British Journal of Nutrition (2024), 131, 276–285 doi:10.1017/S0007114523001885

Effects of branched-chain amino acids supplementation on patients undergoing hepatic intervention: a meta-analysis of randomised controlled trials

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(Submitted 18 February 2023 – Final revision received 3 August 2023 – Accepted 20 August 2023 – First published online 29 August 2023)

Abstract

The benefits of branched-chain amino acid (BCAA) administration after hepatic intervention in patients with liver diseases remain unclear. We conducted a systematic review and meta-analysis to evaluate the effects of BCAA on patients undergoing hepatectomy, trans-arterial embolisation and radiofrequency ablation. Relevant randomised controlled trials (RCT) were obtained from PubMed, EMBASE and Cochrane Library databases. A meta-analysis was performed to calculate the pooled effect size by using random-effects models. The primary outcomes were survival and tumour recurrence. The secondary outcomes were hospital stay, nutrition status, biochemistry profile, complication rate of liver treatment and adverse effect of BCAA supplementation. In total, eleven RCT involving 750 patients were included. Our meta-analysis showed no significant difference in the rates of tumour recurrence and overall survival between the BCAA and control groups. However, the pooled estimate showed that BCAA supplementation in patients undergoing hepatic intervention significantly increased serum albumin (mean difference (MD): 0·11 g/dl, 95 % CI: 0·02, 0·20; 5 RCT) at 6 months and cholinesterase level (MD: 50·00 U/L, 95 % CI: 21·08, 78·92; 1 RCT) at 12 months and reduced ascites incidence (risk ratio: 0·39, 95 % CI: 0·21, 0·71; 4 RCT) at 12 months compared with the control group. Additionally, BCAA administration significantly increased body weight at 6 months and 12 months and increased arm circumference at 12 months. In conclusion, BCAA supplementation significantly improved the liver function, reduced the incidence of ascites and increased body weight and arm circumference. Thus, BCAA supplementation may beneficial for selected patients undergoing liver intervention.

Keywords: **Branched-chain amino acids: Liver disease: Hepatocellular carcinoma: Nutrition**

Although multiple treatment procedures have evolved with time, interventions for liver diseases such as are hepatectomy, trans-arterial embolisation and radiofrequency ablation (RFA) inevitably associated with some postoperative morbidities due to liver function damage. Liver function parameters such as plasma total bilirubin, alanine aminotransferase, aspartate transaminase (AST), serum albumin and Child–Pugh score could be transiently deteriorated due to inevitable reduction in the functional liver mass[(1)]. Generally, malnutrition is frequently associated with liver disease, and therefore, proper nutritional support might be necessary to improve the outcomes of liver disease treatment[(1)].

Branched-chain amino acid (BCAA), an amino acid having an aliphatic side chain with a branch, is made up of three essential amino acids, namely leucine, isoleucine and valine. BCAA

Abbreviations: AST, aspartate transaminase; BCAA, branched-chain amino acid; HCC, hepatocellular carcinoma; MD, mean difference; RCT, randomised controlled trials; RFA, radiofrequency ablation.

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supplementation improves cellular metabolism, amino acid transport and protein turnover[1]. Moreover, BCAA activate mammalian target of rapamycin signalling, stimulating the synthesis of glycogen and of proteins such as albumin, cell growth and proliferation, insulin resistance and phosphoinositide-3-kinase-protein kinase B (PI3K-Akt) signalling pathway[2]. Therefore, it might promote liver regeneration and accelerate liver recovery after treatment-related damage[2]. Hepatocellular carcinoma (HCC) is associated with cirrhosis and poor nutritional status, since the liver damage due to HCC would decrease the cellular metabolism of carbohydrate, protein and lipid[1]. BCAA administration in patients undergoing intervention for HCC might reduce malnutrition and improve treatment outcome[3,4]. The nutritional status of patients is associated with their liver transplantation outcome, and BCAA supplementation may ameliorate metabolic abnormalities and improve health recovery post-transplantation[5].

Studies have shown that BCAA supplementation has beneficial effects on patients undergoing liver interventions in terms of overall survival rate, complication rate and nutritional status[2]. However, other studies have failed to show a significant difference between BCAA supplement and control groups[1]. Therefore, we conducted a comprehensive systematic review of randomised controlled trials (RCT) to evaluate the effects of BCAA supplementation during the peri-treatment phase on patients undergoing hepatic intervention.

Methods

Selection criteria

We included RCT that compared the outcomes of BCAA supplementation with those of no dietary intervention in patients scheduled for liver treatment, including hepatectomy, trans-arterial embolisation, RFA and liver transplantation. We excluded non-peer-reviewed articles, conferential abstracts and studies consisting of patients aged < 18 years.

Search strategy

Studies were selected based on a search of the PubMed, EMBASE and Cochrane Library databases. The following search headings were used: (hepatic resection OR hepatectomy OR liver resection OR liver surgery OR trans-arterial embolisation and radiofrequency ablation) AND (branched chain amino acid). Furthermore, these terms were searched in full texts (Methods in online Supplementary Table 1). The 'related articles' function was used to find more studies and all abstracts, studies and citations retrieved were reviewed. More articles were identified through a manual search of references by experts in the field. Finally, unpublished trials were collected from the ClinicalTrials.gov registry (http://clinicaltrials.gov/). No language limitation was applied. The final search was conducted in October 2022. This systematic review was accepted by PROSPERO, an online international prospective register of systematic reviews curated by the National Health Service (registration number: CRD4202021917).

Study selection and data extraction

Two reviewers independently extracted the following information from each trial: first author, publication year, study population characteristics, study design, selection criteria, treatment procedure, dosage and duration of BCAA supplementation and post-treatment condition. The data recorded by the two reviewers were compared, and any disagreement was resolved by a third reviewer.

