

1 **IMPORTANCE OF BRANCHED-CHAIN AMINO ACIDS IN PATIENTS WITH**  
2 **LIVER CIRRHOSIS AND ADVANCED HEPATOCELLULAR CARCINOMA**  
3 **RECEIVING HEPATIC ARTERIAL INFUSION CHEMOTHERAPY**

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19 **Running title:**

20 BCAA for HCC patients receiving HAIC.

21 **Key words:**

22 BCAA, HCC, liver cirrhosis, hepatic arterial infusion chemotherapy

23

1 **ABSTRACT**

2 **PURPOSE:** The aim of this retrospective cohort study was clarify the effect of a  
3 branched-chain amino acids (BCAA) on the liver function and the prognosis of  
4 Child-Pugh class (C-P) A and B liver cirrhosis (LC) patients with advanced  
5 hepatocellular carcinoma (aHCC) undergoing hepatic arterial infusion chemotherapy  
6 (HAIC).

7 **METHODS:** Ninety-two adult Japanese patients with LC and aHCC underwent HAIC.  
8 They were in C-P A or B, and they showed multiple partial responses or stable disease.  
9 We excluded 11 patients classified as C-P C and 47 patients who showed no response.  
10 The patients were divided into an HAIC group receiving HAIC alone (n = 43) and a  
11 BCAA group treated with HAIC plus BCAA (n = 49). HAIC was delivered via the  
12 proper hepatic artery. The BCAA group also received oral administration of BCAA.

13 **RESULTS:** In the BCAA group, serum albumin increased significantly after HAIC,  
14 while there were no significant changes of serum total bilirubin, serum  
15 aminotransferases, prothrombin time, ascites, and hepatic encephalopathy. The C-P  
16 score decreased significantly after HAIC compared with before HAIC in C-P B patients,  
17 although there was no significant change in C-P A patients. Survival of the BCAA group  
18 was significantly longer than that of the HAIC group, with the median survival time  
19 being 426 versus 272 days for C-P B patients, although there was no significant  
20 difference for C-P A patients.

21 **CONCLUSIONS:** BCAA might improve the survival and C-P score by increasing  
22 serum albumin in C-P B patients with aHCC receiving HAIC.

23

## 1 I. INTRODUCTION

2 Sorafenib is an oral multikinase inhibitor that shows strong in vitro activity by  
3 targeting the Raf/mitogen-activated protein kinase/extracellular signal-related kinase  
4 signaling pathway, and it is used to treat advanced hepatocellular carcinoma (aHCC). In  
5 the Sorafenib HCC Assessment Randomised Protocol (SHARP) study, 602 patients  
6 (mainly Europeans) were randomized to receive sorafenib therapy or placebo therapy.  
7 They had an Eastern Cooperative Oncology Group performance status of 0 - 2 and were  
8 all in Child-Pugh (C-P) class A. The sorafenib group achieved a median overall survival  
9 time of 10.7 months versus 7.9 months for the placebo group [1]. Sorafenib has also  
10 demonstrated significant clinical activity against HCC in phase II and phase III studies  
11 [2, 3], with sorafenib-treated patients having a longer median survival time and longer  
12 time to radiologic progression compared with placebo-treated patients. However, Pinter  
13 et al. reported that complications of sorafenib therapy may occur more frequently  
14 among patients in C-P classes B or C [4]. In the most recent Japan Society of  
15 Hepatology treatment algorithm for HCC (2010 update), transcatheter arterial  
16 chemoembolization (TACE) (for HCC with Vp1 or Vp2) and hepatic arterial infusion  
17 chemotherapy (HAIC) are recommended for liver cirrhosis (LC) patients (C-P classes A  
18 and B) with four or more tumors, thrombus involving major portal vein branches, or  
19 portal trunk thrombus, while sorafenib is only recommended for patients in C-P class A  
20 [5]. Therefore, HAIC is still one of the few remaining options for treating aHCC in  
21 patients with LC who are in C-P class A or B, as well as LC patients with thrombus  
22 involving major branches of the portal vein or the portal trunk. Improvement of  
23 implantable drug delivery systems has made it possible to perform repeated hepatic

1 arterial infusion of anticancer agents in patients with aHCC, and HAIC has been  
2 demonstrated to improve both survival and the quality of life [6]. HAIC with  
3 5-fluorouracil (5-FU) and cisplatin (CDDP) using an infuser pump and an implanted  
4 reservoir has been related to prolong the survival of aHCC patients [6-8]. We have also  
5 reported that combined intra-arterial therapy with low-dose 5-FU, CDDP, and  
6 leucovorin (LV) prolongs the survival of aHCC patients [9]. Moreover, we have shown  
7 that continuous intra-arterial infusion for 24 hr is more effective than infusion for 6 hr in  
8 patients with HCV-related LC and aHCC, although 24-hr infusion also causes stronger  
9 hematologic toxicity [10]. Even when dietary intake is adequate, deficiency of  
10 branched-chain amino acids (BCAA) can occur due to enhanced uptake and  
11 consumption of these amino acids by skeletal muscle for ammonia metabolism and  
12 energy generation [11, 12]. Supplementation of BCAA has been reported to improve the  
13 nutritional status and prevent hepatic complications in patients with decompensated  
14 cirrhosis [13-15]. In addition, Hayashi et al. reported that BCAA supplementation was  
15 associated with a lower incidence of HCC in cirrhosis patients and appeared to prevent  
16 liver-related events in C-P class A patients [16]. Furthermore, Harima et al. reported that  
17 a BCAA-enriched late evening snack improves energy metabolism and glucose  
18 tolerance in cirrhosis patients with advanced HCC undergoing HAIC [17]. Therefore,  
19 we investigated the effect of BCAA on liver function and the prognosis of LC patients  
20 (C-P classes A and B) with aHCC undergoing HAIC in the present retrospective cohort  
21 study.

