REVIEW

Intravenous branched-chain amino acid administration for the acute treatment of hepatic encephalopathy: a systematic review and meta-analysis

Shoji Yokobori[1]*[iD], Tomoaki Yatabe[2], Yutaka Kondo[3], Yasuhiko Ajimi[4], Manabu Araki[5], Norio Chihara[6], Masao Nagayama[7], Tetsuya Samkamoto[8] and the Japan ResuscitationCouncil (JRC) Neuroresuscitation Task Force and the Guidelines Editorial Committee

Abstract

Background Hepatic encephalopathy (HE) is a severe complication of acute hepatic failure requiring urgent critical care management. Branched-chain amino acids (BCAAs) such as leucine, isoleucine, and valine have been investigated as potential treatments to improve outcomes in patients with acute HE. However, the effectiveness of BCAA administration during the acute phase remains unclear. This study aimed to evaluate the effect of intravenous BCAA (IV-BCAA) treatment on clinical outcomes in patients with acute HE by systematically reviewing and analyzing randomized controlled trials (RCTs).

Methods We conducted a comprehensive literature search of MEDLINE, the Cochrane Central Register of Controlled Trials, and Igaku Chuo Zasshi (ICHUSHI), a Japanese database for medical literature. We included RCTs involving adult patients with acute HE who received IV-BCAA or placebo during the acute phase after admission (< 7 days). Two reviewers independently screened the citations and extracted data. The primary "critical" outcomes were mortality from any cause and improvement in disturbance of consciousness. The secondary "important" outcome included the incidence of complications such as nausea and diarrhea. Risk ratios (RRs) were calculated using random effects models with inverse variance weighting.

Results Among the 2073 screened records, four met the criteria for quantitative analysis. The analysis included 219 patients: 109 received IV-BCAA, and 110 received placebo. Improvement in the disturbance of consciousness and mortality were not significantly different between the two groups (RR, 1.26; 95% confidence interval [CI], 0.96–1.66; RR, 0.90; 95% CI 0.70–1.16, respectively). Following IV-BCAA administration, the absolute differences of improvement in the disturbance of consciousness and mortality were 118 more per 1000 (95% CI 18 fewer–300 more) and 55 fewer per 1000 (95% CI 165 fewer–88 more), respectively. No significant differences were observed in the incidence of nausea or diarrhea between the two groups.

Conclusions Our meta-analysis demonstrates that all outcomes were not significantly different between IV-BCAA treatment and placebo for acute HE. Further RCTs are required to better understand IV-BCAA treatment potential in patients with HE.

Keywords Hepatic encephalopathy, Branched-chain amino acid, Acute care, Randomized controlled trial, Meta-analysis, Systematic review, Intravenous infusion

---

†Shoji Yokobori and Tomoaki Yatabe contributed equally to this work.

*Correspondence:
Shoji Yokobori
shoji@nms.ac.jp
Full list of author information is available at the end of the article

Yokobori *et al. Journal of Intensive Care* (2025) 13:2

Page 2 of 10

Background

Hepatic encephalopathy (HE) is a complex neuropsychiatric syndrome resulting from acute liver failure. It is characterized by symptoms ranging from subtle cognitive impairments to severe alterations in consciousness, significantly impacting quality of life and increasing mortality rates. The pathogenesis of HE involves a combination of metabolic disturbances, including elevated serum ammonia levels, which disrupt neurotransmission and neuronal function [1].

The development of HE marks a significant transition in the natural history of cirrhosis. Following a diagnosis of HE, the median survival for persons with cirrhosis is substantially reduced to 2 years, 1 year if over 65 years old. HE occurs in as many as 40% of patients with cirrhosis [2]. Thus, cirrhosis was associated with 2.4% of global deaths [3].

Amino acids, particularly branched-chain amino acids (BCAAs), such as leucine, isoleucine, and valine, have been investigated for their potential therapeutic benefits in the management of HE. BCAAs are essential amino acids that are metabolized primarily in the muscles and influence brain function and neurochemistry [4]. The role of BCAAs in HE management stems from the hypothesis that BCAAs can provide neuroprotective effects and counteract some of the adverse effects of elevated ammonia levels [4]. An imbalance between BCAAs and aromatic amino acids (AAAs) is thought to contribute to the neurotoxic effects of HE. Thus, BCAAs may help restore balance by competing with AAAs for transport across the blood–brain barrier, potentially reducing the neurotoxic impact of AAAs.

Several studies have explored the efficacy of BCAA supplementation in improving HE symptoms, particularly cognitive function and overall clinical outcomes [5–9]. Compared with placebo or no intervention, oral BCAA supplementation in the chronic phase is more effective in treating overt HE [10]. However, evidence for this treatment in the acute resuscitative phase of HE with intravenous administration of BCAA (IV-BCAA) is lacking.

This systematic review and meta-analysis aimed to evaluate the existing evidence on the effectiveness of IV-BCAA administration for resuscitative acute HE treatment. By synthesizing data from multiple studies, we sought to determine whether IV-BCAA administration improves clinical outcomes in patients with acute HE, identifying potential benefits or limitations associated with this therapeutic approach.

