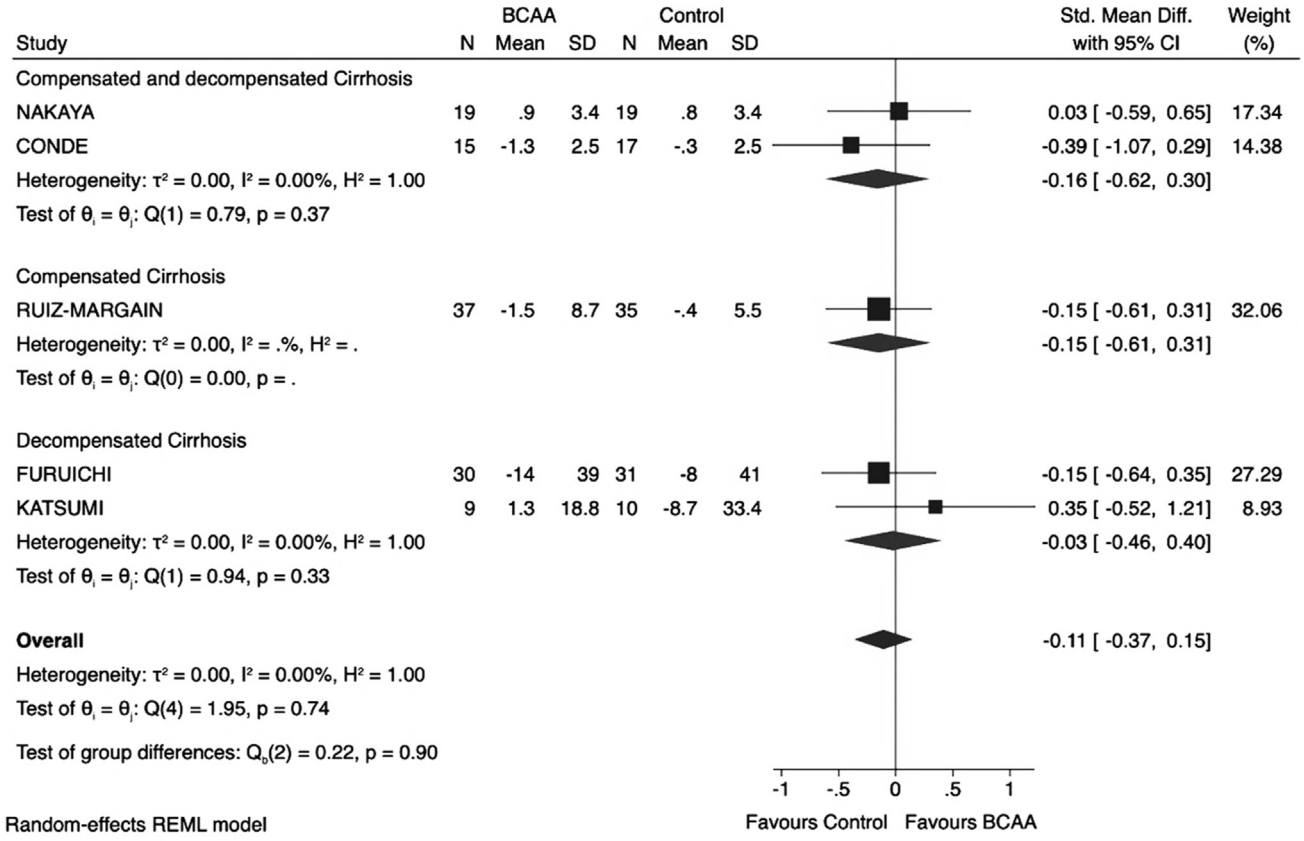

Fig. 10. Effect of BCAAs on fat mass, subgroup stage of cirrhosis.

