New Evidence of Oral Branched-Chain Amino Acid Supplementation on the Prognosis of Patients With Advanced Liver Disease

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INTRODUCTION: **Oral branched-chain amino acids (BCAAs) might benefit patients with advanced liver disease. We assess its effects on prognosis compared with control from the meta-analysis.**

METHODS: **Study end points were development of hepatic encephalopathy (HE), hepatocellular carcinoma (HCC), mortality, and overall liver-related events (LREs). Risk ratios (RRs) and hazard ratios (HRs) were calculated using random effects model and heterogeneity using I^2 statistic.**

RESULTS: **Twenty-eight studies were included in this meta-analysis; 1,578 and 1,727 patients in oral BCAAs and control groups, respectively. From studies using RRs as outcome measures, oral BCAAs were better in preventing HE and LRE than controls, with RRs 0.684 (95% confidence interval [CI] 0.497–0.941; $P = 0.019$) and 0.788 (95% CI 0.585–0.810; $P < 0.001$), respectively. Oral BCAAs had marginal effect on preventing HCC compared with control, with RR 0.791 (95% CI 0.619–1.011; $P = 0.061$); no significant difference in mortality was detected. From studies using HRs as outcome measures, oral BCAAs were superior to control in preventing LRE with adjusted HR 0.497 (95% CI 0.321–0.770; $P = 0.002$). In subgroups undergoing HCC resection, oral BCAAs had beneficial effect in preventing HE (RR 0.716, 95% CI 0.514–0.996; $P = 0.047$) and LRE (RR 0.716, 95% CI 0.595–0.860; $P < 0.001$).**

DISCUSSION: **Oral BCAAs could afford clinical benefits in reducing HE and LRE risks, especially among patients undergoing HCC resection.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A887

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INTRODUCTION

Patients with liver cirrhosis can develop various hepatic decompensation events (1). Among them, hepatic encephalopathy (HE), a complex and reversible neuropsychiatric syndrome caused by hepatic insufficiency, is a major complication associated with poor prognosis, reduced quality of life, and enhanced risk of recurrence. Clinical manifestations of HE range from minutely altered mental status to deep coma, negatively affecting the overall quality of life (2,3). Moreover, the 1-year mortality rate in patients with severe HE in the intensive care unit was up to 54% (4). To manage patients with overt HE, oral administration of branched-chain amino acids (BCAAs) could be considered as an adjuvant to nonabsorbable disaccharides and rifaximin.

Patients with liver cirrhosis have decreased serum concentrations of BCAAs; a group of 3 essential amino acids comprising valine, leucine, and isoleucine; and a reduced Fischer ratio (serum BCAA/aromatic amino acids), which are associated with the pathogenesis of protein-energy malnutrition and HE (5). The main pathogenesis of BCAA deficiency is that BCAA is used as donor of amino group to alpha-ketoglutarate for synthesis of glutamate, which is a direct precursor for ammonia detoxification to glutamine in muscles. Such a process leads to so-called cataplerosis, the loss of alpha-ketoglutarate from citric cycle, subsequently decreasing adenosine triphosphate production by mitochondria (6). Furthermore, given that patients with cirrhosis exhibit portosystemic shunts and hypermetabolic states, BCAA deficiency is also attributed to the enhanced uptake and consumption of BCAA by the skeletal muscle for energy generation (7). Furthermore, BCAA accounts for approximately 30% of essential amino acids in skeletal muscle proteins (8,9). Hence, muscle protein breakdown occurs through persistent skeletal muscle consumption of BCAA, ultimately resulting in sarcopenia, which is

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closely associated with the major life-threatening complications of liver cirrhosis, such as ascites, spontaneous bacterial peritonitis, HE, and hepatorenal syndrome (10,11).

Theoretically, the beneficial effects of BCAA supplementation during chronic liver disease include improvements in body composition and nitrogen balance, liver cell regeneration, protein and albumin synthesis, symptoms of HE, and immune function (12). Nevertheless, the use of oral BCAA to improve the overall prognosis in patients with cirrhosis remains controversial, and a recent Cochrane review has concluded that oral BCAA might be useful in managing overt HE with no beneficial effects on mortality or nutritional parameters noted (13). This finding might be due to the wide variability in dose, duration, and mode of administration, as well as the clinical setting, sample size, and study design. To our knowledge, no present study has examined the preventive effect of oral BCAA supplementation on either newly developed HE or HE recurrence after recovery, so far.

In this systematic review and meta-analysis, we aimed to review the extant literature on oral BCAA in patients with liver cirrhosis and quantitatively assess its efficacy on the development of HE, hepatocellular carcinoma (HCC), mortality, and liver-related events (LREs).

METHODS

Literature search strategy

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (14) and not registered in publicly available databases. We searched the PubMed, Embase, and Cochrane Library databases to identify studies that investigated the effects of BCAA in patients with advanced liver diseases compared with a control group in December 2020. There were no restrictions on the year or language of publication. The following search terms were used as medical subject headings terms in PubMed: "liver cirrhosis," "liver diseases," "HE," "liver failure," "amino acids, branched-chain," along with individual free terms. In the Embase database, Emtree terms such as "liver cirrhosis," "liver disease," "HE," "liver failure," "liver fibrosis," "liver dysfunction," "hepatic coma," and "BCAA" were used as search terms. Furthermore, we reviewed the references of searched and identified articles and added relevant articles to the review list during the first screening. Supplementary Table S1 presents the detailed search strategy used (see Supplementary Table 1, http://links.lww.com/CTG/A887).