22

## 1 II. METHODS

### 2 *Patients*

3 Review of the medical records identified 92 adult Japanese LC patients with LC  
4 and aHCC who were managed at Toho University Medical Center Omori Hospital  
5 between 2000 and 2011, and who were not eligible for surgical resection or for  
6 interventions such as transcatheter arterial embolization, percutaneous ethanol injection,  
7 microwave coagulation therapy, or radiofrequency ablation because they had multiple  
8 tumors in both lobes of the liver. All 92 patients received HAIC. These patients were all  
9 in C-P classes A or B, and they showed multiple partial responses or stable disease. We  
10 excluded 11 patients were classified as C-P class C and 47 patients (19 patients were  
11 classified as C-P class A and 28 patients were classified as C-P class B) who showed no  
12 response because of liver damage caused by tumor progression. The patients were  
13 divided into two groups, which were the HAIC group treated by HAIC alone (n = 43)  
14 and the BCAA group treated by HAIC plus BCAA (n = 49). HAIC was delivered via the  
15 proper hepatic artery at 5-day intervals for 4 weeks. The BCAA group also received oral  
16 administration of BCAA (12 g/day of Livact Granules; Ajinomoto Co., Inc., Tokyo,  
17 Japan or 3 packets/day of Aminoreban EN powder mix; Otsuka Co., Inc., Tokyo, Japan).  
18 Livact Granules contain 952 mg of L-isoleucine, 1904 mg of L-leucine and 1144 mg of  
19 L-valine per packet, while one packet of Aminoreban EN contains as follows 1922,  
20 2037, and 1602 mg, respectively. Patients were administered 1 packet of Livact  
21 Granules or Aminoreban EN three times a day after meals from the first therapy of  
22 HAIC. Blood samples were collected from the patients in the morning before and after  
23 chemotherapy.

1

2 **Drug delivery system**

3 In all patients, an intra-arterial catheter was inserted via the femoral artery and  
4 was attached to a subcutaneously implanted reservoir [18]. In principle, the  
5 gastroduodenal artery and the right gastric artery were occluded with steel coils to  
6 prevent gastroduodenal injury by the anticancer agents. Informed consent to these  
7 procedures was obtained from all of the patients.

8

9 **Treatment**

10 All patients were treated by 24-hrs HAIC (LV at 12 mg / hr, CDDP at 10 mg / hr,  
11 and 5-FU at 250 mg / m<sup>2</sup> / 22 hrs) via the proper hepatic artery at 5-day intervals for 4  
12 weeks using a catheter connected to a subcutaneously implanted drug reservoir. The  
13 doses of these chemotherapy agents were set according to a previous report [19], and  
14 treatment was continued to enforce as much as possible every 3 or 4 months at the same  
15 intensity.

16

17 **Evaluation of Efficacy**

18 On CT scans obtained after 4 weeks of treatment, the 2 longest perpendicular  
19 diameters of the largest tumor were measured and the product was calculated. A  
20 complete response (CR) was defined as disappearance of this tumor (decrease of the  
21 product to 0), while a partial response (PR) was defined as reduction of the product by  
22 more than 50%. An increase of more than 25% was defined as progressive disease (PD),  
23 and smaller changes between PR and PD were defined as stable disease (SD).

1

2 **Statistical Analysis**

3 Statistical analysis was performed by using the Statistical Package for the Social  
4 Sciences (SPSS version 11.0; SPSS, Chicago, IL, USA). Results are expressed as the  
5 mean  $\pm$  standard deviation (SD). The  $\chi^2$  test was employed to assess differences of  
6 patient distribution. Normally distributed variables were compared between the two  
7 groups with Student's test and other variables were compared by the Mann-Whitney U  
8 test, while Wilcoxon's signed rank sum test was used to compare patient characteristics  
9 within the same group. Survival was evaluated by the Kaplan-Meier method, and the  
10 significance of differences in survival was determined by the log-rank test. The Cox  
11 proportional hazards model was employed for multivariate analyses of factors  
12 associated with survival. A probability of less than 0.05 was considered to indicate  
13 statistical significance in all analyses.

