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**Effect of oral branched chain amino acids enriched snack
in the cirrhotic patient with sleep disturbance**

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Running title; Effect of BCAA supplement for LC with sleep disturbance

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Abbreviations used in this paper:

ESS: Epworth Sleepiness Scale

BCAA: Branched chain amino acid

LES: Late evening snack

LC: Liver cirrhosis

QOL: Quality of life

WBC: White blood cells

RBC: Red blood cells

Plt: Platelets

PT: prothrombin time

BUN: blood urea nitrogen

Cr: creatinine

AST: Aspartate aminotransferase

ALT: Alanine aminotransferase

γ -GTP: γ -glutamyltranspeptidase

ALP: Alkaline phosphatase

TB: Total bilirubin

TP: Total protein

Alb: Albumin

TC: Total cholesterol

ChE: Cholinesterase

TG: Triglyceride

FPG: Fasting blood glucose

NH₃: Ammonia

BTR: BCAA/tyrosine ratio

MHE: minimal hepatic encephalopathy

PBC: primary biliary cirrhosis

TACE: Trans-arterial chemoembolization

Key words:

BCAA supplement

ESS

LC

LES

ABSTRACT

Aim; Sleep is closely related to physical and mental health. Sleep disturbance is reported to the patient without encephalopathy. We made an original symptom evaluation question item, and examined the relation among cirrhotic symptoms, laboratory data and sleep disturbance. .Next, we examined the influence that a BCAA supplement gave the sleep disturbance of cirrhotic patients.

Methods; We investigated a total of 21 patients at Nagasaki University Hospital, including 9 men and 11 women from January to June 2009. We constructed questionnaire items for evaluation of cirrhotic symptom. The items, as major symptoms of cirrhotic patients, are follows; hands tremor, appetite loss, muscle cramp of foot, fatigue, decreased strength, become anxious, abdominal fullness, abdominal pain and feel of low energy. We used the Epworth Sleepiness scale (ESS) for evaluation of daytime hyper-somnolence. Energy supplementation of BCAA snack was performed as late evening snack (LES). All patients were assessed at entry, 4 weeks and 8 weeks.

Result; It was presented that BCAA snack, was taken orally as LES, improved the ESS for cirrhotic patients without encephalopathy. This beneficial result was recognized in short term, 4 weeks after beginning of treatment. This study demonstrates availability of BCAA supplementation for cirrhotic patients with sleep disturbance. However, the cirrhotic symptom related score was positively relation with Child-Pugh score at entry, we were not able to find the item that related to ESS.

Conclusion; BCAA snack is the useful drug for cirrhotic patients whom do not have overt encephalopathy but suffered sleep disturbance.

INTRODUCTION

The patients with liver cirrhosis (LC) has a widely spread symptom. A few cirrhotic patients has sleep disturbance (1). In recent years, it has been reported that sleep is closely related to physical and mental health (2. 3). Sleep disturbance is one of the symptoms of overt hepatic encephalopathy (4), but is reported to the patient without encephalopathy (1). In previous report (1), the questionnaire indicated the elevated number (47.7%) of cirrhotic patient who complained of unsatisfactory sleep compared with healthy control (4.5%). Additionally, global sleep quality was significantly lower in the primary biliary cirrhosis group (5) and the non-alcoholic fatty liver disease group (6) compared to control. In Japan, the overall prevalence of insomnia during the preceding month was 21.4% among the Japanese general population (7). In this study, we examined the actual circumstance of the sleep disturbance in Japanese cirrhotic patients.

The relation among the sleep disturbance and a variegated cirrhotic symptom are not yet clear. Previous reports indicated that sleep disturbance is not related to liver function (1. 8). It is reported that fatigue in non-alcoholic fatty liver disease is significant and associates with excessive daytime sleepiness but not insulin resistance (6). Because of emergence of sleep disturbance in cirrhotic patient without encephalopathy, the relation between the sleep disturbance and cirrhotic symptom exclude encephalopathy should be examined. In this study, we made an original symptom evaluation question item, and examined the relation between sleep disturbance and other cirrhotic symptoms.