Study selection

We included randomized clinical trials (RCTs) and observational studies describing the effects of BCAAs on HE or relevant health outcomes among patients with advanced liver diseases. Four study end points were classified into 1 primary and 3 secondary outcomes. The primary outcome was the occurrence of (i) HE, defined as a newly developed or recurrence after remission. Secondary outcomes were the incidence of (ii) HCC, defined as a newly developed case or recurrence after curative treatment; (iii) mortality; and (iv) LRE, defined as all composite outcomes, including hepatic decompensation (e.g., HE, ascites, variceal bleeding, hepatorenal syndrome, spontaneous bacterial peritonitis, and liver transplant), HCC, and mortality. Studies were excluded based on the following exclusion criteria: (i) use of intravenous BCAA, (ii) studies that failed to include health outcomes associated with BCAA, (iii) outcomes not of interest, (iv) article type not of interest (e.g., reviews, editorials, conference abstracts, and letters to the editor), (v) duplicates, and (vi) inability to access the full text. Using the predefined selection criteria, 2 reviewers (H.L. and B.K.K.) evaluated the titles and abstracts of identified articles for first-stage selection. If the abstract did not contain full content to determine whether the article was included, the reviewers then independently assessed the full text of the article. Disagreements between the 2 reviewers were resolved by discussion.

Data extraction and quality assessment

The following variables were extracted: (i) location, (ii) study design, (iii) study population, (iv) the number of samples in both intervention and comparator arms, (v) age, (vi) the percentage of men, and (vii) the number of events for each outcome. For obtaining any missing or additional data, we contacted authors, if eligible, via e-mail. Quality assessment of RCTs was performed using the version 2 of the Cochrane risk-of-bias (RoB) tool (15). Observational studies were evaluated using the Risk of Bias Assessment Tool for Nonrandomized Studies (16). RoB is the recommended tool for assessing the risk of bias in RCTs and consists of 5 domains as follows: randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. In addition, based on the results of the 5 domains, the overall risk is judged. The Risk of Bias Assessment Tool for Nonrandomized Studies consists of the following 6 domains: selection of participants, confounding variables, measurement of exposure, blinding of outcome assessments, incomplete outcome data, and selective outcome reporting. Two reviewers independently assessed the risk of bias as high risk, low risk, or unclear risk according to the contents of the study text for each domain. Any disagreements were resolved by reaching a consensus.

Statistical analysis

The random effects model was selected because underlying heterogeneity was expected from the various study locations, designs, and clinical characteristics of the study population. Risk ratio (RR) estimates and associated 95% confidence intervals (CIs) were pooled using the DerSimonian-Laird estimator for τ^2 with inverse variance weights (17). We considered 4 outcomes, recorded as hazard ratios (HRs) or adjusted HRs and their 95% CIs on the log-scale, and weighted by the inverse of their corresponding variances to obtain pooled estimates.

Heterogeneity was assessed using the *P* value by Q statistic and I^2 statistic categorized as follows: $<$30%, not important; 30%–50%, moderate; 50%–75%, substantial; and $>$75%, considerable I^2 (18). To explore the sources of heterogeneity, a subgroup analysis was performed to examine the relationship between RRs and the study population (liver cirrhosis, HCC, and surgical resection of HCC), design (RCT, prospective cohort, and retrospective cohort), and ethnicity (Asian and non-Asian). The mean age or SD, which was not reported in original articles, was estimated using median, range, and interquartile range (19). Even when the number of studies was less than 10, publication bias was assessed using funnel plots and the Peter test (20).

All statistical analyses were performed using R (version 4.0.4; The R Foundation for Statistical Computing, Vienna, Austria) and Review Manager software (version 5.4; Copenhagen, Denmark; Cochrane Collaboration). A forest map was used to plot the meta-analysis results, and a funnel map was used to present

