

**Original Paper**

# Beneficial Effect of Maintaining Hepatic Reserve during Chemotherapy on the Outcomes of Patients with Hepatocellular Carcinoma

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**Keywords**

Hepatocellular carcinoma · Hepatic reserve · Child-Pugh score · Hepatic arterial infusion chemotherapy · Sorafenib

**Abstract**

Hepatocellular carcinoma (HCC) usually develops in chronically damaged liver. We investigated hepatic reserves during chemotherapy of patients with advanced HCC and compensated liver function to evaluate the effect on patients' outcomes of maintaining hepatic reserve after chemotherapy. We retrospectively reviewed the medical records of 190 patients with Child-Pugh A with advanced HCC who were treated with sorafenib or hepatic arterial infusion chemotherapy (HAIC). We investigated the Child-Pugh score and albumin-bilirubin grade for hepatic reserve, and evaluated the effect of the change in Child-Pugh scores on patients' outcomes. Subjects were treated with sorafenib ( $n = 59$ ) or HAIC ( $n = 131$ ). Of patients with Child-Pugh data, 66.7% maintained or improved their Child-Pugh score after 4 weeks. Treatment with HAIC was the only factor that significantly contributed to maintaining Child-Pugh scores after 4 weeks. The overall survival of patients with a higher Child-Pugh score after 4 weeks was shorter than that of patients whose Child-Pugh classification was unchanged. Multivariate analysis demonstrated that an increased Child-Pugh score after 4 weeks was one of the independent unfavorable prognostic factors. The change of hepatic reserve as a function of albumin-bilirubin grade did not significantly correlate with patients' outcomes. Maintaining the Child-Pugh score during chemotherapy benefits the outcomes of patients with advanced HCC, even those with sufficient hepatic reserve.

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## Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer-related mortality worldwide [1]. Surveillance of high-risk patients with hepatitis virus infection or liver cirrhosis who are at risk for HCC occurrence and new imaging techniques have enabled the detection of HCC at an early stage [2], and advances in therapeutic procedures have improved curability [3]. However, patients who receive curative treatment frequently experience multicentric recurrence and intrahepatic metastases. Consequently, recurrent HCC invades the intrahepatic vasculature or metastasizes to extrahepatic sites and becomes refractory to transarterial chemoembolization. Administration of sorafenib or hepatic arterial infusion chemotherapy (HAIC) to such patients benefits their survival [4, 5].

Impaired hepatic reserve caused by advanced chronic liver disease is another crucial factor that significantly affects patients' outcomes [6]. For example, patients with more advanced stages of HCC may experience deterioration of hepatic reserve [7], possibly due to a progressive tumor burden directly affecting hepatic function, or impaired blood supply of the portal vein caused by vascular invasion damages. Although hepatic reserve before treatment affects the outcome of a patient with advanced HCC when subsequently treated with chemotherapy, there have been no relevant studies focusing on hepatic reserve during treatment of patients with sufficient hepatic reserve.

Therefore, the aim of the present study was to investigate the hepatic reserves after sorafenib treatment or HAIC of patients with advanced HCC and compensated liver function. We further analyzed the effect on patients' outcomes of maintaining hepatic reserve after chemotherapy that was associated with changes of hepatic reserve after administration of sorafenib or HAIC.