Methods

We organized a systematic review team in the Japan Resuscitation Council (JRC) Neuroresuscitation Task Force. The JRC 2025 Neuroresuscitation Task Force and the Guidelines Editorial Committee were established in 2024 and organized by the Japan Society of Neuroemergencies and Critical Care, the Japanese Society of Intensive Care Medicine, the Japan Society of Neurosurgical Emergency, and the Japanese Society of Neurological Therapeutics. The JRC Neuroresuscitation Task Force established six clinically relevant questions and performed a systematic review.

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses standards [11]. This study was registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry, the largest clinical trial registry in Japan (UMIN000054559).

Based on the discussion in the JRC Neuroresuscitation Task Force, the population intervention comparator outcome study design and timeframe to guide a systematic review search was set as follows:

> P (patients): All adults ($\geq$ 18 years old) with HE.
> I (interventions): Initial administration of IV-BCAA during the in-hospital acute phase ($<$ 7 days or in the acute hospitalized phase, not in outpatient clinics). The doses of BCAA used were not limited.
> C (comparisons, controls): Placebo or non-intervention.
> O (outcomes): Primary, "critical" outcome was mortality from any cause and improvement in consciousness. Secondary, "important" outcomes were nausea and diarrhea, which are common side effects.
> S (study design): Randomized controlled trials (RCTs).
> T (timeframe): All published literature up to June 4, 2024.

We identified RCTs investigating the effects of IV-BCAA in patients with acute HE by searching PubMed, the Cochrane Library, and Igaku Chuo Zasshi (ICHUSHI) web up till June 4, 2024. ICHUSHI web is the largest database of Japanese medical journals, containing approximately 10 million manuscripts from 6,000 journals.

We included studies that fulfilled the following criteria: (1) RCT, (2) full-text publications in English or Japanese, (3) included adult patients with acute, worsened HE, (4) included comparisons between IV-BCAA and placebo or non-intervention, and (5) initial administration of IV-BCAA during the acute phase (within 7 days

Yokobori *et al. Journal of Intensive Care*   (2025) 13:2

Page 3 of 10

after admission). The dose of administration and components of BCAA were not limited; however, the method of administration was limited to transvenous infusion because of the limitations of the acute resuscitation phase.

Two reviewers (TY and SY) independently extracted the data and assessed the methodological quality of eligible studies. They reached a consensus on literature selection, resolving disagreements through discussion. Data extracted from each study included the first author's name, year of publication, number of study sites, number of patients, patient age, proportion of males, definition of HE, precipitating factors (infection, GI bleeding, and alcohol abuse), initial serum ammonia, administration of BCAA, dose of BCAA, and other treatments. Methodological quality was evaluated using the Cochrane risk-of-bias (RoB) assessment tool [12], which assesses the randomization process, derivations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. The two reviewers reached a consensus on RoB 2, and any discrepancy in judgment was resolved through discussion.

The grade of recommendation, assessment, development, and evaluation (GRADE) approach was also used to evaluate the certainty of the available evidence, such as inconsistency, indirectness, imprecision, and publication bias. We provided an evidence profile table using the GRADE pro GDT (GRADEpro GDT: GRADEpro Guideline Development Tool [Software]) and McMaster University, 2015 (developed by Evidence Prime Inc.). The table is available at gradepro.org. To apply the GRADE system, we received guidance from the Medical Information Network Distribution Service (MINDS), a Japanese center for GRADE education. The two reviewers also discussed the results of the RoB and reached a consensus on the final decision.

According to the GRADE approach, the JRC neuroresuscitation task force determines the importance of each outcome as critical, important, or not important [12, 13]. We defined critical outcomes as hospital mortality and improvements in disturbance of consciousness, and important outcomes as common side effects such as nausea and diarrhea.

We performed the meta-analysis using Review Manager (version 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Comparative risk ratios (RRs) were reported with 95% confidence intervals (CIs). We selected a random-effects model. Statistical heterogeneity was determined by assessing values that were interpreted as follows: 0–40%, not important; 30–60%, moderate heterogeneity; 50–90%, substantial heterogeneity; and 75–100%, considerable heterogeneity.