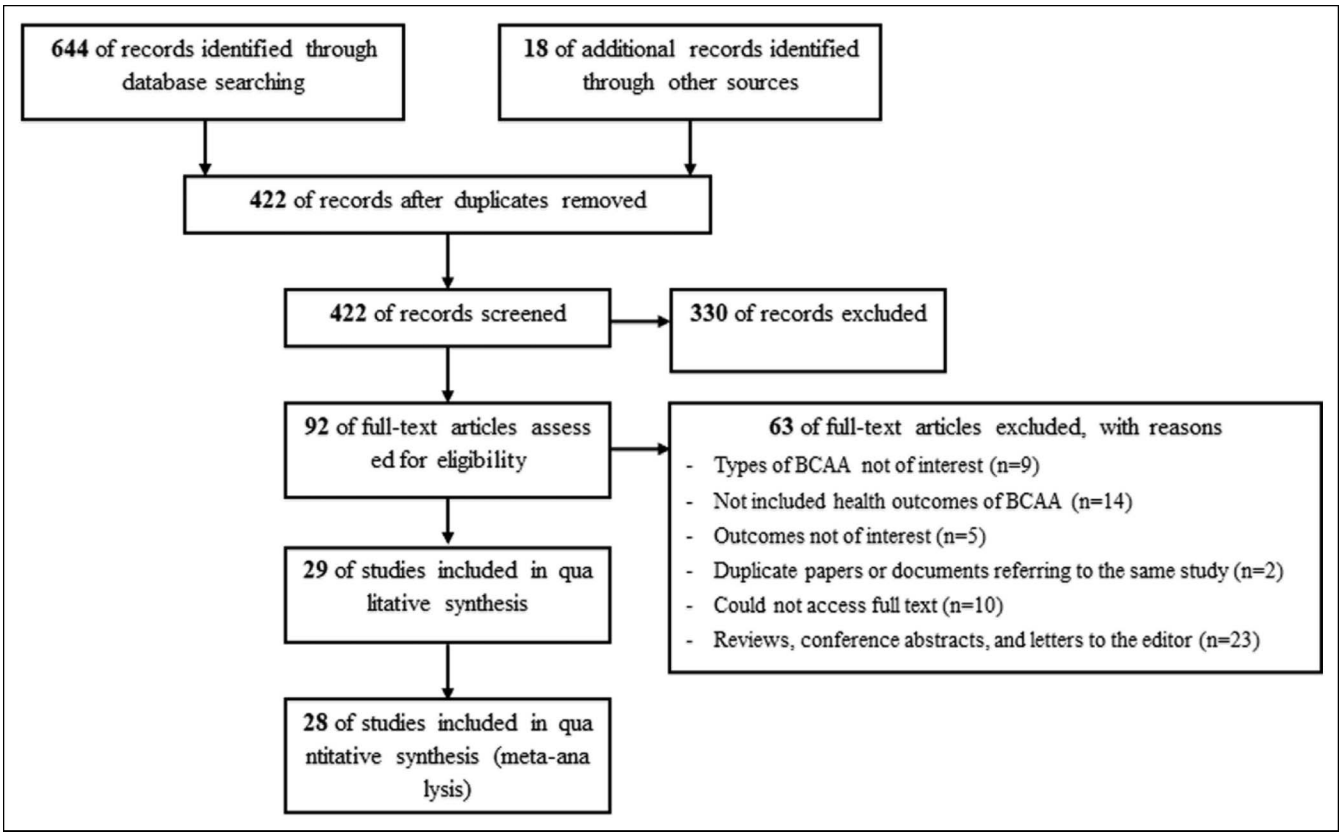

Figure 1. Flowchart for identifying relevant studies. BCAA, branched-chain amino acids.

publication bias. A P value of <0.05 was considered statistically significant.

Certainty of evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was applied to assess the certainty of evidence across 4 outcomes by the study type (21). Using the GRADE profiler (22), 4 domains (risk of bias, inconsistency, indirectness, and imprecision) and other considerations (publication bias, large effect, plausible confounding, and dose response gradient) were assessed, and the certainty of evidence was classified into 1 of 4 grades: high, moderate, low, and very low.

RESULTS

Summary of included articles

In this study, our search yielded 422 original articles after excluding duplicates. After screening titles and abstracts, 92 articles were included in the full-text review. Finally, we included 28 articles that met the inclusion criteria established for the meta-analysis (23–50) (Figure 1). Among included articles, 20 were RCTs, whereas the remaining were observational studies (retrospective cohort, 6; prospective cohort, 2). Among these, 22 were published in Asia (Japan [n = 18], South Korea [n = 2], and Hong Kong [n = 2]). Overall, 3,305 patients with liver diseases were considered, 1,578 in the BCAA group and 1,727 in the control group. The characteristics of selected studies are presented in Supplementary Table S2 (see Supplementary Table 2, http://links.lww.com/CTG/A887).

The quality assessment results are presented in Supplementary Table S3 and Supplementary Figures S1 and S2 (see Supplementary Table 3, Figures 1 and 2, http://links.lww.com/CTG/A887). In the quality assessment of RCTs, the risks in most domains were assessed as "low risk," except for "allocation concealment" and "blinding of participants and personnel." Given the paucity of clear descriptions regarding allocation and blinding of participants in several RCTs, the risks in "allocation concealment" and "blinding of participants and personnel" were evaluated as "unclear risk" and "high risk," respectively. The quality of observational studies included was deemed as low risk of bias; however, a few studies were rated as "high-risk" in the domain of "confounding variables."

Because of the GRADE approach, all evidence of RCTs was rated with high certainty, but the certainty of evidence synthesized from observational studies was rated low.

Effect of oral BCAAs on HE

The pooled outcomes for treatment efficacy of oral BCAA supplementation at each study end point are summarized in Table 1 and Figure 2 (Table 1, Figure 2). In the pooled analysis for HE, 41 of 274 patients in the BCAA group developed HE when compared with 65 of 276 patients in the control group. Both fixed effect and random effect meta-analyses revealed that oral BCAA supplementation had a beneficial effect on HE, with RRs of 0.684 (95% CI 0.497–0.941; $P = 0.019$) and 0.684 (95% CI 0.497–0.941; $P = 0.019$), respectively (Figure 2a). Heterogeneity between trials was not significant, with an I^2 of 0%, and no evidence of publication bias observed ($P = 0.357$ by the Peter test) (Figure 3a).

Table 1. Pooled analysis for each outcome using studies with RR as an outcome measure

