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# Comparison of the Effect of Oral Supplementation with Branched–Chain Amino Acid on Serum Albumin Level between Decompensated Cirrhosis and Compensated Cirrhosis

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## ABSTRACT

**Background/Aims:** We designed a randomized trial to examine whether increase or preservation of serum albumin levels was attained with administration of branched-chain amino acid (BCAA) granules for compensated cirrhosis, compared with decompensated cirrhosis.

**Methodology:** Sixty-five patients with HCV-related cirrhosis with serum albumin level less than 4.0 g/dl were enrolled in this study. Half of the patients were randomly assigned to receive 14.22 g/day of BCAA granules orally, and half were assigned to a control group. Patients were evaluated at entry and at 1-year intervals for at least 2 years. The parameters were divided into 3 categories. Class 1 was decompensated cirrhosis with serum albumin level less than 3.5 mg/dl. Class 2 was compensated cirrhosis with serum albumin

level over 3.6 mg/dl and molar ratio of BCAA to tyrosine (BTR) less than 4. Class 3 was compensated cirrhosis with serum albumin level over 3.6 mg/dl and BTR over 4.

**Results:** In class 1 and class 2, the BCAA group exhibited significantly higher rates of maintaining serum albumin level than the control group for 2 years. In contrast, there was no significant difference between the BCAA group and control group in rate of maintaining serum albumin levels in class 3.

**Conclusions:** Those results suggested that if cirrhotic patients were in the compensated stage at the entry but with lower BTR, as for decompensated cirrhosis, oral BCAA supplementation might be effective in maintaining serum albumin level for 2 years.

## INTRODUCTION

Oral administration of BCAA for the purpose of improving hepatic encephalopathy or hypo- albuminemia with decompensated cirrhosis is generally accepted in Japan (1, 2). We have suspected that, for at least some patients oral supplementation of BCAA for compensated cirrhosis can maintain serum albumin level and hinder dropping into the decompensated stage. We therefore planed the randomized control trial with HCV-related cirrhosis to compare the effect of oral supplementation of BCAA between decompensated cirrhosis and compensated cirrhosis in changes in serum albumin level over 2 years.

## METHODOLOGY

### Patients and Methods

Sixty-five patients with HCV-related cirrhosis with serum albumin level under 4.0 g/dl who visited our hospital between December 1998 and November 1999 were enrolled in this study. None of the patients had previously been given BCAA supplementation. No patients had hepatocelluar carcinoma, hepatitis B virus infection or other liver diseases such as autoimmune hepatitis, primary biliary cirrhosis and alcoholic liver disease at entry. Diagnosis of cirrhosis was made based on the council system by not less than three hepatologists based on abdominal ultrasonography (3). Entry characteristics of the patients are shown in **Table 1**.

Half of the patients were randomly assigned to receive 14.22 g/day of BCAA granules (Livact; Ajinomto Co. Tokyo, Japan) orally (BCAA group), and half were assigned to a controls (control group). All patients were underwent diet education to maintain total calorie: 30 kcal/kg and protein 1.3g/kg (includ-

| TABLE 1 Baseline Characteristics of the Patients | |
| --- | --- |
| | **Patients** |
| Sex (male/female) | 22/38 |
| BCAA/Control | 28/32 |
| Average age | 65.1 + 6.9 |
| Average BTR | 3.6 + 1.0 |
| BTR<4 / BTR>4 | 38/22 |
| Albumin (g/dl) | 3.6 + 0.3 |
| Alb<3.5 / Alb>3.5 | 25/35 |
| Platelets (10$^4$/mm$^3$) | 11.0 + 5.5 |
| Pl<10 / Pl>10 | 29/31 |
| ALT (IU/l) | 100.8 + 63.4 |
| ALT>80 / ALT<80 | 36/24 |
| Average T-bilirubin (mg/dl) | 1.1 + 0.5 |
| T-Bil>1.0 / T-Bil<1.0 | 26/34 |

ing BCAA granules 14.22 g/day for BCAA group) a day for standard body weight (height(m)2x22) and in principal kept this diet through the study period. All patients gave written informed consent. The procedures used accorded with the Helsinki Declaration (1996) and were approved by the Ethics Committee of Osaka City University Medical School.

Patients were evaluated at entry and at 1-year intervals for at least 2 years. We evaluated results as follows: Increase in serum albumin level over 0.2mg/dl compared with serum albumin level at entry was evaluated as "increased". Decrease in serum albumin level over 0.2mg/dl compared with serum albumin level at entry was evaluated as "decreased". Other patients were in the "unchanged group".

At entry, we measured serum molar concentrations of branched-chain amino acids divided by those of tyrosine (branched-chain tyrosine ratio; BTR). BTR were measured by an enzymatic method (Ono Pharmaceutical Co., Ltd., Osaka, Japan). Normal range of BTR is from 5.82 to 8.64. The clinical significance of the results obtained resemble those for Fisher's ratio (4-7).

We divided the parameters into 3 categories. Class 1 was de-compensated cirrhosis with serum albumin level less than 3.5 mg/dl. Class 2 was compensated cirrhosis with serum albumin level over 3.6 mg/dl and BTR less than 4. Class 3 was compensated cirrhosis with serum albumin level over 3.6 mg/dl and BTR over 4. For division of patients into class 2 and class 3, we chose a BTR of 4.0 (which corresponds roughly to Fischer's ratio of 2.0), for two reasons. First, 4.0 is the lower limit of the reference range (4). Second, another cross-sectional study showed that a significantly larger population of patients with cirrhosis (mostly viral) and with a BTR of less than 4 had esophageal varices or portal hypertension (or both) than similar patients with higher BTR (unpublished). A scatter graph representing the relationship between serum albumin level and BTR of the parameters is shown in **Figure 1**.

The number of patients in class 2 was almost equal to that in class 3. Twenty-eight patients in the BCAA group and 32 in the control group completed 2 years of treatment. Four patients in the BCAA group and one in the control group dropped out.

At entry, we measured serum albumin, total bilirubin, ALT and platelets. Baseline characteristics of the 3 groups are shown in **Table 2**.

**Statistical analysis**

For statistical testing, the chi-square test for independence was used. Differences with $p < 0.05$ were considered statistically significant. Five baseline variables were assessed in the study, including serum albumin, BTR, total bilirubin, ALT level and platelet cell counts. Multivariate analysis was performed to determine the significance of the parameters using a proportional odds model.

**RESULTS**

Comparison of serum albumin levels at 2 years since enrollment between BCAA group and control group in class 1 (**Table 3**).

The BCAA group exhibited a significantly higher rate of maintenance of serum albumin level compared with enrollment than the control group (chi-square test for independence: $p$ =0.02).

Comparison of serum albumin levels at 2 years since enrollment between BCAA group and control group in the class 2 (**Table 4**).

The BCAA group exhibited a significantly higher rate of maintenance of serum albumin level compared with enrollment than the control group (chi-square test for independence: $p$=0.02).

Comparison of serum albumin levels at 2 years since enrollment between BCAA group and control group in the class 3 (**Table 5**).

There was no significant difference between the BCAA group and control group in rate of maintenance of serum albumin levels (chi-square test for independence).