Results

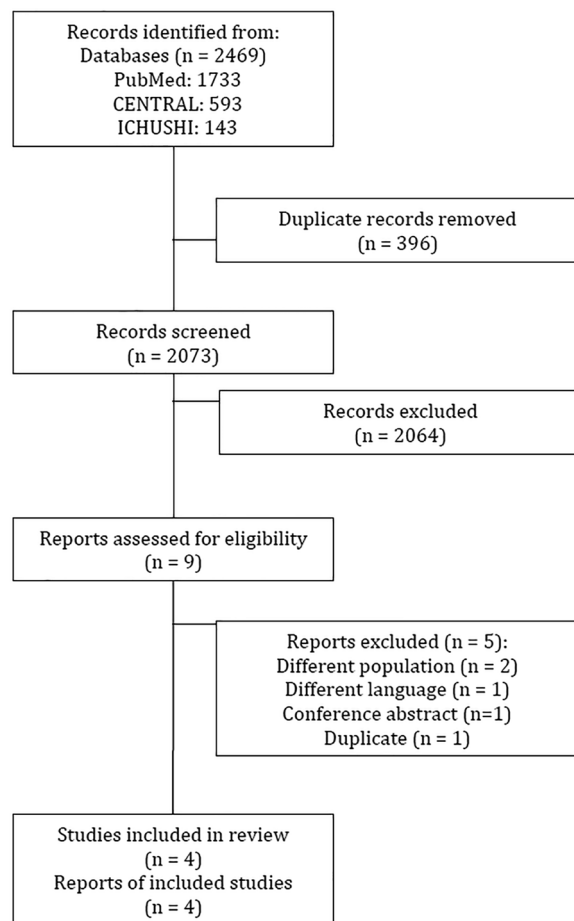### Literature search strategy

A total of 2469 studies were identified using the database search. After removing 396 duplicate studies, 2073 studies were eligible for the first screening. Based on the assessment of title and abstract, 2064 study records were excluded, and nine full-text articles were included for the second assessment as the full-text article assessment. After assessing the eligibility of the records, five reports were excluded for the following reasons; two studies were excluded because of different patient populations, one study was excluded because of different languages, one study was excluded because it was a conference abstract, and one study was excluded because of duplication. Thus, four RCTs were ultimately included in this meta-analysis (Fig. 1) [14–17]. The search formulae and results are listed in Additional file 1.

Patient characteristics

The characteristics of studies included in this meta-analysis are summarized in Table 1. Overall, 219 patients selected from four RCTs were assigned to the IV-BCAA treatment group ($n=109$) or placebo group ($n=110$) for critical outcome analysis. Each study included 34–70 patients, with average age ranging from 45.3 to 58.9 years. The proportion of males was 56.0–88.6%. The largest RCT population was an open-label RCT published in 2023 [17]. Three studies were multicenter RCTs. In all studies, BCAA was administered intravenously. The most common precipitating factor was gastrointestinal bleeding (27.9%; n=61).

Critical outcome: improvement in the disturbance of consciousness

Improvement in the disturbance of consciousness was evaluated in all four RCTs (Fig. 2a). The evidence profiles are shown in Table 2. This set of four RCTs had less publication bias with a symmetric distribution in the funnel plot (Additional file 2a). The forest plot of one of the critical outcomes, improvement in the disturbance of consciousness, is shown in Fig. 2a. During the observation period, 59 patients (57.8%) in the BCAA-treated group and 45 patients (45.5%) in the placebo group recovered their mental status. Although this difference did not reach significance (RR, 1.26 [95% CI 0.96–1.66], $P=0.09$; Fig. 2a), the absolute differences in improvement in the disturbance of consciousness were 118 more per 1000 (95% CI 18 fewer–300 more) as a result of BCAA administration.

Yokobori *et al. Journal of Intensive Care*   (2025) 13:2

Page 4 of 10

Fig. 1 Flow chart of the search strategy and study selection

Critical outcome: all-cause mortality

Mortality from any cause was evaluated in three RCTs (Fig. 2b). The evidence profiles are presented in Table 2. This set of three RCTs had less publication bias with a symmetric distribution in the funnel plot (Additional file 2b). During the observation period, 46 patients (50.0%) died in the IV-BCAA-treated group, and 51 patients (54.8%) died in the placebo group. Although this difference did not reach significance (RR, 0.90 [95% CI 0.70–1.16], p = 0.42), the absolute differences in mortality were 55 fewer per 1000 (95% CI 165 fewer–88 more) as a result of IV-BCAA administration.

Important outcome: adverse effects (nausea and diarrhea)

The incidence rates of the adverse effects of IV-BCAA treatment, nausea, and diarrhea were determined for each RCT [16] (Fig. 2c, d). With respect to nausea, three (8.6%) of the 35 patients who received BCAAs experienced nausea, and the same number (8.6%) of patients in the placebo group experienced nausea. No significant

difference was observed in the incidence of nausea between the BCAA and placebo groups (RR, 1.00; 95% CI [0.22–4.62]; *P* = 1.00) (Fig. 2c).

Regarding the incidence of diarrhea, it occurred in four (11.4%) patients in the IV-BCAA group and five (14.3%) patients in the placebo group. No significant difference was observed in the incidence of nausea between the BCAA and placebo groups (RR, 0.80; 95% CI [0.23–2.73]; *P* = 0.72). (Fig. 2d). As a result of BCAA administration, the absolute differences in nausea and diarrhea were 0 fewer per 1000 (95% CI 67 fewer–310 more) and 29 fewer per 1000 (95% CI 110 fewer–427 more), respectively.