14

15 **III. RESULTS**

16 The HAIC group (n = 43) included 34 men and 9 women with LC who were  
17 treated for aHCC by HAIC at our hospital between 2000 and 2011, while the BCAA  
18 group (n = 49) comprised 43 men and 6 women with LC who were treated for aHCC by  
19 HAIC during the same period and also received BCAA. In the HAIC group, 30 patients  
20 were in C-P class A and 13 patients were in class B, while the respective numbers were  
21 23 and 26 in the BCAA group. There was a significant difference in the severity of liver  
22 damage between the two groups ( $p = 0.028$ ). In the HAIC group, 14 patients had stage  
23 III disease, 21 patients had stage IVA disease, and 8 patients had stage IVB disease,

1 while the respective numbers were 8, 36, and 5 in the BCAA group. There was a  
2 significant difference of tumor stage between the two groups ( $p = 0.039$ ). In the HAIC  
3 group, 22 patients achieved PR and 21 patients showed SD, while 15 patients showed  
4 PR and 34 patients had SD in the BCAA group. There was a significant difference of the  
5 tumor response between the two groups ( $p = 0.046$ ). Moreover, there was a significant  
6 difference of the serum albumin level between the HAIC and BCAA groups ( $p = 0.006$ )  
7 (Table 1). We calculated propensity scores to identify factors with an influence on the  
8 survival of the subjects. After excluding serum albumin, the propensity score for  
9 treatment with or without BCAA showed  $< 0.001$  based on the Humster-Lemeshow test  
10 and the area under the curve (AUC) of the propensity score was 34.2338 (95%  
11 confidence interval [CI], 7.0966-175.9901). When serum albumin was included, the  
12 propensity score for BCAA still had a significant influence, with  $p < 0.0002$  and an  
13 AUC of 17.2676 (95% confidence interval [CI], 3.8766-81.5265) (Table 2). These  
14 findings indicated that treatment with BCAA might improve the survival of LC patients  
15 with aHCC undergoing HAIC. Therefore, we separately investigated patients in C-P  
16 classes A and B to more clearly define the influence of BCAA on survival after HAIC  
17 for aHCC.

18

### 19 *Analysis of patients in Child-Pugh class A*

20 Table 3 shows the characteristics of the 53 LC patients with advanced HCC classified as  
21 C-P class A. The C-P class A patients of the HAIC group and the BCAA group showed  
22 no significant differences of gender, age, etiology of cirrhosis, stage, response,  $\text{NH}_3$ ,  
23 total bilirubin (T-Bil), direct bilirubin (D-Bil), alanine aminotransferase (ALT), total



1 cholesterol, white blood cell count, platelet count, prothrombin time (PT), creatinine  
2 (Cr), alfa-fetoprotein (AFP), AFP-L3, and des-gamma carboxyprothrombin (DCP).  
3 Serum albumin was significantly higher in the HAIC group than in the BCAA group ( $p$   
4 = 0.009).

5

6 **Multivariate analysis of factors associated with the survival of patients in Child-Pugh**  
7 **class A**

8 Univariate analysis of factors associated with survival revealed a significant  
9 influence of  $\text{NH}_3$  (hazard ratio [HR], 1.0184,  $p = 0.008$ ), AFP (HR, 1.0000,  $p = 0.019$ ),  
10 and AFP-L3 (HR, 1.0215,  $p = 0.007$ ). However, there was no significant difference in  
11 relation to BCAA supplementation (HR, 1.3325,  $p = 0.374$ ) (Table 4). On multivariate  
12 analysis with Cox proportional hazards model, BCAA supplementation was also not  
13 significantly associated with the survival time of C-P class A patients (HR, 1.4804; 95%  
14 CI, 0.7365-3.07580;  $p = 0.273$ ), while tumor stage (HR, 2.81397; 95% CI,  
15 1.29716-6.53700;  $p = 0.008$ ) and AFP (HR, 2.2080; 95% CI, 1.0056-5.3843;  $p = 0.048$ )  
16 had a significant influence on the survival time (Table 5).

17

18 **Analysis of patients in Child-Pugh class B**

19 Table 6 shows the characteristics of the 39 patients with advanced HCC in C-P  
20 class B. Patients in the HAIC group and the BCAA group showed no significant  
21 differences of gender, etiology of cirrhosis, stage, response,  $\text{NH}_3$ , T-Bil, D-Bil, albumin,  
22 ALT, total cholesterol, WBC count, PLT count, PT, AFP, AFP-L3, and DCP. The mean  
23 age was significantly higher in the HAIC group than in the BCAA group ( $p = 0.028$ ).

1

2 **Multivariate analysis of factors associated with the survival of patients in Child-Pugh**  
3 **class B**

4 Univariate analysis of factors associated with survival revealed a significant influence  
5 of NH<sub>3</sub> (hazard ratio [HR], 0.9742,  $p = 0.030$ ) and BCAA supplementation (HR, 2.3018,  
6  $p = 0.039$ ) (Table 7). Multivariate analysis with the Cox proportional hazards model  
7 confirmed that BCAA supplementation was associated with the survival time of C-P  
8 class B receiving HAIC for aHCC (HR, 2.7889; 95% CI, 1.2247-6.3213;  $p = 0.015$ ),  
9 while tumor stage (HR, 1.9823; 95% CI, 0.5536-12.7597;  $p = 0.328$ ) and AFP (HR,  
10 2.1735; 95% CI, 0.8776-6.3353;  $p = 0.097$ ) were not determinants of the survival time  
11 (Table 8).