The energy balance of LC was characterized as protein-energy malnutrition (PEM),

involved disorder of glycolysis, decline of glycogenesis, negative nitrogen balance and hyper-lipolysis (9. 10. 11). PEM carries a high risk of morbidity and mortality by increasing the risk of life-threatening complications, which in turn reduce quality of life (QOL), independent of liver function (12. 13). Recently, branched-chain amino acids (BCAA) supplementation in patients with liver disease is paid attention. The administration of BCAA has been shown to correct malnutrition associated with LC in both animal and human studies (14. 15) Additionally, it has been reported that long-term nutritional BCAA supplementation is useful to prevent prognosis hepatic failure and to improve surrogate markers in advanced LC (15. 16. 17). It is described that BCAA supplement is effective in down-regulating protein metabolism in LC, improving nitrogen balance, and finally resulting in better clinical outcomes (15. 18. 19). It is also speculated that the mechanisms for beneficial effects of BCAA might be mediated by their stimulating activity on hepatocyte growth factor, favoring liver regeneration (20). Previously, we indicate that a BCAA supplement taken orally as a late evening snack prevents suppression of liver function by TACE in patients with LC complicated with HCC during the 2-week period after TACE (21). However, BCAA is the useful drug for hepatic malnutrition and encephalopathy (4), the influence of BCAA given to sleep disturbance has not been reported. Therefore, we examined the influence that a BCAA supplement gave the sleep disturbance of cirrhotic patients.

PATIENTS AND METHODS

Patients

We investigated a total of 21 patients at Nagasaki University Hospital, including 9 men and 11 women from January to June 2009 (table 1). All patients were LC without hepatocellular carcinoma, history of hepatic encephalopathy, chronic renal failure, internal use of BCAA drug, refill of the albumin preparation and alcohol drinking. The diagnosis of hepatocellular carcinoma was based on findings on contrast enhancement computed tomography scan and magnetic resonance imaging. Hepatic encephalopathy was diagnosed by clinical findings. All patients had diagnosed LC by laboratory data and imaging findings at entry of study and not prescribed BCAA supplement before this study. After balancing of the both groups for sex, age, Child-Pugh score, cirrhotic symptom related score and albumin level, patients were randomized into two group, BCAA enriched supplementation group and control group. All patients in both groups did not suffered overt hepatic encephalopathy and HCC during observation period. We had followed all patients in our hospital.

Laboratory measurements

Laboratory data, anthropometric measurements and survey by questionnaire were performed at the day of entry (at entry), 4 weeks later (4 weeks) and 8 weeks later (8 weeks). Body mass index, BMI, was calculated as weight (kg) divided by the square of height (m). Laboratory measurements were as follow; white blood cell (WBC), red blood cell (RBC), platelet (Plt),

prothrombin time (PT), blood urea nitrogen (BUN), creatinine (Cr), aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ -glutamyltranspeptidase (γ -GTP), alkaline phosphatase (ALP), total bilirubin (TB), total protein (TP), albumin (Alb), total cholesterol (TC), cholinesterase (ChE), triglyceride (TG), fasting blood glucose (FPG), ammonia (NH₃) and BCAA/tyrosine ratio (BTR).

Survey by questionnaire

We constructed questionnaire items for evaluation of cirrhotic symptom. The items, as major symptoms of cirrhotic patients, are follows; hands tremor, appetite loss, muscle cramp of foot, fatigue, decreased strength, become anxious, abdominal fullness, abdominal pain and feel of low energy. For each items, we calculated an “impact factor”, the product of proportion of patients identified the item as a problem (frequency), and the mean importance attributed to that item. The impact factor for each item could range from 0 to 6. We investigate total of impact factors (cirrhotic symptom related score). Next, we used the Epworth Sleepiness scale (ESS) (22) for evaluation of daytime hyper-somnolence. ESS score rang is from 0 to 24, a score of 10 or more being indicative of significant of daytime hyper-somnolence. All patients were assessed by cirrhotic symptom related score and ESS at entry, 4 weeks and 8 weeks.

