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Oral Branched-Chain Amino Acids as a Cost-Effective Option for Managing Hepatic Encephalopathy

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Purpose: Oral branched-chain amino acids (BCAAs) may benefit patients with cirrhosis, especially those with hepatic encephalopathy (HE). We analyzed the cost-effectiveness of BCAAs in improving the prognosis of patients with HE.

Materials and Methods: We compared the total costs and effectiveness of oral BCAA treatment (Scenario 1) versus no BCAA supplementation (Scenario 2) in a virtual cohort of 10000 patients who had experienced HE over a 5-year period. A nested Markov model consisting of four health states (remission, recurrence, stabilization after recurrence, and death) for decompensated cirrhosis was used. Effectiveness was estimated as the cumulative number of HE recurrences and deaths. Additionally, the number of life-years and quality-adjusted life-years (QALYs) and incremental cost-effectiveness ratio (ICER) were analyzed. Deterministic and probabilistic sensitivity analyses were also performed.

Results: Oral BCAA treatment prevented 34% of HE recurrences and reduced the number of HE-related deaths by 18%. Although patients in the BCAA-treated group spent an additional 4086 USD on average compared with their counterparts in the non-treated group ($27088 vs. $23003), they experienced 0.34 more QALYs (2.77 vs. 2.43) over the 5-year period. The ICER for BCAA treatment was 12017 USD/QALY, indicating the high cost-effectiveness of the therapeutic option. Moreover, the sensitivity analyses showed that its economic feasibility was robust. With the willingness-to-pay threshold set at 1 GDP per capita, the probability of cost-effectiveness of BCAA treatment exceeded 80%.

Conclusion: Oral BCAAs for HE prevention may contribute positively to both the clinical status of the patient and the national healthcare budget.

Key Words: Branched-chain amino acids, hepatic encephalopathy, prevention, liver cirrhosis, cost-effectiveness analysis

INTRODUCTION

Hepatic decompensation in patients with liver cirrhosis can lead to the development of various life-threatening conditions, including hepatic encephalopathy (HE), spontaneous bacterial peritonitis, variceal bleeding, and hepatorenal syndrome.[1-4] HE, which is a complex and reversible neuropsychiatric syndrome with clinical manifestations ranging from a minutely altered mental status to deep coma, negatively impacts mortality and the overall quality of life.[5-7] Currently, non-absorbable disaccharides, with or without rifaximin, are used to manage HE.[8]

Branched-chain amino acids (BCAAs) refer to a group of three essential amino acids: valine, leucine, and isoleucine. Patients with cirrhosis have decreased serum concentrations of BCAAs and a reduced Fischer's ratio (serum BCAA/aromatic amino acids) caused by protein-energy malnutrition.[9] Moreover, BCAA deficiency in these patients may be further exacerbated by clinical conditions such as portosystemic shunts, hypermetabolic states, and increased skeletal muscle uptake and

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consumption for amino acids ammonia metabolism and energy production. BCAAs account for approximately 35% of essential amino acids in skeletal muscle proteins. Sarcopenia, defined as an age-related loss of muscle mass resulting from muscle protein breakdown due to persistent skeletal muscle consumption of BCAAs, is closely associated with major life-threatening complications of liver cirrhosis, such as ascites, spontaneous bacterial peritonitis, HE, and hepatorenal syndrome.[10-12]

Theoretically, oral BCAA supplementation in patients with cirrhosis may offer several beneficial effects, including improvements in body composition, nitrogen balance, liver cell regeneration, protein and albumin synthesis, HE symptoms, and immune function. However, despite a recent Cochrane review concluding that oral BCAAs may be useful for managing overt HE,[8] their role in improving the overall prognosis (including mortality) of patients with cirrhosis remains controversial. Long-term treatment with oral BCAAs may be required to manage repeated events of HE that occur during the clinical course of decompensated cirrhosis, which could progressively increase the overall socioeconomic burden. However, the cost-effectiveness of prescribing oral BCAAs to patients with HE has not been thoroughly analyzed to date. Therefore, in this study, we evaluated whether oral BCAA treatment is a cost-effective option for improving the overall prognosis of patients with HE.