12

13 **Serum alanine aminotransferase**

14 Figure 1 summarizes the changes of ALT in each group. In the HAIC group, there  
15 were no significant changes of serum ALT after chemotherapy among patients in either  
16 C-P class A (before:  $46.0 \pm 20$  IU/l, after:  $45.7 \pm 47$  IU/l) or class B (before:  $48.3 \pm 37$   
17 IU/l, after:  $45.0 \pm 38$  IU/l). In the BCAA group, there were also no significant changes  
18 of serum ALT after chemotherapy among patients in C-P class A (before:  $46.7 \pm 47$  IU/l,  
19 after:  $37.6 \pm 37$  IU/l) or class B (before:  $51.5 \pm 45$  IU/l, after:  $49.4 \pm 47$  IU/l).

20

21 **Serum albumin**

22 Figure 2 summarizes the changes of serum albumin in each group. In the HAIC  
23 group, there were no significant changes of serum albumin after chemotherapy among

1 the patients in C-P class A (before:  $3.58 \pm 0.4$ , after:  $3.66 \pm 0.4$  g/dl) or those in class B  
2 (before:  $2.81 \pm 0.6$ , after:  $2.99 \pm 0.6$  g/dl). In the BCAA group, however, serum albumin  
3 showed a significant increase after chemotherapy compared with before chemotherapy  
4 for patients in C-P class B (before:  $2.85 \pm 0.4$ , after:  $3.09 \pm 0.5$  g/dl,  $p = 0.009$ ), while  
5 there was no significant change of albumin after chemotherapy in C-P class A patients  
6 (before:  $3.29 \pm 0.3$ , after:  $3.51 \pm 0.4$  g/dl).

7

### 8 **Total bilirubin**

9 Figure 3 summarizes the changes of serum T-Bil. In the HAIC group, there was no  
10 significant change of serum T-Bil after chemotherapy among patients in C-P class A  
11 (before:  $0.79 \pm 0.4$  IU/l, after:  $0.76 \pm 0.3$  IU/l) or those in class B (before:  $1.15 \pm 0.5$   
12 IU/l, after:  $1.21 \pm 0.5$  IU/l). In the BCAA group, there was also no significant change of  
13 serum T-Bil after chemotherapy among patients in C-P class A (before:  $0.82 \pm 0.3$  IU/l,  
14 after:  $0.81 \pm 0.3$  IU/l) or patients in class B (before:  $1.16 \pm 0.4$  IU/l, after:  $1.28 \pm 0.4$   
15 IU/l).

16

### 17 **Prothrombin time**

18 Figure 4 summarizes the %PT data. There was no significant change of %PT after  
19 chemotherapy among patients from the HAIC group in C-P class A (before:  $87.1 \pm 14$  %,  
20 after:  $83.7 \pm 10$  %) or class B (before:  $74.9 \pm 15$  %, after:  $74.4 \pm 16$  %). Likewise, there  
21 was no significant change of %PT after chemotherapy among patients from the BCAA  
22 group in C-P class A (before:  $84.8 \pm 11$  %, after:  $82.9 \pm 11$  %) or class B (before:  $75.5 \pm$   
23  $11$  %, after:  $74.8 \pm 13$  %).

1

2 **Child-Pugh score**

3 Figure 5 compares C-P scores. In the HAIC group, there was no significant  
4 difference of the C-P score between before and after chemotherapy in class A or class B  
5 patients (C-P class A:  $5.53 \pm 0.5$  vs.  $5.50 \pm 0.6$ , C-P class B:  $7.30 \pm 1.3$  vs.  $7.08 \pm 1.3$ ).  
6 In the BCAA group, however, the C-P score showed a significant decrease after  
7 chemotherapy compared with before chemotherapy for patients in C-P class B ( $7.12 \pm$   
8  $1.0$  vs.  $7.44 \pm 0.7$ ,  $p = 0.011$ ), while there was no significant difference between before  
9 and after chemotherapy for C-P class A patients (before:  $5.58 \pm 0.5$ , after:  $5.46 \pm 0.7$ ).

10

11 ***Survival***

12 Among patients in C-P class A from the two groups, there was no significant  
13 difference of the median survival time (HAIC group:  $626 \pm 29$  days vs. BCAA group:  
14  $653 \pm 127$  days) (Fig. 6). Among patients in C-P class B, however, the median survival  
15 time of those from the BCAA group ( $426 \pm 30$  days) was significantly longer than that  
16 of those from the HAIC group ( $272 \pm 65$  days) ( $p = 0.0294$ , Kaplan-Meier method and  
17 log-rank test)(relative hazard ratio: 1.36, 95% confidence interval: 1.06-4.98) (Fig. 7).