Risk of bias assessment

Two reviewers independently assessed the risk of bias of each trial by using the revised tool for assessing the risk of bias in randomised trials (RoB 2·0). Five domains of bias were assessed, namely bias due to the randomisation process, bias due to deviation from the intended intervention, bias due to missing outcome data, bias in the outcome measurement and bias in the selection of reported results. Each trial was awarded an overall risk of bias according to the most severe risk involved in the trial[6].

Outcome measures

The primary outcomes were overall survival and tumour recurrence. The secondary outcomes were nutritional status, including serum albumin, cholinesterase level and liver function represented by alanine aminotransferase and AST, hospital stay, the complication rate of liver treatment and adverse effect of BCAA supplementation.

Grading evidence quality

Two reviewers independently assessed evidence quality for each outcome by using the Grading of Recommendations Assessment, Development, and Evaluation guidelines[7]. Evidence quality was classified as high, moderate, low or very low on the basis of judgments concerning risk of bias, inconsistency, indirectness, imprecision and publication bias. We resolved discrepancies through consensus.

Statistical analysis

The meta-analysis was performed according to recommendations of the Cochrane Collaboration and the Quality of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines[8]. Statistical analyses were performed using the statistical program Review Manager, version 5·3 (Cochrane Collaboration, Oxford, UK). The effect sizes of dichotomous outcomes were reported as risk ratios or OR, and continuous outcomes were reported as mean differences (MD). The effect size precision was reported as 95 % CI. The SD was calculated using provided CI limits, SE or interquartile ranges[9]. The pooled estimates of RR, OR and MD were calculated using the DerSimonian and Laird random-effects model[10]. If an RCT included more than two treatment arms, all data were used, as appropriate, without the repeated use of any arm. The χ^2 and I^2 statistics were used to assess statistical heterogeneity. Statistical significance was set at 0·10 for Cochran's Q tests. The proportion of the total outcome variability attributable to variability across the studies was quantified as I^2. Meta-analyses of subgroups

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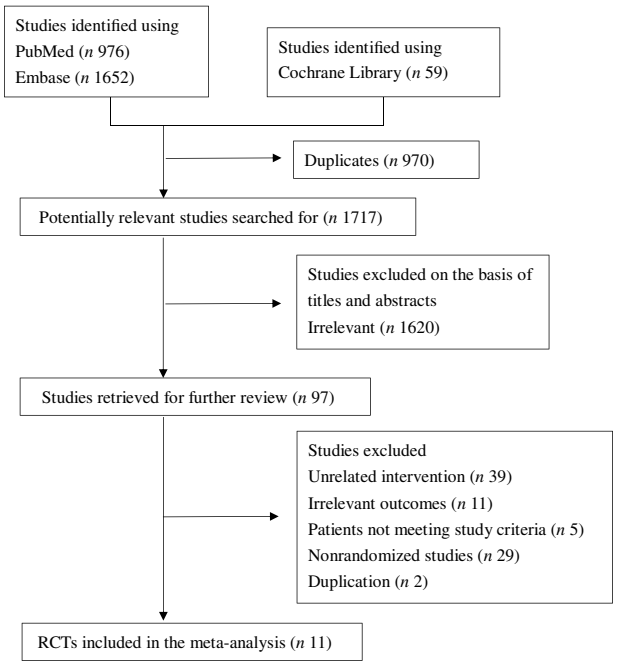

Fig. 1. Flow chart of study selection.

were conducted according to the control strategy used in the trials, either placebo or fasting.

Results

Fig. 1 presents a flow chart of study selection. We excluded duplications twice and excluded unrelated citations through the screening of titles and abstracts. Furthermore, after screening the full texts of retrieved records, we excluded studies that were duplicates, consisting patients that failed to meet the study criteria, having irrelevant interventions or outcomes and the studies that were non-RCT. Finally, eleven RCT were included in the meta-analysis[11–21].

The characteristics of all the included RCT are presented in Table 1. The studies were published between 1997 and 2020, with sample sizes ranging from 24 to 154. The liver disease status of patients in most of the included studies was evaluated according to the Child–Pugh classification and albumin level. The liver treatments included hepatectomy[11,13,14,16–18,20,21], liver transplantation[19], transcatheter arterial chemoembolisation[12] and RFA[15]. All studies include two supplements: LIVACT®[11,13,18,21] and Aminoleban EN®[12,14–17,19,20]. Two supplementations both contain three main BCAA: isoleucine, leucine and valine. The details of BCAA supplementation are provided in Table 1.

The methodological quality of included trials is summarised in online Supplementary Table 2. In total, eleven trials reported acceptable randomisation methods, and five trials did not describe allocation concealment[13–15,17,20]. All trials used the intention-to-treat analysis. One trial did not describe participant blinding[18]. A high loss to follow-up was reported in three trials[14,18,20], and outcome measurement in one study might have caused potential bias[20].

Overall survival and tumour recurrence

Six RCT compared the overall survival between the BCAA groups and control groups that take conventional diet without supplementation for liver disease[11–13,15–17]. The meta-analysis revealed no significant difference in overall survival (OR 0·75: 95 % CI: 0·39 to 1·44; Fig. 2). Moreover, five studies reported the recurrence rate of HCC after intervention[11–13,16,17]. The pooled estimate showed no significant difference in tumour recurrence rates (OR 0·69: 95 % CI: 0·40 to 1·18; Fig. 3) between the BCAA and control groups.

Post-treatment complication

Eight trials reported post-hepatic-intervention complications, including encephalopathy, edema, ascites, post-operation infection, bleeding, effusion and liver abscess[11–13,15–17,19,21]. Three trials reported that encephalopathy incidence at a 12-month follow-up showed no significant difference between the BCAA and control groups (RR: 0·48, 95 % CI: 0·12, 1·83; Fig. 4)[12,15,17]. The pooled estimate of two trials revealed significant differences in the incidence of oedema at 3 and 12 months[15,17]. Six trials reported ascites, with two trials[13,17] showing no significant difference at 6 months (RR: 0·83, 95 % CI: 0·25, 2·75), and the pooled estimate of four trials[12,15,17,21] showed that the BCAA group exhibited a significantly reduced incidence of ascites at 12 months compared with the control group (RR: 0·39, 95 % CI: 0·21, 0·71; Fig. 5).