Protocol for intake of branched chain amino acids enriched snack

We used a branched chain amino acids enriched snack (Aminoleban EN, Otsuka

Pharmaceutical Co., Tokyo) for supplementation of the LC patients. The treated patients were started once a day of orally 50g as BCAA snack at 22:00 of the one day at entry and continued after the entry for 8 weeks. Aminoleban EN was snack, contained 13.5g protein, high levels of BCAA and low levels of the other amino acids, as Fischer ration 38, and 210 kcal of energy per 50g on one pack. Energy supplementation of BCAA snack was performed as late evening snack (LES) (21). Patients in the BCAA group carried on intake of BCAA snack afteryears. Beside, patients in the control group did not take BCAA snack. Patients were instructed to maintain a diet containing 30–35 kcal and 1.2–1.3 g of protein per kilogram of ideal body weight per day. In the BCAA group, the patients were educated to adjust their total energy intake by subtracting 210 kcal of BCAA snack from the meals. In the control group, the control rice ball as late evening snack provided 210 kcal of energy with 9 g of protein. Nutritional intake was evaluated to all patients by dietitians at initial period, 4 weeks after and 8 weeks after.

Statistical analysis

Data were processed on a personal computer and analyzed using StatView 5.0 (SAS Institute, Inc., Cary, NC). The differences of each laboratory data were analyzed by Mann-Whitney U test and χ -square test for number. In addition, relation with items was evaluated by coefficient of correlation. Values of $P < 0.05$ were considered statistically significant.

RESULTS

This study included 21 patients, randomized either to the BCAA group, n=12, and the control group, n=9. Baseline clinical characteristics were revealed the table 1. The Child– Pugh classification A: B: C is 6: 5: 1 and 5: 3: 1 in the BCAA and control group, respectively. Hepatitis B virus infection and hepatitis C virus infection in BCAA and control group are at equal rate, respectively. The other etiology is one of autoimmune hepatitis and one of cryptogenic in the BCAA group and one of primary biliary cirrhosis and one of non-alcoholic steatohepatitis in the control group and all other etiology patients are female. All patients were outpatient during observation period and not were admitted to a hospital. In the BCAA group, adverse effects of BCAA snack were not found. Nutritional intake was not difference among initial period, 4 weeks after and 8 weeks after. The LES of BCAA snack were well tolerable diets and had good compliance in all patients of BCAA group.

Laboratory data at 8 weeks and variation between at entry and 8 weeks were showed in table 2. In 8 weeks analysis, levels of all laboratory data were equivalent between the BCAA and control group. In the variation between entry and 8 weeks in groups, all laboratory data were equivalent between the BCAA and control group. BMI at 8 weeks and variation of BMI did not have significant difference between both groups, too.

Although, laboratory data and BMI did not changed between entry and 8 weeks, cirrhotic symptom related score and ESS were influenced by BCAA snack (fig. 1). Cirrhotic symptom related score (mean±SD) is 17.12±7.76 and 16.7±10.1 at entry, 16.08±5.94 and 18.3±10.4 at 4

weeks and 11.7 ± 5.23 and 17.9 ± 10.5 at 8 weeks (fig. 1A). At 8 weeks, in the BCAA group, score is declining trend from at entry. The evaluation of difference among entry, 4 weeks and 8 weeks speculated declining trend in the BCAA group (fig. 1B). “4W-entry”, “8W-entry” and “8W-4W” also were -1.08 ± 7.60 and 1.667 ± 2.96 , -4.42 ± 5.57 and -0.444 ± 2.79 , -5.50 ± 10.3 and 1.22 ± 4.32 in the BCAA and control group, respectively. On the contrary, ESS is recognized statistically significant by BCAA treatment (fig. 1C, D). ESS (mean \pm SD) is 7.67 ± 4.21 and 4.67 ± 3.35 at entry, 5.50 ± 3.15 and 5.78 ± 3.528 at 4 weeks and 4.81 ± 2.19 and 5.78 ± 3.27 at 8 weeks (fig. 1C). However, the value of ESS is not detected significant difference at indicated period in both group. The difference among entry, 4 weeks and 8 weeks were calculated (fig. 1B). “4W-entry”, “8W-entry” and “8W-4W” also were -2.16 ± 3.46 and 1.11 ± 1.364 , -0.917 ± 1.78 and -0.00 ± 0.866 , -3.08 ± 3.66 and 1.11 ± 1.17 in the BCAA and control group, respectively. It was understood that a significant decrease of ESS had already started on the fourth week of beginning of the treatment. A significant decrease became more eminent on the eighth week of beginning of the treatment (fig. 1D).