18

19 **IV. DISCUSSION**

20 The liver plays an important role in energy metabolism, and liver diseases can lead  
21 to abnormalities of nutrient metabolism and malnutrition [20]. Among attempts to  
22 improve such malnutrition, intake of a late evening snack (LES) by patients with LC has  
23 been demonstrated to be beneficial for energy substrate metabolism [21-24]. It has also

1 been reported that an LES containing BCAA improves malnutrition, amino acid  
2 imbalances, and glucose intolerance in patients with LC [25-27]. In present study, an  
3 LES was not used and BCAA were administered three times a day after meals. In  
4 addition, whether BCAA supplementation improves energy metabolism was not  
5 determined. Harima et al. reported that an LES containing BCAA improves energy  
6 metabolism and glucose tolerance in LC patients with aHCC undergoing HAIC [17].  
7 However, they did not discuss whether BCAA had an influence on the prognosis of their  
8 patients and did not investigate any patients in C-P class B. In the present study, we not  
9 only assessed LC patients in C-P class A with aHCC undergoing HAIC, but also those  
10 in C-P class B. We investigated who showed multiple partial responses or had stable  
11 disease and we excluded patients in C-P class C and patients with no response. Because  
12 liver damage caused by tumor progression should influence the prognosis of LC  
13 patients with aHCC undergoing HAIC, we calculated propensity scores to find other  
14 factors with an influence on survival. Our results showed that treatment with BCAA  
15 might improve the survival time of aHCC patients undergoing HAIC. We also  
16 investigated in C-P classes A and B separately to confirm that treatment with BCAA  
17 was associated with the survival of these patients. Multivariate analysis with the Cox  
18 proportional hazards model showed that BCAA supplementation was not associated  
19 with the survival time of aHCC patients in C-P class A undergoing HAIC, while tumor  
20 stage and AFP were associated with their survival. However, BCAA supplementation  
21 was associated with the survival time of aHCC patients in C-P class B receiving HAIC,  
22 whereas tumor stage and AFP did not influence the survival of these patients. In C-P  
23 class B patients from the BCAA group, serum albumin was significantly increased after

1 HAIC, while there was no significant change in serum T-Bil, serum ALT, %PT, ascites,  
2 or hepatic encephalopathy. Therefore, the C-P score showed a significant decrease after  
3 HAIC compared with before HAIC in C-P class B patients from this group, although  
4 there was no significant change in C-P class A patients from the same group. Moreover,  
5 the survival time of C-P class B patients from the BCAA group was significantly longer  
6 than that of class B patients from the HAIC group, while the median survival time  
7 showed no significant difference for C-P class A patients from the 2 groups. The  
8 increasing of serum albumin by BCAA treatment might have improved C-P score and  
9 might have extended the period which can be treated by HAIC. These might contribute  
10 it to extension of survival time. Vincent et al. reported a decreased frequency of LC  
11 complications and an improved nutritional status when BCAA were prescribed as  
12 maintenance therapy for LC patients [28]. They also reported that nutritional  
13 supplementation with oral BCAA is beneficial for increasing the serum albumin level,  
14 reducing morbidity, and improving quality of life in patients undergoing TACE for HCC  
15 [29]. In the present study, BCAA improved the survival time and C-P score by  
16 increasing serum albumin in C-P class B patients receiving HAIC for aHCC. These  
17 findings might have reflected improvement of energy metabolism and glucose tolerance  
18 in our LC patients with advanced HCC undergoing HAIC, although we did not  
19 investigate nutritional parameters.

20 BCAA (LIVACT granules) were reported to improve the plasma albumin level in  
21 LC patients with hypoalbuminemia [30, 31]. A BCAA-enriched snack (Aminoreban EN  
22 powder mix) was superior to ordinary food as a late evening snack for improving the  
23 serum albumin level and energy metabolism of LC patients [24]. Ijichi et al. reported

1 that BCAA, especially leucine, promote the production of albumin by rat hepatocytes  
2 via the mammalian target of rapamycin (mTOR) signal transduction system [32].  
3 Furthermore, it has been reported that oral administration of BCAA augments hepatic  
4 albumin synthesis, not only by supplementation of substrates for protein synthesis, but  
5 also by induction of mTOR signaling that is critical for initiation of translation, and that  
6 activation of the mTOR pathway is one of the major mechanisms by which BCAA  
7 treatment reverse hypoalbuminemia in LC patients [33].

8 In conclusion, the present study showed that BCAA treatment can improve the liver  
9 function and prognosis of LC patients in C-P class B undergoing HAIC for aHCC. It  
10 was suggested that BCAA might increase the serum albumin level by promoting hepatic  
11 albumin production and might thus allow the prolongation of HAIC. These effects  
12 might improve the prognosis of LC patients with aHCC in C-P class B.

13

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17

## 18 **Figure legends**

19

20 Figure 1. Changes of serum alanine aminotransferases (ALT) in the two groups. In the  
21 HAIC group, there were no significant changes of serum ALT after  
22 chemotherapy among patients in Child-Pugh class A or class B. In the  
23 BCAA group, there were also no significant changes of serum ALT after

1 chemotherapy among patients in Child-Pugh class A or class B.

2

3 Figure 2. Changes of serum albumin in the two groups. In the HAIC group, there were  
4 no significant changes of serum albumin after chemotherapy among  
5 patients in Child-Pugh class A or class B. In the BCAA group, serum  
6 albumin was significantly increased after chemotherapy compared with  
7 before chemotherapy for patients in Child-Pugh class B, while there was no  
8 significant difference of serum albumin between before and after  
9 chemotherapy for Child-Pugh class A patients.