Regeneration

Beppu et al. used the single-photon emission computed tomography system to assess liver volume and function in patients with HCC undergoing portal vein embolisation and subsequent hepatectomy. They found that the BCAA group had a significantly higher percentage of liver volume and functional liver volume than did the control group at 6 months after hepatectomy[18]. Yoshida et al. compared BCAA supplementation with ordinary diet in patients undergoing living donor liver transplantation. The ordinary diet was based on European Society for Parental and Enteral Nutrition guidelines. The liver regeneration rate was calculated using a formula consisting of the measurements of liver graft weight obtained from CT and actual graft weight. However, no significant difference was observed between the BCAA and control groups at 4 weeks after living donor liver transplantation [19].

Post-intervention liver function

Six RCT reported the serum albumin level post-intervention[12,13,15–17,20]. The pooled analysis showed a significantly higher serum albumin level in the BCAA group than in the control group at 6 months post-intervention (MD: 0·11 g/dl, 95 % CI: 0·02, 0·20). No significant differences were observed in the serum albumin level at 2 (MD: 0·09, 95 % CI: −0·11, 0·29), 4 (MD: 0·11, 95 % CI: −0·07, 0·30) and 12 (MD: 0·14, 95 % CI: −0·03, 0·32) months post-intervention (Fig. 6).

Serum cholinesterase levels were similar in two trials[13,20]. The pooled estimate showed no significant difference at 2 (MD: −3·41 U/L, 95 % CI: −25·31, 18·49), 4 (MD: 6·10, 95 % CI: −16·39,

Table 1. Characteristics of selected randomised controlled trials

Study	Selection criteria	No. of patients (% male)	Age, year, mean ± SD	Child–Pugh class A/B/C, %	Albumin, g/dl (mean ± SD)	Treatment procedure	Intervention
Hepatectomy							
Beppu et al. (2015)	History of PVE; Child–Pugh class A or B	B: 13 (69) C: 15 (67)	B: 64 (47–83)* C: 72 (56–78)*	NA	NA	B: RH 89 %, LH 0 %, LH + S 0 %, S 11 % C: RH 58 %, LH 8 %, LH + S 8 %, S 25 %	B: Livact 4·15 g BID, post-op PVE 6 m C: Conventional diet
Hachiya et al. (2020)	Curative hepatic resection for HCC	B: 74 (80) C: 80 (82)	B: 69 (47–85)* C: 70 (47–85)*	B: 82/18/0 C: 80/20/0	B: 3·7 (2·1–4·9)* C: 3·6 (1·5–4·6)*	B: AR 74 %, NAR 26 % C: AR 68 %, NAR 32 %	B: Livact 4 g TID, 4 y C: Surgery only
Ichikawa et al. (2013)	First hepatic resection for solitary HCC	B: 26 (69) C: 30 (67)	B: 64·7 ± 9·8 C: 64·5 ± 11·4	B: 81/19/0 C: 83/17/0	B: 0·6 ± 0·3 C: 0·8 ± 0·4	B: 2 Seg or extended: 10, Seg: 16 C: 2 Seg or extended: 14, Seg: 16	B: Livact 4·74 g TID, pre-op 2 w and post-op 6 m C: Conventional diet
Ishikawa et al. (2010)	Surgery for liver neoplasm	B: 11 (55) C: 13 (62)	B: 63·1 ± 12·5 C: 61·3 ± 11·3	B: 91/9/0 C: 92/8/0	NA	B: 3–4 Seg: 3, 1–2 Seg: 8 C: 3–4 Seg: 2, 1–2 Seg: 11	B: Aminoleban EN + usual diet pre-op 2 w and post-op 7 d C: Usual diet
Kikuchi et al. (2016)	Liver resection for HCC	B: 39 (79) C: 38 (76)	B: 69·4 ± 7·5 C: 71·9 ± 7·4	B: 100/0/0 C: 100/0/0	NA	B: Partial 33 %, Seg 0 %, 2 Seg/Seg 33 %, bisections or more 33 % C: Partial 32 %, Seg 16 %, 2 Seg/Seg 26 %, bisections or more 26 %	B: Livact 4·74 g TID, pre-op 1 m and post-op 1 y C: Post-op BCAA 1 y
Meng et al. (1999)	Curative hepatic resection for HCC	B: 21 (90) C: 23 (78)	B: 51·5 ± 10·8 C: 53·3 ± 12·8	B: 81/19/0 C: 87/13/0	B: 3·4 ± 0·5 C: 3·3 ± 0·5	B: Major: 13, Minor: 8 C: Major: 18, Minor: 5	B: Aminoleban EN 50 g TID plus protein 40 g/d, 12 w C: Normal diet (protein 80 g/d)
Okabayashi et al. (2011)	Hepatectomy for HCC	B: 40 (73) C: 36 (69)	B: 68·7 ± 7·6 C: 65·1 ± 11·3	B: 70/30/0 C: 71/29/0	B: 3·7 ± 0·5 C: 3·7 ± 0·5	B: Hemi: 10, Seg: 30, Limited: 60 C: Hemi: 11, Seg: 28, Limited: 61	P: Aminoleban EN 50 g BID pre-op 2 w and post-op 6 m C: Conventional diet
San-in group (1997)	Curative hepatic resection for HCC	B: 67 (81) C: 65 (85)	B: < 50:5 50–70:55 > 70:7‡ C: < 50:7 50–70:45 > 70:13‡	B: 79/19/1 C: 77/22/2	B: 3·5 ± 0·5 C: 3·5 ± 0·4	B: 1 Seg or more: 19, limited: 48 C: 1 Seg or more: 26, limited: 39	B: Aminoleban EN 50 g BID, post-op 1 y C: Usual diet
Liver transplantation							
Yoshida et al. (2012)	Elective LDLT	B: 12 (58) C: 12 (33)	B: 52·6 ± 10·2 C: 48·5 ± 4·4	B: 10·8 ± 2·1 C: 10·0 ± 2·4	NA	LDLT	B: Aminoleban EN 1 pack BID, 1–7 d before LDLT, 3 d to 4 w after LDLT C: Ordinary diet
RFA or TACE							
Nojiri et al. (2017)	≤ 3 tumours; size ≤ 3 cm for TACE or RFA	B: 25 (60) C: 26 (58)	B: 69·7 ± 9 C: 69·1 ± 11	B: 84/16/0 C: 88/12/0	B: 3·72 ± 0·5 C: 3·71 ± 0·4	TACE or RFA	B: Aminoleban EN 1 pack BID, 2 w before and to 5 y C: Usual diet
Poon et al. (2004)	TACE for unresectable HCC	B: 41 (95) C: 43 (91)	B: 59 (24–84)* C: 59 (27–80)*	NA	B: 3·5 (2·5–4·8)* C: 3·6 (2·4–4·6)*	TACE	B: Aminoleban EN 50 g BID plus usual diet, 1 w before first TACE, continued 1 y C: Usual diet