Discussion

In this systematic review and meta-analysis, we aimed to clarify the efficacy of IV-BCAA administration compared to placebo in patients with acute HE. Several systematic reviews of BCAA treatment in HE patients have been published [8, 16–19]. However, in these meta-analyses, most RCTs did not mention acute HE, which requires urgent care and intravenous administration in the emergency room or intensive care unit. Therefore, this study is the first systematic review and meta-analysis of RCTs comparing IV-BCAA treatment and placebo in acute-phase HE care.

Our meta-analysis demonstrates that all outcomes were not significantly different between IV-BCAA treatment and placebo for acute HE. Therefore, the benefit of IV-BCAAs remains unclear. However, our meta-analysis indicated the possibility that IV-BCAA treatment might have potential benefits in this population because improvements in the disturbance of consciousness in the IV-BCAA group tended to be higher.

BCAAs, including leucine, isoleucine, and valine, play various roles in the body, which include supporting protein synthesis and energy production. With regard to the pathophysiology of HE, BCAAs play a crucial role in ammonia metabolism [21]. In patients with liver disease, the protein breakdown in muscles leads to an increase in ammonia levels. BCAAs can provide an alternative nitrogen source that is converted into glutamine in muscles, thereby reducing the level of toxic ammonia in the blood [20].

In HE, there is often an imbalance between neurotransmitters in the brain, particularly a decrease in excitatory neurotransmitters such as glutamate and an increase in inhibitory neurotransmitters such as gamma-aminobutyric acid [22]. BCAAs can also help restore this balance by serving as precursors of excitatory neurotransmitters, potentially improving cognitive function. Additionally, patients with liver disease are often malnourished, and

**Table 1** Characteristics of the included studies

Author, year	No. of sites	No. of patients (BCAA vs Control)	Mean Age (years)	Definition of HE	Male n, (%)	Precipitating factor, n (%)			Initial Mean Serum Ammonia	Intervention BCAA Type and dose	Methods of BCAA administration	Comparison/ Control	Outcomes
						Infection	GI Bleeding	Alcohol Abuse					
Rossi-Fanelli et al. 1982 [14]	4	34 (17vs17)	58.9	Grade 3–4 (Adams and Foley classification)	21 (61.8)	12 (35.3)	7 (20.6)	1 (2.9)	172.4 (g/dL)	BS 692[a] + 20% dextrose	60 ml/L for the first 24 h (1500 ml/day), and thereafter at 80 ml/hr (2500 ml/day) until 48 h after mental recovery	Lactulose via a nasogastric tube (30–40 g every 4 h) or via the rectal route (200–300 g/day). Dextrose in isocaloric amounts and the same rate of as in intervention group	Improvement in HE (Grade 0) during 48 h
Wahren et al. 1983 [15]	5	50 (25vs25)	56	Grade II–IV (Denis classification)	28 (56.0)	12 (24.0)	20 (40.0)	2 (4.0)	2.4 times local laboratory's upper normal limit	BCAA 20 g/L (70% leucine, 20% valine, and 10% isoleucine) in 5% glucose	2L of BCAAs (40 g)/ day. Infusions were given for 20 h/day, and therapy was continued for 1 day after HE improved to Grade 0 or I, or for a maximum of 5 days	Glucose (5%) alone, 2 L/day	Improvement in HE (Grade 0–II) during 5 days 30-day mortality
Vilstrup 1990 [16]	3	65 (32vs33)	55.5	Grade II–IV (Fogarty classification)	47 (72.3)	15 (23.1)	20 (31.0)	3 (4.6)	N/A	1 g/kg/day of amino acid with 40% branched chain contents	Central venous infusion	Isocaloric 8% glucose	Improvement in HE (Grade 0–I) during 16 days 16-day mortality
Mehtani et al. 2023 [17]	1	70 (35vs35)	47	EASL-CLIF-defined ACLF with HESA grades > 2	62 (88.6)	19 (27.1)	14 (20.0)	28 (40.0)	134 (μmol/L)	BCAA 500 mL/day for 3 days + Lactulose 30–60 mL three times a day	Intravenous infusion	Lactulose alone 30–60 mL three times a day	Improvement in HE at day 28[b] 28-day mortality

SD, Standard Deviation; HE, Hepatic Encephalopathy; GI, Bleeding, Gastrointestinal Bleeding; BCAA, Branched Chain Amino Acid; EASL-CLIF, European Association for the Study of the Liver–Chronic Liver Failure Consortium; ACLF, Acute-on-Chronic Liver Failure; HESA, hepatic encephalopathy scoring algorithm; hr, hours

[a] Composition of BCAA Mixture (BS692): L-Isoleucine 9 g/L, L-Leucine 11 g/L, L-Valine 8.4 g/L (Total BCAA 28.4 g). Dextrose 200 g/L (Total BCAA 8.4 g/L, Total Nitrogen 4.54 g/L, Total calorie: 814.2 kcal/L