10

11 Figure 3. Changes of serum total total bilirubin (T-Bil) in the two groups. In the  
12 HAIC group, there were no significant changes of serum T-Bil after  
13 chemotherapy among patients in Child-Pugh class A or class B. In the  
14 BCAA group, there were also no significant changes of serum T-Bil after  
15 chemotherapy among patients in Child-Pugh class A or class B.

16

17 Figure 4. Changes of the prothrombin time (%PT) in the two groups. In the HAIC  
18 group, there were no significant changes of the %PT after chemotherapy  
19 among patients in Child-Pugh class A or class B. In the BCAA group, there  
20 were also no significant changes of the %PT after chemotherapy among  
21 patients in Child-Pugh class A or class B.

22

23 Figure 5. Changes of the Child-Pugh score in the two groups. In the HAIC group,

1           there was no significant difference of the Child-Pugh score between before  
2           and after chemotherapy. In the BCAA group, however, the Child-Pugh  
3           score was significantly lower after chemotherapy compared with before  
4           chemotherapy for patients in Child-Pugh class B, although there was no  
5           significant difference between before and after chemotherapy in  
6           Child-Pugh class A patients.

7  
8   Figure 6.   Survival time of patients with advanced hepatocellular carcinoma from  
9           Child-Pugh class A in each group. There was no significant difference of  
10          the median survival of class A patients between the two groups.

11  
12   Figure 7.   Survival time of patients with advanced hepatocellular carcinoma in  
13          Child-Pugh class B from each group. The median survival time of class B  
14          patients from the BCAA group was significantly longer than that of those  
15          from the HAIC group.

**Table 1.**  
**Comparison of clinical characteristics between the BCAA and HAIC groups**

	BCAA group	HAIC group	P value
No. of patients	49	43	
Mean age	66.3 ± 7	68.0 ± 7	0.209
Gender (M/F)	43/6	34/9	0.283
Etiology of cirrhosis (HBV/HCV/non Bnon C)	8/30/11	6/30/7	0.745
Child-Pugh classification (A/B)	23/26	30/13	0.028*
Stage (IV/III)	41/8	29/14	0.070
Stage (III/IVA/IVB)	8/36/5	14/21/8	0.039*
Response(PR/SD)	15/34	22/21	0.046*
NH <sub>3</sub> (μg/dl)	67.5 ± 40	56.3 ± 30	0.268
total bilirubin (g/dl)	1.03 ± 0.4	0.92 ± 0.5	0.236
direct bilirubin (g/dl)	0.34 ± 0.2	0.31 ± 0.3	0.495
albumin (mg/dl)	3.04 ± 0.4	3.33 ± 0.5	0.006*
ALT (IU/l)	50.0 ± 45	44.5 ± 20	0.473
total cholesterol (mg/dl)	152.0 ± 56	157.0 ± 66	0.758
white blood cell (/mm <sup>3</sup> )	4057 ± 1661	4714 ± 2509	0.154
platelets (X 10 <sup>4</sup> /mm <sup>3</sup> )	11.76 ± 6.8	14.52 ± 8.0	0.087
prothrombin time (%)	80.0 ± 12	84.8 ± 14	0.083
BUN (mg/dl)	13.9 ± 6	13.4 ± 6	0.067
Cr (mg/dl)	0.76 ± 0.3	0.69 ± 0.2	0.131
AFP (ng/ml)	15260 ± 55227	36790 ± 161779	0.412
AFP (<20 / ≥20 ng/ml)	9/34	9/32	0.909
AFP-L3 (%)	35.6 ± 26	26.9 ± 25	0.163
DCP (AU/ml)	75263 ± 330127	9712 ± 26423	0.226

HBV: hepatitis B virus, HCV: hepatitis C virus, NH<sub>3</sub>: ammonia, ALT: alanine aminotransferase, BUN: blood urea nitrogen, Cr: creatine, AFP: alpha-fetoprotein, DCP: Des-gamma carboxyprothrombin

\*Statistically difference compared between BCAA group and HAIC group (the Mann-Whitney U test)

**Table 2.**

**Propensity scores of factors related to the survival of 92 advanced HCC patients treated by HAIC**

**Excluding albumin**

	Hazard ratio	95% confidence interval		<i>P value</i>
		Lower limit - upper limit		
with or without BCAA	0.4816	0.2705 - 0.8537		0.0124*
propensity score	34.2338	7.0966 - 175.9901		< 0.001**

**Including albumin**

	Hazard ratio	95% confidence interval		<i>P value</i>
		Lower limit - upper limit		
with or without BCAA	0.5567	0.3203 - 0.9682		0.0038*
propensity score	17.2676	3.8766 - 81.5265		< 0.0002**

\*Statistically difference compared by the Cox proportional hazards model for multivariate analyses of factors associated with survival.

\*\*Statistically difference compared by the propensity score for treatment with or without BCAA showed < 0.001 based on the Humster-Lemeshow test and the area under the curve (AUC) of the propensity score.