## Materials and Methods

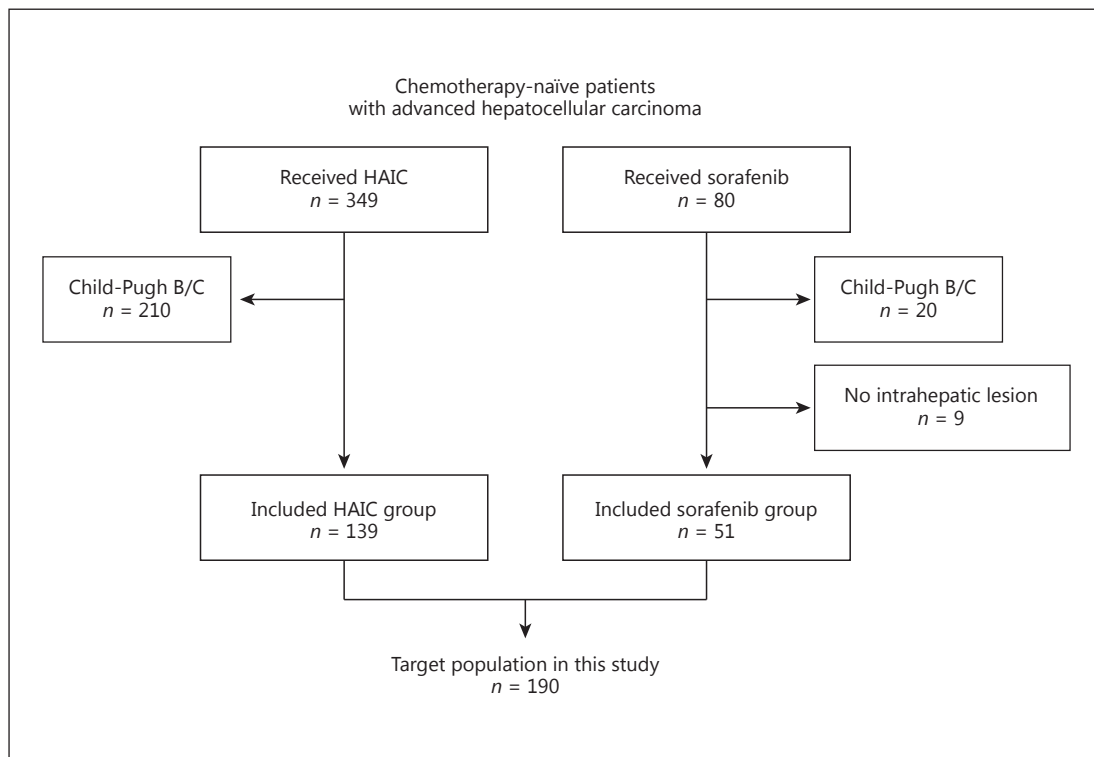
### *Patients*

We studied chemotherapy-naïve patients with advanced HCC who were treated with sorafenib or HAIC at the Kanazawa University Hospital from March 2003 to December 2015. All patients underwent dynamic computed tomography or magnetic resonance imaging to diagnose and assess the extent of HCC. HCC was diagnosed according to the guidelines of the American Association for the Study of Liver Disease, and histological examination was performed if required [8]. If the radiological findings showed vascular invasion, multiple intrahepatic lesions, or both, patients were judged to be unsuitable for surgery, locoregional therapy, and transarterial chemoembolization. If patients met these criteria, further inclusion criteria were as follows: (1) without prior chemotherapy, (2) without cirrhosis or with Child-Pugh A cirrhosis, and (3) presence of intrahepatic lesions (Fig. 1). Patients with extrahepatic lesions were judged to be eligible for HAIC if the extrahepatic lesions were mild and not prognostic, e.g. small tumor burden, slowly growing tumor, and no effect of the tumor on the patient's symptoms.

### *Treatment*

Patients in the sorafenib group received 400 mg of sorafenib orally twice daily. Patients in the HAIC group received 5-fluorouracil as follows: 5-fluorouracil (330 mg/m<sup>2</sup>/day) was administered continuously on days 1–5 and days 8–12. Some patients received cisplatin injection (20 mg/m<sup>2</sup>/day) into the hepatic artery for 10 min before administration of 5-fluorouracil. Interferon- $\alpha$ -2b or pegylated interferon- $\alpha$ -2b was used at the physician's discretion. Pegylated interferon- $\alpha$ -2b (1.0  $\mu$ g/kg) was administered subcutaneously on days 1, 8, 15, and 22, and interferon- $\alpha$ -2b ( $3 \times 10^6$  U) was administered intramuscularly 3 times each week. The administration of drugs was followed by a 14-day rest period. The implantation of a drug-delivery reservoir system was established before treatment as previously described [9].

Both treatments were temporarily interrupted, or the dose of the drugs was reduced according to toxicity. Treatment was subsequently continued until confirmation of tumor progression, unacceptable toxicity, a patient's refusal of treatment, or death.



**Fig. 1.** Flow diagram of the study.

#### *Effects of Treatment*

At each visit, a patient's Child-Pugh score was assessed according to physiological, laboratory, and radiological findings. The albumin-bilirubin (ALBI) grade, a simple assessment criterion for hepatic reserve, was calculated as previously reported [10]. We used dynamic computed tomography or dynamic magnetic resonance imaging every 4–6 weeks during treatment to assess the efficacy of treatment. The antitumor effects of treatment were assessed according to the Response Evaluation Criteria in Solid Tumors v1.1 [11]. The disease control rate was defined as the sum of the rates of complete response, partial response, and stable disease. Progression-free survival (PFS) was defined as the time from the start of treatment until the date of radiological progression and death. Overall survival (OS) was defined as the time from the start of treatment until death.

#### *Data Collection*

We reviewed patients' medical records and collected demographic, clinical, and laboratory data, which included age, sex, Eastern Cooperative Oncology Group performance status (ECOG PS), hepatitis virus status, hepatic reserve, consumption of branched-chain amino acids, imaging data (vascular invasion and extrahepatic lesions), analyses of tumor markers, and response to treatment. The Institutional Review Board at Kanazawa University approved the study, which was conducted in accordance with the Declaration of Helsinki.

#### *Statistical Analysis*

Categorical variables were compared using the  $\chi^2$  test when appropriate for univariate analysis, and logistic regression analysis was used to perform multivariate analysis. Cumulative survival was calculated using the Kaplan-Meier method, and differences were evaluated using the log-rank test. Only variables with statistically significant values determined using univariate analysis were subsequently evaluated using multivariate analysis with the Cox proportional hazards regression model.  $p < 0.1$  and  $p < 0.05$  were considered statistically significant in univariate analysis and multivariate analysis, respectively. All statistical analyses were performed using SPSS statistical software (v21.0; SPSS, Chicago, IL, USA).

**Table 1.** Demographic characteristic of the patients according to the type of treatment

	All (n = 190)	Treatment		p value <sup>a</sup>
		sorafenib (n = 51)	HAIC (n = 139)	
Age				
Median, years	69	69	69	
≥69 years	101 (53.2)	27 (52.9)	74 (53.2)	0.97
Male	156 (82.1)	45 (88.2)	111 (79.9)	0.18
ECOG performance status				
0	175 (92.1)	46 (90.2)	129 (92.8)	0.55
1–3	15 (7.9)	5 (9.8)	10 (7.2)	
Hepatitis B virus surface antigen	52 (27.4)	16 (31.4)	36 (25.9)	0.45
Hepatitis C virus antibody	99 (52.1)	24 (47.1)	75 (54.0)	0.40
Child-Pugh score				
5	93 (48.9)	28 (54.9)	65 (46.8)	0.32
6	97 (51.1)	23 (45.1)	74 (53.2)	
Branched-chain amino acid	30 (15.8)	9 (17.6)	21 (15.1)	0.67
Maximum tumor size ≥50 mm	59 (31.1)	8 (15.7)	51 (36.7)	0.006
Tumor number ≥6	133 (70.0)	30 (58.8)	103 (74.1)	0.042
Vascular invasion	75 (39.5)	18 (35.3)	57 (41.0)	0.48
Extrahepatic spread	49 (25.8)	25 (49.0)	24 (17.3)	<0.001
AFP ≥400 ng/mL	69 (36.3)	16 (31.4)	53 (38.1)	0.39
Crossover second-line chemotherapy	50 (26.3)	28 (54.9)	22 (15.8)	<0.001