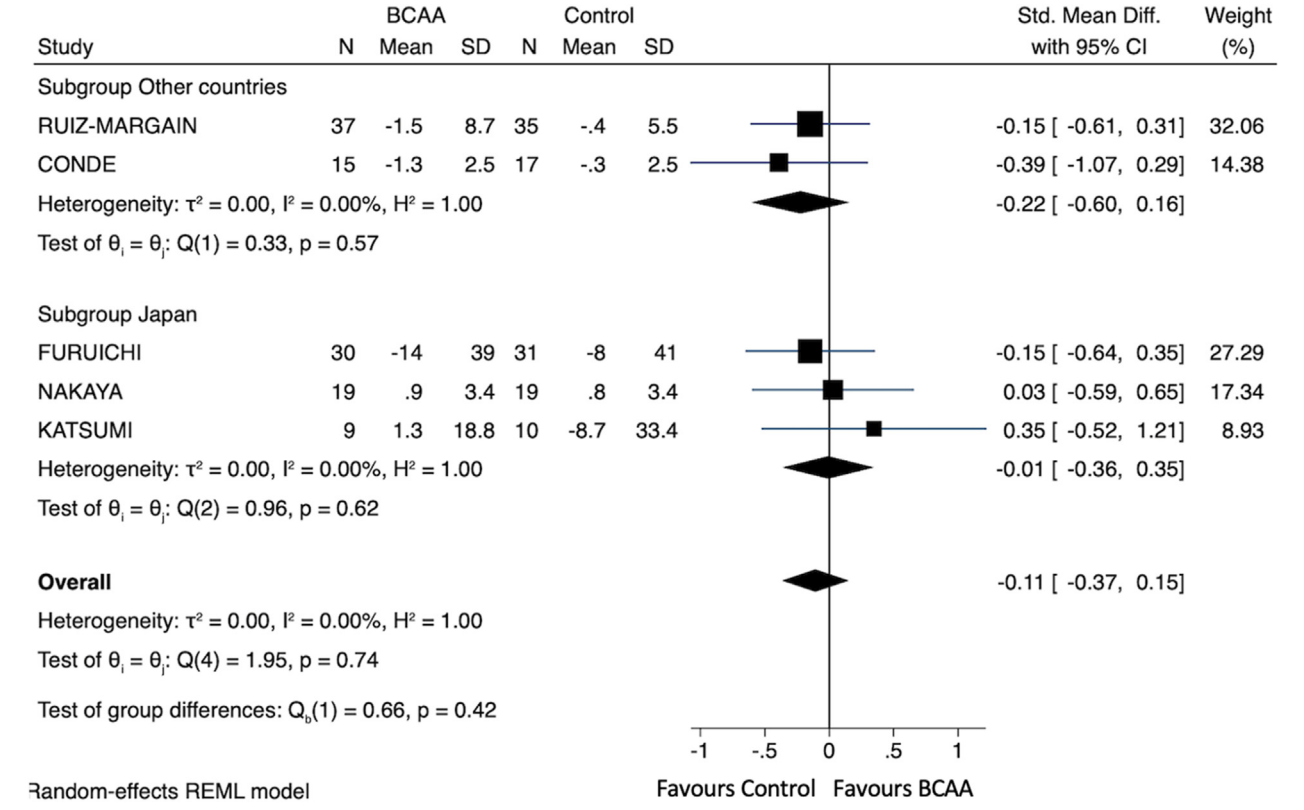

Fig. 11. Effect of BCAAs on fat mass, subgroup country.

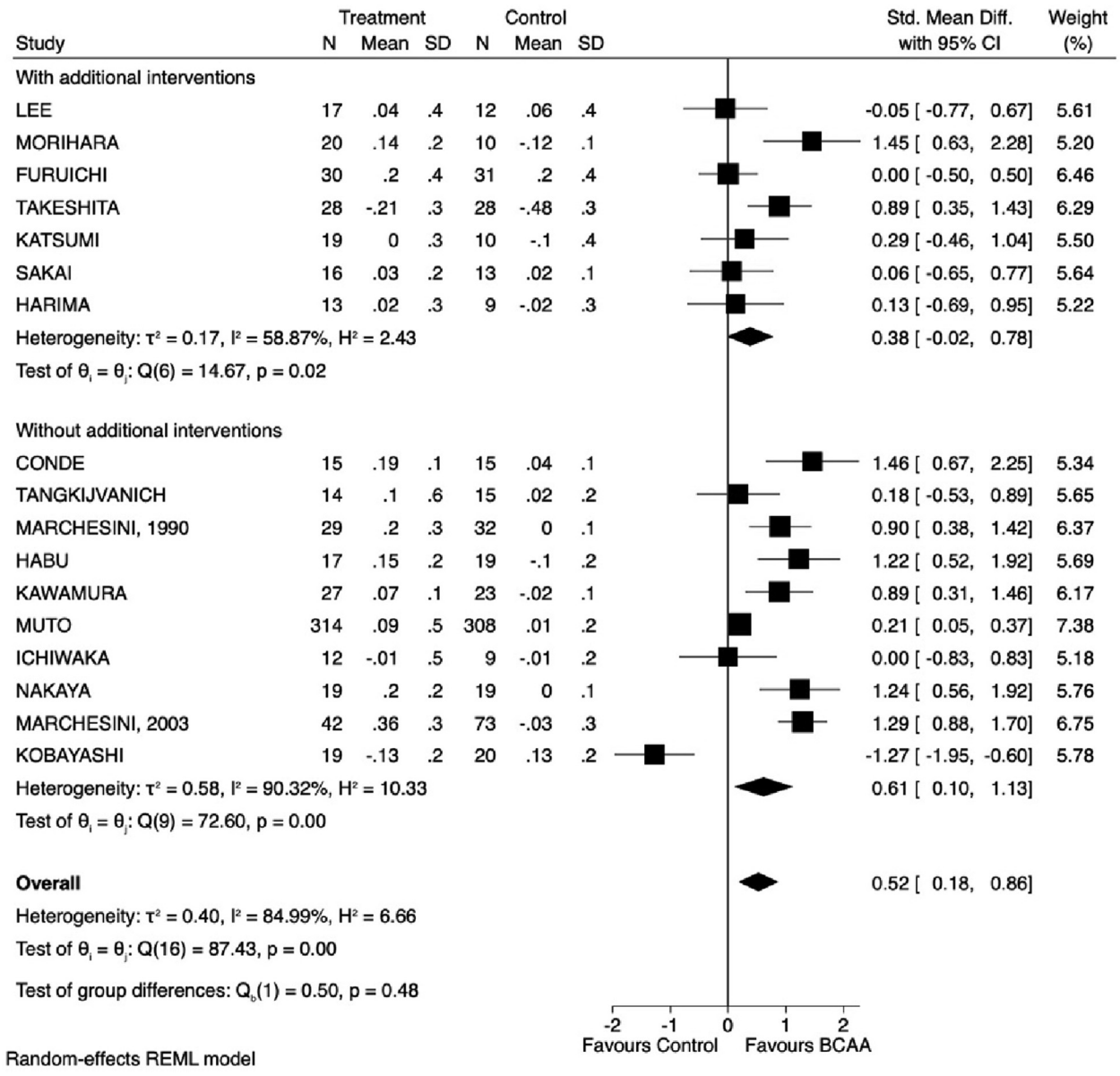

Fig. 12. Effect of BCAAs on change from baseline albumin concentration, subgroup additional interventions for cirrhotic complications.

patients at different stages of disease, were included. Dosage of BCAA varied between 5.25 and 30 g (mean circa 11.5 g), whereas duration of the supplementation ranged from 1 to 168 weeks. Compared with various interventions, BCAAs increased muscle mass, evaluated through various methods, albumin concentration, BMI, and reduced the incidence of serious cirrhotic complications. BCAAs were not more efficacious than other interventions in decreasing % of body fat and only showed a trend in reducing mortality among cirrhotic patients.

Seventeen studies [20–28,30–34,37–39] evaluated the effect of BCAA supplementation in albumin serum concentration, which can be regarded as an trustworthy indicator of patient's protein state and acts as an independent prognostic factor [40]. Our analysis showcased a significant effect in change from baseline albumin concentration in patients under BCAA supplementation, after excluding the only trial [37] reporting results with percentage changes. Due to variations in supplementation's duration among included studies we conducted subgroup analyses (by length of duration), which showed a stronger effect for data associated with more than 12 weeks duration [20,21,23,26,27,30–34], a finding which was further validated through cumulative analysis by duration. Moreover, as the stage of liver cirrhosis is an additional factor able to affect our results, a subgroup analysis with baseline albumin concentration (with a cutoff of 3.5 g/dL) was performed, showing that BCAA supplementation is more effective in the presence of hypoalbuminemia [21,22,25,30,33,34]. To examine the robustness of our results, a re-analysis excluding data extracted from plots and graphs was conducted [20,28,30,32,33,37], that agreed with the main analysis.