MATERIALS AND METHODS

Model structure and validation

A nested Markov model consisting of four health states (remission, recurrence, stabilization after recurrence, and death) was used to simulate the cost-effectiveness of oral BCAA treatment in patients who had experienced HE, with two scenarios modeled from a healthcare perspective: Scenario 1, patients receiving oral BCAAs (BCAA group); and Scenario 2, those not receiving oral BCAAs (non-BCAA group). The health states are represented by circles in Fig. 1. State 1 (remission) represents the beginning of the simulation, when the health state of the starting cohort has already resolved after first experiencing HE. State 2 (recurrence) occurs when HE-related symptoms reappear and require treatment. In State 3 (stabilization after recurrence), the acute HE-related symptoms that had recurred disappear again; therefore, the cohort can only enter this state from State 2. State 4 (death) is an absorbing state and includes HE-related deaths. Since patients with advanced cirrhosis who have experienced HE cannot return to a reversible state, the Markov model was constructed in a nested form, with three health states classified within the advanced cirrhosis state. A 5-year time horizon was applied, and the analytical cycle length was 4 weeks. The discount rate for the base-case analysis was 4.5%,[13] and a half-cycle correction was used.

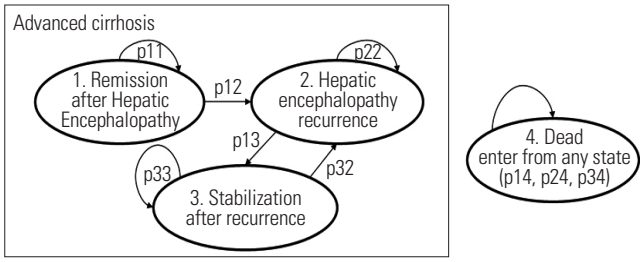

Fig. 1. Markov model structure for evaluating the cost-effectiveness of branched-chain amino acid treatment in patients with advanced cirrhosis.

The external validity of the model was confirmed using results from a previous literature review[14] that evaluated the cost-effectiveness of interventions in patients with HE, as well as through consultation with clinical experts. Similar to this study, that previous review had employed overt (recurrence) HE, remission, and death as the main health states in the Markov model.[14] The operational and computational validity of our simulation model was verified by checking the results when extreme values were inserted.

Characteristics of the cohort

The number of patients was calculated on the basis of the representative sample data of South Korean patients provided by the Health Insurance Review and Assessment Service.[15,16] Approximately 10000 patients were estimated to be part of the initial cohort after extracting those with records of both liver cirrhosis (K74 of the International Classification of Diseases codes) and HE diagnoses, and then multiplying them by a sampling weight. Consistent with the characteristics of patients in our recent meta-analysis study,[17] the mean age of this cohort was 58 years, and 70% were male.

Transition probabilities

Transition probabilities are key parameters for determining the distribution of cohorts in each scenario over time. In this study, this was defined as the probability of the cohort transitioning from one health state to another in a fixed period of time (i.e., 4 weeks). Four hazard ratios (HRs) were calculated for the two scenarios to determine the effectiveness of oral BCAAs on transition probabilities. Our previous meta-analysis comparing the BCAA group with the non-BCAA group showed that the HRs for preventing HE recurrence and mortality were 0.716 [95% confidence interval (CI): 0.502–1.020] and 0.902 (95% CI: 0.746–1.091), respectively.[17] The Cochrane group reported that oral BCAAs had a positive effect on recovery from overt HE, with an HR of 0.670 (95% CI: 0.520–0.880); however, the treatment showed no statistically significant effect in preventing death from HE recurrence, with an HR of 0.90 (95% CI: 0.500–1.630).[8]

To estimate transition probabilities for the BCAA group, we obtained transition probabilities for the non-BCAA groups from previous studies with a cohort similar to that of this study and then multiplied those values by the four HRs mentioned

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above. In the 4-week analytical cycle, transition probabilities in the recurrence state were applied to the first 2 weeks as the acute phase, taking into account the length of hospital stay due to overt HE,[18,19] whereas those in the remission state were applied to the last 2 weeks as the subacute phase. The transition probabilities were obtained by mathematically converting the rate values reported in previous studies. For example, the 2-week transition probability from the remission state (State 1) or stabilization state (State 3) to the recurrence state (State 2) in the non-BCAA group was calculated to be 0.038; this was converted from the rate (45.9%) at which HE recurrence occurred over 128 days[20] [probability up to time t=1–exp(-rate× t)=1–exp(-0.459)/(168/14)]. In the BCAA group, the probability of transition from States 1 or 3 to State 2 was 0.027 (=0.038× 0.716). In the non-BCAA group, the mortality rates due to HE were 0.009 from States 1 or 3[14] and 0.139 in State 2.[21] Therefore, the transition probability from State 2 to State 3 was calculated to be 0.413 by mathematically transforming the patient recovery rate of 53.3%[22] (Table 1).