Data are presented as n (%). ECOG, Eastern Cooperative Oncology Group; AFP,  $\alpha$ -fetoprotein; HAIC, hepatic arterial infusion chemotherapy. <sup>a</sup>  $\chi^2$  test.

## Results

### Characteristics of Patients

We retrospectively reviewed the records of 80 and 349 chemotherapy-naïve patients with advanced HCC who were treated with sorafenib or HAIC, respectively, at Kanazawa University Hospital between March 2003 and December 2015. Overall, 190 patients (51 treated with sorafenib [sorafenib group] and 139 treated with HAIC [HAIC group]) met the inclusion criteria (Fig. 1). Patients' characteristics are summarized in Table 1. We determined that 54.9 and 45.1% of patients in the sorafenib group and 46.8 and 53.2% of patients in the HAIC group had Child-Pugh scores of 5 and 6, respectively. Other factors associated with general condition, hepatic reserve, and tumors were similarly distributed between groups, except that extrahepatic metastases were observed more frequently in patients in the sorafenib group than in the HAIC group (49.0 vs. 17.3%;  $p < 0.001$ ), and maximum tumor size of 50 mm or larger and tumor number of 6 or more were observed more frequently in patients in the HAIC group than in the sorafenib group (36.7 vs. 15.7%,  $p = 0.006$ ; 74.1 vs. 58.8%,  $p = 0.042$ , respectively).

### Treatment

When data collection terminated on 18 March, 2016, 177 patients (93.2%) had discontinued treatment, and 153 patients (80.5%) had died. The median follow-up was 12.9 months (range, 0.5–151.3 months). Both treatments were well tolerable, although 2 patients, 1 patient in each group, discontinued treatment because of liver failure. Both of them had numerous small HCCs in the liver, portal vein tumor thrombus and extrahepatic lesion, and their Child-Pugh scores were 6 before treatment. However, the liver function of a patient treated with HAIC deteriorated to Child-Pugh score 11 after 4 weeks, and she stopped HAIC on day 35.

**Table 2.** Response to treatment according to the type of treatment

	Treatment		p value <sup>b</sup>
	sorafenib (n = 51)	HAIC (n = 139)	
<b>a Radiological assessment<sup>a</sup></b>			
Complete response	0 (0%)	12 (8.6%)	
Partial response	3 (5.9%)	37 (26.6%)	
Stable disease	23 (45.1%)	45 (32.4%)	
Progressive disease	23 (45.1%)	41 (29.5%)	
Objective response rate	5.9%	35.3%	<0.001
Disease control rate	51.0%	67.6%	0.035
<b>b Change of AFP</b>			
Before treatment, median	72	74	
After 4 weeks, median	63.5	47	
≥50% decreased after 4 weeks/patients with ≥20 ng/mL before treatment	1/30 (3.3%)	37/95 (38.9%)	<0.001

AFP, α-fetoprotein; HAIC, hepatic arterial infusion chemotherapy. <sup>a</sup> According to RECIST v1.1. <sup>b</sup>  $\chi^2$  test.

Another patient treated with sorafenib also developed impaired liver function with a Child-Pugh score of 9 after 8 weeks, and he stopped sorafenib on day 57. Both impaired liver functions were irreversible.

#### Response to Treatment

Responses to treatment are shown in Table 2. Objective responses to treatment were achieved by 5.9% (3/51) and 35.3% (49/139) of patients treated with sorafenib and HAIC, respectively. The disease control rates were 51.0 and 67.6% in the sorafenib and HAIC groups, respectively. Responsiveness to treatment in the HAIC group was better than that in the sorafenib group (objective response:  $p < 0.001$ , disease control rate:  $p = 0.035$ ) (Table 2a). Changes of α-fetoprotein (AFP) are shown in Table 2b. The median AFP before treatment and 4 weeks after treatment start were 72 and 63.5 ng/mL, respectively, in the sorafenib group, whereas they were 74 and 47 ng/mL, respectively, in the HAIC group. AFP was 20 ng/mL or more before treatment among 30 (58.8%) and 95 patients (68.3%) treated with sorafenib and HAIC, respectively. AFP decreased by 50% or more after 4 weeks after treatment in only 1 (3.3%) patient of the sorafenib group, and 37 patients (38.9%) of the HAIC group ( $p < 0.001$ ).

The median PFS of all patients was 4.4 months. The median PFS values of patients treated with HAIC and sorafenib were 4.8 and 2.8 months, respectively. The PFS of the patients treated with HAIC was better compared with that of patients treated with sorafenib ( $p = 0.0032$ ) (Fig. 2).