Caution should accompany the interpretation and implication at a clinical level of these results due to the great heterogeneity that was noted. Despite sensitivity analyses and meta-regression, taking into account risk of bias, morbidity, duration and dosage of BCAAs used in each trial, heterogeneity between studies remained high probably because of differences in study design and administration protocol, thus impairing the applicability of our findings.

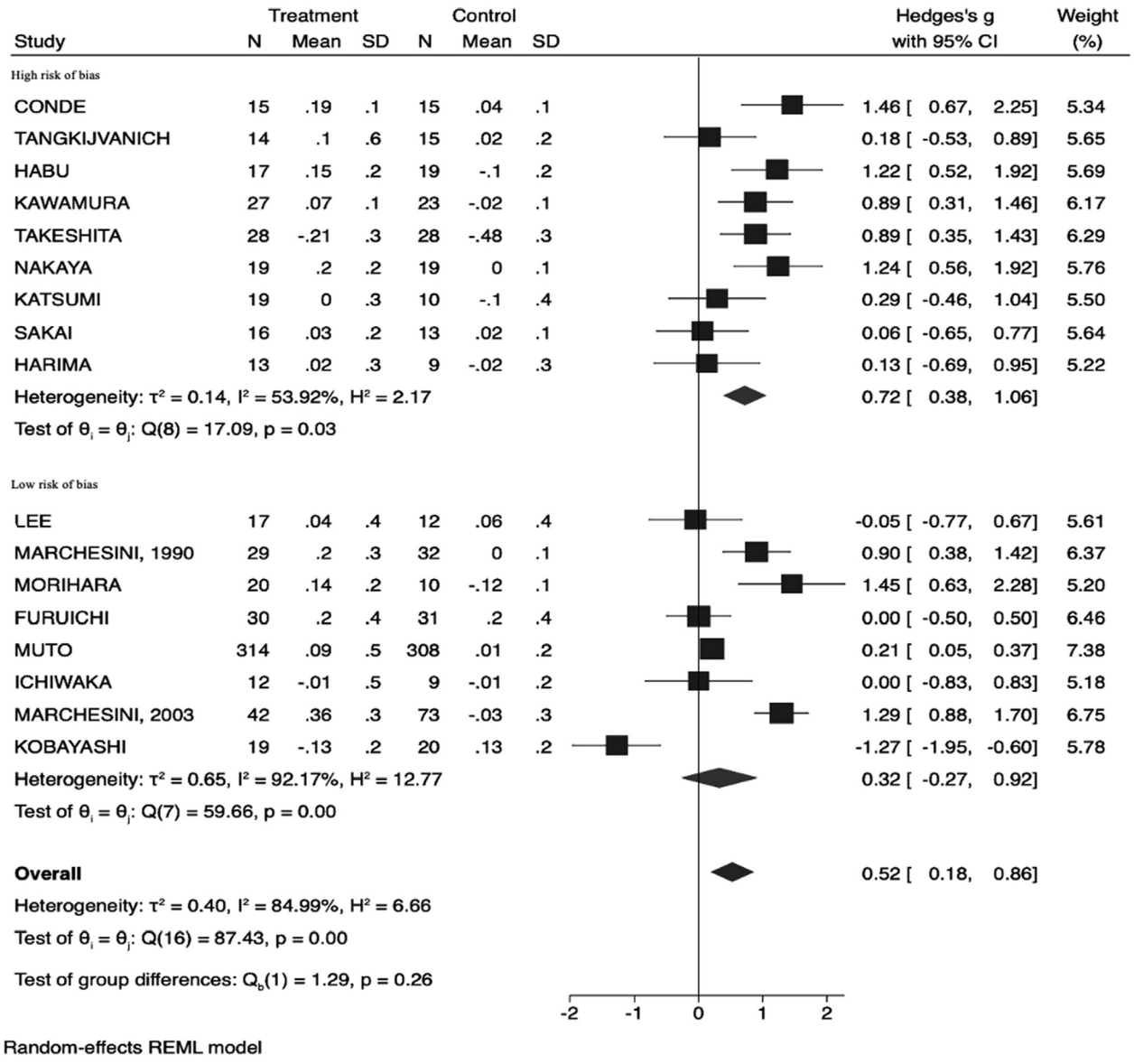

Fig. 13. Effect of BCAAs on change from baseline albumin concentration, risk of bias.

The effect of BCAA supplementation in body composition was the second major outcome that our analysis examined. Cirrhosis is characterized by changes in body composition with concurrently depletion of muscle mass and adipose tissue being observed among cirrhotic patients. Muscle mass loss, also defined as sarcopenia, is being acknowledged as a major cirrhotic complication, accompanied by worsening prognosis and lower survival [41]. In their latest clinical guidelines both EASL [6] and ESPEN [42] recommend for cirrhotic patients a thorough nutritional assessment for the diagnosis of malnutrition. Moreover, EASL suggests utilization of different tools from simple bedside anthropometric measurements to computed topographic image analysis at the L3 vertebra, tetrapolar Bioelectrical Impedance Analysis (BIA) and whole-body dual energy X-ray absorptiometry, while ESPEN encouraging only the latter. Among bedside tools, MAMC and TSF display high diagnostic agreement with the more advanced methods. Eight [20,23,25,29,34–36,39] of the 20 studies included in our analysis, reported numeric data on various methods assessing muscle mass. Among them, one study [35] reported muscle mass changes as AMA percentage changes, four studies reported MAMC cm changes [29,34,36,39], two studies reported MAMC percentage changes [20,25], and one study employed muscle mass index [23]. BIA was used in four eligible studies [20,22,28,30], but data were accessible to only two of them [20,28]. According to our analysis incorporating pooled data assessed through different methods and unit of measurements, BCAA supplementation increased muscle mass. When we examined data only from studies reporting MAMC (cm) changes [29,34,36,39], results showed only a trend in increasing muscle mass. With respect to adipose tissue changes, five studies reported data. Four of them [20,25,34,36], used TSF as a fat mass indicator and one [23] of them used CT measurements. Analysis showed only a trend for BCAAs in lowering body fat mass. Results should be approached with caution, due to inconsistency during sensitivity analyses, a phenomenon most likely attributed to different methods and different unit of measurements employed to evaluate body composition parameters.