Results of multivariate analysis of BCAA sup-



**FIGURE 1** Scatter graph representing the relationship between serum albumin level and BTR of the parameters
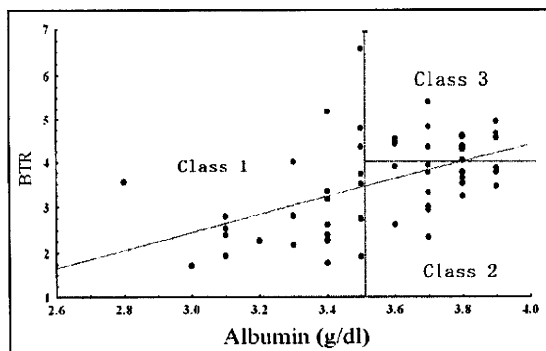
| TABLE 2 Baseline Characteristics of 3 Classes | | | |
|---|---|---|---|
| | Class 1 (Alb < 3.5) | Class 2 (Alb>3.5, BTR<4) | Class 3 (Alb>3.5, BTR > 4) | |
| Sex (male/female) | 11/14 | 6/12 | 5/12 | ns |
| BCAA / Control | 13/12 | 9/9 | 6/11 | ns |
| Average age | 64.3 + 4.9 | 63.8 + 7.0 | 67.5 + 8.8 | ns |
| Average BTR | 3.1 + 0.2 | 3.4 + 0.5** | 4.6 + 0.3** | $p<0.001$ |
| Albumin (g/dl) | 3.3 + 0.2 | 3.8 + 0.1** | 3.8 + 0.1** | $p<0.001$ |
| Platelets ($10^4/mm^3$) | 8.6 + 4.8 | 10.4 + 3.9* | 15.1 + 5.8* | $p<0.01$ |
| ALT (IU/l) | 117.0 + 84.0 | 98.4 + 42.7 | 79.4 + 38.1 | ns |
| Bilirubin (mg/dl) | 1.3 + 0.5 | 1.0 + 0.3 | 0.9 + 0.4 | ns |

Wilcoxon rank-sum test for age, BTR, serum albumin, platelets, alanine aminotransferase (ALT) and total bilirubin; chi-square test for sex ratio and BCAA/Control ratio.

plementation using proportional odds model (**Table 6**).

No factors were selected as significant independent risk factors for maintenance of serum albumin levels by oral supplementation of BCAA granules.

Results of multivariate analysis of maintenance of serum albumin levels in the control group using a proportional odds model (**Table 7**).

BTR only was selected as an independent risk factor for maintenance of serum albumin levels 2 years after enrollment in the control group.

## DISCUSSION

As liver function deteriorates, ammonia metabolism in the liver slows downs, and in compensation muscles begin to detoxify ammonia, consuming serum BCAA (8). Another reason for low BTR is that tyrosine (in the denominator of the equation) increases as cirrhosis worsens because of protein breakdown (9). BCAA, especially leucine, help regulate gene expression and protein turnover. In the control group, BTR alone was selected as an independent risk factor for maintenance of serum albumin levels 2 years after the enrollment because lower level of BCAA might not trigger albumin synthesis (10).

It has been reported that correction of the BCAA to aromatic amino acid (AAA) ratio improves protein synthesis and that BCAA supplementation prevents degeneration of body protein in cirrhosis (11-13). The clinical safety and usefulness of supplementation of BCAA granules for decompensated cirrhosis has already been established (1, 14). The short-term usefulness of BCAA administration for liver cirrhosis has also already been reported (15, 16).

In this prospective trial, the results of patients in class 2 (with higher serum albumin and lower BTR) and those of patients in class 1 (decompensated cirrhosis with lower serum albumin level), were almost the same. In both classes, the BCAA group exhibited a significantly higher rate of maintenance of serum albumin levels compared with that at en-

| TABLE 3 Effect of Oral BCAA Supplementation on Serum Albumin Level at 2 Years since Enrollment in Class 1 | | | |
|---|---|---|---|
| | Alb>0.2 | 0.1>Alb>-0.1 | Alb<-0.2 |
| BCAA | 46% (6/13) | 38% (5/13) | 15% (2/13) |
| Control | 8% (1/12) | 25% (3/12) | 67% (8/12) |

The BCAA group exhibited a significantly higher rate of maintaining serum albumin levels compared with that at enrollment than the control group (chi-square test for independence: $p = 0.02$).

| TABLE 4 Effect of Oral BCAA Supplementation on Serum Albumin Level at 2 Years since Enrollment in Class 2 | | | |
|---|---|---|---|
| | Alb>0.2 | 0.1>Alb>-0.1 | Alb<-0.2 |
| BCAA | 44% (4/9) | 44% (4/9) | 11% (1/9) |
| Control | 0% (0/9) | 33% (3/9) | 67% (6/9) |

The BCAA group exhibited a significantly higher rate of maintaining serum albumin levels compared with that at enrollment than the control group (chi-square test for independence: $p = 0.02$).

| TABLE 5 Effect of Oral BCAA Supplementation on Serum Albumin Level at 2 Years since the Enrollment in Class 3 | | | |
|---|---|---|---|
| | Alb>0.2 | 0.1>Alb>-0.1 | Alb<-0.2 |
| BCAA | 67% (4/6) | 17% (1/6) | 17% (1/6) |
| Control | 36% (4/11) | 55% (6/11) | 9% (1/11) |

There was no significant difference between the BCAA group and control group in rate of maintaining serum albumin levels (chi-square test for independence).

rollment than the control group.

In contrast, there was no significant difference between the BCAA group and control group in rate of maintenance of serum albumin level in class 3. These results suggested that if cirrhotic patients are in compensated stage at entry but with lower BTR, as for decompensated cirrhosis, oral BCAA supplementation might be effective in maintaining serum albumin level for 2 years.

TABLE 6 Risk Ratio of Increase or Decrease in Serum Albumin Level after 2 Years of Supplementation of Oral BCAA Granules

| | Risk ratio | 95% CI | p - value |
|---|---|---|---|
| Serum albumin | 0.813 | 0.161 – 4.099 | 0.8016 |
| BTR | 0.788 | 0.117 – 5.299 | 0.8063 |
| Total bilirubin | 3.131 | 0.659 – 14.872 | 0.1510 |
| ALT | 1.400 | 0.291 – 6.736 | 0.6749 |
| Platelet count | 2.002 | 0.324 – 12..72 | 0.4553 |

Odds ratios are expressed as per 1 year for age. Since albumin value was categorized into two groups, >3.5 and <3.5g/dl, as were BTR > 4.0 and < 4, Total bilirubin < 1.0 and >1.0, ALT level < 80 and > 80 IU/ml, platelet count >100 and < 100 thousand / mm$^3$, odds ratios are indicated between each set of two groups.

TABLE 7 Risk Ratio of Increase or Decrease in Serum Albumin Level after 2 Years since Enrollment in Control Group

| | Risk ratio | 95% CI | p - value |
|---|---|---|---|
| Serum albumin | 1.586 | 0.281 – 8.960 | 0.6015 |
| BTR | 9.444 | 1.524 – 58.521 | 0.0158 |
| Total bilirubin | 0.463 | 0.071 – 3.028 | 0.4214 |
| ALT | 1.549 | 0.322 – 7.452 | 0.5849 |
| Platelet count | 5.619 | 0.954 – 33.101 | 0.0564 |

Odds ratios are expressed as per 1 year for age. Since albumin value was categorized into two groups, >3.5 and <3.5 g/dl, as were BTR > 4.0 and < 4, Total bilirubin < 1.0 and >1.0, ALT level < 80 and > 80 IU/ml, platelet count >100 and < 100 thousand / mm$^3$, odds ratios are indicated between each set of two groups.