Author (yr)	No. of patients		HE		HCC		Mortality		LRE	
	BCAA	Control	RR (95% CI)	*P* value	RR (95% CI)	*P* value	RR (95% CI)	*P* value	RR (95% CI)	*P* value
Horst (1984) (23)	17	20	0.168 (0.023–1.233)	0.079	—	—	—	—	—	—
Calvey (1985) (24)	21	43	—	—	—	—	0.896 (0.437–1.838)	0.764	—	—
Kanematsu (1988) (25)	29	27	0.931 (0.205–4.223)	0.926	—	—	1.862 (0.179–19.380)	0.603	—	—
Yoshida (1989) (26)	20	20	—	—	—	—	—	—	1.100 (0.609–1.986)	0.752
Nagasue (1997)	67	65	—	—	0.970 (0.730–1.289)	0.834	1.031 (0.733–1.450)	0.862	—	—
Meng (1999) (28)	21	23	—	—	1.643 (0.537–5.027)	0.384	1.917 (0.653–5.625)	0.236	—	—
Marchesini (2003) (29)	58	115	—	—	—	—	—	—	0.525 (0.270–1.019)	0.057
Poon (2004) (30)	41	43	0.349 (0.015–8.337)	0.516	—	—	0.845 (0.667–1.071)	0.163	0.459 (0.211–0.999)	0.05
Muto (2005) (31)	320	326	—	—	—	—	1.019 (0.332–3.126)	0.974	0.674 (0.521–0.872)	0.003
Togo (2005) (32)	21	22	—	—	1.048 (0.162–6.774)	0.961	—	—	—	—
Muto (2006) (33)	227	204	—	—	0.719 (0.470–1.099)	0.128	—	—	—	—
Kobayashi (2008) (34)	20	20	—	—	—	—	—	—	—	—
Okabayashi (2008) (35)	40	72	—	—	—	—	0.771 (0.322–1.850)	0.561	0.394 (0.192–0.810)	0.011
Kawamura (2009) (36)	27	23	—	—	—	—	—	—	0.487 (0.163–1.456)	0.198
Ishikawa (2010) (37)	11	13	—	—	—	—	—	—	0.788 (0.159–3.898)	0.77
Kuroda (2010) (38)	20	15	—	—	—	—	0.750 (0.051–11.046)	0.834	0.375 (0.079–1.784)	0.218
Hayaishi (2011) (39)	56	155	—	—	—	—	—	—	—	—
Les (2011) (40)	58	58	0.750 (0.511–1.101)	0.142	—	—	—	—	1.000 (0.720–1.388)	1
Ichikawa (2013) (41)	26	30	—	—	0.557 (0.290–1.070)	0.079	1.538 (0.378–6.250)	0.547	—	—
Yoshiji (2013) (42)	29	22	—	—	0.559 (0.370–0.844)	0.006	—	—	—	—
Kanekawa (2014a) (43)	23	30	—	—	—	—	—	—	—	—
Kanekawa (2014b) (43)	26	13	—	—	—	—	—	—	—	—
Hanai (2015) (44)	94	36	—	—	—	—	—	—	—	—
Kikuchi (2016) (45)	39	38	—	—	—	—	2.924 (0.123–69.592)	0.507	0.688 (0.382–1.239)	0.213
Nojiri (2017) (46)	25	26	0.693 (0.126–3.806)	0.673	—	—	0.312 (0.097–1.003)	0.051	0.578 (0.335–0.996)	0.048
Park (2017) (47)	41	41	1.250 (0.361–4.326)	0.725	—	—	1.000 (0.352–2.845)	1	0.833 (0.490–1.417)	0.501
Tada (2019) (48)	27	51	—	—	—	—	—	—	—	—
Hachiya (2020) (49)	74	80	—	—	—	—	0.309 (0.066–1.440)	0.135	—	—
Park (2020) (50)	63	61	0.387 (0.161–0.933)	0.034	—	—	0.646 (0.244–1.705)	0.377	0.596 (0.413–0.860)	0.006
Overall by fixed effect model			0.684 (0.497–0.941)	0.019	0.804 (0.665–0.975)	0.026	0.887 (0.749–1.049)	0.199	0.665 (0.578–0.766)	<0.001
Overall by random effect model			0.684 (0.497–0.941)	0.019	0.791 (0.619–1.011)	0.061	0.887 (0.749–1.049)	0.175	0.688 (0.585–0.81)	<0.001
Heterogeneity, I2 (%)			0.0 (0.0–67.6)	0.636	24.7 (0.0–68.3)	0.248	0.0 (0.0–40.6)	0.706	16.1 (0.0–55.0)	0.282

BCAA, branched-chain amino acids; CI, confidence interval; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; LRE, liver-related event; RR, risk ratio.

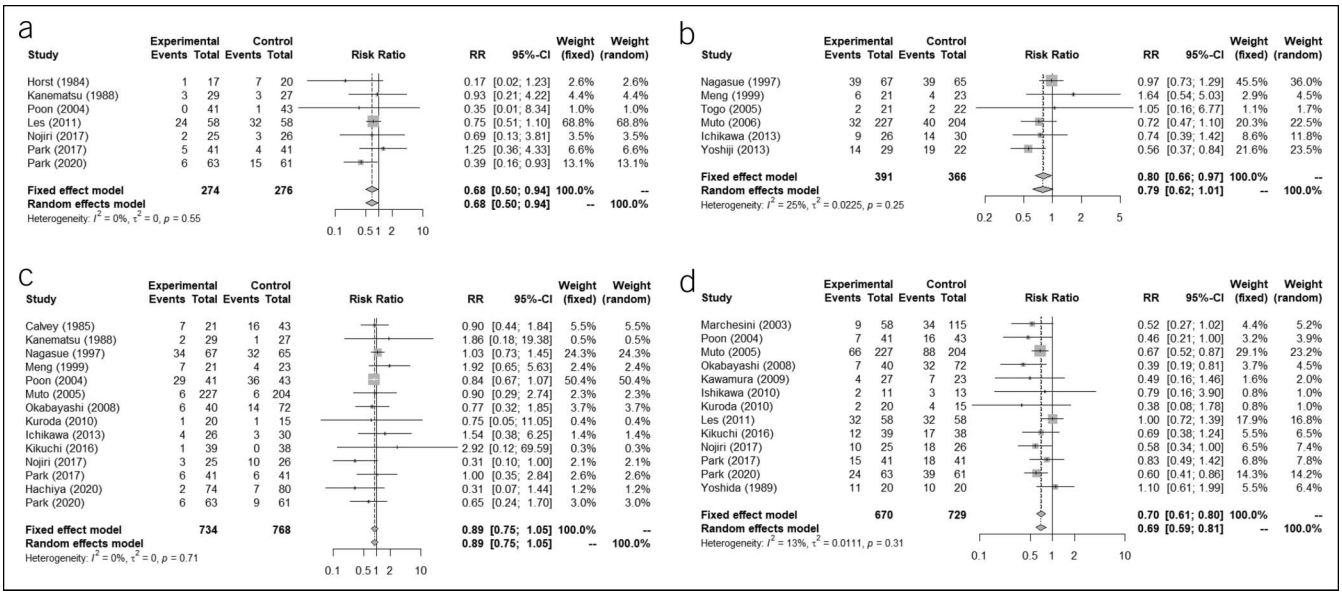

Figure 2. Effects of oral BCAA supplements on the development of HE (**a**), HCC (**b**), mortality (**c**), and LRE (**d**) by forest plots. BCAA, branched-chain amino acids; CI, confidence interval; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; LRE, liver-related events; RR, risk ratios.