BMI is a readily accessible tool, able not only to assess cirrhotic patients' nutritional status but also appreciate malnutrition's

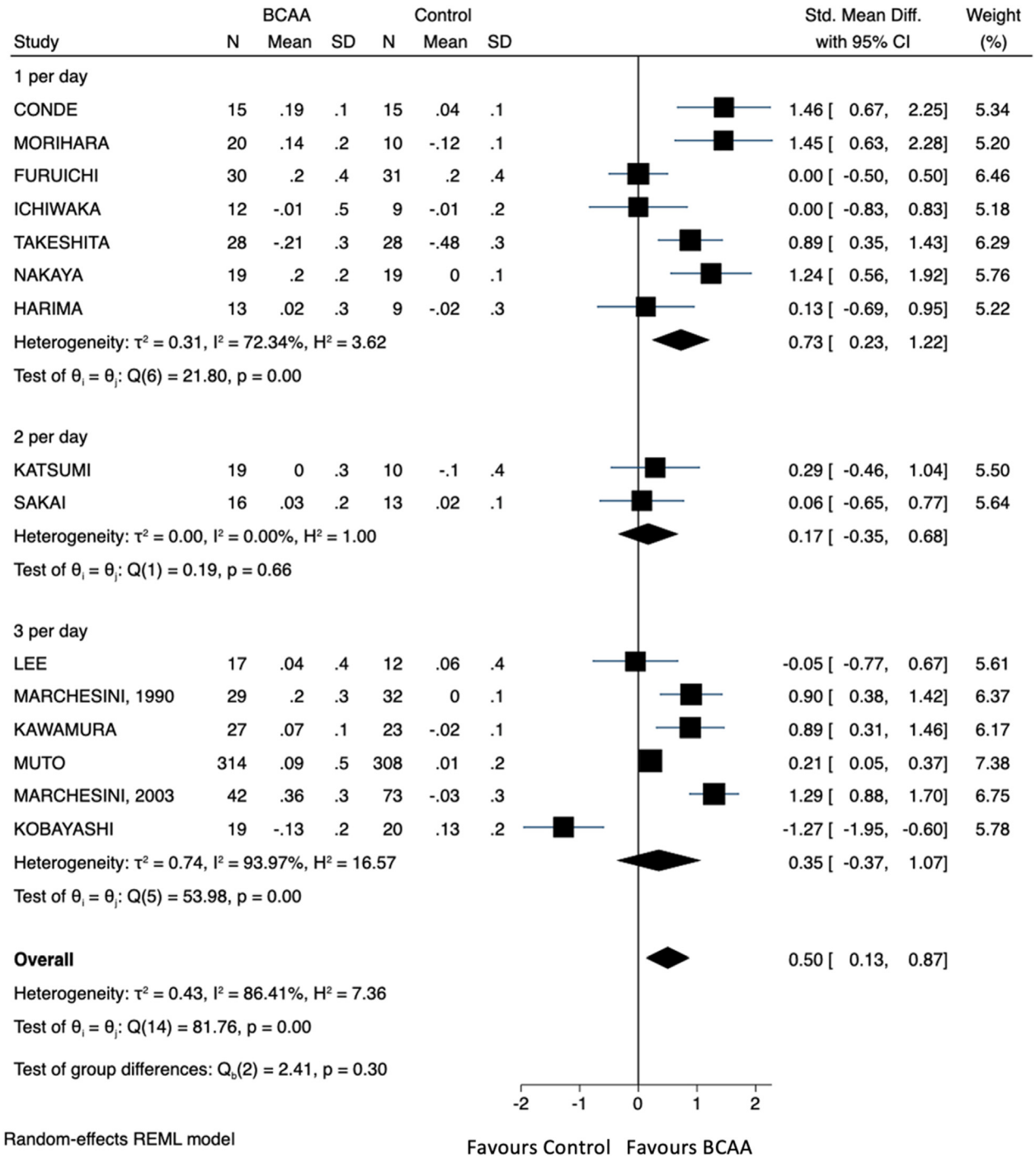

Fig. 14. Effect of BCAAs on change from baseline albumin concentration, subgroup frequency of BCAA administration.

progress. However, in cirrhotic patients it is affected by other factors, such as the development of peripheral edema and ascites. Nevertheless, its value in the prognosis and diagnosis of malnutrition in patients with liver cirrhosis is not diminished as it is stated in the guidelines of EASL [6]. In fact, Campillo et al. [9] reported that BMI is not affected by the presence of peripheral edema or treatment for ascites. Our meta-analyses showed that BCAA supplementation benefits patients with cirrhosis as the body mass index increased in contrast to the control groups in which the majority showed a decrease. However, because it was not reported whether patients experienced an increase in total water in the form of edema or worsening of ascites, results require validation from well-designed clinical trials that address this issue.

Data from eight [22,23,28–31,33,34] and six studies [23,26,27,30,33,34] were used to assess death from all causes and incidence of serious cirrhotic complications respectively. Overall, 33 deaths from all causes in 498 patients under BCAA supplementation versus 51 deaths from all causes in 555 patients in control groups were noted. Odds ratio was not significant in favor of BCAAs. In contrast, patients being treated with BCAAs were less likely to suffer from major cirrhotic complications according to data