Cost estimations

From a limited societal perspective, direct medical costs, direct non-medical costs, and indirect costs were included in the analysis. Medication (drug and prescription costs) and medical costs for the treatment of advanced cirrhosis in each health state were included in the estimation of direct medical costs. To estimate the BCAA acquisition cost, the average price of these products in South Korea was used (5.1 USD/day),[23] and the prescription fee was calculated on a 4-week cycle. Medical costs were classified into those covered by National Health Insurance (NHI) and those not covered. The NHI-covered medical costs of each health state were obtained from our previous study, using data from nationally representative health insurance claims.[15] To estimate the costs for State 1 and State 3, we used the outpatient costs of patients with advanced liver cirrhosis and a history of HE (285.6 USD/4-week). For the State 2 cost, the hospitalization costs of the patients were used (3477.6 USD/4-week). The non-NHI-covered medical costs were calculated by multiplying the NHI-covered medical costs for each health state by the non-NHI-covered rate (8.5%).[24] Direct non-medical costs, including transportation for outpatient visits (10.0 USD/4-week) and time loss costs during a 14-day admission (141.1 USD), were calculated using national employment survey data.[25,26] All costs were adjusted for inflation and expressed in the overall US dollar rate of 2021 (1 USD=1200 Korean won) (Table 2).

Utility weight estimation

Utility weights are health-related quality-of-life measurements on a scale from 0 (death) to 1 (perfect health). The values were obtained from a previous study in which they had been derived according to Conn grades (0–4) using the standard gamble method.[27] The mean values of Conn grades 0 and 1 (0.876) were used for State 1 and State 3, and those of Conn grades 2, 3, and 4 (0.462) were used for the State 2 hospitalization period (2 weeks). As the model cycle was set at 4 weeks, the utility value for State 2 was calculated as the average value (0.669) for the 2-week hospitalization period (0.462) and 2-week non-hospi-

Table 1. Cohort Characteristics and Transition Probabilities

Variables	Value		Source
Cohort characteristics			
No. of patients in cohort	10000		15
Age (yr)	58		17
Male (%)	70		17
HR (BCAA vs. No BCAA)			
HE remission to HE recurrence (HR1)	0.716		17
HE remission/stabilization to death (HR2)	0.902		17
HE recurrence to remained HE recurrence (HR3)	0.670		8
HE recurrence to death (HR4)	0.900		8
Monthly transition probability	**Scenario 1 (BCAA group)**	**Scenario 2 (No BCAA group)**	**Source**
From HE remission (State 1)			
to HE recurrence (State 2, p12)	0.027	0.038	20
to death (State 4, p14)	0.008	0.009	14
From HE recurrence (State 2)			
to stabilized HE (State 3, p23)	0.575	0.413	22
to death (State 4, p24)	0.125	0.139	21
From stabilized HE (State 3)			
to recurrence HE (State 2, p32)	0.027	0.038	
to death (State 4, p34)	0.008	0.009	

BCAA, branched-chain amino acids; HR, hazard ratio; HE, hepatic encephalopathy.