BCAA, branched-chain amino acid; B, BCAA group; C, control group; NA, not available; y, year; m, month; w, week; d, day; BID, twice per day; TID, thrice per day; PVE, portal vein embolisation; HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; TACE, transcatheter arterial chemoembolisation; RFA, radiofrequency ablation; RH, right hemihepatectomy; LH, left hemihepatectomy; S, sectionectomy; Hemi, hemihepatectomy; Seg, segmentectomy; AR, anatomical resection; NAR, nonanatomical resection; SD, standard deviation; op, operation.
* Median (range).
‡ Patient numbers from different age ranges.

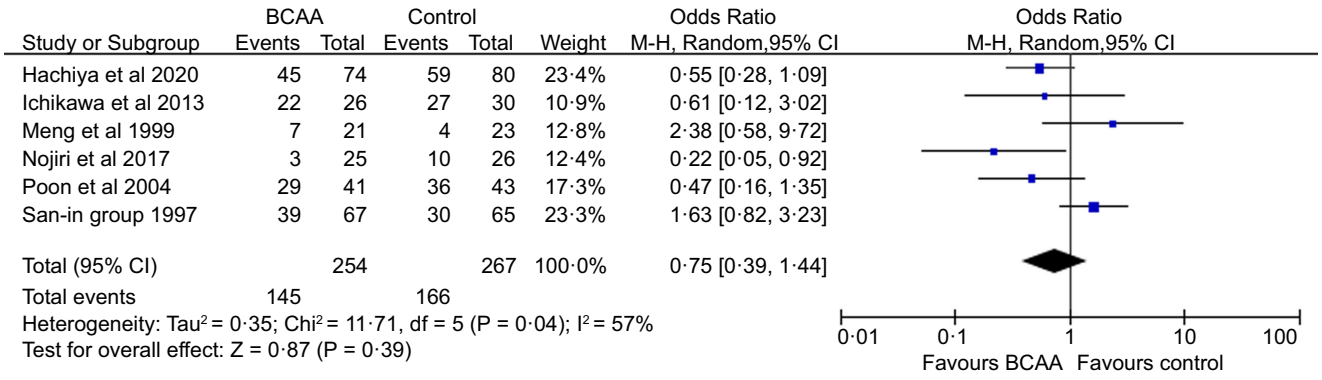

Fig. 2. Forest plot comparing the overall survival between the BCAA supplement and control groups. BCAA, alanine aminotransferase

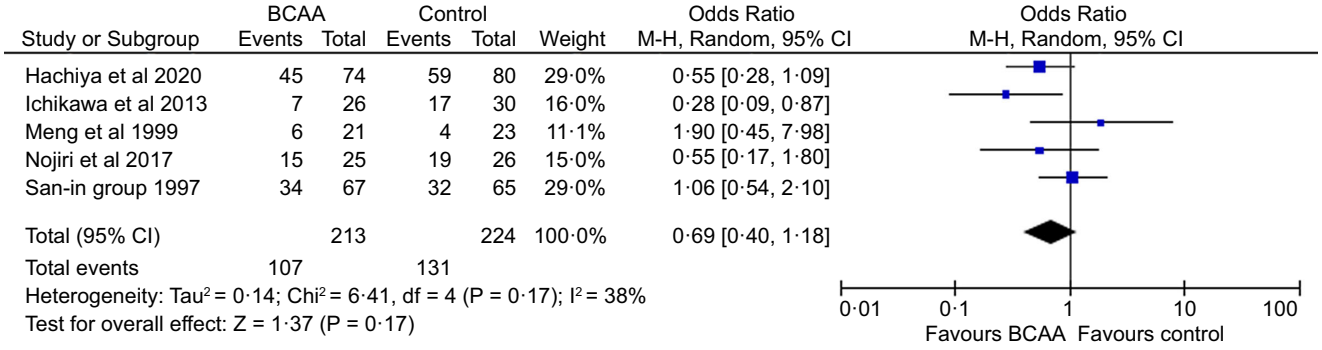

Fig. 3. Forest plot comparing the tumour recurrence between the BCAA supplement and control groups. BCAA, alanine aminotransferase