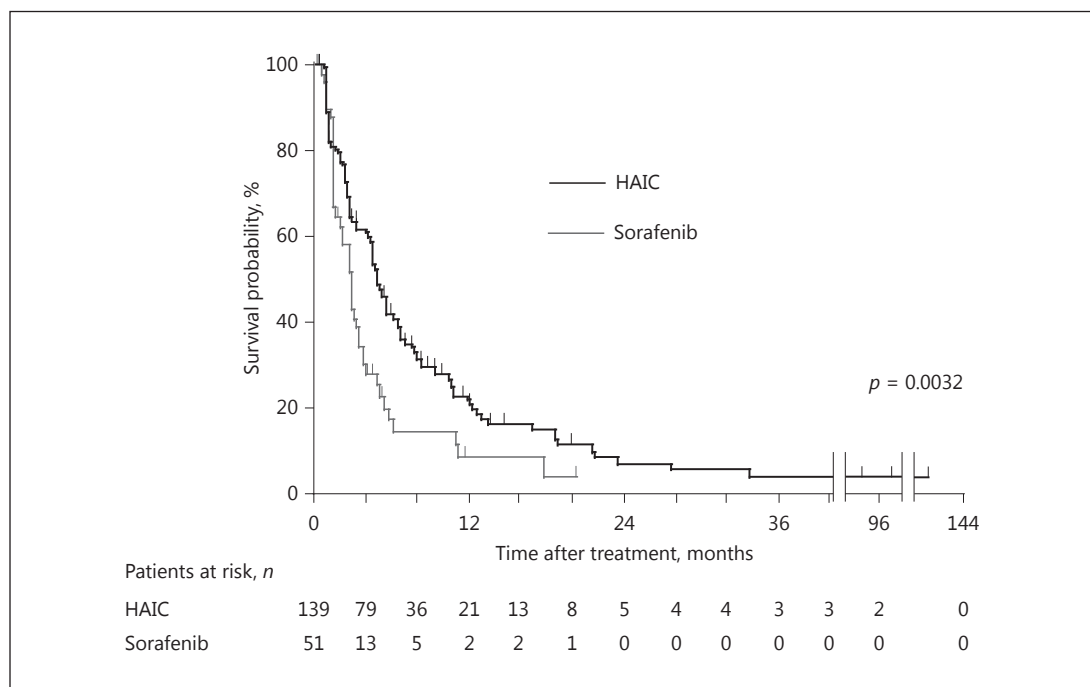
#### Effect of Chemotherapy on Child-Pugh Scores

Child-Pugh data after treatment were available for 183 (96.3%) and 162 patients (85.3%) at 4 and 12 weeks, respectively. The Child-Pugh scores of 122 patients (66.7%) were maintained or improved after 4 weeks (50.0 and 72.3%) among patients treated with sorafenib or HAIC, respectively (Table 3). Similarly, the Child-Pugh scores of 21 (47.7%) and 84 patients (71.2%) were unchanged or improved after 12 weeks among patients treated with sorafenib or HAIC, respectively. The Child-Pugh scores of more patients treated with HAIC were significantly maintained or improved after 4 and 12 weeks compared with those who were treated

**Table 3.** Correlation of Child-Pugh scores with the type of treatment at 4 and 12 weeks after treatment commencement

	All	Treatment		p value <sup>a</sup>
		sorafenib	HAIC	
<i>Four weeks after treatment commenced</i>				
Evaluable	183	46	137	
Maintained or improved	122 (66.7%)	23 (50.0%)	99 (72.3%)	0.006
Deteriorated	61 (33.3%)	23 (50.0%)	38 (27.7%)	
<i>Twelve weeks after treatment commenced</i>				
Evaluable	162	44	118	
Maintained or improved	105 (64.8%)	21 (47.7%)	84 (71.2%)	0.005
Deteriorated	57 (35.2%)	23 (52.3%)	34 (28.8%)	

HAIC, hepatic arterial infusion chemotherapy. <sup>a</sup>  $\chi^2$  test.



**Fig. 2.** Kaplan-Meier plots of progression-free survival (PFS) after treatment commencement. The median PFS was 4.8 months for patients treated with HAIC, which was significantly better compared with that of patients treated with sorafenib ( $p = 0.0032$ , log-rank test).

with sorafenib ( $p = 0.006$  and  $p = 0.005$ , respectively) (Table 3). This tendency was also observed among the patients whose best response to treatment was complete response, partial response, or stable disease (online suppl. Table 1; for all online suppl. material, see [www.karger.com/doi/10.1159/000472262](http://www.karger.com/doi/10.1159/000472262)).

Univariate analysis revealed that Child-Pugh scores before treatment, extrahepatic spread, and treatment correlated significantly with unchanged Child-Pugh scores ( $p = 0.037$ ,  $p = 0.020$ , and  $p = 0.0056$ , respectively), and multivariate logistic regression analysis revealed that HAIC was the only variable that was significantly associated with unchanged Child-Pugh