Effect of oral BCAA on HCC

Based on the pooled analysis for HCC (Table 1), 101 of 391 patients developed HCC in the BCAA group when compared with 121 of 366 patients in the control group; a fixed effects meta-analysis revealed that oral BCAA supplementation had a benficial effect on this outcome measure, with an RR of 0.804 (0.665–0.975; $P = 0.026$). However, the observed benefit was marginal in the random effects meta-analysis, with an RR of 0.791 (95% CI 0.619–1.011; $P = 0.061$) (Figure 2b). The heterogeneity between trials was not significant, with an I^2 value of 24.7%, and no evidence of publication bias detected ($P = 0.797$ by the Peter test) (Figure 3b).

From another pooled analysis based on 5 studies with outcomes recorded as HR (95% CIs), both fixed effect and random effect meta-analyses showed that oral BCAA supplements had benficial effects on HCC, with HRs of 0.713 (95% CI 0.550–0.924; $P = 0.01$) and 0.637 (95% CI 0.410–0.988; $P = 0.044$), respectively (Table 2). However, the heterogeneity between trials was substantial, with an I^2 value of 57.6%.

Effect of oral BCAAs on mortality

Regarding mortality, 114 of 827 patients in the BCAA group and 145 of 890 patients in the control group developed HCC (Table 1). Based on both fixed effect (RR 0.887, 95% CI 0.749–1.049; $P = 0.199$) and random effect (RR 0.887, 95% CI 0.749–1.049; $P = 0.175$) meta-analyses, no significant difference was observed between the 2 groups (Figure 2c). The heterogeneity between trials was not significant, with an I^2 of 0%, and no evidence of bias observed ($P = 0.972$ by Peter's test) (Figure 3c).

On analyzing 1 study which recorded outcomes as HR (95% CIs), both fixed effect and random effect meta-analyses showed clinical benefits after oral BCAA supplementation, with HRs of 0.514 (95% CI 0.300–0.882; $P = 0.016$) and 0.509 (95% CI 0.275–0.942; $P = 0.032$), respectively (Table 2). Heterogeneity between trials was not significant, with an I^2 of 22.5%. Furthermore, a pooled analysis of 3 studies with adjusted HRs (95% CIs) demonstrated similar results, with adjusted HRs of 0.322 (95% CI 0.259–0.40; $P < 0.001$) and 0.324 (95% CI 0.109–0.963; $P = 0.042$) by fixed effect and random effect meta-analyses, respectively. However, the heterogeneity between trials was considerable, with an I^2 value of 94.9%.

Effect of oral BCAAs on LRE

In the pooled analysis for LRE, 201 of 763 patients in the BCAA group and 318 of 851 patients in the control group developed HCC (Table 1). Both fixed effect and random effect meta-analyses showed that oral BCAA supplementation had a benficial effect on LRE, with RRs of 0.665 (0.578–0.766; $P < 0.001$) and 0.688 (95% CI 0.585–0.81; $P < 0.001$) (Figure 2d). The heterogeneity between trials was not significant, with an I^2 value of 16.1%, and no evidence of publication bias documented ($P = 0.644$ by Peter's test) (Figure 3d).

Based on the analysis of 1 study recording outcomes as HR (95% CIs), both fixed effect and random effect meta-analyses revealed clinical benefits of oral BCAA supplementation, with HRs of 0.468 (95% CI 0.264–0.831; $P = 0.010$) and 0.468 (95% CI 0.264–0.831; $P = 0.010$), respectively (Table 2). Heterogeneity was not significant, with an I^2 value of 0.0%. Similar results were observed on analyzing 2 studies with adjusted HRs (95% CIs), presenting adjusted HRs of 0.497 (95% CI 0.321–0.770; $P = 0.002$) and 0.497 (95% CI 0.321–0.770; $P = 0.002$), respectively. Heterogeneity was not significant, with an I^2 value of 0.0%.

Subgroup analysis according to study design, study population, and ethnicity

In addition, we performed a subgroup analysis according to the study design, study population, and ethnicity (Table 3). On stratifying by study design, oral BCAA supplementation was associated with a lower risk of LRE (pooled RR from 9 RCTs 0.725, 95% CI 0.597–0.879; $P = 0.001$).