Table 2. Input Costs and Utility Weights

Input parameters	Value	Source
Direct medical costs (USD)*		
BCAA medication cost		
BCAA acquisition costs	143.6	23
BCAA prescription costs	10.7	23
Advance cirrhosis treatment cost		
NHI-covered medical costs		
HE remission/stabilization state	285.6	15
HE recurrence state	3477.6	15
Non-NHI-covered health state costs		
HE remission/stabilization	24.2	
HE recurrence	294.2	
Non-NHI covered rate (%)	8.5	24
Non-direct medical costs (USD)*		
Transportation cost	10.0	Assumption
Time loss cost (during a 14-day admission for HE recurrence)	141.1	25, 26
Utility weight		
HE remission/stabilization	0.876	27
Hospitalization for HE recurrence†	0.462	27
Length of stay due to HE recurrence	2 weeks	15

BCAA, branched-chain amino acids; HE, hepatic encephalopathy.
*All costs are estimated on a monthly basis and expressed in 2022 values. One U.S. dollar (USD) is approximately equal to 1200 Korean won; †Utility in the HE recurrence state over the 4-week model cycle was estimated as the average of the 2-week hospitalization period and the 2-week non-hospitalization period.

talization period (0.876) (Table 2).

Health outcomes and analysis

Health outcomes were measured using four main results: the cumulative number of HE recurrences, deaths, life-years (LYs), and quality-adjusted life-years (QALYs). QALYs capture both the quality and quantity of health outcomes and are calculated by multiplying the utility weight by life expectancy. One QALY equates to 1 year of living with full health. The cost-effectiveness of BCAA treatment compared with no BCAA treatment was measured using the incremental cost-effectiveness ratio (ICER), calculated as incremental costs divided by incremental QALYs. The decision rule for determining cost-effectiveness was applied when the ICER was within the willingness-to-pay (WTP) threshold(represented as the λ value), which was set as 1 GDP per capita in South Korea (34866 USD in 2021).[28]

One-way and probabilistic sensitivity analyses (SAs) were also performed. Clinically meaningful variables (i.e., four HRs and transition probabilities), costs, utilities, and model-setting values were selected as the SA parameters. For the one-way SA, changes in the ICER resulting from substituting each parameter's point estimate with its lower and upper limits (i.e., 95% CI) were illustrated in a tornado diagram. For the probabilistic SA, random values were generated by applying probability distributions defined by the lower and upper limits of each parameter (Table 3). ICER scatter plots and cost-effectiveness acceptance curves (CEACs) were generated from a total of 1000 simulation runs. A CEAC illustrates how the probability of cost-effectiveness of the simulation results changes as the λ value increases.

This study does not require an IRB approval number because it is not based on the direct use of human-derived materials or personal information. Instead, it utilizes data derived from previously published studies and publicly available sources.

RESULTS

Base-case analysis

When 10000 patients with HE received oral BCAA treatment for 5 years, the cumulative number of HE recurrences was 16471 (1.6 cases per person), and the 5-year cumulative mortality rate was 55.3%. In the non-BCAA group, the number of HE recurrences was 24915 (2.5 cases per person), and the cumulative mortality rate was estimated to be 67.5%. Therefore, oral BCAA treatment prevented 34% of HE recurrences and reduced the number of deaths related to the condition by 18% (Supplementary Fig. 1, only online).

Patients in the BCAA group spent 4086 USD more (27088 USD vs. 23003 USD) and gained 0.34 more QALYs (2.77 vs. 2.43) than those in the non-BCAA group over the 5-year period. The base-case ICER was calculated as 12017 USD/QALY, demonstrating that oral BCAA treatment was cost-effective (Table 4). When health outcomes were measured in terms of LYs, the BCAA group gained 0.37 more LYs (3.19 vs. 2.81). ICER, an indicator that does not consider the quality of life, was calculated as 10933 USD/LY gained.

Sensitivity analyses

The tornado diagram generated from the one-way SA results (Fig. 2) showed that the HR of the BCAA group for the transition from State 1 to State 2 was the most influential parameter affecting the base-case ICER. Upon input of the upper value for the transition from HE remission to recurrence, the ICER value increased by 27876 USD/QALY. However, when the lower value was applied, the ICER was reduced to 6724 USD/QALY (almost half of the base-case ICER). Although other HRs, oral BCAA costs, and medical costs for managing HE recurrence were also key parameters, all one-way SA results were below the λ value (i.e., WTP threshold) and had minimal impact on cost-effectiveness decisions. Additionally, the impact of the change in the utility value was negligible. The average ICER of the one-way SA results was computed to be 12318 USD/QALY, which was very similar to the base-case ICER. All SA results were below the λ value, supporting the conclusion that BCAA is a cost-effective alternative with low uncertainty.