HCV-related cirrhosis with BTR less than 4 might be a stage in which insufficiency of BCAA has clearly occurred, and therefore oral supplementation of BCAA granules might be effective in maintaining serum albumin levels. In contrast, BTR over than 4 might be a stage in which insufficiency of BCAA has not clearly occurred yet, and therefore oral supplementation of BCAA granules might not significantly affect the synthesis of albumin.

Serum albumin level is an important regula-

tory factor for liver cirrhosis, and compensated cirrhosis with serum albumin level above 3.5g/dl appears to have a better prognosis (17-21). This trial suggested that oral supplementation of BCAA for compensated cirrhosis with BTR less than 4, which may have accounted for about half of patients with compensated cirrhosis in our study, was effective in maintaining serum albumin level and thus might improve prognosis, as well as it dose that of decompensated cirrhosis.

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been shown to be important in animal models of glomerulonephritis, restenosis, asthma and fibrosarcoma,[3] might be as important. From a clinical perspective, one might even argue that FXa is a more attractive therapeutic target for liver fibrosis than thrombin. This notion is not only based on the fact that FXa inhibitors are more effective at lower doses than thrombin inhibitors but also on the fact that FXa inhibitors block both FXa-dependent profibrotic signalling and thrombin generation.

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Competing interests: None.

Provenance and peer review: Not commissioned; not externally peer reviewed.

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# Applicability of BARD score to Japanese patients with NAFLD

We read the article by Harrison et al[1] with great interest. The authors proposed an easily calculated composite score for predicting the risk of advanced fibrosis in patients with non-alcoholic fatty liver disease (NAFLD), called the BARD score: the weighted sum of the three variables (body mass index (BMI) ≥28 = 1 point, aspartate aminotransferase/alanine aminotransferase ratio (AAR) ≥0.8 = 2 points, diabetes = 1 point). When a BARD score of 2–4 was used, the area under the receiver operating characteristic curve (AUROC) was found to be 0.81 with an odds ratio (OR) of 17 (95% CI 9.2 to 31.9) for detecting advanced fibrosis. The positive predictive value (PPV) and negative predictive value (NPV) were 43% and 96%, respectively. We studied the reliability of the BARD score for identifying the risk of advanced fibrosis in Japanese patients with NAFLD.
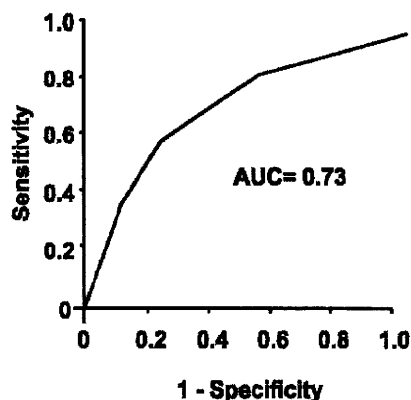


**Figure 1** Simple steatosis plus non-alcoholic steatohepatitis (NASH) with fibrosis stages 0–2 vs NASH with fibrosis stages 3–4. AUC, area under the curve.

A total of 122 patients (61% female; median age, 59 years) with NAFLD who underwent liver biopsy at our hospital were studied. Median BMI was 26 kg/m² (range, 18–45); 33% of patients had a normal BMI of <25, whereas 46% were overweight (BMI 25–29), 21% were obese (BMI ≥30) and 1% were extremely obese (BMI ≥40). Common co-morbidities included hypertension (30%), diabetes (37%) and hyperlipidaemia (59%). Liver biopsy showed that 9 (7%) had simple steatosis, and 113 (93%) had non-alcoholic steatohepatitis, including 67 (55%) with mild fibrosis (stage 0–2) and 46 (38%) with advanced fibrosis (stage 3–4). When a BARD score of 2–4 was used, the AUROC was 0.73 (fig 1) with an OR of 4.9 (95% CI 2.2 to 10.8) for detecting advanced fibrosis. The PPV and NPV were 59% and 77%, respectively.

The BARD score was less predictive of advanced fibrosis in Japanese patients than in the study by Harrison et al, probably because of two major reasons. First, their subjects were predominantly Caucasians; only 2% were Asian Pacific Islanders. Although mean BMI is lower in Asian populations than in non-Asian populations, Asians have a higher percentage of body fat for a given BMI than non-Asians.[2] In a study

conducted in Japan,[3] nearly half of the subjects with NAFLD were not overweight or obese, suggesting that different genetic and environmental factors are related to susceptibility to hepatic steatosis in the Japanese population. In our cohort, BMI was similar in patients with and without advanced fibrosis, as shown in table 1. Our results are consistent with those of Hashimoto et al,[4] who found that older age, the presence of diabetes and elevated AAR were significantly associated with more advanced fibrosis in Japanese patients, whereas higher BMI was not. Secondly, Harrison et al assessed only AAR, glycated haemoglobin (HbA1c) and the quantitative assessment check index score among laboratory variables as potential risk factors for advanced fibrosis. Since decreased platelet count and decreased albumin concentration were significantly associated with more advanced fibrosis in our cohort (table 1), we assessed the value of the NAFLD fibrosis score,[5] which includes these two variables, for the detection of advanced fibrosis. The AUROC for the NAFLD fibrosis score was 0.84, with a PPV and NPV of 59% and 89%, respectively (data not shown). Albeit slightly more complex, the NAFLD fibrosis score more accurately detected advanced fibrosis in our patients than the BARD score.

In summary, the BARD score can be easily derived from readily available clinical data, but may be less reliable for excluding the presence of advanced fibrosis in Japanese patients with NAFLD than in the study by Harrison et al.

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Competing interests: None.

Provenance and peer review: Not commissioned; not externally peer reviewed.

**Table 1** Risk assessments of clinical parameters for advanced fibrosis

| Characteristics | Simple steatosis and NASH fibrosis 0–2 (n = 76) n (%) | NASH fibrosis 3–4 (n = 46) n (%) | p Value | OR (95% CI) |
|---|---|---|---|---|
| Age ≥50 years | 45 (59) | 37 (80) | 0.016 | 2.8 (1.2 to 6.7) |
| Female gender | 42 (55) | 33 (72) | 0.070 | 2.1 (0.9 to 4.5) |
| Body mass index ≥28 kg/m² | 24 (32) | 15 (33) | 0.906 | 1.0 (0.5 to 2.3) |
| Hypertension | 18 (24) | 18 (39) | 0.070 | 2.1 (0.9 to 4.6) |
| Diabetes | 21 (28) | 24 (52) | 0.007 | 2.9 (1.3 to 6.1) |
| Hyperlipidaemia | 52 (68) | 20 (43) | 0.007 | 0.4 (0.2 to 0.8) |
| AST/ALT ≥0.8 | 16 (21) | 27 (59) | <0.0001 | 5.3 (2.4 to 11.9) |
| Platelets <200×10⁹ cells/l | 25 (33) | 36 (78) | <0.0001 | 7.3 (3.1 to 17.1) |
| Albumin <4.1 g/dl | 24 (32) | 32 (70) | <0.0001 | 5.0 (2.2 to 10.9) |

ALT, alanine aminotransferase; AST, asparate aminotransferase; NASH, non-alcoholic steatohepatitis.

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## Authors' reply

We appreciate the comments by Fujii and colleagues in reference to our manuscript on the development and validation of the BARD score for identifying patients with non-alcoholic steatohepatitis (NASH) without advanced fibrosis[1] and applaud efforts by other investigators to apply the BARD score to their patient populations. The authors conclude that in a study of 122 Japanese patients with non-alcoholic fatty liver disease (NAFLD) the BARD score was less predictive of advanced fibrosis.