At the last, we examined the factor that related to ESS at entry. At entry, the cirrhotic symptom related score was positively relation with Child-Pugh score ($R=0.545$), but not relation with ESS (fig. 2A, B). Additionally, ESS was not relation with Child-Pugh score (fig. 2C), each items of the cirrhotic symptom related score and laboratory data (BMI, WBC, RBC, Plt, PT, BUN, Cr, AST, ALT, γ -GTP, ALP, TB, TP, Alb, TC, ChE, TG, FPG, NH₃ and BTR) at entry. In the comparison at entry and 8 weeks after, ESS has been improved only by the BCAA treatment group and we found only one case who increment of ESS or cirrhotic symptom related score gone

negative in the control group (fig. 2D).

There are four cases, has 10 or more score of ESS, in BCAA group. ESS at entry, 4 weeks and 8 weeks is 17, 7, 5 in 50 years old female suffered hepatitis B virus infection (Child-Pugh score (CPS) 6 and cirrhotic symptom related score (CSS) 15), 10, 6, 6 in 55 years old male suffered alcohol drinking (CPS 7 and CSS 30), 12, 13, 9 in 71 years old female suffered hepatitis B virus infection (CPS 5 and CSS 23) and 10, 5, 5 in 73 years old male suffered alcohol drinking (CPS 5 and CSS 6). Three of four patients were diminished ESS score at 4 weeks compared with at entry, all patients were improved to below 10 of ESS. ESS at entry, 4 weeks, 8 weeks is 11, 13, 12 in 77 years old male suffered hepatitis C virus infection (CPS 7 and CSS 30) in control group.

DISCUSSION

In this study, it was presented that BCAA snack, was taken orally as late evening snack (LES), improved the ESS for cirrhotic patients without encephalopathy, recently. This beneficial result was recognized in short term, 4 weeks after beginning of treatment. This study demonstrates availability of BCAA supplementation for cirrhotic patients with sleep disturbance. However, the cirrhotic symptom related score was positively relation with Child-Pugh score at entry, we were not able to find the item that related to ESS.

The frequency of sleep disturbance in cirrhotic patients can not be evaluated in this study, because we did not set the normal healthy control group. 10 or more ESS, as significant of daytime hyper-somnolence, is 5 cases of 21 cirrhotic patients (23.8%), and all cirrhotic patients have a mean ESS of 6.38 in this study. In Japanese previous report (23), it is described that a mean ESS of 5.6 in 144 healthy control cases are lower than Parkinson disease group. In Italian study (8), it is reported that cirrhotic patients had a mean ESS of 6.66 (6.17 in health control), and 15.7% of them had a higher than 10 of ESS (12.9% in healthy controls). In primary biliary cirrhosis study (5), it is reported that patients had a mean ESS of 9 (5 in health control), and more than 50% of them had a higher than 10 of ESS (15% in healthy controls). We think that our ESS data of cirrhotic patient is not very different from the previous study. And, all of the patients with significant of daytime hyper-somnolence were improved by BCAA snack in this study.

The mechanism of sleep disturbance in cirrhotic patient is still unclear. Thus far, it has been considered that sleep disturbance is the early sing of hepatic encephalopathy and symptom of

“minimal hepatic encephalopathy (MHE)” which is characterized by cognition dysfunction without overt encephalopathy (24). There is no current consensus on how MHE should be diagnosis. However, there are the following several requirements to diagnosis of MHE; 1. Normal mental status on clinical examination. 2. Documentation of neurological impairment by the multiple methods. 3. Exclusion of other disturbance that may cause the neurological impairment (25). In this study, our patients have normal mental status and do not have other neurological impairment, but did not documented neurological impairment. Therefore, our patients could not diagnose to MHE. However, we think that an enough evaluation for the relation with MHE and sleep disturbance is necessary. Previous report described that the psychometric test were not correlated with ESS (26), there was no relationship between sleep and cognitive performance either at baseline or in relation to treatment (27). There is a positive correlation in HME and Child-Pugh score(25), but is no correlation in sleep disturbance and Child-Pugh score (1). In this study, ESS is not relation with liver function and cirrhotic symptom related score. It has been considered that MHE is a part of cause for sleep disturbance in cirrhotic patient, but we think that another inducer of sleep disturbance is existence.