The probabilistic SA proved that the cost-effectiveness of oral

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Table 3. Input Parameters for Sensitivity Analysis

Input parameters	One-way sensitivity analysis		Probabilistic sensitivity analysis	Source
	Lower limit	Upper limit	Distribution (parameters)*	
Hazard ratio (BCAA vs. No BCAA)				
HE remission to HE recurrence (HR1)	0.502	1.020	Lognormal (-0.334, 0.181)	[17]
HE remission/stabilization to death (HR2)	0.746	1.091	Lognormal (-0.103, 0.097)	[17]
HE recurrence to remained HE recurrence (HR3)	0.520	0.880	Lognormal (-0.400, 0.134)	[8]
HE recurrence to death (HR4)	0.500	1.630	Lognormal (-0.105, 0.301)	[8]
Transition probabilities in scenario 2				
From HE remission (State 1)				
to HE recurrence (State 2)	0.034	0.041	Beta (96, 2468)	Assumption (±10% of base-case value)
to death (State 4)	0.008	0.010	Beta (99, 10961)	Assumption (±10% of base-case value)
From HE recurrence (State 2)				
to stabilized HE (State 3)	0.370	0.450	Beta (58, 82)	Assumption (±10% of base-case value)
to death (State 4)	0.130	0.150	Beta (86, 531)	Assumption (±10% of base-case value)
From stabilized HE (State 3)				
to recurrence HE (State 2)	0.034	0.041	Beta (96, 2468)	Assumption (±10% of base-case value)
to death (State 4)	0.008	0.010	Beta (99, 10961)	Assumption (±10% of base-case value)
Costs (USD)				
BCAA acquisition costs	114.9	172.3	Gamma (1, 143.6)	Assumption (±20% of base-case value)
NHI-covered HE remission	228.5	342.8	Gamma (1, 286)	Assumption (±20% of base-case value)
NHI-covered HE recurrence	2782.1	4173.1	Gamma (1, 3478)	Assumption (±20% of base-case value)
NHI-covered HE stabilization	228.5	342.8	Gamma (1, 286)	Assumption (±20% of base-case value)
Transportation cost	8.0	12.0	Gamma (1, 10)	Assumption (±20% of base-case value)
Time cost	112.9	169.3	Gamma (1, 141)	Assumption (±20% of base-case value)
Utilities				
HE remission/stabilization	0.857	0.895	Lognormal (-0.132, 0.011)	[26]
Hospitalization for HE recurrence	0.435	0.489	Lognormal (-0.402, 0.010)	[26]
Analysis settings				
Discounted rate for costs	0	5.0	-	Assumption
Discounted rate for effectiveness	0	5.0	-	Assumption

BCAA, branched-chain amino acids; HE, hepatic encephalopathy.
*Parameters for distribution fitting were applied as follows: Lognormal (log mean, log standard deviation); Beta (alpha, beta); Gamma (alpha, beta).

Table 4. Base-Case Results of Cost-Effectiveness Analysis Over a 5-Year Period

Per-patient	Scenario 1 (BCAA group)	Scenario 2 (Non-BCAA group)	Incremental
Cost (USD)*	27088	23003	4086
Medication cost	6398	-	6398
NHI-covered medical cost	16710	17854	-1145
Non-NHI-covered medical cost	1414	1510	-97
Non-direct medical cost	2567	3638	-1071
Effectiveness			
Cumulative number of HE recurrence (episodes)	1.6	2.5	-0.8
Cumulative HE-related mortality rate (%)	55.3	67.5	-18.1
LYG*	3.19	2.81	0.37
QALYs*	2.77	2.43	0.34
Incremental cost-effectiveness ratio			
Incremental costs (USD)/LYG		10933	
Incremental costs (USD)/QALY		12017	

BCAA, branched-chain amino acids; HE, hepatic encephalopathy; LGY, life-years gained; QALY, quality-adjusted life-year.
*Costs and effectiveness (life-years and QALYs) were discounted at a 4.5% annual rate.