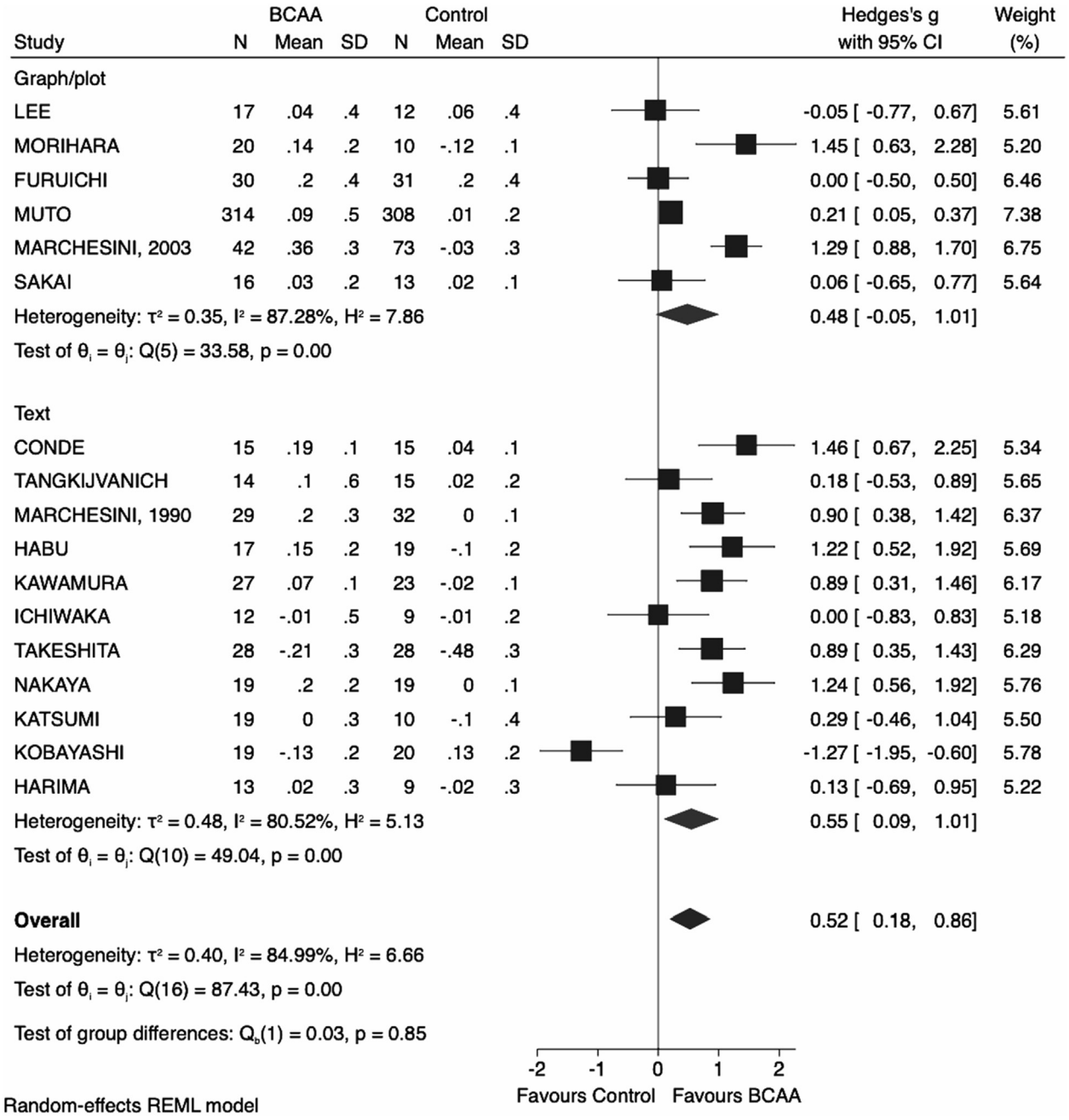

Fig. 15. Effect of BCAAs on change from baseline albumin concentration, subgroup data source.

from 913 patients across six studies. Sensitivity analyses supported the aforementioned results.

In order to address the fact that many studies were conducted in Japan as potential factor of heterogeneity and to increase the applicability of our results, a post-hoc subgroup analysis, taking into account the country of each study, was performed with most results being in agreement with the main analysis.

Furthermore, great variability was noted regarding the total dosage of BCAAs among eligible studies. This issue was addressed through the performance of meta-regression analysis using total dosage as a parameter for muscle mass, fat mass, serum albumin, and mortality. No significant relationship was observed between total BCAA dosage and magnitude of effect. Thus, no optimal dose recommendation can be made from this systematic review and meta-analysis. Nonetheless, we recommend adopting the ESPEN guidelines proposal for BCAA intake of 0.25 g/kg/day for cirrhotic patients [42]. Significant variability was also observed in terms of frequency of administration and the ratio of each individual BCAA to the overall supplement mixture. In the view of the fact that these parameters were not taken into consideration by this study results should be interpreted cautiously since these variances may affect the overall BCAA-induced protein synthesis.

Two other meta-analyses [13,43] and two systematic reviews [44,45] have been published recently, regarding BCAAs and liver disease. It needs to be noted that these studies had disparities in design and examined different outcomes of interest. One meta-analysis examined the effect of BCAAs in hepatic encephalopathy [13] and the other [43] examined the effect of various diet

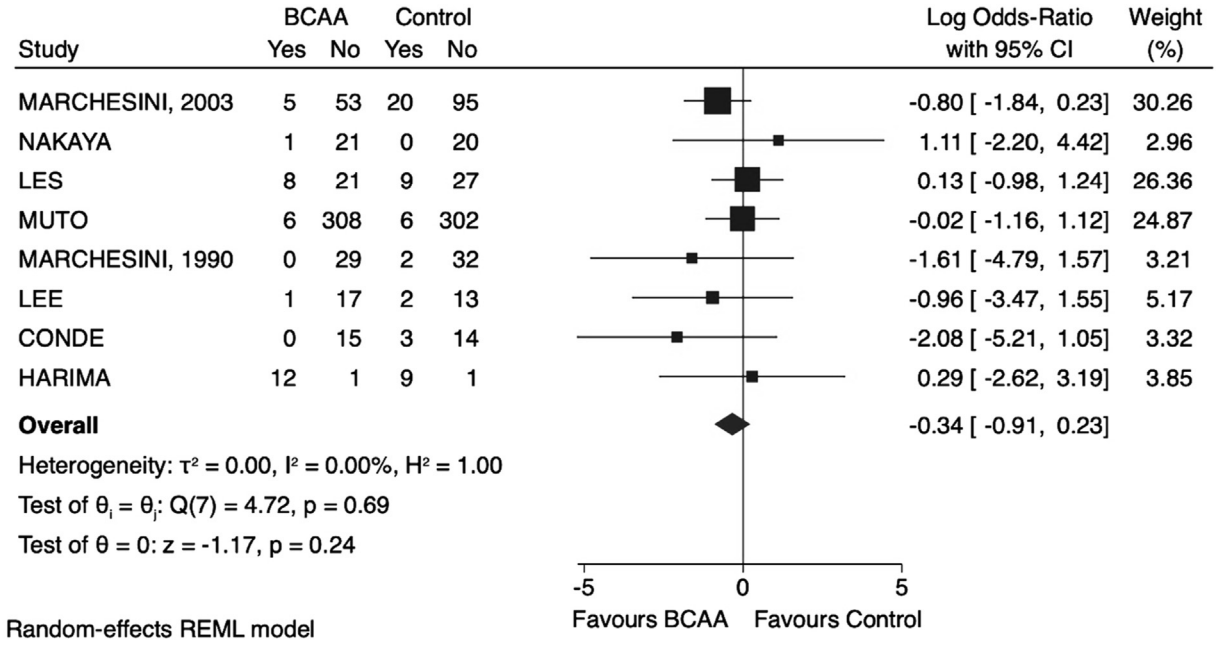

Fig. 16. Effect of BCAAs on mortality, main analysis.