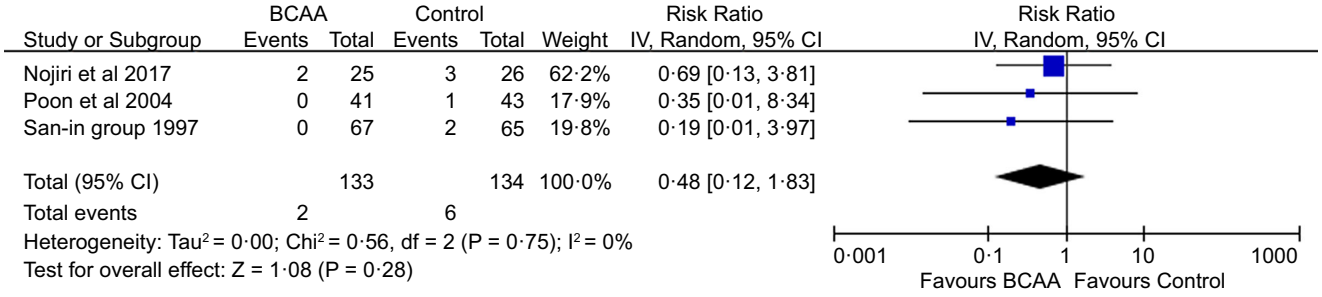

Fig. 4. Forest plot comparing the encephalopathy incidence between the BCAA supplement and control groups. BCAA, alanine aminotransferase

28·59) and 6 (MD: 21·69, 95 % CI: −4·99, 48·38) months post-intervention between the BCAA and control groups. However, one trial reported that the BCAA group expressed a significantly higher cholinesterase level than did the control group 12 months after the intervention (MD: 50·00, 95 % CI: 21·08, 78·92; Fig. 7)[20].

Three RCT reported AST and alanine aminotransferase serum levels[12,15,17]. The pooled estimate showed no significant differences between the BCAA and control groups in terms of AST (MD: 3·42 μg/l, 95 % CI: −20·99, 27·82) and alanine aminotransferase (MD: −3·56, 95 % CI: −15·18, 8·06) levels at 12 months post-intervention (Fig. 8).

Hospitalisation duration

In total, four trials compared the hospitalisation duration between the BCAA and control groups[13,16,19,21]. The pooled results showed that the BCAA group had a non-significant shorter hospitalisation length (MD: −2·36 d, 95 % CI: −4·78, 0·07) than did the control group (online Supplementary Fig. 1).

Body weight and arm circumference

In total, three trials investigated the body weight between the BCAA and control groups[13,15,20]. Poon et al.[15] measured the aforementioned parameters at 3, 6, 9 and 12 months post-treatment, whereas Ichikawa et al.[13] recorded the parameters at 2, 4 and 6 months. The pooled result showed that the BCAA group had significantly more weight gain that did the control group in 6 months (MD: 4·03 kg, 95 % CI: 0·63, 7·42) and 12 months (MD: 5·50 kg, 95 % CI: 1·42, 9·58; online Supplementary Fig. 2). The trial that used percentage changes for comparison demonstrated that body weight was greater in the treatment

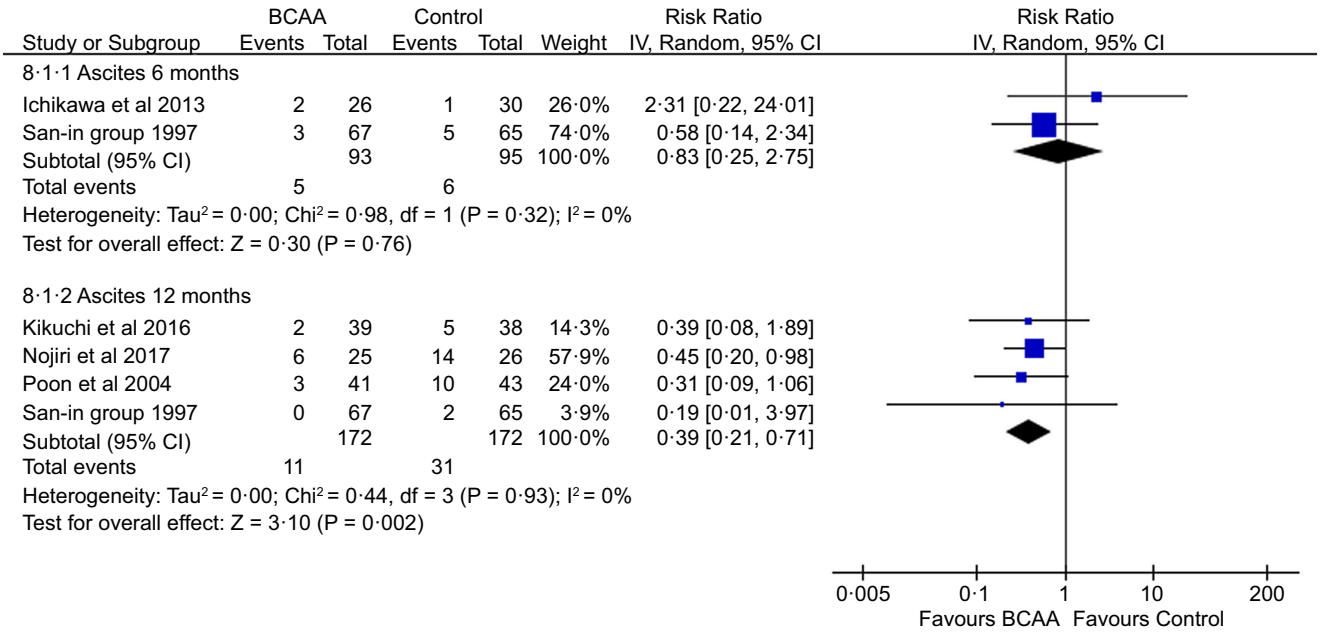

Fig. 5. Forest plot comparing the ascites incidence between the BCAA supplement and control groups. BCAA, alanine aminotransferase

group than in the control group at all time points in the first year[20].