It is speculated by groups that think relationship between sleep disturbance and MHE that the mechanism of sleep disturbance in cirrhotic patient is the deterioration of circadian rhythm (1. 24). Specially, melatonin and that metabolite, brain hormone, common pacemaker of circadian rhythm, are hepatic metabolism, and it caused sleep disturbance for delayed sleep phase that the melatonin levels of peak significantly delayed in cirrhotic patient (28). However, contrary, it is

reported that cirrhosis does not shift the circadian phase of plasma fibrinolysis (29). Because we did not evaluate sleep phase in our cirrhotic patients, it is necessary to wait for the evaluation in the future about an abnormal circadian variation. However, we learnt that BCAA snack is effectiveness for sleep disturbance in cirrhotic patient. Tryptophan, aromatic amine acid, elevated in cirrhotic patient, is the precursor for the neurotransmitter 5-hydroxytryptamine (5-HT), which is involved in fatigue and sleep (30, 31). In previous report (31), it is suggested that BCAA supplementation may help to counteract the effects of an increase in plasma free tryptophan. It has been suggested that the plasma BCAA concentration may influence brain function and affect appetite, physical and mental fatigue, mental performance and physical endurance (32). In other report, it has been described that oral intake of BCAA may reduce tryptophan uptake and 5-HT synthesis and release, thereby delaying fatigue (30). Recently, it is reported that fatigue in liver disease is significant and associates with excessive daytime sleepiness and high average of ESS (6). In this study, ESS is not related with our indicated data, but it will be necessary to examine the participations of the factor, for instance, fatigue, other than having examined in this study.

In our study, the difference of BTR with BCAA group and control group was not founded. We speculated that the cause is the short treatment period. In previous reports, the elevation of BTR was observed at 3 month (33) and 1 year (34) after BCAA supplementation group (Aminoleban EN). We think that elevation of BTR in BCAA group at 8 week might be caused by an increase in number of entry cases.

Since benzodiazepines should not be used for cirrhotic patients with sleep disturbance (35), availability of orally taken BCAA snack for cirrhotic patient with sleep disturbance will be necessary to verify. Previous report showed that BCAA can be a psychotropic drug which directly acts on the central nervous system (4). The restless legs syndrome and obstructive sleep apnea syndrome are known as the cause of sleep disturbance in cirrhotic patients (6. 36). The cause of sleep disturbance and the relationship with prognosis and sleep disturbance will be subjective of future research.