The authors suggest that two reasons exist for the disparity. First, only 2% of our 827 patients were Asian Pacific Islanders. This explanation seems plausible as the mean body mass index (BMI) of this cohort of patients is typically less than that of Western patients. Indeed, in their study, the mean BMI was 26 kg/m² compared with a BMI of 33 kg/m² in our study. Only 3% of our study cohort had a BMI of <25 kg/m², while 33% of the Japanese cohort had a BMI of <25 kg/m². Perhaps consideration should be given to performing BARD analyses on Asian populations using lower setpoints.[2] This finding is paramount, as one of the three criteria for the BARD score includes a BMI of ⩾28. Secondly, we did not utilise platelet count or albumin in our study, and in the Japanese cohort both of these variables were found to be significantly associated with advanced fibrosis.

A few other differences between the two study populations are worth mentioning. The Japanese cohort was roughly 10 years older on average and included more females. This probably contributed to the higher percentage of advanced fibrosis in their cohort compared with ours, 38% vs 22%. Finally, the Japanese study had only 46 patients with advanced fibrosis, compared with 182 patients in our study cohort, increasing the chance of statistical error.

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## Gastrointestinal manifestations among Chilean patients infected with novel influenza A (H1N1) 2009 virus

Influenza A (H1N1) viruses have been widely found in different species, hence different strains have been demonstrated to infect various species such as birds, pigs and humans. During this year a new influenza virus has recently emerged from a reassortment between triple reassortant swine virus and the Eurasian influenza A swine virus lineage.[1] Since the World Health Organisation's declaration of a new pandemic, the virus has continued to spread to different countries, with a higher number of cases in North and South America, of which Chile has emerged as one of the most affected countries worldwide[2] (fig 1).

Sentinel respiratory viral surveillance has been performed routinely in Chile over the last 7 years and, since 27 April 2009, all influenza-like cases in Chile were immediately notified to the Health Secretary. This notification included a complete report of demographic data, signs and symptoms such as fever, headache, respiratory symptoms, myalgias and the following gastrointestinal symptoms: nausea, diarrhoea and vomiting. Respiratory samples were obtained from all patients with influenza-like illness, and real-time reverse transcription–PCR (RT–PCR) confirmation was performed by Instituto de Salud Pública of Chile following the Centers for Disease Control (CDC; USA) protocol of real-time RT–PCR for novel influenza A (H1N1) virus.[3] The first 500 Chilean patients with a confirmed influenza A (H1N1) 2009 virus infection were detected between 17 and 31 May 2009. A febrile respiratory infection was the most common clinical manifestation and ranged from self-limited to severe illness. This group of patients included four critically ill patients, and one of them died, representing an overall mortality of 0.2%. Gastrointestinal manifestations due
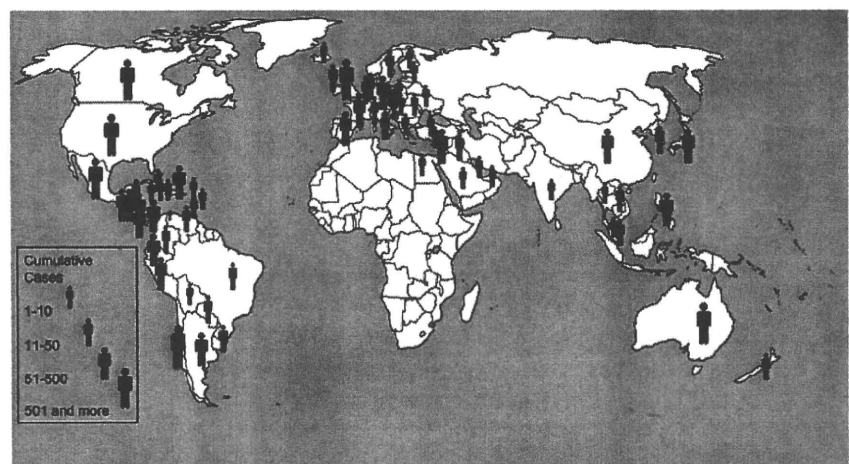
**Table 1** Clinical features of the first 500 Chilean patients infected with novel influenza A (H1N1) 2009 virus

| Sign/symptom | n (%) |
|---|---|
| Fever | 486 (97.1) |
| Headache | 486 (97.1) |
| Myalgias | 468 (93.5) |
| Cough | 450 (90) |
| Sore throat | 442 (88.3) |
| Rhinorrhea | 421 (84.1) |
| Joint pain | 219 (43.8) |
| **Nausea** | **182 (36.4)** |
| **Diarrhoea** | **147 (29.4)** |
| Conjunctivitis | 94 (18.8) |
| **Vomiting** | **72 (14.3)** |
| Seizures | 42 (8.3) |



**Figure 1** New influenza A (H1N1) 2009. The number of laboratory-confirmed cased worldwilde reported by the World Health Organisation on 10 June 2009. The most affected countries were Mexico, the USA, Canada, Chile (red figure), Australia and the UK.

# Applicability of BARD score to Japanese patients with NAFLD

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ORIGINAL ARTICLE

# A Randomized Pilot Trial of Oral Branched-Chain Amino Acids in Early Cirrhosis: Validation Using Prognostic Markers for Pre–Liver Transplant Status

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Because of the chronic shortage of liver donors, hepatologists are required to prolong the liver transplant waiting period by preserving the hepatic reserve of scheduled recipients. This study examined the effectiveness of oral branched-chain amino acids (BCAAs), using outcome markers indicating pretransplant hepatic reserve. Fifty-six consecutive eligible patients with Child class A cirrhosis without major complications were randomly assigned to receive oral BCAA granules (12.45 g/day) for least 1 year or no BCAAs. Differences between groups in the Model for End-Stage Liver Disease (MELD) score, Child-Turcotte-Pugh (CTP) score, asialoscintigraphic clearance index (CI), and complications were examined. Of 50 remaining patients, 27 received BCAAs, and 23 received no BCAAs (mean duration, 3.2 years). The mean annual changes in the MELD score, CTP score, and asialoscintigraphic CI were smaller in the BCAA group than in the control group ($-0.06 \pm 0.23$ versus $0.10 \pm 0.40$, $P = 0.024$, $0.06 \pm 0.30$ versus $0.30 \pm 0.48$, $P = 0.037$, and $0.00 \pm 0.02$ versus $0.02 \pm 0.04$, $P = 0.040$, respectively). The mean annual changes in the serum total bilirubin and the serum albumin in the BCAA group were better preserved than those in the control group ($-0.07 \pm 0.20$ versus $0.12 \pm 0.18$ mg/dL, $P < 0.001$, and $0.07 \pm 0.13$ versus $-0.02 \pm 0.19$ g/dL, $P = 0.005$, respectively); other laboratory variables were not significant. The incidence of overall major cirrhotic complications was lower in the BCAA group than in the control group [14.8% (4 of 27 patients) versus 30.4% (7 of 23 patients) at 3 years, $P = 0.043$]; only ascites was significant individually. In conclusion, early interventional oral BCAAs might prolong the liver transplant waiting period by preserving hepatic reserve in cirrhosis. *Liver Transpl 15:790-797, 2009.* © 2009 AASLD.