[b] Resolution of HE was defined as an improvement in HESA to grade 0 or 2 consecutive days when HESA grade remained at 1 after an initial improvement in at least 1 full grade
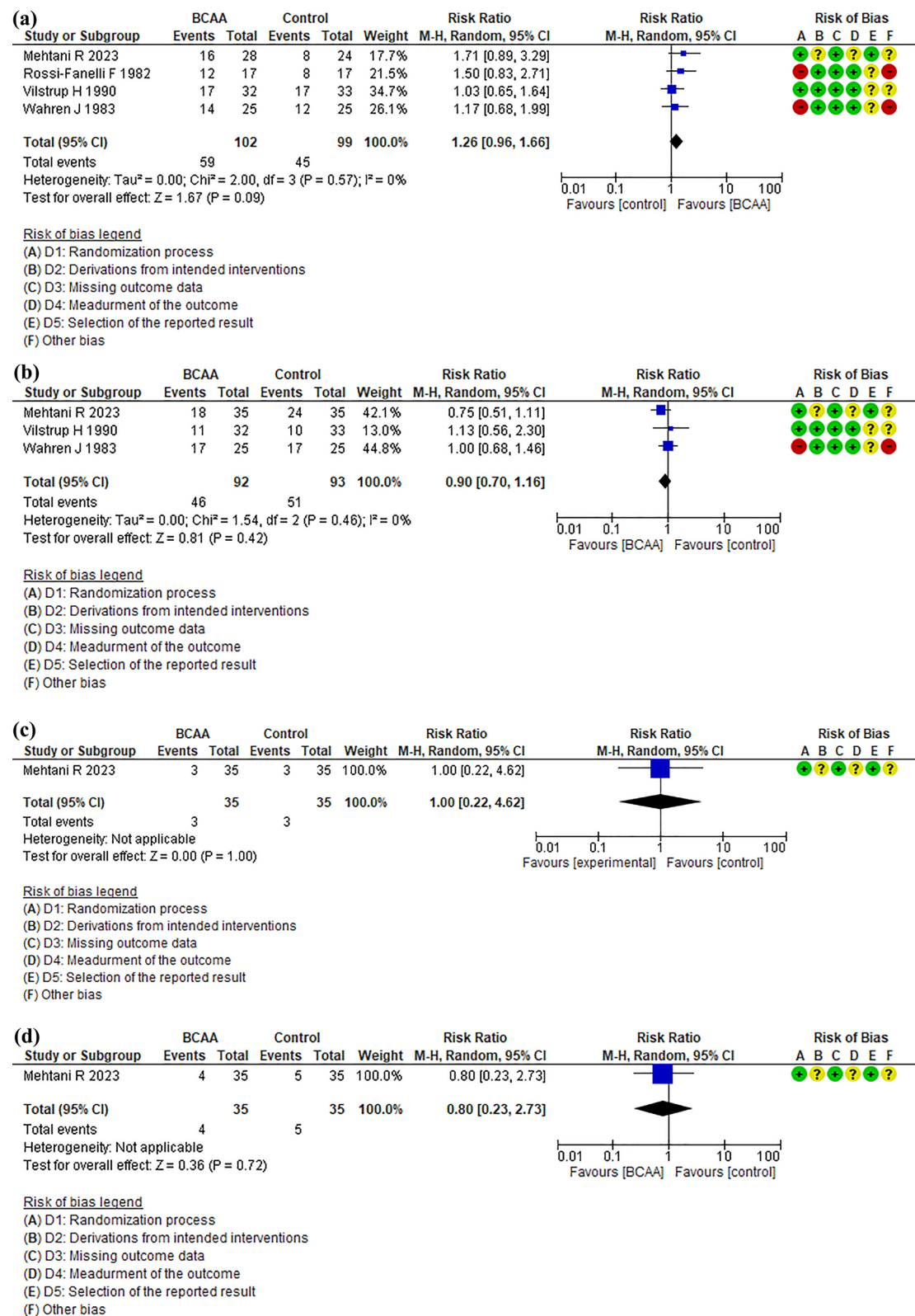
Fig. 2 Forest plot of (**a**) Improvement in the disturbance of consciousness (**b**) All-cause mortality (**c**) Nausea, and (**d**) Diarrhea. The risk of bias summary is listed as follows: **A** D1 Randomization process; **B** D2 Derivations from intended interventions; **C** D3 Missing outcome data; **D** D4 Measurement of the outcome; **E** D5 Selection of the report result; **F** other bias. BCAA, branched-chain amino acid; CI, confidence interval