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Figure legend

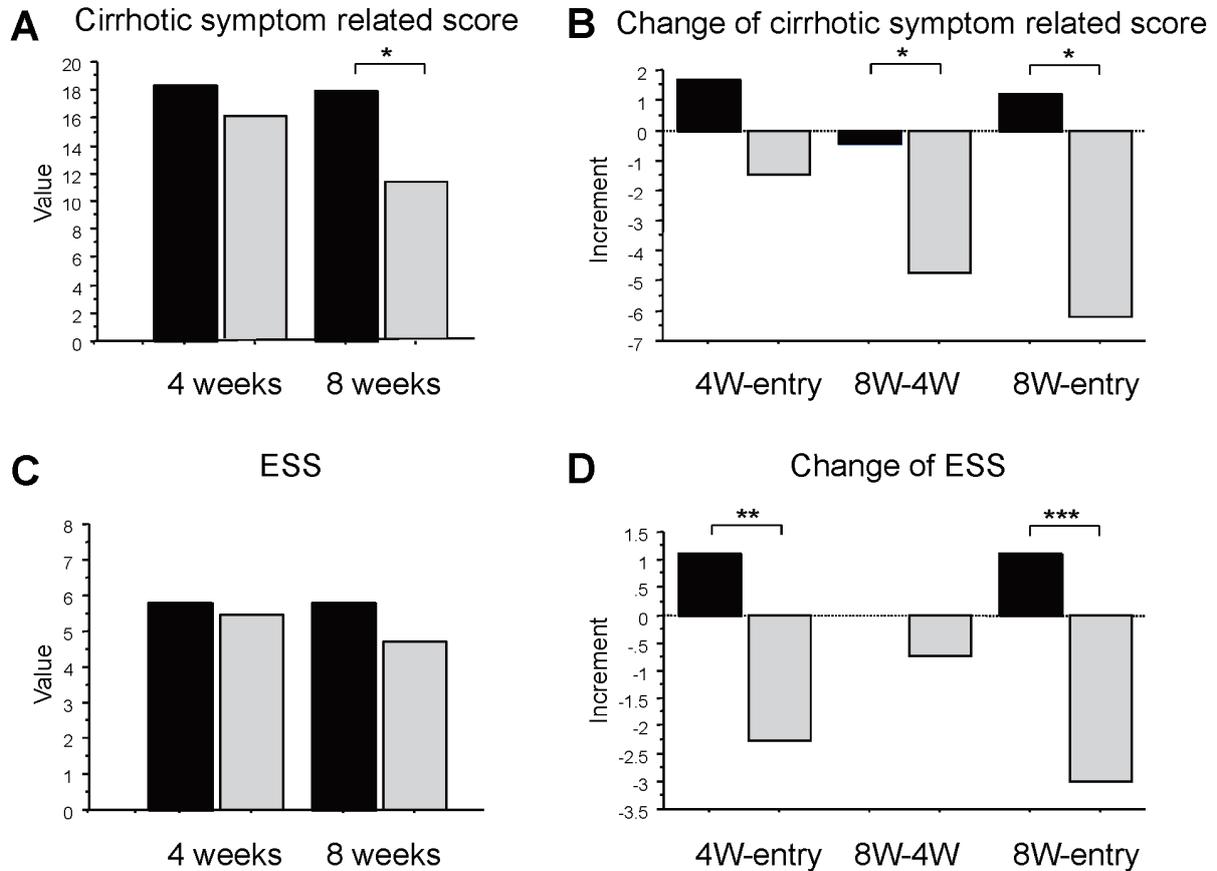


Figure 1. The transition of cirrhotic symptom related score and ESS during the follow up period.

Value of cirrhotic symptom related score (A) and ESS (C) at 4 weeks and 8 weeks. Change of cirrhotic symptom related score (B) and ESS (D). “4W-entry” is an increment value in which the data of pre-treatment is pulled from the data of 4 weeks after the observation beginning. “8W-entry” and “8W-4W” also were calculated the increment between two indicated period. Black box is the mean value in observation group. Gray box is the mean value in BCAA group. * is $p < 0.1$. ** is $p < 0.05$. *** is $p < 0.01$.