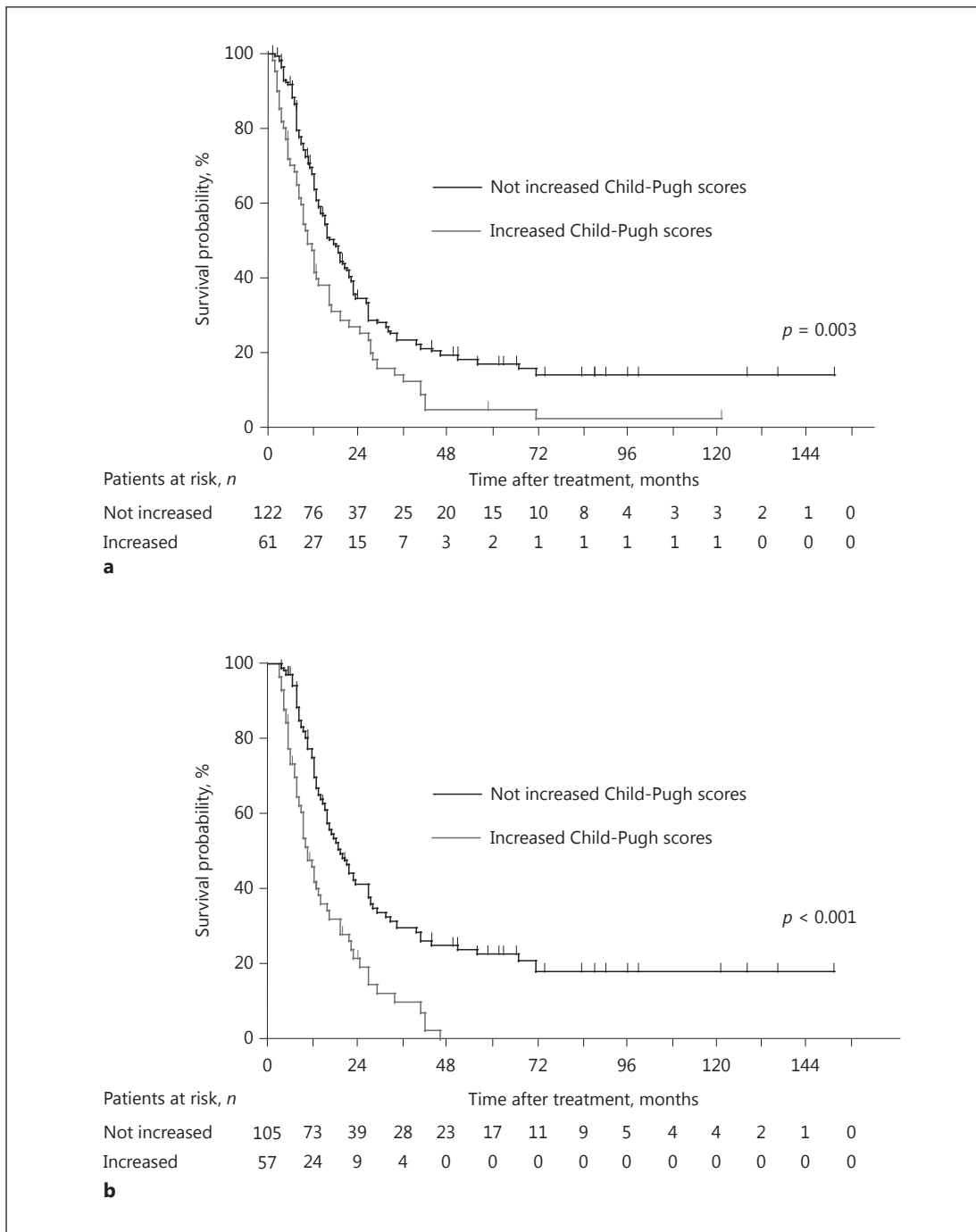
**Table 4.** Factors that contributed to maintaining Child-Pugh scores at 4 weeks

	<i>n</i>	Maintaining Child-Pugh scores, %	Univariate <i>p</i> value <sup>a</sup>	Hazard ratio (95% CI)	Multivariate <i>p</i> value <sup>b</sup>
Age					
≥69 years	97	66.0	0.83		
<69 years	86	67.4			
Gender					
Male	149	66.4	0.89		
Female	34	67.6			
ECOG performance status					
0	169	68.0	0.17		
1–3	14	50.0			
Hepatitis B virus surface antigen					
Positive	51	70.6	0.48		
Negative	132	65.2			
Hepatitis C virus antibody					
Positive	94	64.9	0.60		
Negative	89	68.5			
Child-Pugh score					
6	91	73.9	0.037	1.898 (0.996–3.610)	0.052
5	92	59.3			
Branched-chain amino acid					
Positive	28	57.1	0.25		
Negative	155	68.4			
Maximum tumor size					
<50 mm	126	67.5	0.73		
≥50 mm	57	64.9			
Number of tumors					
<6	54	64.8	0.73		
≥6	129	67.4			
Vascular invasion					
Negative	110	69.1	0.39		
Positive	73	63.0			
Extrahepatic lesion					
Negative	139	71.2	0.020	1.861 (0.883–3.923)	0.10
Positive	44	52.2			
AFP					
<400 ng/mL	116	69.0	0.39		
≥400 ng/mL	67	62.7			
Treatment					
HAIC	137	72.3	0.0056	2.119 (1.021–4.399)	0.044
Sorafenib	46	50.0			
Best response to treatment <sup>c</sup>					
Complete response, partial response, or stable disease	119	69.7	0.23		
Progressive disease or not evaluable	64	60.9			

AFP, α-fetoprotein; HAIC, hepatic arterial infusion chemotherapy; ECOG, Eastern Cooperative Oncology Group. <sup>a</sup> log-rank test. <sup>b</sup> Cox proportional hazards regression model. <sup>c</sup> Based on RECIST v1.1.

scores after 4 weeks (hazard ratio [HR], 2.119; *p* = 0.044) (Table 4). HAIC was also one of the contributing factors to maintaining Child-Pugh scores at 12 weeks (HR, 2.852) as well as Child-Pugh score 6 before treatment (HR, 3.086), maximum tumor size <50 mm (HR, 3.417), and best response to treatment of complete response, partial response, or stable disease (HR, 2.364) (online suppl. Table 2).