Table 2 Evidence profiles

Certainty assessment							No of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BCAA	placebo	Relative (95% CI)	Absolute (95% CI)		
Improvement of the disturbance of consciousness												
4	Randomized trials	Very serious[a]	Not serious	Not serious	Serious[b]	None	59/102 (57.8%)	45/99 (45.5%)	RR 1.26 (0.96 to 1.66)	118 more per 1000 (from 18 fewer to 300 more)	⊕◯◯◯ Very low	CRITICAL
All-cause mortality												
3	Randomized trials	Very serious[c]	Not serious	Not serious	Serious[b]	None	46/92 (50.0%)	51/93 (54.8%)	RR 0.90 (0.70 to 1.16)	55 fewer per 1000 (from 165 fewer to 88 more)	⊕◯◯◯ Very low	CRITICAL
Nausea												
1	Randomized trials	Serious[c]	Not serious	Not serious	Serious[b]	None	3/35 (8.6%)	3/35 (8.6%)	RR 1.00 (0.22 to 4.62)	0 fewer per 1000 (from 67 fewer to 310 more)	⊕⊕◯◯ Low	IMPORTANT
Diarrhea												
1	Randomized trials	Serious[c]	Not serious	Not serious	Serious[b]	None	4/35 (11.4%)	5/35 (14.3%)	RR 0.80 (0.23 to 2.73)	29 fewer per 1000 (from 110 fewer to 247 more)	⊕⊕◯◯ Low	IMPORTANT

Reasons of downgrade:

a. "There are two studies with a high risk of bias."

b. "There is a high possibility that the optimal amount of information is not met."

c. "There is one study with a high risk of bias, and its contribution rate is high."

CI: Confidence interval; RR: Risk ratio; RoB: Risk of Bias

BCAAs are important for maintaining muscle mass and overall nutritional status [23]. Several clinical studies have shown that oral BCAA supplementation can improve mental health and reduce the severity of HE symptoms via the above pathophysiological mechanisms [5, 24–26]. However, the benefits are often modest, and BCAAs are usually part of a broader treatment plan rather than a standalone solution [27]. BCAA supplementation is often used as an adjunct therapy in the management of chronic phase HE, particularly in patients who are unresponsive to standard treatments such as lactulose or rifaximin [28]. Thus, BCAA administration is usually transoral during the chronic phase of HE management [27]. Recent guidelines from the European Association for the Study of the Liver and American Association for the Study of Liver Diseases recommend routine oral BCAA treatment for patients with overt HE [29, 30]. However, the effect of IV-BCAA on episodic bouts of HE has not been proven [31].

Our findings support the safety of IV-BCAA in clinical practice because of the equal incidence of side effects in the IV-BCAA and placebo groups. However, we found only one RCT that mentioned side effects (nausea and diarrhea). Generally, the adverse effects of BCAA treatment are listed as hypoglycemia, nausea, and diarrhea [32].

Indeed, prophylactic glucose administration may be applied; however, the incidence of these adverse effects is still not well understood.

Moreover, we could not find sufficient evidence to evaluate the benefit of IV-BCAA compared with other interventions because improvements in the disturbance of consciousness and mortality were not significantly different between the two groups.

We also could not discuss the cost-effectiveness of the interventions for the management of HE because all four RCTs did not evaluate it. An economic study revealed that the total cost related to HE in the United States increased from USD 4676.7 million in 2005 to USD 7244.7 million in 2009 [33]. Therefore, it is necessary to assess the cost-effectiveness of IV-BCAA treatment for HE from the standpoint of medical economics, benefits, and harm.

This meta-analysis has some limitations. First, only four RCTs were included in our systematic review, with limited information on a small number of patients because of the inclusion criteria of patients who received IV-BCAAs in emergency care. Second, the severity of HE differed across the four RCTs; that is, the definition of the inclusion of patients with HE may have differed across the RCTs. Thus, the features of the targeted patients may have been heterogeneous in our meta-analysis. Finally, the underlying conditions that precipitated HE varied,

as shown in Table 1. However, we could not perform a subgroup analysis based on these underlying conditions because the four RCTs did not provide data for each of these subgroups. Therefore, the balance between the risks and benefits of IV-BCAA might differ depending on the underlying conditions that precipitate HE. Well-designed RCTs are needed in the future to determine the indications for IV-BCAA in acute HE care and support our findings.

Conclusions

Our meta-analysis demonstrates that all outcomes were not significantly different between IV-BCAA treatment and placebo for acute HE. However, improvements in the disturbance of consciousness in the IV-BCAA group tended to be higher. These findings highlight the need for further RCTs to better understand the potential benefits of IV-BCAA treatment in this population.

Abbreviations
HE   Hepatic encephalopathy
BCAA   Branched-chain amino acid
IV-BCAA   Intravenous BCAA treatment
RCTs   Randomized controlled trials
AAA   Aromatic amino acid

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s40560-024-00771-x.

Additional file 1. Search strategy and results.

Additional file 2. Funnel plot. (a) Critical outcome: Improvement in the disturbance of consciousness. (b) Critical outcome: All-cause mortali

Additional file 3.

Author contributions
All authors were involved in the study design. SY and TY identified the studies included in the meta-analysis and analyzed the data. SY drafted the manuscript, and TY supervised it. All authors were involved in data interpretation and discussion. All the authors have read and approved the final manuscript.

Yokobori *et al. Journal of Intensive Care*   (2025) 13:2

Page 9 of 10

Availability of data and materials

Not applicable.

Declarations

Declarations

This manuscript has not been published or presented elsewhere in part or in entirety and is not under consideration by another journal. There are no conflicts of interest to declare.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflicts of interest.