The 5-year survival rate after liver transplantation has recently been improved to 70% to 75%.[1] Liver transplantation is the only means available for the radical treatment of severe liver cirrhosis. All patients with liver cirrhosis have the potential to become liver recipients in the near future. Furthermore, the 5-year survival rate

following liver transplantation has been improved to 65% to 80% even in patients whose condition is complicated by hepatocellular carcinoma (HCC).[2] Liver transplantation thus appears to be the best means of dealing with HCC satisfying the Milan criteria.[3] However, because of the shortage of liver donors with respect to the growing demand for liver transplantation, the mortality rate of patients during the liver transplant waiting period has been rising markedly (currently about 20%-30%) across the world.[4] The posttransplant survival rate decreases as the pretransplant waiting period lengthens, with a reduction of hepatic reserve.[5] Hepatologists thus need to suppress the reduction of hepatic reserve as long as possible in patients with liver cirrhosis awaiting liver transplantation.

Pre–liver transplant nutritional status is one of the major factors associated with outcome after transplantation. Protein-energy malnutrition associated with liver cirrhosis is already observed in the compensated phase.[6] Controversy continues because of the limited clinical evidence available to clarify the optimal time for initiation of oral branched-chain amino acid (BCAA) supplementation for cirrhosis,[7,8] although anecdotal findings suggest that nutritional intervention should begin in an early stage of disease.[9] It is clear that liver transplantation has been carried out with inadequate nutritional control. We believe that improving nutritional status helps to delay a fatal reduction of hepatic reserve in patients with early liver cirrhosis registered in waiting lists for liver transplantation. We planned a pilot study to examine whether oral BCAA treatment, begun in the early stages of liver cirrhosis, can preserve hepatic reserve until a liver donor becomes available.

In the present study, we used the Model for End-Stage Liver Disease (MELD) and Child-Turcotte-Pugh (CTP) scores, the asialoscintigraphic clearance index (CI), and major cirrhotic complications as markers for pretransplant status.[10-12] The natural course of hepatic reserve is transient in cirrhosis, and the disease rapidly becomes worse with Child class B cirrhosis.[13] The present study was designed to use these markers to evaluate the efficacy of oral BCAAs for patients with uncomplicated Child class A cirrhosis who may be registered in transplantation waiting lists.

## PATIENTS AND METHODS

The study was performed at the Department of Hepatology of Osaka City University Hospital in an open-label, randomized, controlled parallel group design. The inclusion criteria were as follows: (1) an age of 20 to 75 years; (2) Child class A cirrhosis; and (3) hepatitis C virus, hepatitis B virus, or alcohol-related cirrhosis. Patients with other types of cirrhosis were excluded because of their extremely low prevalence in Japan. Patients were also excluded if they (1) had received an albumin infusion at least once per week for 1 month or longer, (2) had a history of oral BCAA supplementation/dietary protein restriction for 6 months or longer, (3) had major complications of cirrhosis such as HCC, ascites, esophagogastric varices, or hepatic encephalopa-

thy, or (4) had other nonhepatic major diseases. The study protocol agreed with the Helsinki Declaration and was approved by the Ethics Committee of Osaka City University Medical School. Each patient provided written informed consent.

### Study Design

Eligible patients were randomly assigned to receive oral BCAAs or no BCAAs by the study investigators according to a computer-generated list. The date of study entry was defined as the date of initial asialoscintigraphy. Investigators were informed of treatment assignments on the same day, and BCAA therapy was started within 1 week.

The primary endpoint of the study was the incidence of cirrhosis-related complications after enrollment. Such complications included the first confirmation of HCC, ascites, esophagogastric varices, and hepatic encephalopathy. Eligible patients had to undergo the assigned treatment for at least 1 year. Secondary endpoints were defined as the receipt of any of the following treatments, which can influence outcome markers, including the MELD score, CTP score, and asialoscintigraphic CI: (1) an albumin infusion for ascites; (2) endoscopic sclerotherapy/ligation for varices; (3) open surgery, interventional radiological procedures, or percutaneous local ablation for HCC; and (4) parenteral BCAAs for hepatic encephalopathy.

### Baseline Assessments

All patients underwent a pretrial evaluation that included an evaluation of hepatic reserve as follows: laboratory studies and assessment of physical findings required to calculate the MELD score and CTP score, abdominal ultrasonography or dynamic computed tomography to assess the extent of ascites or the existence of HCC, endoscopy to evaluate esophagogastric varices, and scintigraphy with technetium-99m diethylenetriaminepentaacetic acid galactosyl human serum albumin (99mTc-GSA; Asialoscinti Injectable, Nihon Medi-Physics., Inc., Tokyo, Japan). For scintigraphy, computer acquisition of data with a gamma camera (Vertex-Plus, ADAC Laboratories Inc., Silicon Valley, CA) was started just before the injection of 185 MBq of 99mTc-GSA. After the acquisition of 20-minute summed digital images (128 × 128 pixels), the asialoscintigraphic CI was calculated by the division of the radioactivity in the region of interest in the heart 15 minutes after injection by that in the heart region of interest 3 minutes after injection.[14]

### Contents of the Daily Nutritional Treatment

Patients in the BCAA group received a cirrhotic diet supplemented with a Japanese nutritional preparation (LIVACT, Ajinomoto Co., Inc., Tokyo, Japan; 4.15 g of BCAA granules per sachet containing 952 mg of L-isoleucine, 1904 mg of L-leucine, and 1144 mg of L-valine) 3 times daily. The daily cirrhotic diet consisted of a total caloric intake of 25 to 35 kcal/kg and a protein intake of
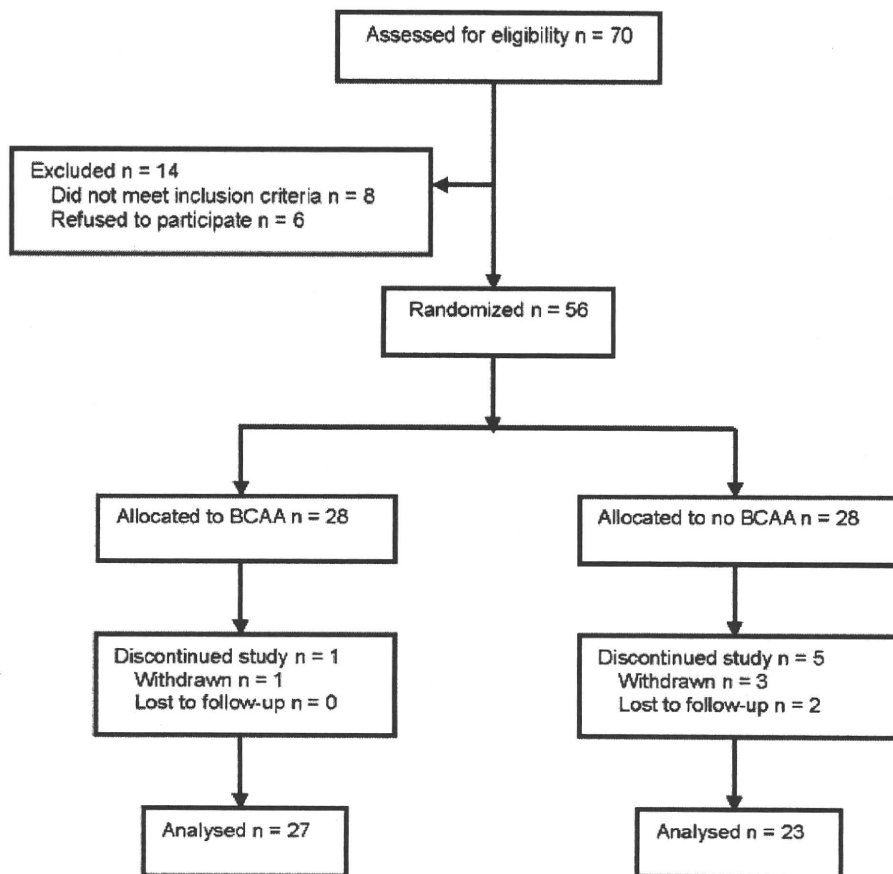
**Figure 1. Flow chart of the participants in the study. Abbreviation: BCAA, branched-chain amino acid.**

1.0 to 1.2 g/kg (including 12.45 g/day BCAAs in the BCAA group), and it was adjusted to the standard body weight [height (m)$^2$ × 22] according to the guidelines of the European Society of Parenteral and Enteral Nutrition.[15] All patients received the same dietary instructions throughout the study. Patients in the control group received the same dietary instructions without BCAAs. All patients completed questionnaires on their diet at 6-month intervals after enrollment. Patients with excessive or deficient dietary intakes of energy or protein were given written dietary instructions prepared by the dietitians at our hospital.