On stratifying studies by characteristics of the study population, oral BCAA supplementation was efficacious in preventing HE

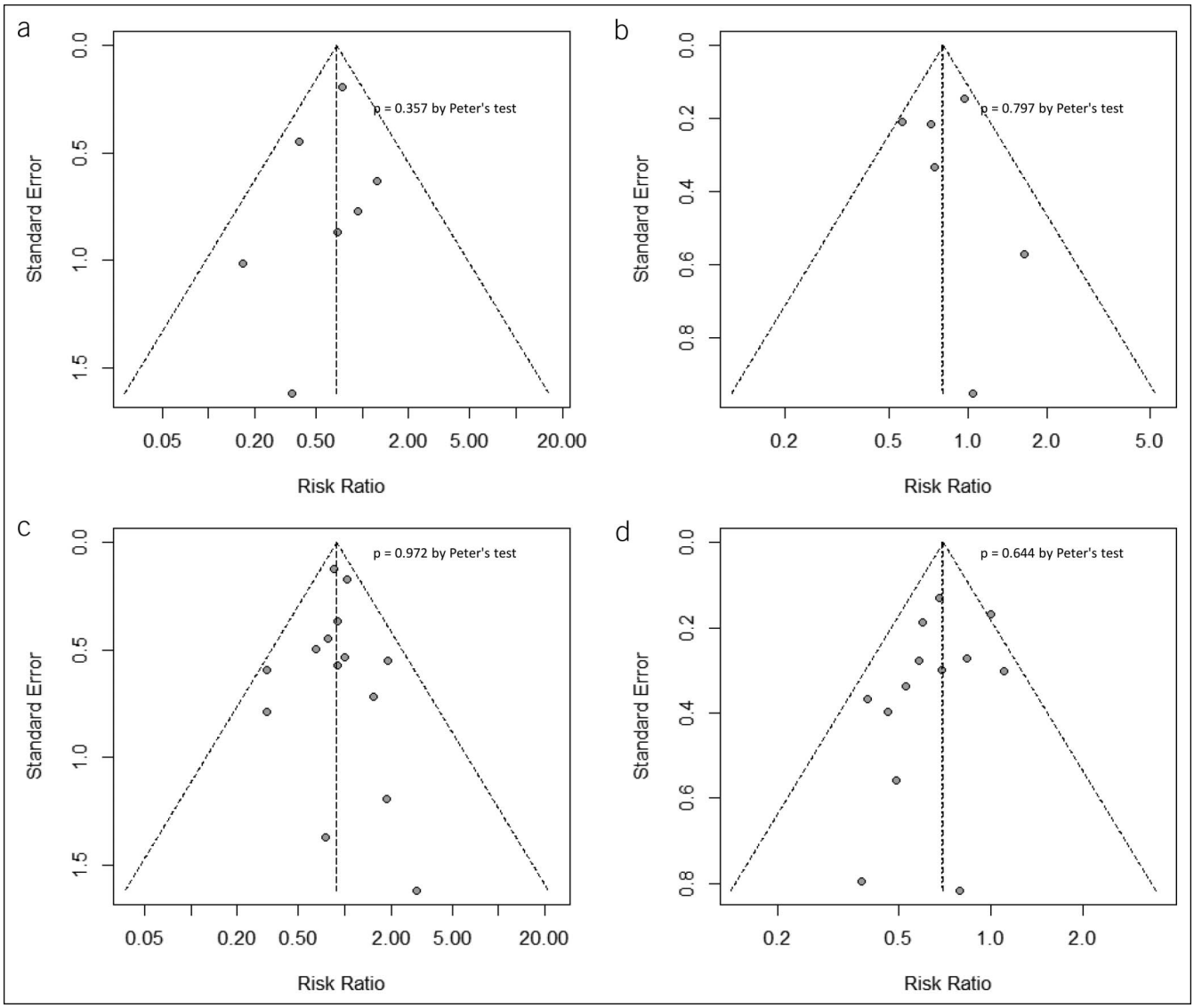

Figure 3. Funnel plots for publication bias: (**a**) HE, (**b**) HCC, (**c**) mortality, and (**d**) LRE. HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; LRE, liver-related events.

(pooled RR from 4 studies of 0.716, 95% CI 0.514–0.996; $P = 0.047$) and LRE (pooled RR from 10 studies 0.716, 95% CI 0.595–0.860; $P < 0.001$) in patients who underwent HCC resection. However, oral BCAA supplementation showed no statistically significant improvements in preventing HCC and mortality in patients who underwent HCC resection. In addition, on analyzing 3 studies, oral BCAA supplementation was associated with a lower risk of LRE (pooled RR 0.521, 95% CI 0.340–0.801; $P = 0.003$) in patients with HCC.

On stratifying by ethnicity, Asian subjects showed a lower risk of LRE (pooled RR from 10 studies 0.652, 95% CI 0.57–0.763; $P < 0.001$) after oral BCAA supplementation.

DISCUSSION

To manage patients with hepatic decompensation events who are subject to both morbidity and mortality (51–54), liver transplantation might be eventually required (55–57). However, primarily owing to the shortage of donor, other medical treatments are required (54,56,58). In this systematic review and meta-analysis, we observed that oral BCAA supplementation could improve the prognosis of patients with advanced liver disease. More importantly, oral BCAA supplementation afforded benefits that could significantly prevent the development of HE, with an RR of 0.684 (95% CI 0.497–0.941; $P = 0.019$), and LRE, with an RR of 0.688 (95% CI 0.585–0.81; $P < 0.001$). Although previous meta-analyses have shown that oral BCAA supplements can facilitate recovery of clinical manifestations of HE (13,59,60), no previous study has examined the prevention of either newly developed HE or HE recurrence after recovery. To our knowledge, this study is the first meta-analysis to assess the preventive effect of oral BCAA supplementation on future HE development. In particular, patients who underwent surgical HCC resection might benefit from oral BCAA supplementation, effectively reducing the risk of developing HE or LRE. Given that these patients experience various kinds of morbidities after hepatic resection, preemptive oral BCAA supplementation might contribute to a

Table 2. **Pooled analysis for each outcome using studies with HR as an outcome measure**