Four trials compared the arm circumference between the BCAA and control groups. Among them, three clearly described statistical data included for the analysis[13,15,20]. The arm circumference was higher in the BCAA group than in the control group at both 6 and 12 months, with an average increase of 0·84 and 3·29 cm, respectively. However, only the increase in arm circumference at 12 months was statistically significant (MD: 3·29, 95 % CI: 1·07, 5·50; online Supplementary Fig. 3). In the trial that did not report statistical data, arm circumference was not significantly different between the groups[16].

Adverse effect of BCAA

Only one trial reported the adverse effect of BCAA on patients undergoing hepatectomy. Among the sixty-seven patients in the BCAA group, seven patients experienced adverse reactions, namely four had nausea and vomiting, one had diarrhea, one had abdominal distension and one had hypertension[17].

Grading evidence quality

Grading of Recommendations Assessment, Development, and Evaluation evidence quality for the main outcomes is listed in online Supplementary Table 3. We classified evidence quality as high, moderate, low or very low on the basis of judgements on study design, risk of bias, inconsistency, imprecision, indirectness and publication bias. The risk of biases was rated as serious among the outcomes. In the inconsistency domain, we rated the overall survival as serious because $I^2 > 50\,\%$ indicated high heterogeneity. In the imprecision domain, we rated the cholinesterase level at 12 months as serious because of insufficient number of trials. Thus, we obtained low evidence of certainty for the overall survival and cholinesterase level at 12 months (online Supplementary Table 3).

Discussion

Our study showed that BCAA supplementation in patients undergoing hepatic intervention is advantageous in terms of improvement in serum albumin and cholinesterase levels, increase in body weight and arm circumference and reduction in ascites incidence. Additionally, BCAA supplementation shortens the hospitalisation duration by 2·36 d. However, no significant difference was noted in tumour recurrence rate and overall survival rate between the groups.

BCAA enrichment formulas used were similar to supplemental parenteral nutrition, and BCAA supplementation changed the adipose–muscle–liver triangle in the metabolic pathway, for example, delayed-onset muscle soreness[22,23], insulin resistance of type 2 diabetes, decreased obesity risk[24] and clinical side effect of hepatic encephalopathy. Ooi et al. revealed that forty studies on BCAA supplementation in adults with liver cirrhosis showed improvement in muscle strength, ascites and oedema, whereas children with liver cirrhosis showed improvement in body weight, fat mass, fat-free mass and serum albumin level[25]. Furthermore, previous reviews have indicated favourable effects of BCAA on patients with hepatic encephalopathy[26,27]. Therefore, BCAA is an alternative for nutrition supplementation in patients with liver disease or patients undergoing liver surgery.

Different BCAA formulations were noted in our included RCT, namely Livact in four trials and Aminoleban EN in eight trials. Sato et al. compared the effects of BCAA granules Livact and an enteral nutrient Aminoleban EN on serum albumin in patients with decompensated liver cirrhosis and revealed that changes in serum albumin levels were similar between the two