**Fig. 3.** Kaplan-Meier plots of overall survival (OS) after treatment commencement. **a** The median OS was 17.7 months for patients with not increased Child-Pugh scores 4 weeks after treatment, which was significantly better compared with that of patients with increased Child-Pugh scores ( $p = 0.003$ , log-rank test). **b** Similarly, the median OS was 19.4 months for patients with not increased hepatic reserve 12 weeks after treatment, which was significantly better compared with that of patients with increased Child-Pugh scores ( $p < 0.001$ , log-rank test).



**Table 5.** Effect of maintaining Child-Pugh scores on patients' outcomes in each subgroup 4 weeks after treatment commencement

	<i>n</i>	Median overall survival, months	Hazard ratio (95% CI)	<i>p</i> value <sup>a</sup>
Age				
<69 years	86	13.1	1.281 (0.785–2.091)	0.32
≥69 years	97	16.1	2.120 (1.336–3.365)	0.001
Gender				
Female	34	12.0	1.646 (0.749–3.619)	0.21
Male	149	15.6	1.654 (1.142–2.396)	0.008
ECOG performance status				
1–3	14	7.1	1.199 (0.363–3.955)	0.77
0	169	15.5	1.601 (1.125–2.278)	0.009
Hepatitis B virus surface antigen				
Positive	51	12.2	1.265 (0.662–2.415)	0.48
Negative	132	16.2	1.832 (1.237–2.712)	0.003
Hepatitis C virus antibody				
Negative	89	12.4	1.663 (1.025–2.699)	0.039
Positive	94	16.6	1.739 (1.090–2.773)	0.020
Child-Pugh score				
6	92	13.0	1.407 (0.851–2.326)	0.18
5	91	15.6	1.996 (1.251–3.187)	0.004
Branched-chain amino acid intake				
Positive	28	12.0	1.232 (0.546–2.778)	0.62
Negative	155	15.2	1.684 (1.163–2.440)	0.006
Vascular invasion				
Positive	73	9.0	1.468 (0.888–2.429)	0.13
Negative	110	19.2	1.777 (1.134–2.784)	0.012
Extrahepatic lesion				
Positive	44	7.7	1.256 (0.661–2.390)	0.49
Negative	139	17.2	1.624 (1.089–2.422)	0.017
AFP				
≥400 ng/mL	67	10.5	2.069 (1.215–3.523)	0.0079
<400 ng/mL	116	18.6	1.439 (0.934–2.217)	0.099
Treatment procedure				
Sorafenib	46	13.0	1.195 (0.620–2.301)	0.59
HAIC	137	15.6	1.709 (1.144–2.552)	0.009
Best response to treatment				
Progressive disease or not evaluable	64	7.7	1.458 (0.869–2.445)	0.15
Complete response, partial response, or stable disease	119	22.0	1.667 (1.072–2.593)	0.023

AFP, α-fetoprotein; HAIC, hepatic arterial infusion chemotherapy; ECOG, Eastern Cooperative Oncology Group. <sup>a</sup> Cox proportional hazards regression model.

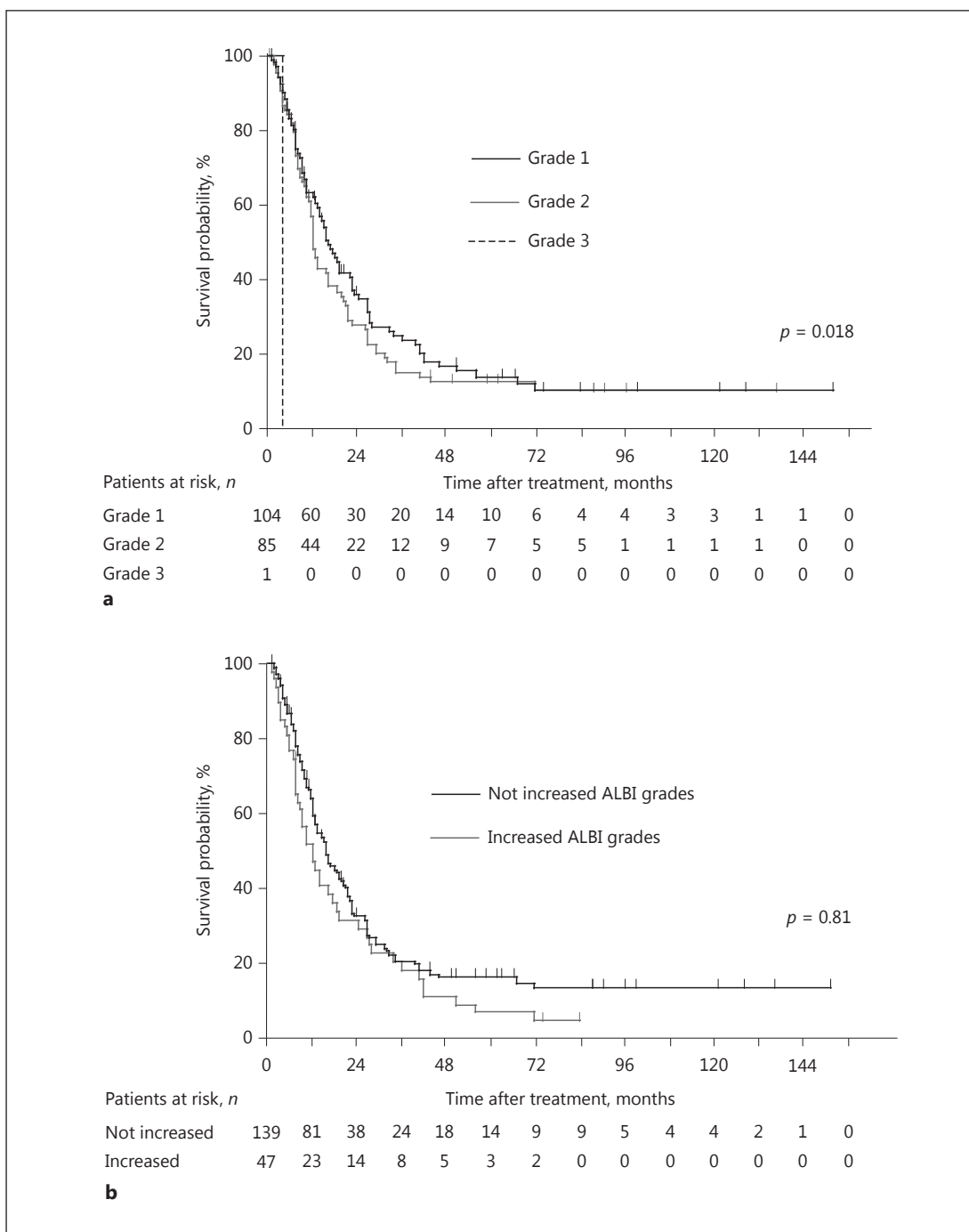
*Impact of Maintaining the Child-Pugh Score on Patients' Outcomes*