	HCC		Death		Death		LRE		LRE	
Author (yr)	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**	**Adjusted HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**	**Adjusted HR (95% CI)**	***P* value**
Marchesini (2003) (29)	—	—	—	—	—	—	0.43 (0.191–0.967)	0.041	—	—
Marchesini (2003) (29)	—	—	—	—	—	—	0.51 (0.226–1.150)	0.105	—	—
Muto (2005) (31)	—	—	—	—	0.670 (0.486–0.923)	0.014	—	—	—	—
Muto (2006) (33)	0.660 (0.415–1.049)	0.079	—	—	—	—	—	—	—	—
Kobayashi (2008) (34)	0.606 (0.145–2.536)	0.493	—	—	—	—	—	—	—	—
Hayaishi (2011) (39)	0.416 (0.216–0.801)	0.009	—	—	—	—	—	—	0.585 (0.336–1.018)	0.058
Kanekawa (2014a)	—	—	0.675 (0.330–1.380)	0.281	—	—	—	—	—	—
Kanekawa (2014b)	—	—	0.359 (0.158–0.816)	0.015	—	—	—	—	—	—
Hanai (2015) (44)	—	—	—	—	—	—	—	—	0.380 (0.186–0.775)	0.008
Nojiri (2017) (46)	0.402 (0.184–0.878)	0.022	—	—	0.160 (0.117–0.219)	<0.001	—	—	—	—
Tada (2019) (48)	—	—	—	—	0.317 (0.123–0.815)	0.017	—	—	—	—
Hachiya (2020) (49)	1.125 (0.742–1.705)	0.579	—	—	—	—	—	—	—	—
Overall by fixed effect model	0.713 (0.55–0.924)	0.01	0.514 (0.30–0.882)	0.016	0.322 (0.259–0.40)	<0.001	0.468 (0.264–0.831)	0.01	0.497 (0.321–0.77)	0.002
Overall by random effect model	0.637 (0.41–0.988)	0.044	0.509 (0.275–0.942)	0.032	0.324 (0.109–0.963)	0.042	0.468 (0.264–0.831)	0.01	0.497 (0.321–0.77)	0.002
Heterogeneity, I^2 (%)	57.6 (0.0–84.3)	0.051	22.5 (NA–NA)	0.256	94.9 (88.4–97.8)	<0.001	0.0 (NA–NA)	0.771	0.0 (NA–NA)	0.349

CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; LRE, liver-related event.

Table 3. Subgroup analysis according to study design, study population, and ethnicity

Group	HE			HCC			Mortality			LRE		
	N[a]	Pooled RR (95% CI)	*P* value	N[a]	Pooled RR (95% CI)	*P* value	N[a]	Pooled RR (95% CI)	*P* value	N[a]	Pooled RR (95% CI)	*P* value
Study population												
Surgical resection of HCC	4	0.716 (0.514–0.996)	0.047	5	0.890 (0.717–1.105)	0.29	10	0.992 (0.764–1.287)	0.949	10	0.716 (0.595–0.86)	<0.001
HCC	2	0.595 (0.133–2.667)	0.497	1	0.559 (0.37–0.844)	0.006	3	0.637 (0.289–1.402)	0.262	3	0.521 (0.34–0.801)	0.003
Liver cirrhosis	1	0.168 (0.023–1.233)	0.079	—	—	—	1	0.896 (0.437–1.838)	0.764	—	—	—
		P = 0.366			*P* = 0.05			*P* = 0.543			*P* = 0.183	
Study design												
RCT	5	0.716 (0.502–1.02)	0.065	6	0.791 (0.619–1.011)	0.061	10	0.902 (0.746–1.091)	0.289	9	0.725 (0.597–0.879)	0.001
Prospective cohort	1	0.387 (0.161–0.933)	0.034	—	—	—	2	0.657 (0.263–1.637)	0.367	2	0.582 (0.407–0.831)	0.003
Retrospective cohort	1	1.25 (0.361–4.326)	0.725	—	—	—	2	0.858 (0.439–1.679)	0.656	2	0.596 (0.281–1.263)	0.176
		P = 0.275			NA			*P* = 0.796			*P* = 0.531	
Ethnicity												
Asian	5	0.621 (0.343–1.126)	0.117	6	0.791 (0.619–1.011)	0.061	13	0.887 (0.746–1.054)	0.172	11	0.652 (0.557–0.763)	<0.001
Non-Asian	2	0.633 (0.306–1.309)	0.217	—	—	—	1	0.896 (0.437–1.838)	0.764	2	0.769 (0.397–1.489)	0.435
		P = 0.969			NA			*P* = 0.978			*P* = 0.635	

P value was computed by the comparison between subgroups.
CI, confidence interval; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; LRE, liver-related event; RR, risk ratio.
[a]N, number of studies.

better clinical prognosis, resulting in fewer morbidities, a better quality of life, and reduced hospital stay and medical costs. Additional studies focusing on the cost-effectiveness and quality of life of oral BCAA supplementation among patients with advanced liver disease are required to establish a more generalized application of these supplements in routine clinical practice. Based on our findings, oral BCAA supplements, in addition to nonabsorbable disaccharides and/or rifaximin, which remain the mainstay to prevent HE in patients with cirrhosis, might help improve patient prognosis. Further RCTs with long-term follow-up are warranted to validate our hypothesis.

Hepatic malnutrition, resulting from decreased intake, increased requirements, and altered amino acid metabolism, is an important adverse prognostic factor. Although the precise mechanism of action of oral BCAA supplements in HE needs to be comprehensively elucidated, several mechanisms supporting our findings can be suggested. First, BCAA facilitates ammonia detoxification by supporting glutamine synthesis in the skeletal muscles and brain, normalizing plasma amino acid concentrations and decreasing the brain influx of aromatic amino acids (61). Because BCAA acts as a nitrogen donor for neurotransmitter synthesis in the brain, anaplerotic reactions that involve the conversion of glutamate may be important (62). Furthermore, studies have reported the beneficial effects of BCAA supplements on additional clinical aspects, including insulin resistance, metabolic profile, and immune response (54,63–66). Despite these favorable mechanisms, no other benficial effects on clinical outcomes other than HE-related outcomes (e.g., HCC and mortality) were identified in this meta-analysis.