### Follow-Up

Patients underwent the following follow-up examinations: laboratory studies, including serum total bilirubin, albumin, and creatinine levels, prothrombin activity, and other clinical findings at a mean interval of 0.3 years; abdominal ultrasonography or dynamic computed tomography at a mean interval of 0.4 years; endoscopy at a mean interval of 0.5 years; and asialoscintigraphy at a mean interval of 1.0 year. Needle biopsy specimens of the liver were obtained and examined histologically as needed in patients with suspected liver tumors.

### Statistical Analysis

Results were analyzed with SAS 9.1 statistical software (SAS Institute, Inc., Cary, NC). Continuous variables were expressed as mean ± standard deviation and were compared with the Mann-Whitney $U$ test. Categorical variables were compared with Fisher's exact test or the chi-square test. Annual changes in the MELD score, CTP score, asialoscintigraphic CI, and laboratory results related to hepatic function were calculated by the division of the difference between the results of the first examination and those of the last examination by the interval (ie, duration of follow-up in years) between these 2 examinations. The cumulative rates of complications were calculated and plotted with the Kaplan-Meier method and compared with the log-rank test. A 2-tailed $P$ value of <0.05 was considered to indicate statistical significance.

Given the magnitude of this sample size and the lack of definitive evidence establishing that early interventional oral BCAAs reduce risk,[16] we decided to perform a pilot study in 70 patients.

### RESULTS

Of 70 outpatients with liver cirrhosis, 14 were ineligible, and 56 (27 men and 29 women; mean age, 62.52 years)

| TABLE 1. Pretrial Characteristics of the Patients | | | |
|---|---|---|---|
| | BCAA Group (n = 27) | Control Group (n = 23) | P |
| Age (year)* | 62.70 ± 10.08 | 62.30 ± 7.30 | 0.537 |
| Sex ratio (male:female) | 13:14 | 12:11 | >0.999† |
| Etiology (HCV:HBV:alcohol) | 22:3:2 | 19:2:2 | 0.951‡ |
| Total bilirubin (mg/dL)* | 0.97 ± 0.51 | 0.96 ± 0.34 | 0.550 |
| Albumin (g/dL)* | 3.70 ± 0.38 | 3.81 ± 0.32 | 0.230 |
| Platelets (×10⁴/μL)* | 11.52 ± 4.85 | 11.10 ± 5.01 | 0.616 |
| Alanine aminotransferase (IU/L)* | 70.92 ± 17.96 | 64.17 ± 13.51 | 0.095 |
| Prothrombin activity (%)* | 81.52 ± 10.55 | 84.39 ± 13.39 | 0.802 |
| Creatinine (mg/dL)* | 0.68 ± 0.16 | 0.63 ± 0.13 | 0.230 |
| Cholinesterase (IU/L)* | 349.07 ± 151.57 | 322.83 ± 116.92 | 0.616 |
| Cholesterol (mg/dL)* | 153.19 ± 25.64 | 156.05 ± 42.12 | 0.913 |
| BCAA/tyrosine ratio* | 4.11 ± 0.20 | 3.98 ± 0.91 | 0.712 |
| α-Fetoprotein (ng/mL)* | 10.93 ± 5.12 | 14.1 ± 2.43 | 0.805 |
| Body mass index (kg/m²)* | 22.55 ± 2.10 | 24.01 ± 0.29 | 0.707 |
| MELD score* | 6.88 ± 0.98 | 7.01 ± 0.72 | 0.187 |
| CTP score* | 5.41 ± 0.50 | 5.22 ± 0.42 | 0.253 |
| Asialoscintigraphic clearance index* | 0.61 ± 0.09 | 0.60 ± 0.11 | 0.685 |
| Hepatocellular carcinoma (absence:presence) | 27:0 | 23:0 | >0.999† |
| Ascites (absence:presence) | 27:0 | 23:0 | >0.999† |
| Esophagogastric varices (absence:presence) | 27:0 | 23:0 | >0.999† |
| Hepatic encephalopathy (absence:presence) | 27:0 | 23:0 | >0.999† |

NOTE: Unless otherwise indicated, comparisons were made by the Mann-Whitney U test.
Abbreviations: BCAA, branched-chain amino acid; CTP, Child-Turcotte-Pugh; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, Model for End-Stage Liver Disease.
*Data are shown as mean ± standard deviation.
†Fisher's exact test.
‡Chi-square test.

were randomly assigned to receive oral BCAAs (n = 28, BCAA group) or no BCAAs (n = 28, control group; Fig. 1). The diagnosis of liver cirrhosis was made clinically by a team of 3 or more hepatologists. Because liver biopsy is invasive, it is difficult to perform this test in all patients. Of the 56 patients, 41 (22 from the BCAA group and 19 from the control group) underwent liver biopsy. In the remaining 15 patients, the diagnosis was made with the findings of diagnostic imaging (eg, abdominal ultrasonography) and hematological and biochemical tests taken into account.[17] Six patients were lost to follow-up. The remaining 50 patients were included in the final analysis. The mean duration of therapy was 3.2 years (range, 1.0-6.3 years). The BCAA group and control group were similar with respect to the virus type, total bilirubin, albumin, prothrombin activity, MELD score, CTP score, asialoscintigraphic CI, and other variables (Table 1).
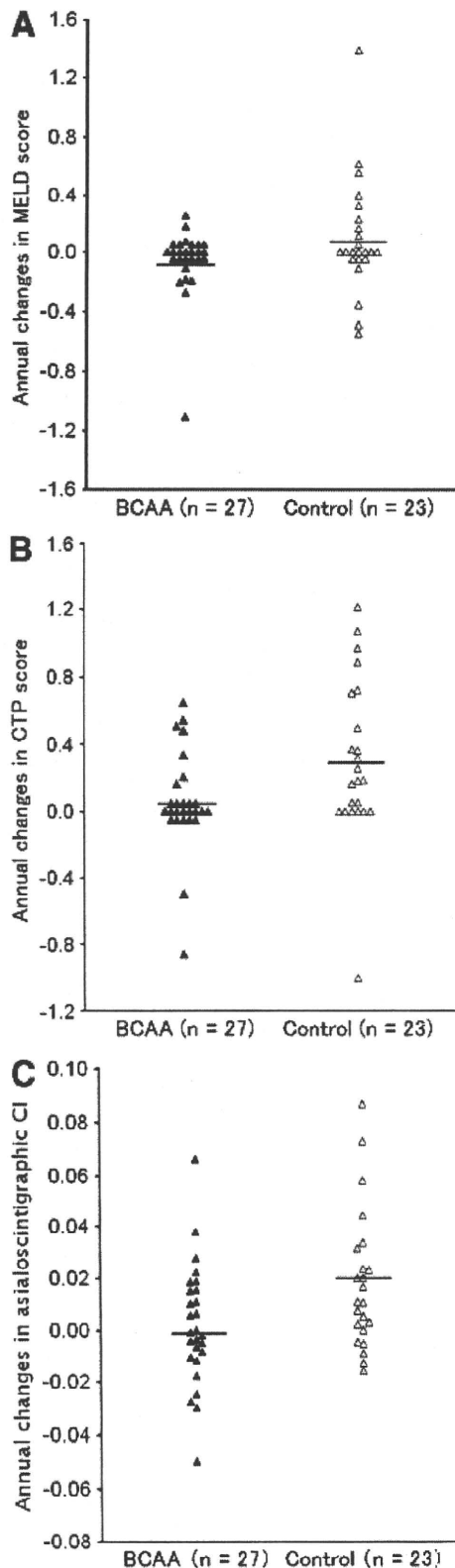
## Compliance and Adverse Effects of BCAA Treatment

Of 28 patients in the BCAA group, 27 continued to take BCAA granules (12.45 g/day) for at least 1 year [mean duration, 3.3 years (range, 1.3-6.2 years)]. No adverse reactions to the BCAA treatment were found in any patient.