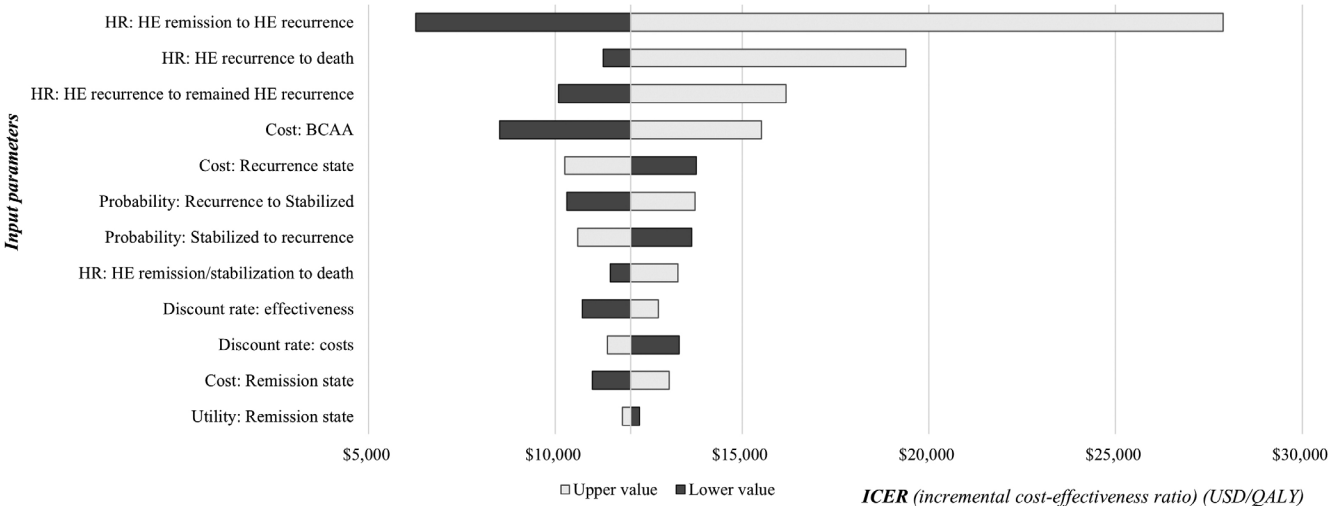

Fig. 2. Tornado diagram showing the impact of key parameters on cost-effectiveness. BCAA, branched-chain amino acids; HR, hazard ratio; HE, hepatic encephalopathy; QALY, quality-adjusted life-year.

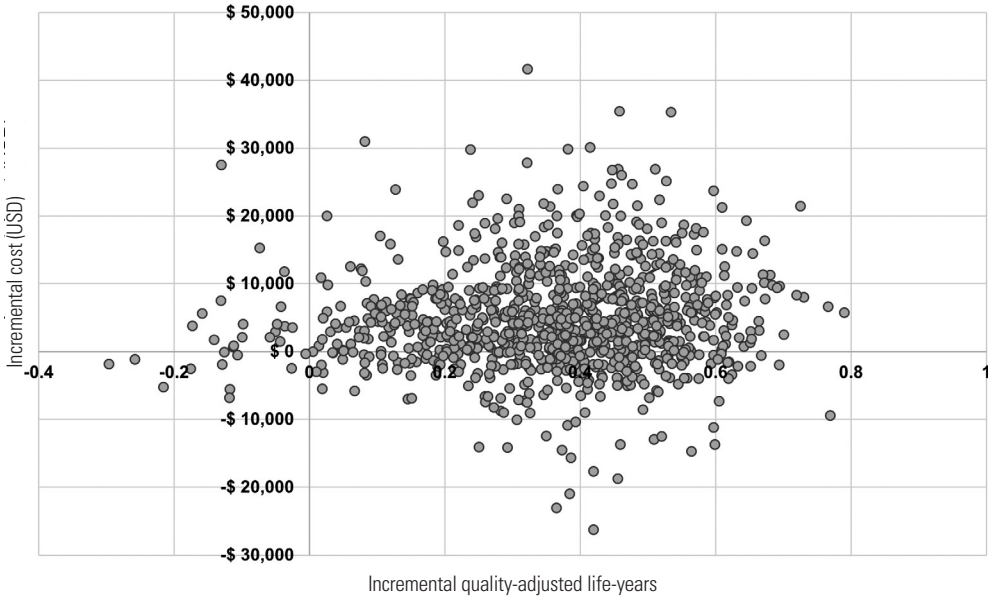

Fig. 3. Incremental cost-effectiveness ratio scatter plot on the cost-effectiveness plane.