The clinical benefits of oral BCAA supplementation on the 2 study end points, i.e., HCC and mortality, differed between the pooled analyses based on RRs and HRs. In the analyses based on studies using RRs, the BCAA group did not exhibit further clinical benefits for these 2 outcomes when compared with the control group. Conversely, analyses based on studies using HRs revealed that the BCAA group had significantly better outcomes than the control group, considering both outcomes. Particularly, we noted a significant discrepancy in mortality based on the type of analysis used. However, considering that analyses using HR for mortality included only 2–3 study findings with considerable heterogeneity from the analysis using adjusted HRs, the hypothesis of a significant association between oral BCAA supplements and a lower risk of mortality should be reserved until the same phenomena can be reproduced using additional large-scale RCTs.

This study has several limitations. First, although 20 of the 28 included articles were RCTs, the sample size of each study was relatively small. Therefore, RCTs with large sample sizes are required to resolve this issue. Second, because the number of studies available for subgroup analyses according to study population, study design, and ethnicity was insufficient, some results might not be generalizable. In particular, among the 3 studies focusing on patients with HCC (30,42,48), treatment modalities were heterogeneous, including surgical resection, radiofrequency ablation, transarterial chemoembolization (TACE), and TACE plus radiofrequency ablation (67–69). Therefore, the results of the subgroup analysis based on the 3 studies should be interpreted with caution. Likewise, because only 7 studies addressed the decreased patterns of serum BCAA level, further studies to identify patients who can benefit from oral BCAA supplementation are required. Third, because LRE was defined as all composite outcomes including hepatic decompensation, HCC, liver transplantation, or mortality, the clinical significance might be confounded in part. Indeed, 7 of 13 studies reported only a single outcome as LRE in which the type of complications could not be distinguished; only from the remaining 6 studies, the reclassification of ascites, variceal bleeding, and hepatorenal syndrome (or renal failure) as a separate outcome was eligible (see Supplementary Table 4, http://links.lww.com/CTG/A887). However, as the number of studies for each outcome was very small and the characteristics of studies were heterogeneous in the study type (e.g. RCT, prospective cohort, or retrospective cohort) and study population (e.g. patients with HCC, patients with HCC receiving surgical resection, or patients with HCC treated with TACE), it is very challenging to synthesize evidence quantitatively by meta-analysis from the methodological viewpoint. Further studies are required to overcome this limitation. Fourth, as a result of quality assessment, some concerns or high risks in RCTs included were observed in the domains of randomization process and deviations from the intended intervention. In addition, from certainty assessment, all evidence synthesized from RCTs was assessed with high certainty, but evidence from observational studies was assessed with low certainty in GRADE. However, because the maximum grade for observational studies begins with a low grade (second level) in GRADE, even a well-designed cohort study (i.e., propensity score matching study) cannot reach a higher grade. Therefore, considering the certainty of evidence by study design, the results of this study should be interpreted carefully. Last, because the primary aim of our study is the meta-analysis about the effect of oral BCAA supplementation among patients with liver disease, further studies are required to address its potential adverse effects, particularly harmful effects on cataplerosis in muscles and ammonia formation from glutamine in visceral tissues. Along with several studies showing the paradoxically increased ammonia levels by BCAA supplementation (70–72), Holeče (73) suggested that supplementation of branched chain keto acids (BCKAs) should offer advantages over BCAAs, on the basis upon that administration of BCKAs might decrease ammonia production, attenuate cataplerosis, correct amino acid imbalance, and improve protein balance. Further studies are required concerning the suitability of BCKAs supplementations in hyperammonemic conditions, along with other treatment modalities (54,58,74).

In conclusion, we propose that oral BCAA supplementation can be a preventive strategy for HE or LRE, especially in patients undergoing surgical HCC resection. Additional RCTs with long-term follow-up, especially those with high-quality and large samples, are required to verify our suggestions.

CONFLICTS OF INTEREST

Guarantor of the article: Beom Kyung Kim, MD, PhD.

Specific author contributions: H.L. and B.K.K.: conception and design. H.L., J.Y., and B.K.K.: development of methodology. H.L., J.Y., and B.K.K.: acquisition, analysis, and interpretation of data. H.L., J.Y., S.H.A., and B.K.K.: writing, review, and/or revision of the manuscript. H.L., J.Y., and B.K.K.: administrative, technical, or material support. B.K.K.: study supervision. All authors have read and agreed to the published version of the manuscript. Please turn to the CRediT taxonomy for the term explanation. Authorship must be limited to those who have contributed substantially to the work reported.

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LIVER

Study Highlights

WHAT IS KNOWN

- ✓ Oral branched-chain amino acids (BCAAs) might benefit patients with advanced liver disease.
- ✓ Nevertheless, the use of oral BCAA to improve the overall prognosis in patients with cirrhosis remains controversial.

WHAT IS NEW HERE

- ✓ From the meta-analysis based upon 28 studies, oral BCAAs were better in preventing hepatic encephalopathy (HE) and over liver-related events (LREs) than controls.
- ✓ However, compared to control, it had only marginal effect on preventing hepatocellular carcinoma (HCC) and no significant difference in mortality.
- ✓ In subgroups undergoing HCC resection, oral BCAAs had beneficial effect in preventing HE and LRE.

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