## Outcome Measures Related to Hepatic Function

The mean annual change in the MELD score was significantly smaller in the BCAA group than in the control group ($-0.06 ± 0.23$ versus $0.10 ± 0.40$, $P = 0.024$; Fig. 2A). The mean annual change in the CTP score was significantly smaller in the BCAA group than in the control group ($0.06 ± 0.30$ versus $0.30 ± 0.48$, $P = 0.037$; Fig. 2B). The mean annual change in the asialoscintigraphic CI was also significantly smaller in the BCAA group than in the control group ($0.00 ± 0.02$ versus $0.02 ± 0.04$, $P = 0.040$; Fig. 2C). The mean annual change in the total bilirubin level in the BCAA group was significantly smaller than that in the control group ($-0.07 ± 0.20$ versus $0.12 ± 0.18$ mg/dL, $P < 0.001$). The mean annual change in the serum albumin level was significantly greater in the BCAA group than in the control group ($0.07 ± 0.13$ versus $-0.02 ± 0.19$ g/dL, $P = 0.005$; Table 2).

## Major Cirrhotic Complications

The cumulative incidence of overall major cirrhotic complications (HCC, ascites, esophagogastric varices, and hepatic encephalopathy) is shown in Fig. 3. The incidence was 14.8% (4 of 27 patients) in the BCAA group and 30.4% (7 of 23 patients) in the control group

**Figure 2. Annual changes in hepatic reserve markers in the 2 groups. Horizontal bars show means. (A) P = 0.024, (B) P = 0.037, and (C) P = 0.040 (Mann-Whitney U test). Abbreviations: BCAA, branched-chain amino acid; CTP, Child-Turcotte-Pugh; CI, clearance index; MELD, Model for End-Stage Liver Diseases.**

at 3 years and 18.5% (5 of 27 patients) in the BCAA group and 47.8% (11 of 23 patients) in the control group at 5 years. The cumulative incidence of complications was significantly lower in the BCAA group than in the control group (P = 0.043). Among specific complications, the incidence of ascites was significantly lower in the BCAA group (P = 0.037), whereas the incidence of varices was slightly but not significantly lower in the BCAA group (P = 0.092). The incidence of HCC did not significantly differ between the groups (P = 0.364). No hepatic encephalopathy developed in either group.

## DISCUSSION

For patients awaiting liver transplantation, it is desirable that the hepatic reserve be preserved even when the waiting period is prolonged. As one measure to achieve this, the present study evaluated the usefulness of pretransplant nutritional therapy. Long-term BCAA therapy, begun in the early stages of liver cirrhosis, as in the present study, involves 2 possible issues. One pertains to facilitation of abnormal glucose tolerance by BCAA therapy, whereas the other pertains to stimulation of HCC growth, also by BCAA therapy. It has been reported that perioperative patients exhibiting malnutrition or abnormal glucose tolerance are at elevated risk for problems such as posttransplant wound infection and anastomotic failure of the operative wound.[18,19] However, BCAA therapy has been reported to be useful not only in correcting malnutrition but also in alleviating abnormal glucose tolerance.[20,21] Furthermore, BCAAs have been shown to exhibit pharmacological activity suppressing the growth of HCC[22] and have been clinically reported to suppress complications of transarterial embolization and the onset of HCC in obese males with liver cirrhosis as well as hepatitis C virus–positive patients with liver cirrhosis.[23-25] These previous reports suggest that long-term BCAA treatment of liver cirrhosis patients does not involve a high risk of significant adverse reactions such as exacerbation of abnormal glucose tolerance and stimulation of liver carcinogenesis.

In previous studies, both pretransplant MELD and CTP scores strongly correlated with pretransplant waiting-list mortality.[26] These scores also positively correlated with posttransplant hepatic decompensation and mortality.[27,28] In the present study, oral BCAA supplementation was useful in maintaining MELD and CTP scores for more than 3 years on average. Our findings suggest that initiation of oral BCAAs in patients with a MELD score of 6 to 9 or a CTP score of 5 to 6 may contribute to solving current problems related to trans-

TABLE 2. Annual Changes in Laboratory Data Related to Hepatic Function

|  | BCAA Group (n = 27) | Control Group (n = 23) | P* |
|---|---|---|---|
| Total bilirubin (mg/dL) | −0.07 ± 0.20 | 0.12 ± 0.18 | <0.001 |
| Albumin (g/dL) | 0.07 ± 0.13 | −0.02 ± 0.19 | 0.005 |
| Platelets (×10⁴/mL) | −0.09 ± 0.85 | −0.32 ± 0.59 | 0.140 |
| Alanine aminotransferase (IU/L) | 1.38 ± 3.32 | 1.81 ± 2.25 | 0.817 |
| Prothrombin activity (%) | −2.20 ± 1.89 | −3.76 ± 7.36 | 0.705 |
| Cholinesterase (IU/L) | −10.69 ± 27.65 | −13.10 ± 42.55 | 0.378 |
| Cholesterol (mg/dL) | 0.74 ± 8.89 | −0.87 ± 11.98 | 0.273 |
| BCAA/tyrosine ratio | 0.10 ± 0.34 | 0.01 ± 0.25 | 0.399 |

NOTE: Data are shown as mean ± standard deviation.
Abbreviation: BCAA, branched-chain amino acid.
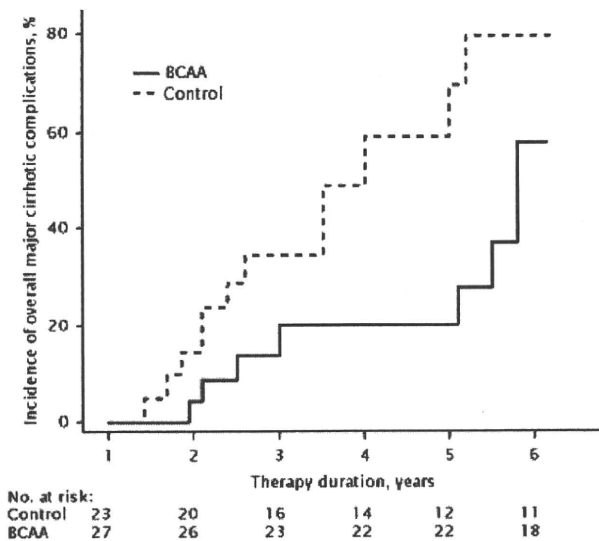*Mann-Whitney U test.