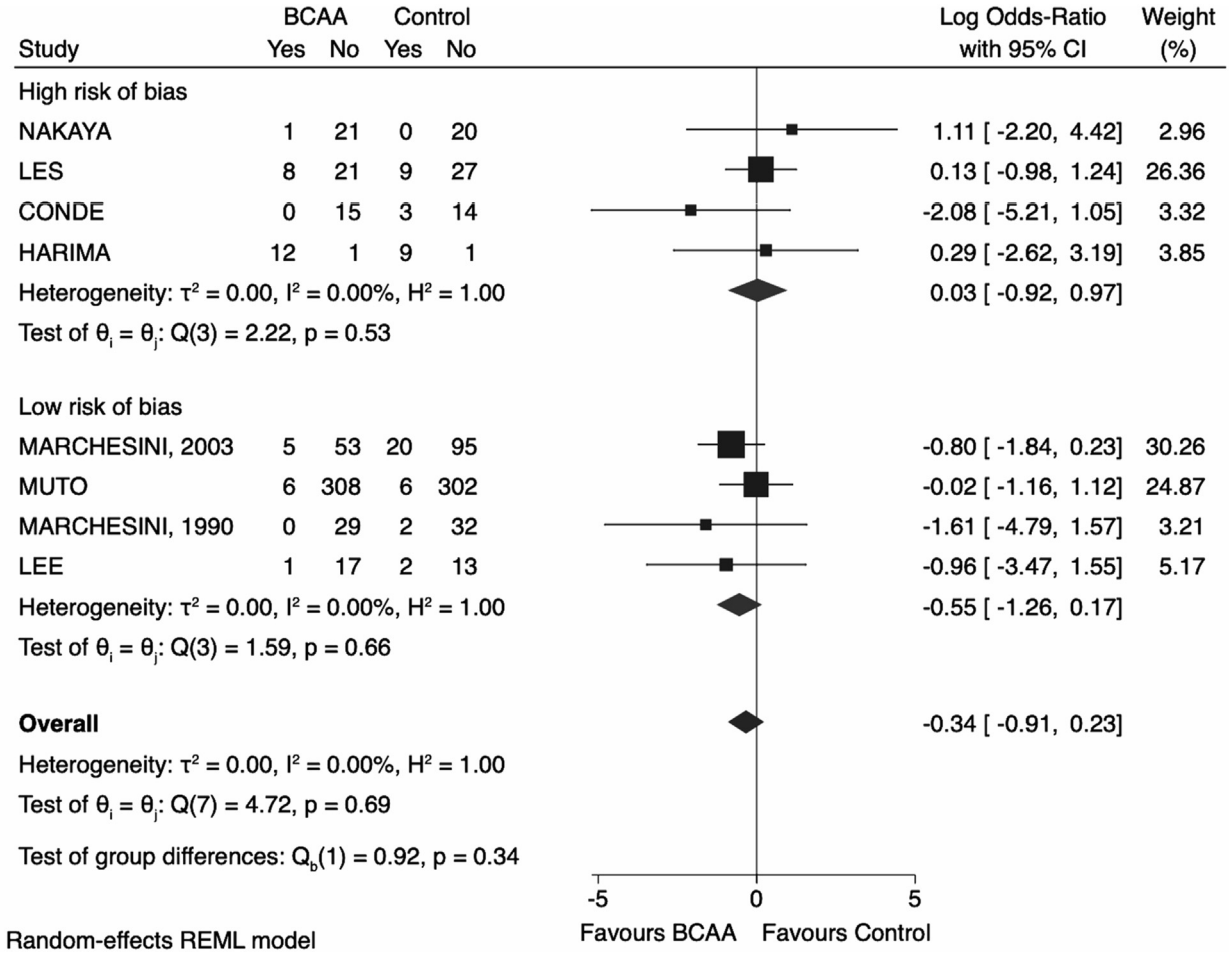

Fig. 17. Effect of BCAAs on mortality, risk of bias.