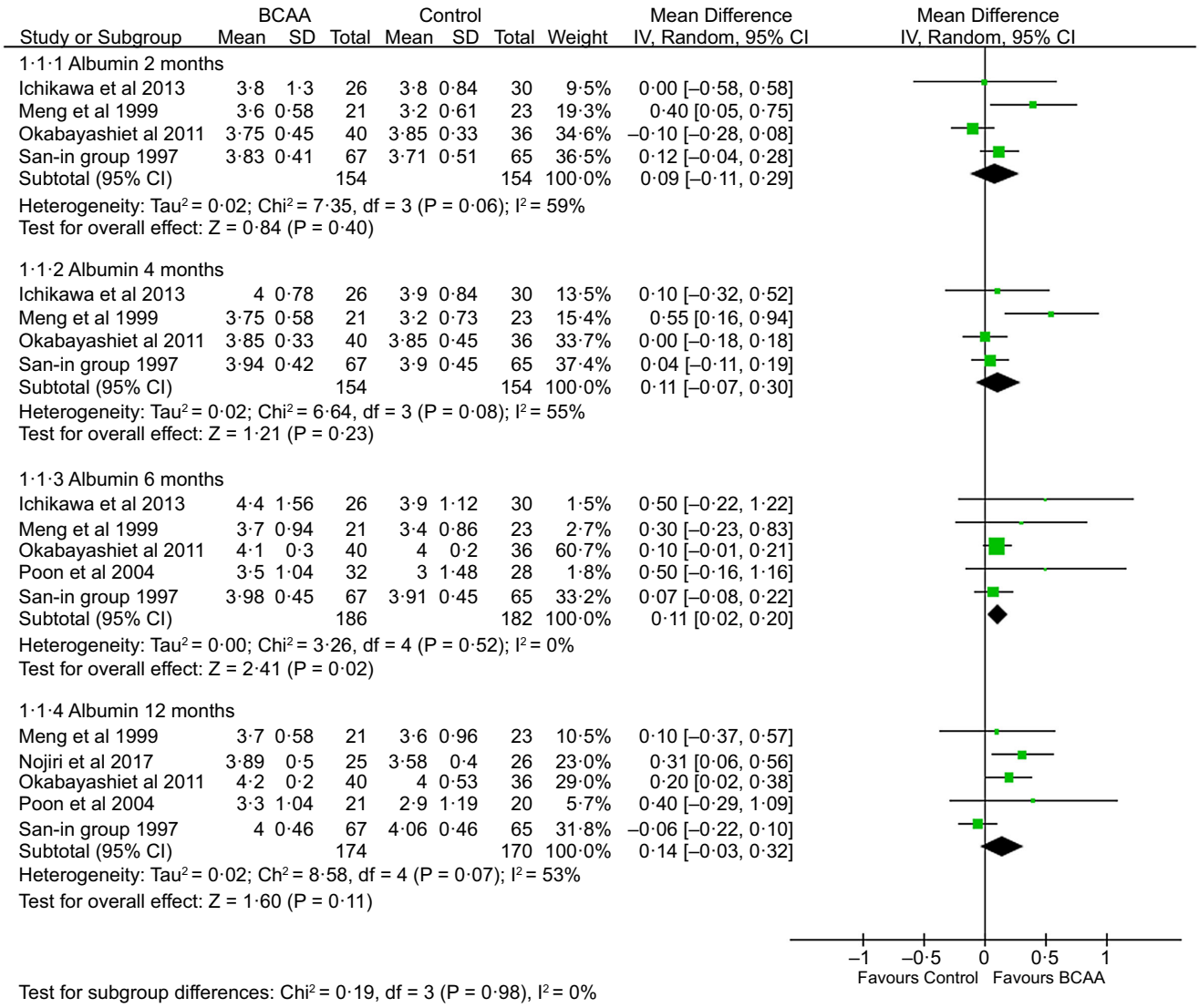

Fig. 6. Forest plot comparing the albumin levels between the BCAA supplement and control groups. BCAA, alanine aminotransferase

groups[28]. Kuroda et al. compared Aminoleban EN and standard diet in thirty-five patients with hepatitis C-related HCC who underwent RFA and revealed that supplementation with BCAA-enriched nutrients for 1 year in patients with cirrhosis with HCC after RFA therapy safely improves both their nutritional status and quality of life[29]. Uchino et al. recruited eighteen patients with heart failure with hypoalbuminaemia and found that Livact supplementation resulted in significantly increased serum albumin and decreased cardiothoracic ratio in comparison with the control group[30]. Similar to our analysis, significant improvement in liver function or serum albumin concentration was noted with both BCAA formulations.

Previous systematic reviews illustrated the benefits of specific HCC treatments. Fan et al. demonstrated significantly increased risks of mortality and recurrence with RFA than liver resection, particularly in patients with up to 2 cm solitary HCC[31]. Huo et al. reviewed twenty-six studies and demonstrated that postoperative adjuvant transcatheter arterial chemoembolisation is safe and improves overall and disease-free survival, with the greatest benefit in microvascular invasion-positive patients[32]. Mckary et al. assessed eleven studies and showed that BCAA supplementation in both pre- and peri-resection hepatic malignancy reduces overall complications[33]. However, the abovementioned studies did not provide supportive evidence regarding the benefits of BCAA supplementation in multiple possible interventions. Therefore, our study comprehensively included trials with operation interventions (e.g. liver transplantation or liver resection), local ablative therapies (e.g. microwave ablation or RFA) or locoregional therapies (e.g. transcatheter arterial chemoembolisation or selective internal radiotherapy). In our analysis of nine studies on hepatectomy, one study on living donor liver transplantation and two studies on RFA or transcatheter arterial chemoembolisation in patients with HCC with pre- and postoperative BCAA supplementation, five studies revealed a significantly decreased postoperative ascites in the BCAA group. Nevertheless, more trials are required

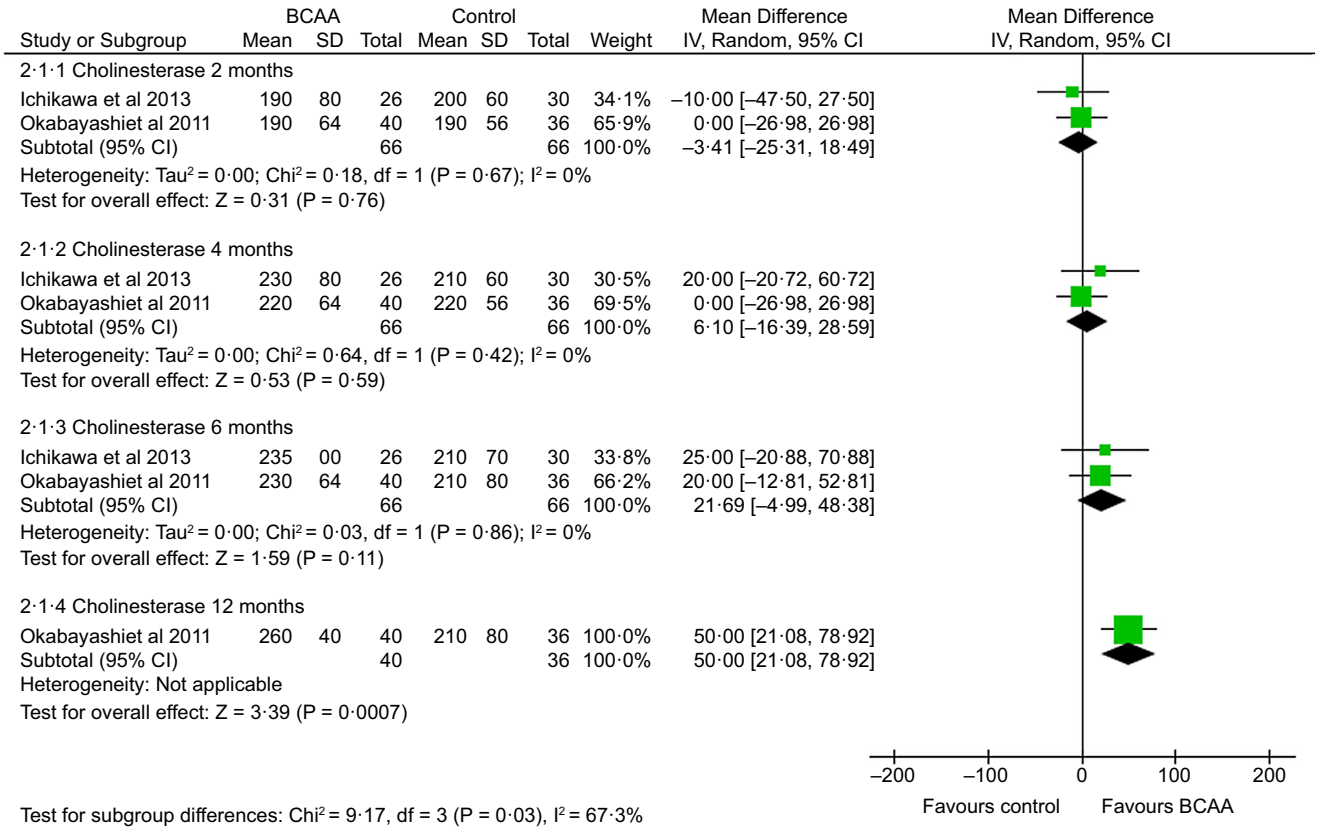

Fig. 7. Forest plot comparing the cholinesterase levels between the BCAA supplement and control groups. BCAA, alanine aminotransferase