Figure 3. **Cumulative incidences of overall major cirrhotic complications diagnosed in patients treated with BCAAs. P = 0.043 (log-rank test). Abbreviation: BCAA, branched-chain amino acid.**

plantation, such as the donor shortage and availability of only small liver grafts (for patients on waiting lists for living-donor liver transplantation)[29] and also to improving posttransplant mortality by preserving the hepatic reserve of scheduled recipients.

The preservation of hepatocyte function in the BCAA group, as indicated by the inhibition of increases in the asialoscintigraphic CI and serum total bilirubin level, might be attributable to the fact that BCAAs can stimulate the regeneration of an injured liver. Asialoscintigraphy is a useful technique for the quantitative estimation of hepatic reserve and more accurately reflects histological hepatic damage than the 15-minute retention rate of indocyanine green in preoperative cirrhosis.[30]

Our study showed that the incidence of major cirrhotic complications accompanying disease progression was significantly lower in patients who received oral BCAAs. The significant suppression of ascites in

the BCAA group may have been related to the inhibition of a decline in the serum level of albumin. Patients with chronic hepatic failure with a low Fischer's ratio due to a decrease in serum BCAAs have been reported to exhibit a concomitant reduction of serum albumin concentrations, which can be improved by oral BCAA administration. The synthesis and secretion of albumin in primary hepatocytes have been reported to be increased when Fischer's ratio is maintained at an appropriate level.[31] BCAAs not only are structural constituents of proteins but also have pharmacological properties. BCAAs have been found to mimic the effects of a complete mixture of amino acids in stimulating protein synthesis both in vivo and in vitro. BCAAs, especially L-leucine, promote albumin synthesis in rat primary hepatocytes through a cell-signaling pathway involving mammalian target of rapamycin (mTOR), a serine/threonine protein kinase and a cellular nutrition sensor for the initiation of protein translation.[32] Although the mTOR signaling pathway is activated by insulin in addition to L-leucine, L-leucine appears to regulate protein synthesis in various tissues by mechanisms independent of insulin. Leucine analogues that are not insulin secretagogues can reproduce the effects of L-leucine.[33] However, it has been reported that inhibition of mTOR by rapamycin is only partially successful in blocking some of the effects of L-leucine, and this suggests that increased albumin synthesis promoted by L-leucine is mediated by at least 2 signaling pathways, one rapamycin-sensitive and the other rapamycin-insensitive.[34] The aforementioned mechanisms may have contributed, at least in part, to the maintenance of serum albumin levels. However, ascites can be due to various other effects on hepatocyte function apart from hypoalbuminemia.[35] Previous studies have reported that L-leucine stimulates hepatocyte growth by promoting the secretion of hepatocyte growth factor (HGF), which regulates cell growth, cell motility, and morphogenesis.[36,37] Administration of HGF has been shown to increase DNA synthesis in the liver and to reduce hepatic injury. L-Leucine has also recently been found to stimulate HGF via hepatic stellate cells through the mTOR pathway.[38]

One of the limitations of the present study is a lack of

placebo. It is ideal to conduct a placebo-controlled, double-blind trial in an assessment of the BCAA granule preparation. In the present study, however, no placebo was given to the control group because the special taste of LIVACT made it impossible to find a placebo with a similar taste that could truly ensure patient blinding. For this reason, the subjects were allocated at random to the BCAA group and diet group, without the inclusion of placebo. Another limitation of this study is that no assessment was performed of protein synthesis, catabolism, balance, and so forth, other than measurements of the serum albumin level. Improvement of nutritional status and recovery of albumin synthesis are pharmacological effects expected with BCAA therapy in patients with liver cirrhosis, as many reports have indicated.[7,16,32] The present study was aimed at demonstrating that BCAAs are useful not only in improving albumin metabolism and nutritional status but also in suppressing the elevation of the serum total bilirubin level and deterioration of the function of residual liver cells, as represented by overall indicators of hepatic failure level such as the MELD score, CTP score, and asialoscintigraphic index.

We believe that our study is the first to provide compelling evidence that early interventional oral BCAAs have favorable effects, when given for a mean period of more than 3 years, on prognostic scores, the results of functional imaging, and complications. A larger multicenter trial is warranted to confirm these findings. We anticipate that oral BCAAs beginning in Child class A cirrhosis will provide additional time and enable surgeons to ensure successful outcomes of liver transplantation.

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## Table 2. Observed vs. expected rates of birth for every season in 340 patients with Crohn's disease

|  | Observed number | Expected number |
|---|---|---|
| Season |  |  |
| Spring | 87 | 85.7 |
| Summer | 99 | 85.7 |
| Autumn | 70 | 84.8 |
| Winter | 84 | 83.8 |
| $\chi^2$(11 d.f.) | 4.66 |  |
| P value | 0.198 |  |

ically predisposed individuals. Exposure to external seasonal factors during the maturation of the immune system is suspected to be an inducing factor for IBD. Perinatal exposure to infections has been proposed as such an environmental factor. Many childhood infections show seasonal variation. Other environmental factors, which are potential trigger factors for IBD, including the use of cigarettes, non-steroidal anti-inflammatory drugs, antibiotics, and contraceptives, have shown seasonal variation since seasonal changes in immune response were first reported (10,11).

In conclusion, in this study, the first performed in Italy, a significant association between the occurrence of CD and birth in the month of July was found. On the other hand, no different seasonal birth patterns were observed. We think that the numerous potential links between the clustering of birth dates and seasonal variations of both immune function and environmental factors should be evaluated by large population-based studies.

### CONFLICT OF INTEREST
The authors declared no conflict of interest.

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# Development of Pouchitis With Combination Therapy With Peg-Interferon α-2b and Ribavirin for Chronic Hepatitis C in a Patient With Ulcerative Colitis Who Underwent Pouch Surgery

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**To the Editor:** A 41-year-old woman was diagnosed with ulcerative colitis (UC), total colitis type, in 2002. She was also infected with hepatitis C virus, genotype 1b, viral load 827 KIU/ml. In April 2004, she had a recurrence of UC that proved refractory to medication, and underwent colectomy with temporary ileostomy in May 2004. Ileal pouch anal canal anastomosis was performed in February 2005. In August 2005, endoscopic examination revealed only some aphthous lesions in the ileal pouch. At that time, she had four defecations per day, but was otherwise asymptomatic. The modified Pouchitis Disease Activity Index (PDAI) score (1) was two points. She had a good clinical course after surgery. Combination therapy for chronic hepatitis C with Peg-interferon (Peg-IFN) α-2b (1.5 μg/kg per week) and ribavirin (600 mg/day) for 24 weeks was started in June 2006.

The frequency of watery diarrhea had gradually increased over 3 months after the initiation of Peg-IFN and ribavirin therapy. However, no abdominal pain, fever, or bloody diarrhea was noted. Bloody diarrhea appeared 6 weeks later. After completion of combination therapy in mid-November 2006, endoscopy revealed erosions, friable mucosa, and purulent mucus in the pouch (**Figure 1a**). The modified PDAI score at that time was 9 points, confirming the diagnosis of pouchitis. Treatment with metronidazole (500 mg/day) was begun, and her symptoms improved rapidly. Endoscopy after treatment with metronidazole revealed only several tiny aphthae in the pouch (**Figure 1b**).

Antiviral treatment appears to have induced pouchitis in the present case, as the patient had been doing well with no pouchitis until antiviral treatment was initiated. Several case reports of development and exacerbation of UC after IFN-α treatment (2,3) also suggest that antiviral treatment can cause pouchitis.

The etiology of pouchitis remains unknown. We previously detected specific