**Table 3.**  
**Comparison of clinical characteristics for 53 patients in Child-Pugh class A**

	BCAA group	HAIC group	P value
No. of patients	23	30	
Mean age	66.8 ± 8	66.7 ± 7	0.644
Gender (M/F)	20/3	23/7	0.343
Etiology of cirrhosis (HBV/HCV/non Bnon C)	3/16/4	4/23/3	0.730
Stage (IV/III)	18/5	17/13	0.100
(IVA/III)	17/5	12/13	0.042*
(IVB/III)	1/5	5/13	0.721
(IVB/IVA)	1/17	5/12	0.232
Response(PR/SD)	8/15	16/14	0.179
NH <sub>3</sub> (μg/dl)	69.2 ± 54	46.8 ± 35	0.267
total bilirubin (g/dl)	0.82 ± 0.3	0.79 ± 0.4	0.781
direct bilirubin (g/dl)	0.27 ± 0.2	0.22 ± 0.2	0.456
albumin (mg/dl)	3.29 ± 0.3	3.58 ± 0.4	0.009*
(<3.5 / ≥3.5 mg/dl)	(13/6)	(10/18)	0.028*
ALT (IU/l)	47.8 ± 48	46.0 ± 20	0.858
total cholesterol (mg/dl)	152.4 ± 48	155.3 ± 35	0.815
white blood cell (/mm <sup>3</sup> )	4044.4 ± 1632	4964.3 ± 2832	0.219
platelets (X 10 <sup>4</sup> /mm <sup>3</sup> )	12.4 ± 8	15.0 ± 8	0.302
prothrombin time (%)	85.4 ± 11	87.1 ± 14	0.654
BUN (mg/dl)	14.7 ± 7	13.1 ± 5	0.366
Cr (mg/dl)	0.81 ± 0.3	0.66 ± 0.2	0.044
AFP (ng/ml)	6400.8 ± 22723	2019.2 ± 6278	0.347
AFP (<20 / ≥20 ng/ml)	(3/14)	(7/20)	0.523
AFP-L3 (%)	30.6 ± 27	27.6 ± 26	0.738
DCP (AU/ml)	131040.1 ± 503988	3517.5 ± 10439	0.220

HBV: hepatitis B virus, HCV: hepatitis C virus, NH<sub>3</sub>: ammonia, ALT: alanine aminotransferase, BUN: blood urea nitrogen, Cr: creatine, AFP: alpha-fetoprotein, DCP: Des-gamma carboxyprothrombin

\*Statistically difference compared between BCAA group and HAIC group (the Mann-Whitney U test).

**Table 4.**  
**Univariate analysis of factors related to the survival of 53 patients in Child-Pugh class A**

<b>Factor</b>	<b>Hazard ratio</b>	<b>P value</b>
Mean age	0.9930	0.721
Gender (M/F)	0.4861	0.080
Etiology of cirrhosis (HBV/HCV/non Bnon C)		
(HBV/nonBnonC)	0.5147	0.339
(HCV/nonBnonC)	0.7945	0.618
Stage (IV/III)	1.5208	0.191
(IVA/III)	1.3799	0.342
(IVB/III)	2.4235	0.094
(IVB/IVA)	1.7562	0.257
Response(PR/SD)	1.7421	0.058
NH <sub>3</sub> (μg/dl)	1.0184	0.008*
total bilirubin (g/dl)	1.6534	0.256
direct bilirubin (g/dl)	2.4874	0.223
albumin (mg/dl)	1.3359	0.517
(<3.5 / ≥3.5 mg/dl)	1.3359	0.517
ALT (IU/l)	1.0112	0.107
total cholesterol (mg/dl)	1.0047	0.300
white blood cell (/mm <sup>3</sup> )	1.0000	0.890
platelets (X 10 <sup>4</sup> /mm <sup>3</sup> )	1.0000	0.801
prothrombin time (%)	1.0025	0.849
BUN (mg/dl)	0.9884	0.701
Cr (mg/dl)	0.3061	0.096
AFP (ng/ml)	1.0000	0.019*
AFP (<20 / ≥20 ng/ml)	1.6020	0.226
AFP-L3 (%)	1.0215	0.008*
DCP (AU/ml)	1.0000	0.169
with or without BCAA	1.3325	0.374

HBV: hepatitis B virus, HCV: hepatitis C virus, NH<sub>3</sub>: ammonia, ALT: alanine aminotransferase, BUN: blood urea nitrogen, Cr: creatine, AFP: alpha-fetoprotein, DCP: Des-gamma carboxyprothrombin

\*Statistically difference compared by the Cox proportional hazards model for univariate analyses of factors associated with survival.

**Table 5.**  
**Multivariate analysis of factors related to the survival of 53 patients in Child-Pugh class A**

Factor	Hazard ratio	95% confidence interval		P value
		Lower limit - upper limit		
Stage (IV/III)	2.8140	1.2972 - 6.5370		0.008*
AFP (< 20 / ≥ 20 ng/dl)	2.2080	1.0056 - 5.3843		0.048*
with or without BCAA	1.4804	0.7365 - 3.0758		0.273

AFP: alpha-fetoprotein

\*Statistically difference compared by the Cox proportional hazards model for multivariate analyses of factors associated with survival.