BCAAs derived from the base-case analysis was robust. The average ICER across 1000 simulation results was 13148 USD/QALY, supporting the robustness of the base-case result. Approximately 25% of the results in the ICER scatter plot (22.6%) demonstrated the likelihood of cost savings from the use of oral BCAAs (Fig. 3). The 95% CI for the ICER derived from the probabilistic SA ranged from 10027 to 16268 USD per QALY, which is below the WTP threshold. This result further supports the robustness of the cost-effectiveness of BCAA. As shown in the CEAC (Fig. 4), the cost-effectiveness of oral BCAA treatment was acceptable, with a probability of approximately 80% when the λ value (WTP threshold) was 1 GDP per capita in South Korea (34866 USD). When the λ value was increased to 2 GDP per capita (69732 USD), the cost-effectiveness probability increased to 93%.

DISCUSSION

Our simulation results suggest that the use of oral BCAAs for preventing HE recurrence is likely a cost-effective treatment option. This result was highly robust in both the one-way and probabilistic SAs, where varying parameters were applied to the model between extreme values. Approximately 25% of the probabilistic simulation results demonstrated that oral BCAA supplementation is a cost-saving option. When the λ value was limited to 1 GDP per capita in South Korea, the probability of accepting BCAA cost-effectiveness was approximately 80%, and the economic feasibility of the treatment was stable. Patients who develop HE typically have various neurological symptoms together with severe liver failure,[29] which inevitably incur transportation and time costs due to hospitalization. Therefore, from

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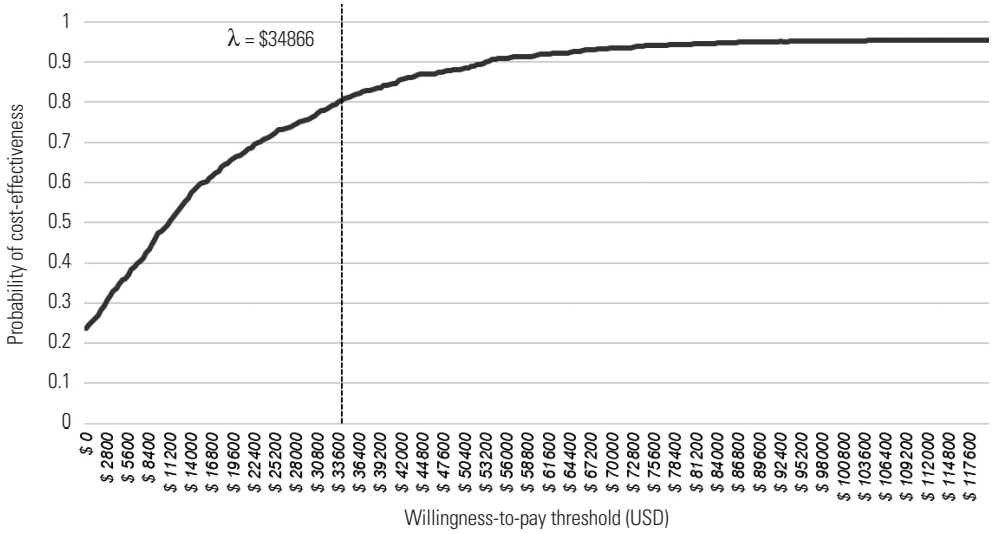

Fig. 4. Cost-effectiveness acceptability curve.

a limited societal perspective, direct non-medical costs were included in the analysis in this study. To conservatively estimate direct non-medical costs, the time cost included only one outpatient visit every 4 weeks and the opportunity cost of hospitalization during a 2-week recurrence period. When analyzed from the healthcare system perspective, the base-case ICER was 15166 USD/QALY, and the highest ICER from the one-way SA was 29596 USD/QALY, an indication of stable cost-effectiveness. According to a recent systematic review of costs incurred by patients with overt HE in the USA, the average annual cost per hospitalization was estimated at 10568–24427 USD,[30] which is 3–7 times higher than the input value used in this study (3477 USD). If the US values were applied to this simulation, the cost-effectiveness of BCAA treatment would be dominant. Based on the literature reporting the preventive effect of BCAAs on HE recurrence stratified by the Model for End-Stage Liver Disease (MELD) score and the number of prior HE episodes, we conducted a scenario analysis. When the MELD score was ≤10, the ICER decreased by 37% compared to the base-case ICER, whereas it nearly doubled in patients with MELD scores of 19–24. In patients with two prior HE episodes, the cost-effectiveness of BCAA improved by 33%, but when the number of episodes exceeded two, the ICER slightly worsened, showing an approximately 4% decrease in cost-effectiveness, which was minimal.