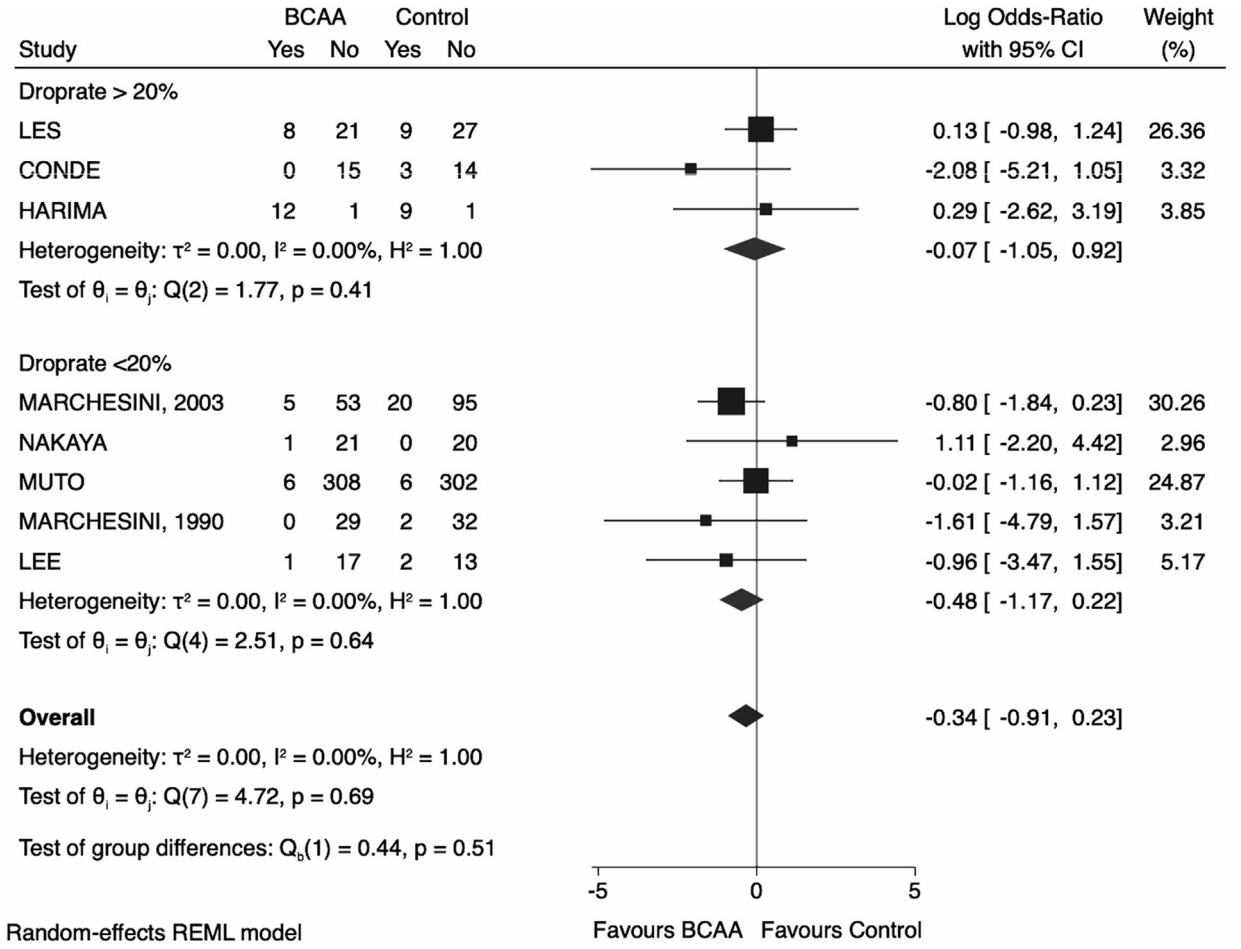

Fig. 18. Effect of BCAAs on mortality, subgroup droprate.

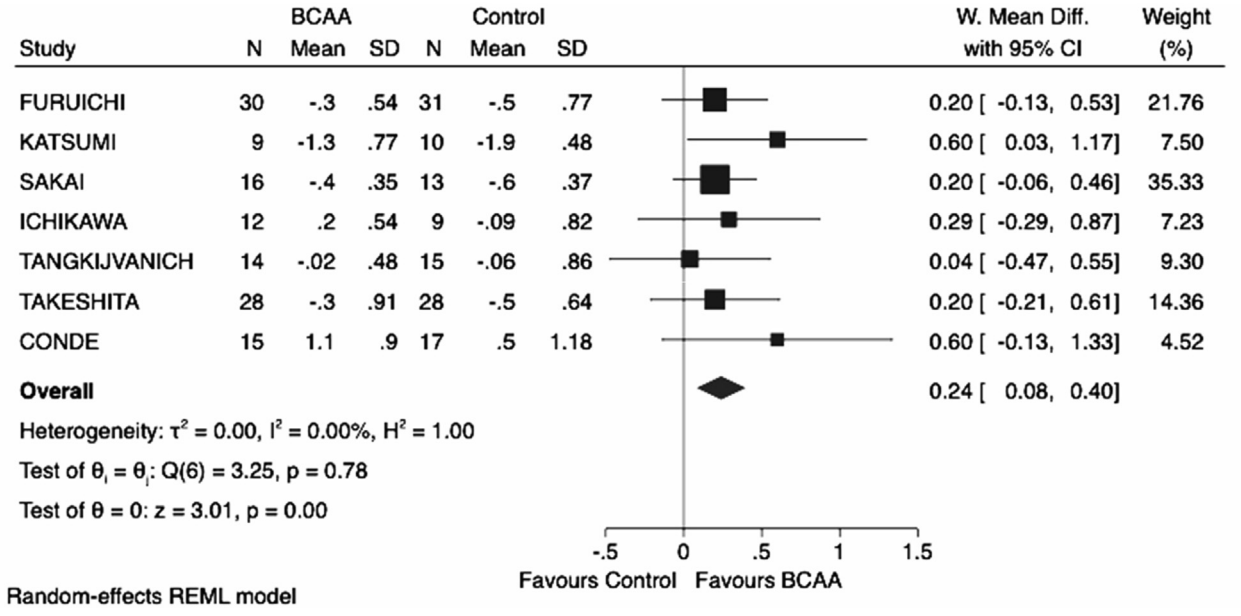

Fig. 19. Effect of BCAA on BMI, main analysis.

interventions in patient with chronic liver diseases, while the two systematic reviews scrutinized pathophysiology and potential therapeutic effects of BCAAs without statistical analyses. Our meta-analysis is the only including data from trials recruiting only patients with cirrhosis and in encompassing up-to-date data from a broad and systematic literature search.