**Table 6.**  
**Comparison of clinical characteristics for 39 patients in Child-Pugh class B**

	BCAA group	HAIC group	P value
No. of patients	26	13	
Mean age	65.8 ± 6	70.4 ± 4	0.028*
Gender (M/F)	23/3	11/2	0.735
Etiology of cirrhosis (HBV/HCV/non Bnon C)	5/14/7	2/7/4	0.943
Stage (IV/III)	23/3	12/1	0.719
(IVA/III)	19/3	9/1	0.889
(IVB/III)	4/3	3/1	0.648
(IVB/IVA)	4/19	3/9	0.159
Response(PR/SD)	7/19	6/7	0.230
NH <sub>3</sub> (μg/dl)	66.3 ± 28	60.9 ± 20	0.582
total bilirubin (g/dl)	1.20 ± 0.4	1.20 ± 0.6	0.981
direct bilirubin (g/dl)	0.40 ± 0.2	0.51 ± 0.4	0.202
albumin (mg/dl)	2.86 ± 0.4	2.91 ± 0.4	0.731
(<3.5 / ≥3.5 mg/dl)	(25/1)	(13/0)	0.474
ALT (IU/l)	51.4 ± 44	42.2 ± 19	0.480
total cholesterol (mg/dl)	153.0 ± 62	132.5 ± 39	0.301
white blood cell ( /mm <sup>3</sup> )	4065.4 ± 1714	4092.3 ± 1672	0.963
platelets ( X 10 <sup>4</sup> /mm <sup>3</sup> )	11.3 ± 6	11.5 ± 4	0.874
prothrombin time (%)	75.9 ± 10	78.6 ± 10	0.500
BUN (mg/dl)	12.4 ± 5	14.1 ± 7	0.725
Cr (mg/dl)	0.73 ± 0.2	0.75 ± 0.2	0.848
AFP (ng/ml)	21052.3 ± 68596	34528.4 ± 79444	0.586
AFP (<20 / ≥20 ng/ml)	(6/20)	(2/11)	0.575
AFP-L3 (%)	39.0 ± 26	27.5 ± 26	0.236
DCP (AU/ml)	40938.9 ± 152033	10819.2 ± 19052	0.484

HBV: hepatitis B virus, HCV: hepatitis C virus, NH<sub>3</sub>: ammonia, ALT: alanine aminotransferase, BUN: blood urea nitrogen, Cr: creatine, AFP: alpha-fetoprotein, DCP: Des-gamma carboxyprothrombin

\*Statistically difference compared between BCAA group and HAIC group (the Mann-Whitney U test)

**Table 7.**  
**Univariate analysis of factors related to the survival of 39 patients in Child-Pugh class B**

<b>Factor</b>	<b>Hazard ratio</b>	<b>P value</b>
Mean age	1.0079	0.779
Gender (M/F)	0.9569	0.929
Etiology of cirrhosis (HBV/HCV/non Bnon C)		
(HBV/nonBnonC)	0.8936	0.841
(HCV/nonBnonC)	1.1923	0.675
Stage (IV/III)	2.0280	0.288
(IVA/III)	1.7541	0.416
(IVB/III)	4.1627	0.060
(IVB/IVA)	2.3732	0.095
Response(PR/SD)	0.7896	0.519
NH <sub>3</sub> (μg/dl)	0.9742	0.030*
total bilirubin (g/dl)	0.5587	0.207
direct bilirubin (g/dl)	0.6267	0.553
albumin (mg/dl)	0.7864	0.629
(<3.5 / ≥3.5 mg/dl)	0.3777	0.413
ALT (IU/l)	0.9961	0.609
total cholesterol (mg/dl)	0.9961	0.386
white blood cell ( /mm <sup>3</sup> )	1.0003	0.052
platelets ( X 10 <sup>4</sup> /mm <sup>3</sup> )	1.0000	0.902
prothrombin time (%)	1.0156	0.456
BUN (mg/dl)	1.0610	0.110
Cr (mg/dl)	1.9773	0.553
AFP (ng/ml)	1.0000	0.759
AFP (<20 / ≥20 ng/ml)	2.0090	0.119
AFP-L3 (%)	1.0117	0.179
DCP (AU/ml)	1.0000	0.057
with or without BCAA	2.3018	0.039*

HBV: hepatitis B virus, HCV: hepatitis C virus, NH<sub>3</sub>: ammonia, ALT: alanine aminotransferase, BUN: blood urea nitrogen, Cr: creatine, AFP: alpha-fetoprotein, DCP: Des-gamma carboxyprothrombin

\*Statistically difference compared by the Cox proportional hazards model for univariate analyses of factors associated with survival.

**Table 8.****Multivariate analysis of factors related to the survival of 39 patients in Child-Pugh class B**

<b>Factor</b>	<b>Hazard ratio</b>	<b>95% confidence interval</b>		<b>P value</b>
		<b>Lower limit - upper limit</b>		
Stage (IV/III)	1.9823	0.5536 - 12.7597		0.328
AFP (< 20 / ≥ 20 ng/dl)	2.1735	0.8776 - 6.3353		0.097
with or without BCAA	2.7889	1.2247 - 6.3213		0.015*

AFP: alpha-fetoprotein

\*Statistically difference compared by the Cox proportional hazards model for multivariate analyses of factors associated with survival.