The median OS of all patients was 14.5 months. The median OS values of patients with an increased Child-Pugh score and those with unchanged or improved Child-Pugh scores after 4 weeks were 10.7 and 17.7 months, respectively. The OS of the patients with increased Child-Pugh scores after 4 weeks was shorter compared with those of patients with unchanged or improved Child-Pugh scores ( $p = 0.003$ ) (Fig. 3a), and the difference was more remarkable 12 weeks after treatment commenced ( $p < 0.001$ ) (Fig. 3b). These differences were more apparent in the subgroups with good prognoses such as the elderly, patients negative for hepatitis B virus surface antigen, patients with Child-Pugh score = 5, absence of vascular invasion, absence of extrahepatic lesions, or tumor control except AFP (Table 5).

**Table 6.** Factors that influenced patients' outcomes

	<i>n</i>	Median over- all survival, months	Univariate <i>p</i> value <sup>a</sup>	Hazard ratio (95% CI)	Multi- variate <i>p</i> value <sup>b</sup>
Age					
<69 years	89	13.1	0.83		
≥69 years	101	16.1			
Gender					
Female	34	12.0	0.058	1.026 (0.653–1.612)	0.91
Male	156	15.6			
ECOG performance status					
1–3	15	7.1	0.0075	1.891 (0.954–3.747)	0.068
0	175	15.5			
Hepatitis B virus surface antigen					
Positive	52	12.2	0.16		
Negative	138	16.2			
Hepatitis C virus antibody					
Negative	91	12.4	0.11		
Positive	99	16.6			
Child-Pugh score					
6	97	13.0	0.49		
5	93	15.6			
Branched-chain amino acid					
Positive	30	12.0	0.086	1.873 (1.157–3.033)	0.011
Negative	160	15.2			
Maximum tumor size					
≥50 mm	59	8.1	<0.001	2.319 (1.476–3.643)	<0.001
<50 mm	131	18.5			
Number of tumors					
≥6	133	15.6	0.47		
<6	57	12.4			
Vascular invasion					
Positive	75	9.0	<0.001	1.145 (0.780–1.681)	0.49
Negative	115	19.2			
Extrahepatic lesion					
Positive	49	7.7	<0.001	1.313 (0.862–2.000)	0.20
Negative	141	17.2			
AFP					
≥400 ng/mL	69	10.5	0.0032	1.233 (0.836–1.820)	0.29
<400 ng/mL	121	18.6			
Treatment					
Sorafenib	51	13.0	0.077	1.240 (0.800–1.922)	0.34
HAIC	139	15.6			
CPS after 4 weeks					
Deteriorated	61	10.7	0.0028	1.425 (1.005–2.021)	0.047
Maintained or improved	122	17.7			
Best response to treatment <sup>c</sup>					
Progressive disease or not evaluable	70	7.7	<0.001	3.150 (2.174–4.566)	<0.001
Complete response, partial response, or stable disease	120	22.0			
Crossover second-line chemotherapy					
Positive	50	15.5	0.25		
Negative	140	14.1			

AFP, α-fetoprotein; HAIC, hepatic arterial infusion chemotherapy; ECOG, Eastern Cooperative Oncology Group. <sup>a</sup> log-rank test. <sup>b</sup> Cox proportional hazards regression model. <sup>c</sup> Based on RECIST v1.1.



**Fig. 4.** Kaplan-Meier plots of overall survival (OS) after treatment commencement. **a** OS was stratified according to ALBI grade when treatment commenced, and median OS times were 16.5, 12.4, and 4.2 months for patients with ALBI grades 1, 2, and 3 ( $p = 0.018$ , log-rank test). **b** OS did not differ between patients with not increased ALBI grades and patients with increased ALBI grades after 4 weeks (median OS times, 16.2 and 13.0 months, respectively,  $p = 0.81$ , log-rank test).