This study has several strengths. Although several studies have assessed the cost-effectiveness of rifaximin for the treatment of HE,[14,31,32] to the best of our knowledge, our study is the first decision analysis to evaluate the cost-effectiveness of oral BCAA treatment in preventing HE recurrence and HE-related deaths compared with no treatment. Given the established role of rifaximin in combination with non-absorbable disaccharides for treating HE, further analysis of the combined effect of oral BCAAs, non-absorbable disaccharides, and rifaximin on this condition is warranted. Since the patient characteristics and cost parameters were derived from a nationwide database in a real-world setting,[14] the results of this study have high generalizability. In many cost-effectiveness analyses, uncertainty unavoidably occurs because the parameter values are obtained from various sources. However, in this study, uncertainty was minimized by directly obtaining key parameters. In particular, as the most influential parameter in this study, an HR of 0.716 for the transition from State 1 to State 2 was derived by pooling randomized clinical trials on the efficacy of BCAAs.[17] In the clinical setting, once patients develop HE, they are more prone to other types of hepatic decompensation, such as ascites.[15] Therefore, in patients with HE, the concomitant use of oral BCAAs with standard HE therapy, along with long-term maintenance of amino acid supplementation, may contribute to improved overall prognosis. Consistent with our hypothesis, Konstantis, et al.[33] also reported the beneficial effects of oral BCAAs in terms of improvements in the muscle mass and plasma albumin concentration and the amelioration of serious cirrhotic complications. We found that oral BCAAs may reduce HE-related deaths by 18%. Finally, as recurrent HE substantially compromises the quality of life of both patients and their caregivers, the preemptive use of oral BCAAs may, at least in part, help reduce the indirect socioeconomic burden.

This study had several limitations, and cautious interpretation is warranted. The cost of non-NHI coverage may have been measured conservatively. To estimate the non-covered costs, the average non-NHI-covered rate in the departments of internal medicine at tertiary hospitals (8.5%) was applied.[24] However, HE episodes are generally more acute and severe than other conditions and may require urgent medical procedures regardless of NHI coverage. Applying a higher non-NHI coverage rate reduces the ICER slightly. Given that this economic evaluation used locally sourced cost data, caution is warranted when generalizing the findings to other countries with different healthcare cost structures.

Because a cohort simulation was performed, it was fairly straightforward to demonstrate the representative health outcomes and economic feasibility in patients who experienced HE. However, individual-level characteristics may not have been fully reflected due to inherent limitations of cohort simulation, such as the assumption of memorylessness.[34] We applied a Markov model using fixed transition probabilities in this study. Although a semi-Markov model better reflects the natural progression HE over time by allowing time-dependent transition probabilities, we adopted a Markov model with constant probabilities, as our study targeted patients with advanced liver diseases who had already experienced HE and were followed over a relatively short time horizon.

In conclusion, the use of oral BCAAs for preventing HE recurrence in patients with a history of the disorder may contribute positively to both individual clinical outcomes and the national healthcare budget. Further well-designed prospective studies are required to validate these results.

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AUTHOR CONTRIBUTIONS

Conceptualization: Hankil Lee and Beom Kyung Kim. Data curation: Hankil Lee and Beom Kyung Kim. Formal analysis: Hankil Lee. Funding acquisition: Hankil Lee. Investigation: all authors. Methodology: all authors. Project administration: all authors. Resources: all authors. Software: Hankil Lee. Supervision: Sang Hoon Ahn and Beom Kyung Kim. Validation: Sang Hoon Ahn and Beom Kyung Kim. Visualization: Hankil Lee. Writing—original draft: Hankil Lee and Beom Kyung Kim. Writing—review & editing: all authors. Approval of final manuscript: all authors.

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