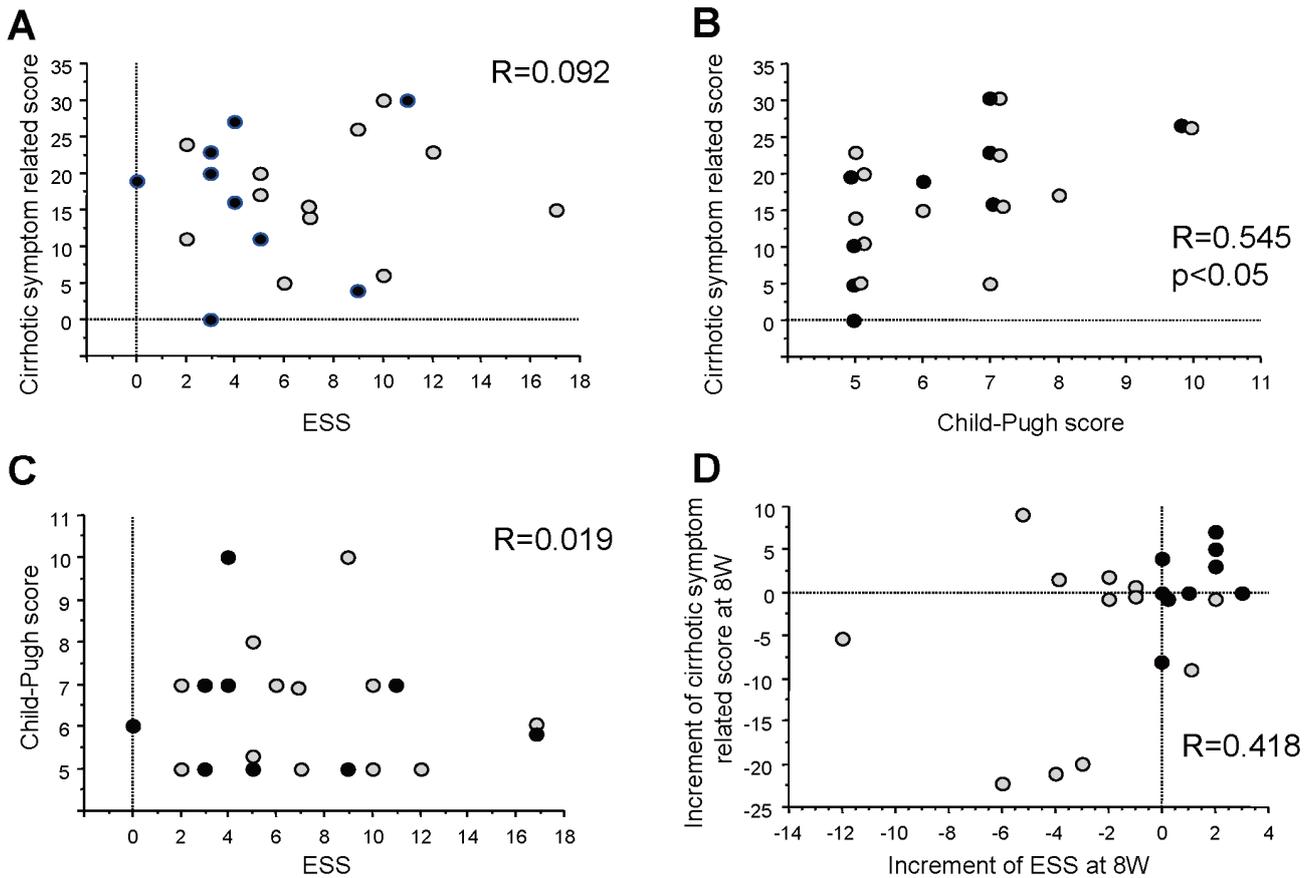


Figure 2. The scatter graph of ESS, cirrhotic symptom related score and Child-Pugh score.

The scatter graph is between cirrhotic symptom related score and ESS (A), cirrhotic symptom related score and Child-Pugh score (B), Child-Pugh score and ESS score (C) and increment of cirrhotic symptom related score from 8 weeks after to entry and increment of ESS from 8 weeks after to entry (D). The increment value calculated the difference from at 8 weeks after to at entry.

Black circle indicated to the patient in observation group. Gray circle indicated to the patient in BCAA group. “R” is correlation coefficient. The relation between cirrhotic symptom related score and Child-Pugh score showed a positive correlation statistically.

Table 1. Clinical characteristics at entry.

Character	BCAA group (n=12)	Control group (n=9)
Disease	Viral 8: Alcoholic 2: other 2	Viral 6: Alcoholic 2: other 2
Sex (Female: Male)	7: 5	4: 5
Child-Pugh score	6.36±1.65	6.33±1.62
BMI	25.6±5.61	23.8±3.86
Age	66.2±8.21	67.4±9.86
TP	7.29±0.65	6.63±0.804
Alb	3.57±0.83	3.44±0.663
WBC	2972±970	2851±940
RBC	381±82.0	359±71.9
Plt	7.01±2.02	9.28±3.86
PT	65.1±15.7	75.3±21.7
BUN	15.4±5.57	17.3±5.22
Cr	0.745±0.112	0.869±0.186
AST	45.1±22.7	47.0±19.3
ALT	35.9±27.0	38.8±20.9
ALP	431.4±217.7	344.8±150.6
γ-GTP	74.0±99.1	69.3±68.2
TB	1.57±0.735	1.01±0.704