Univariate analyses revealed that 10 of the 16 selected variables were significantly associated with OS. They were as follows: sex, ECOG PS, consumption of branched-chain amino acids, maximum tumor size, vascular invasion, extrahepatic lesion, serum AFP levels, treatment procedure, and response to treatment as well as unchanged Child-Pugh scores. Multivariate analysis revealed that an increased Child-Pugh score after 4 weeks was an independent unfavorable predictive factor for OS (HR, 1.425) as well as consumption of branched-chain amino acids (HR, 1.873), maximum tumor size of 50 mm or larger (HR, 2.319), best response to treatment of complete, partial response, or stable disease (HR, 3.150) (Table 6).

#### *Impact of the ALBI Grade on Patients' Outcomes*

We used the ALBI grade as well as the Child-Pugh score to evaluate the effect of a patient's hepatic reserve on outcome. OS was stratified according to ALBI grade at the start of treatment ( $p = 0.018$ ) (Fig. 4a). However, there was no significant difference in median OS times (16.2 vs. 13.0 months, respectively,  $p = 0.81$ ) between patients with and without an unfavorable ALBI grade after 4 weeks (Fig. 4b).

## Discussion

The most important insight provided by the current study is that mild deterioration of hepatic reserve during chemotherapy had an unfavorable effect on a patient's prognosis, even in patients with well-preserved hepatic function before treatment. This result was interesting because it was independent of an antitumor effect as revealed by multivariate analysis. Our recent study of patients with Child-Pugh B found that an improved Child-Pugh score during chemotherapy is a favorable prognostic factor [7], which is reasonable because hepatic failure is often fatal. In contrast, HAIC and sorafenib are well-tolerated by patients with sufficient hepatic reserve [12, 13], and in the present study there were only 3 patients whose Child-Pugh scores rose to  $\geq 9$  after 4 weeks of treatment and 2 patients due to liver failure, suggesting that this result was not caused by lethal hepatic failure. Although we did not definitively identify the reason for these findings, the duration of survival after sorafenib treatment contributes to patients' OS [14], in part, because of increased availability of further treatment options [15, 16]. The present study suggests that a minor change in Child-Pugh score after 4 weeks might have a greater effect on outcome than our assumption related to patients with sufficient hepatic reserve. Although ALBI grade consisting of only 2 factors was simple and useful for the prediction of the patients' outcome before treatment, Child-Pugh score consisting of 5 factors seemed to be more sensitive than ALBI grade to evaluate the change of hepatic reserve contributing patients' outcome during chemotherapy. Therefore, when planning a treatment strategy, we should consider evaluating hepatic reserve using Child-Pugh score as well during the administration of chemotherapy.

Another unique aspect of the present study was that we compared sorafenib with HAIC, focusing on the change of hepatic reserve. Sorafenib has shown survival benefit compared with placebo for patients with advanced HCC in a phase III trial [4], and previous reports compared the outcomes of sorafenib and HAIC treatments. However, the clinical benefits of these treatments for patients with advanced HCC were assessed only in the context of prolonging survival, and it remains unclear which treatment is more useful for patients with advanced HCC [17, 18]. The results of this study demonstrated that HAIC maintained the Child-Pugh scores of patients and had a greater antitumor effect compared with sorafenib. Moreover, the antitumor effect did not significantly affect the Child-Pugh score, because the percentage of patients with unchanged Child-Pugh scores did not differ significantly according to anti-tumor effect, which suggested that the action of sorafenib blocking tumor cell proliferation and

angiogenesis may have some effect on the hepatic damage, although to our knowledge there have been no reports describing that sorafenib worsened the hepatic reserve, and then, further investigation is needed to confirm the damage to normal liver cells by sorafenib.

We further show that there was no significant difference in OS between the 2 treatment groups in multivariate analysis, and the PFS of the patients treated with HAIC was better compared with that of the patients who were treated with sorafenib. This discrepancy was partially because more patients treated with sorafenib also received HAIC as the crossover second-line chemotherapy, and the subsequent therapy especially targeting intrahepatic lesions was suggested to be effective even after systemic chemotherapy, sorafenib [15, 16]. Hepatic reserve closely correlates with the quality of life of patients with HCC [19], and we further showed that it contributed to patients' outcome. The subgroup analysis shown in Table 5 indicated that HAIC may replace sorafenib to treat patients with advanced HCC who were supposed to be long-term survivors because it is relatively more important to maintain hepatic reserve as well as to control tumor in such patients. However, we could not assess this assumption because of the lack of quality of life data for the patients studied here.

The administration of branched-chain amino acid effectively maintains the Child-Pugh score during chemotherapy of patients with advanced HCC [20, 21]. In contrast, the present study did not detect a significant effect of consumption of branched-chain amino acids on maintaining Child-Pugh scores. This apparent discrepancy may be explained by the retrospective nature of this study of patients with Child-Pugh A, the small population that received branched-chain amino acids, and bias introduced by the backgrounds of the groups. Therefore, a prospective trial with a sufficient number of patients is required to confirm the effectiveness of branched-chain amino acids or other factors in maintaining hepatic reserve of during chemotherapy of patients with advanced HCC.

## Conclusions

In conclusion, maintaining Child-Pugh scores contributed to a more favorable outcome of patients with advanced HCC, even if they had sufficient hepatic reserve when chemotherapy commenced. HAIC may therefore have greater potential for maintaining Child-Pugh scores compared with sorafenib.

## Disclosure Statement

The authors declare that they have no conflict of interest.

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