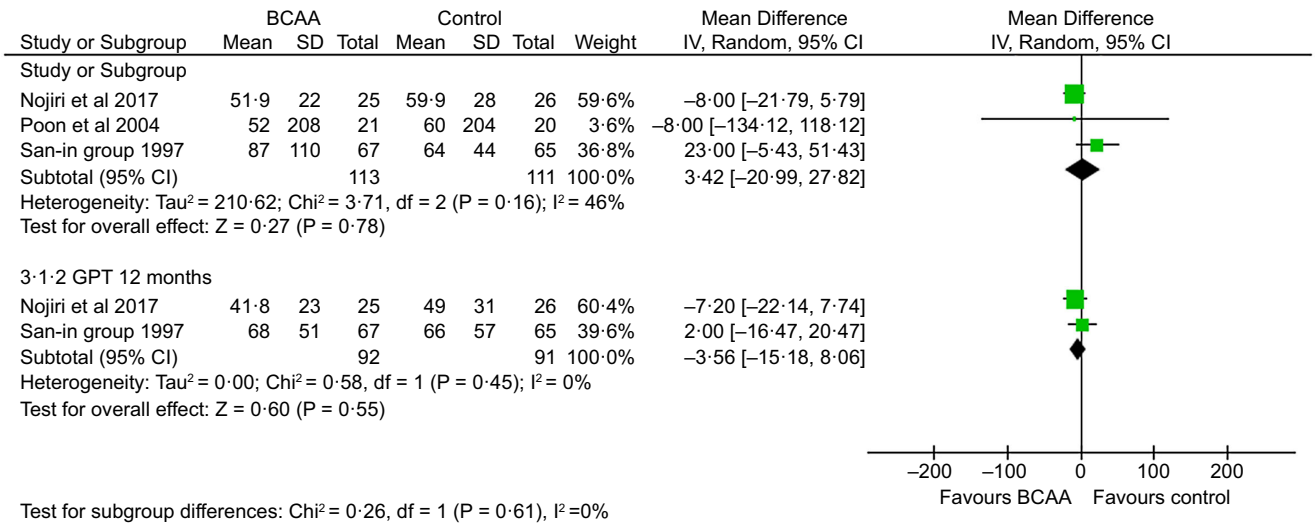

Fig. 8. Forest plot comparing the AST and ALT levels between the BCAA supplement and control groups. AST, aspartate transaminase; ALT, alanine aminotransferase; BCAA, alanine aminotransferase

to provide further evidence regarding each of the analysed factors and to further analyse overall survival and tumour recurrence.

Although BCAA has been used for years, the principle of BCAA supplementation is inconclusive. For example, although both Ichikawa et al.[14] and Kikuchi et al.[21] rendered the same dose of BCAA per day for patients who underwent hepatic resection, the results differed in terms of hospitalisation duration and postoperative ascites. Hence, our study compiled and analysed differences in BCAA supplementation between different trials, including the total dose, use frequency and time taken. Further studies are required to form guidelines based on these factors to maximise the benefits of BCAA in patients undergoing hepatic interventions.

The pros and cons of body weight gain during the peri-treatment phase on patients undergoing hepatic intervention remains unclear. Obesity may increase the risk of type 2 diabetes, CVD and non-alcoholic fatty liver disease. Although such potential complications were not systematically evaluated, adverse effects were not significantly increased in our included trials. In our review, seven trials reported the BMI of the enrolled patients[11–15,20,21], the mean BMI of each group is within 22 to 24·8, revealed that the majority of the patients are not overweight. Therefore, BCAA supplementation is relatively safe to the selected patients to receive interventional therapies.

Considerable heterogeneity was observed across the studies included in our analysis because of various clinical factors. First, most studies recruited patients with liver disease undergoing different interventions. Second, the serum albumin level, serum cholesterol esterase and serum AST were not consistently measured over time. Third, although most studies have used the BCAA diet, the initial intervention and duration of BCAA supplementation and the length of follow-up varied between the studies.

Our study has several limitations. First, certain trials recruited a relatively small sample size of patients per treatment group. Second, the beneficial effects of BCAA on post-treatment liver regeneration or patient's quality of life remain unknown because few studies have addressed these issues. Third, the BCAA diet intervention affects the metabolic pathway, but the effect of BCAA on patients with endocrine or chronic diseases remains unknown. Finally, the compliance of using BCAA could be kept well in the randomised controlled setting, but the BCAA supplementation may be hard to maintain in a real world situation, the impact of the discontinuous supply of BCAA warrants further evaluation.

In conclusion, BCAA supplementation significantly improved the liver function, reduced the incidence of ascites and increased body weight and arm circumference. Thus, BCAA supplementation may be beneficial for non-overweight patients undergoing liver intervention.

Acknowledgement

We acknowledge Wallace Academic Editing for editing this manuscript.

Funding support

This work is supported by a research grant from En Chu Kong Hospital and Shuang Ho Hospital, Taipei Medical University (Grant No.: W192–109). The sponsoring organisation was not involved in the study design, data analysis or interpretation.

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Conflicts of interest

The authors have no conflicts of interest or financial ties to disclose.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114523001885

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