BTR	3.35±1.78	3.50±1.53
NH3	64.9±30.6	75.3±52.3
ChE	176.2±115	150.2±66.4
TC	159.4±30.7	137.1±35.4
TG	63.0±33.2	74.3±23.4
FPG	107.4.8±27.2	115.4±27.2
CSS	17.4±8.1	16.7±10.1
ESS	7.73±4.47	4.67±3.35

Data are shown as means ± standard deviation and numbers, with statistical analysis using a Mann–Whitney test for means and χ -square test for number. Statistical significance difference between BCAA and control group is not detected in this table.

Normal values in laboratory tests: ALT (IU/l), 5–40; AST (IU/l), 10–40; γ -GTP (IU/l), <70 in males, <30 in females; TP (g/dl), 6.7–8.3; ALB (g/dl), 4.0–5.0; WBC (/ μ l), 3500–9000; RBC ($\times 10^4$ / μ l), 450–580 in males, 380–480 in females; Plt ($\times 10^4$ / μ l), 14–33; PT (%), 70-130 ; BUN (mg/dL), 8.0-22.0; Cr (mg/dL), 0.61-1.04 in males, 0.47-0.79 in females; ALP (IU/l), 115-359; LDH (IU/l), 119–229; TB (mg/dl), 0.3–1.5; BTR,5-9.5; NH3 (μ g/dl), <75; ChE (IU/l), 214–466; TC (mg/dl), 128–220; TG (mg/dl), 38–150; FPG (mg/dl), 70–110

BMI; body weight (kg)/ height (m) / height (m)

CSS; cirrhotic symptom related score

Table 2. Variation of laboratory data from at entry to 8 week.

Laboratory data	at 8 weeks after the entry		8 week - entry	
	BCAA	Control	BCAA	Control
BMI	26.1±5.24	23.7±4.00	0.234±0.543	-0.097±0.827
TP	7.18±0.656	6.66±0.835	-0.133±0.42	0.038±0.66
Alb	3.52±0.67	3.43±0.732	-0.017±0.46	-0.013±0.20
WBC	3391±91182	2900±1009	308.3±588	48±560
RBC	385±77.6	353±70.9	6.01±36.6	-6.44±24.4
Plt	7.39±2.44	10.26±5.07	-0.133±0.856	0.978±1.646
PT	66.1±14.7	71.7±15.5	-4.43±27.4	-3.59±8.18
BUN	14.8±4.37	18.3±5.99	-0.58±4.00	1.00±5.41
Cr	0.77±0.112	0.89±0.209	0.23±0.053	0.23±0.063
AST	44.5±15.73	45.0±16.2	-2.00±14.9	-1.50±23.8
ALT	33.3±14.09	29.6±11.0	-2.58±25.0	-9.22±19.3
ALP	412.4±180.1	358.9±150.1	-21.4±141	14.0±64.2
γ-GTP	76.8±103.1	53.1±38.4	6.58±21.3	-16.2±37.2
TB	1.33±0.799	0.80±0.654	-0.25±0.487	-0.21±0.262
BTR	3.69±1.90	3.86±1.50	0.445±1.17	0.364±0.795
NH3	72.6±31.64	63.9±34.0	8.63±21.2	-12.3±18.1
ChE	175.0±94.3	147.7±74.6	2.42±42.4	-2.56±18.7

TC	147.5±30.0	127.6±28.7	-9.67±19.5	-9.56±18.3
TG	52.0±18.2	58.7±42.7	-12.5±12.8	-7.00±23.3
FPG	105.7±73.2	111.6±24.2	21.7±71.3	-45.6±77.6

“8 week - entry” is an increment value in which the data of pre-treatment is pulled from the data of 4 weeks after the observation beginning. Data are shown as means ± standard deviation and numbers, with statistical analysis using a Mann–Whitney test for means. Statistical significance difference between BCAA and control group is not detected in this table. Normal values in laboratory tests are same as table1.