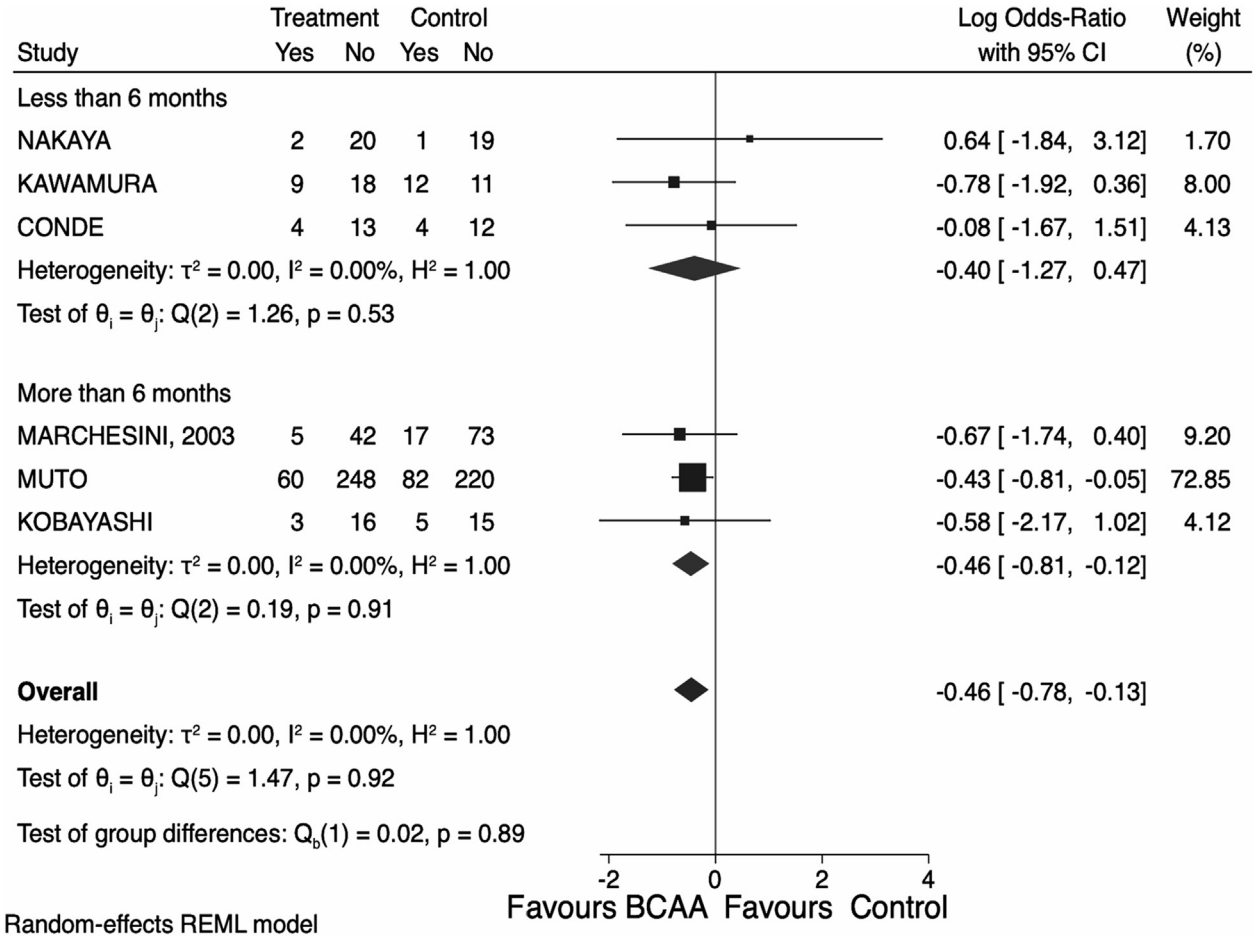

Fig. 20. Effect of BCAAs on incidence of serious complications, subgroup duration.

Cirrhosis is often referred to as a state of protein and energy malnutrition. EASL during the latest consensus [6], advises cirrhotic patients to receive adequate protein through the day, at a range of 1.2–1.5 g/kg/day. However, not all types of protein' intake results to the same effects to a cirrhotic patient. This is particularly true, for animal proteins that are rich in aromatic amino acids (AAA), since the diminished citric acid cycle activity may result in an impaired utilization of amino acids and hyperammonia, which amplify malnutrition, hepatic encephalopathy and sarcopenia.

BCAAs have the major advantage over AAA that are able to completely bypass the hepatic catabolism and get in that way catabolized in muscles through their deamination while also providing adequate substrate for protein synthesis [46].

Additionally, increased physical activity seems to correlate positively with the improvement of muscle mass and strength [6], but adequate information regarding the type and intensity of exercise are not available. From a theoretical basis, excessive physical activity can lead to deterioration of cirrhotic patients, due to the production of muscle ammonia and increased portal pressure [47,48]. Due to the intrinsic properties of BCAAs, i.e., the ability to remove ammonia, the combination of BCAA supplementation and exercise might lead to additional benefits. Promising results have already been shown by a small number of clinical trials [49,50], but RCTs examining the synergistic effect of BCAAs and exercise must be conducted for the potential benefit to be established.

We chose to conduct an available-case meta-analysis and approach missing data as missing at completely random [51] because this method has shown relatively good results, the only negative aspect being loss in power [52]. As suggested in Cochrane's Textbook "*Statistical analysis cannot reliably compensate for missing data while no assumption is likely adequately to reflect the truth* [53]." Duration, dosage of BCAAs, cirrhosis stage and concomitant interventions displayed great variation among eligible studies. Especially in the analysis of albumin concentration, great heterogeneity was noted, that could not be addressed by various sensitivity analyses. As a limitation should also be regarded the fact that some of the main results could not be verified during subgroup or sensitivity analyses. This deviation, in addition to differences in total dose, duration of individual trials and differences in study populations preclude us from drawing robust conclusions concerning BCAAs and from generalizing the results of this study. Cirrhotic sarcopenia is also characterized by reduced contractile muscle strength, a parameter that can easily be assessed though a variety of methods such as handgrip strength or isokinetic knee extensor strength test [54]. An increase in muscle mass alone does not improve the limited functional capacity of patients with cirrhosis and the effect of BCAAs on muscle strength should also be addressed. Due to scarce data an analysis of the effect of BCAAs on muscle strength could not be performed.

5. Conclusions

BCAAs gained a sort of pre-mature recognition as a therapeutical intervention during the 80's when findings from Fisher et al. [55], unraveled the significance of BCAA to AAA ratio in the development and treatment of hepatic encephalopathy. Despite promising

results, perhaps due to lack of insight into how BCAAs intervened with cirrhosis' elaborated mechanisms, attention drifted away from BCAAs to other means of intervention. Our meta-analysis results support supplementation with BCAAs as a concomitant intervention in patients suffering liver cirrhosis, but the lack of homogeneity among available clinical trials, does not allow for robust conclusions. Results must be further validated by well-designed double blind RCTs, characterized by appropriate and standardized means of evaluating cirrhotic malnutrition and sarcopenia, strictly defined diagnostic criteria, similarities in duration, dosage, stage of disease and control arm.

Conflicts of interest

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2022.03.027.

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