Author details

[1]Department of Emergency and Critical Care Medicine, Nippon Medical School, Bunkyo-Ku, Tokyo 113-8603, Japan. [2]Emergency Department, Nishichita General Hospital, Tokai-Shi, Aichi 477-8522, Japan. [3]Department of Emergency and Disaster Medicine, Juntendo University Graduate School of Medicine, Bunkyo-Ku, Tokyo 113-8431, Japan. [4]Department of Emergency Medicine, Teikyo University School of Medicine, Itabashi-Ku, Tokyo 173-8605, Japan. [5]Department of Neurology, Kawakita General Hospital, Tokyo 166-8588, Japan. [6]Division of Neurology, Kobe University Hospital, 7-5-2, Kusunoki-Cho, Chuo-Ku, Kobe 650-0017, Japan. [7]Departments of Neurology, Critical Care Medicine, and the Center for Preventive Medicine, International University of Health and Welfare Narita Hospital, Narita, Chiba 286-8520, Japan. [8]Showa General Hospital, Kodaira-Shi, Tokyo 187-8510, Japan.

References

1. Butterworth RF. Hepatic encephalopathy in cirrhosis: pathology and pathophysiology. Drugs. 2019;79(Suppl 1):17–21. https://doi.org/10.1007/s40265-018-1017-0.
2. Louissaint J, Deutsch-Link S, Tapper EB. Changing epidemiology of cirrhosis and hepatic encephalopathy. Clin Gastroenterol Hepatol. 2022;8(8):S1–8. https://doi.org/10.1016/j.cgh.2022.04.036.
3. The Global Health Observatory. global health estimates: leading causes of death. WHO https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/ ghe-leading-causes-of-death. 2023. Accessed 28 Nov 2024.
4. Colosimo S, Bertoli S, Saffioti F. Use of branched-chain amino acids as a potential treatment for improving nutrition-related outcomes in advanced chronic liver disease. Nutrients. 2023. https://doi.org/10.3390/nu15194190.
5. Les I, Doval E, García-Martínez R, Planas M, Cárdenas G, Gómez P, et al. Effects of branched-chain amino acids supplementation in patients with cirrhosis and a previous episode of hepatic encephalopathy: a randomized study. Am J Gastroenterol. 2011;106:1081–8. https://doi.org/10.1038/ajg.2011.9.
6. Marchesini G, Bianchi G, Merli M, Amodio P, Panella C, Loguercio C, et al. Nutritional supplementation with branched-chain amino acids in advanced cirrhosis a double-blind, randomized trial. Gastroenterology. 2003; 124: 1792–801. https://doi.org/10.1016/s0016-5085(03)00323-8
7. Marchesini G, Dioguardi FS, Bianchi GP, Zoli M, Bellati G, Roffi L, et al. Long-term oral branched-chain amino acid treatment in chronic hepatic encephalopathy. A randomized double-blind casein-controlled trial. The Italian Multicenter Study Group. J Hepatol. 1990;11:92–101. https://doi.org/10.1016/0168-8278(90)90278-y.
8. Dioguardi FS, Brigatti M, Dell'Oca M, Ferrario E, Abbiati R. Effects of chronic oral branched-chain amino acid supplementation in a subpopulation of cirrhotics. Clin Physiol Biochem. 1990;8:101–7.
9. Kawaguchi T, Taniguchi E, Sata M. Effects of oral branched-chain amino acids on hepatic encephalopathy and outcome in patients with liver cirrhosis. Nutr Clin Pract. 2013;28:580–8. https://doi.org/10.1177/0884533613496432.
10. Gluud LL, Dam G, Les I, Marchesini G, Borre M, Aagaard NK, et al. Branched-chain amino acids for people with hepatic encephalopathy. Cochrane Database Syst Rev. 2017;5:CD001939. https://doi.org/10.1002/14651858.CD001939.pub4.
11. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009;62:e1–34. https://doi.org/10.1016/j.jclinepi.2009.06.006.
12. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: arevised tool for assessing risk of bias in randomised trials. BMJ. 2019;366: l4898. https://doi.org/10.1136/bmj.l4898.
13. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. [GRADE guidelines] GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64:383–94. https://doi.org/10.1016/j.jclinepi.2010.04.026.
14. Rossi-Fanelli F, Riggio O, Cangiano C, Cascino A, De Conciliis D, Merli M, et al. Branched-chain amino acids vs lactulose in the treatment of hepatic coma: a controlled study. Dig Dis Sci. 1982;27:929–35. https://doi.org/10.1007/BF01316578.
15. Wahren J, Denis J, Desurmont P, Eriksson LS, Escoffier JM, Gauthier AP, et al. Is intravenous administration of branched chain amino acids effective in the treatment of hepatic encephalopathy? A multicenter study Hepatology. 1983;3:475–80. https://doi.org/10.1002/hep.1840030402.
16. Vilstrup H, Gluud C, Hardt F, Kristensen M, Køhler O, Melgaard B, et al. Branched chain enriched amino acid versus glucose treatment of hepatic encephalopathy. A double-blind study of 65 patients with cirrhosis. J Hepatol. 1990;10:291–6. https://doi.org/10.1016/0168-8278(90)90135-e.
17. Mehtani R, Premkumar M, Garg S, Kajal K, Kulkarni AV, Duseja AK, et al. Intravenous BCAA infusion does not lead to a sustained recovery from overt HE in ACLF–an open label randomized clinical trial. J Clin Exp Hepatol. 2023;13:977–88. https://doi.org/10.1016/j.jceh.2023.05.015.
18. Konstantis G, Pourzitaki C, Chourdakis M, Kitsikidou E, Germanidis G. Efficacy of branched chain amino acids supplementation in liver cirrhosis: a systematic review and meta-analysis. Clin Nutr. 2022;41:1171–90. https://doi.org/10.1016/j.clnu.2022.03.027.
19. Ooi PH, Gilmour SM, Yap J, Mager DR. Effects of branched chain amino acid supplementation on patient care outcomes in adults and children with liver cirrhosis: a systematic review. Clin Nutr ESPEN. 2018;28:41–51. https://doi.org/10.1016/j.clnesp.2018.07.012.
20. Gluud LL, Dam G, Borre M, Les I, Cordoba J, Marchesini G, et al. Oral branched-chain amino acids have a beneficial effect on manifestations of hepatic encephalopathy in a systematic review with meta-analyses of randomized controlled trials. J Nutr. 2013;143:1263–8. https://doi.org/10.3945/jn.113.174375.
21. Zhu GQ, Shi KQ, Huang S, Wang LR, Lin YQ, Huang GQ, et al. Systematic review with network meta-analysis: the comparative effectiveness and safety of interventions in patients with overt hepatic encephalopathy. Aliment Pharmacol Ther. 2015;41:624–35. https://doi.org/10.1111/apt.13122.
22. Butterworth RF. The neurobiology of hepatic encephalopathy. Semin Liver Dis. 1996;16:235–44. https://doi.org/10.1055/s-2007-1007236.
23. Marrone G, Serra A, Miele L, Biolato M, Liguori A, Grieco A, et al. Branched chain amino acids in hepatic encephalopathy and sarcopenia in liver cirrhosis: evidence and uncertainties. World J Gastroenterol. 2023;29:2905–15. https://doi.org/10.3748/wjg.v29.i19.2905.
24. Bianchi GP, Marchesini G, Zoli M, Abbiati R, Ferrario E, Fabbri A, et al. Oral BCAA supplementation in cirrhosis with chronic encephalopathy: effects on prolactin and estradiol levels. Hepatogastroenterology. 1992;39:443–6.
25. Malaguarnera M, Risino C, Cammalleri L, Malaguarnera L, Astuto M, Vecchio I, et al. Branched chain amino acids supplemented with L-acetyl-carnitine versus BCAA treatment in hepatic coma: a randomized and controlled double blind study. Eur J Gastroenterol Hepatol. 2009;21:762–70. https://doi.org/10.1097/MEG.0b013e328309c791.
26. Nakaya Y, Okita K, Suzuki K, Moriwaki H, Kato A, Miwa Y, et al. BCAA-enriched snack improves nutritional state of cirrhosis. Nutrition. 2007;23:113–20. https://doi.org/10.1016/j.nut.2006.10.008.

Yokobori *et al. Journal of Intensive Care*   (2025) 13:2

Page 10 of 10

27. Fallahzadeh MA, Rahimi RS. Hepatic encephalopathy: current and emerging treatment modalities. Clin Gastroenterol Hepatol. 2022;20:S9–19. https://doi.org/10.1016/j.cgh.2022.04.034.

28. Mohammad RA, Regal RE, Alaniz C. Combination therapy for the treatment and prevention of hepatic encephalopathy. Ann Pharmacother. 2012;46:1559–63. https://doi.org/10.1345/aph.1R146.

29. American Association for the Study of Liver Diseases, European Association for the Study of the Liver. Hepatic encephalopathy in chronic liver disease. practice guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. J Hepatol. 2014;2014(61):642–59. https://doi.org/10.1016/j.jhep.2014.05.042.

30. Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology. 2014;60:715–35. https://doi.org/10.1002/hep.27210.

31. Naylor CD, O'Rourke K, Detsky AS, Baker JP. Parenteral nutrition with branched-chain amino acids in hepatic encephalopathy. A Meta-Analy Gastroenterol. 1989;97:1033–42. https://doi.org/10.1016/0016-5085(89)91517-5.

32. Holeček M. Side effects of amino acid supplements. Physiol Res. 2022;71(1):29–45. https://doi.org/10.33549/physiolres.

33. Stepanova M, Mishra A, Venkatesan C, Younossi ZM. In-hospital mortality and economic burden associated with hepatic encephalopathy in the United States from 2005 to 2009. Clin Gastroenterol Hepatol. 2012;10:1034-41.e1. https://doi.org/10.1016/j.cgh.2012.05.016.

Publisher's Note