TABLE 1 Comparison of patients' characteristics based on grade of microvascular invasion

	No MVI ($n = 103$)	Mild MVI ($n = 59$)	Severe MVI ($n = 45$)	P value
Age, year (range)	65.5 (16–82)	67.0 (34–83)	65.0 (33–81)	0.599
Gender (male/female)	79/24	46/13	37/8	0.754
HCV (positive/negative)	74/29	38/21	35/10	0.319
HBV (positive/negative)	22/81	13/46	11/34	0.917
AST, U/L (range)	43 (15–153)	39.0 (14–137)	41.5 (13–160)	0.838
AFP, ng/ml (range)	11.5 (1–20,764)	10.6 (1.7–5,372)	100.3 (2.8–6,385)†‡	0.001
(≤100/>100)	82/21	45/14	23/22	0.001
DCP, AU/ml (range)	34.5 (10–2,529)	54.5 (10–4,761)	209.5 (13–20,919)†‡	<0.001
(≤100/>100)	77/23	36/23	16/29	<0.001
Tumor size, mm (range)	23.5 (12–50)	26.5 (12–50)†	29 (18–50)†	<0.001
(≤30/>30)	83/20	37/22	25/20	0.002
Number of tumors (single/2–3)	83/20	43/16	34/11	0.505
Histological grade (well/moderate/poorly)	10/92/1	0/52/7	0/33/12	<0.001
Background liver (normal+CH/cirrhosis)	60/43	39/20	27/18	0.61
Intrahepatic micrometastasis (present/absent)	2/101	12/47	23/22	<0.001
Capsular formation (present/absent)	62/41	44/15	25/20	0.09
Type of surgical resection (Major/minor)	57/46	35/24	31/14	0.304

Continuous variables presented as median (range)

MVI microvascular invasion, *HCV* hepatitis C virus, *HBV* hepatitis B virus, *AST* aspartate aminotransferase, *AFP* alpha-fetoprotein, *DCP* des-gamma-carboxy prothrombin, *CH* chronic hepatitis, *well* well differentiated, *moderate* moderately differentiated, *poorly* poorly differentiated

† $P < 0.05$ for post hoc test comparison without MVI

‡ $P < 0.05$ for post hoc test comparison with mild MVI

patients without MVI and with mild MVI who underwent resection for recurrence had intrahepatic recurrence with no more than three tumors (more than 50 % patients had a single tumor) and had no macroscopic VI or extrahepatic metastasis. Consequently, 41 (86 %) patients without MVI and 29 (76 %) patients with mild MVI underwent curative treatment for first recurrence, which included resection, RFA, microwave coagulation therapy (MCT), and percutaneous ethanol injection (PEI). In contrast, patients with severe MVI who underwent resection experienced a high frequency of fatal recurrence, including 22 (61 %) patients with multiple intrahepatic tumors, 6 (17 %) patients with macroscopic VI, and 11 (31 %) patients with extrahepatic metastasis. As a result, curative treatment for first recurrence could only be performed in 15 (42 %) patients with severe MVI.

Disease-Specific Survival and Predictive Factors

Of the total 207 patients, 58 patients died during follow-up. Of these 58 patients, 50 patients died from HCC-related causes. Factors associated with disease-specific survival were evaluated by univariate and multivariate analyses. Univariate analysis showed that presence of cirrhosis, elevated AFP level, elevated DCP level, tumor size >20 mm, presence of multiple tumors, presence of MVI, and presence of intrahepatic metastasis were significant variables affecting disease-specific survival (Table 2). By multivariate analysis, presence of MVI (mild MVI; HR: 2.4, 95 % CI: 1.09–5.26, $P = 0.029$ and severe MVI; HR: 6.06, 95 % CI: 2.93–12.53, $P < 0.001$), background liver (cirrhosis; HR: 2.54, 95 % CI: 1.42–4.55, $P = 0.002$), and tumor size (>30 mm; HR: 3.19, 95 % CI: 1.67–8.71, $P = 0.024$) were identified as independent predictors of disease-specific survival (Table 3). Disease-specific survival curves of patients stratified by grade of MVI are shown in Fig. 2b. Patients with worse MVI grades experienced significantly shorter disease-specific survival (no MVI vs. mild MVI, $P = 0.0017$; no MVI vs. severe MVI, $P < 0.0001$; mild MVI vs. severe MVI, $P = 0.0057$).

DISCUSSION

In our previous study, we demonstrated that MVI was a strong risk factor for poor outcome following curative resection in HCC patients within the Milan criteria.[22] The 3-year, recurrence-free survival rates for patients with and without MVI were 27.7 and 62.5 %, respectively. Thus, the presence of MVI was previously known to lead to a high frequency of recurrence of HCC after liver resection in the

TABLE 2 Univariate analyses of recurrence-free survival and disease-specific survival for hepatocellular carcinoma

	Recurrence-free survival HR (95 % CI)	*P* value	Disease-specific survival HR (95 % CI)	*P* value
Gender				
Male	1.26 (0.79–2)	0.325	1.36 (0.64–2.9)	0.426
Age (year)				
>65	1.71 (1.19–2.46)	0.004	1.03 (0.59–1.79)	0.92
HCV				
Positive	1.73 (1.13–2.65)	0.011	1.16 (0.625–2.16)	0.635
HBV				
Positive	0.58 (0.37–0.93)	0.022	0.95 (0.50–1.83)	0.885
AST, U/L				
>50	1.4 (0.97–2.01)	0.069	1.42 (0.82–2.49)	0.215
AFP, ng/mL				
>100	1.36 (0.93–2)	0.115	1.77 (1–3.12)	0.048
DCP, AU/mL				
>100	1.63 (1.14–2.32)	0.008	1.78 (1.02–3.11)	0.042
Tumor size, mm				
>30	1.64 (1.13–2.38)	0.009	2.66 (1.53–4.64)	0.001
Number of tumors				
2–3	1.93 (1.3–2.87)	0.001	1.92 (1.59–3.5)	0.032
Histological grade				
Moderate	1.56 (0.64–3.84)	0.331	2.78 (0.38–20.19)	0.312
Poorly	1.8 (0.64–5.13)	0.268	3.69 (0.43–31.7)	0.234
Background liver				
Cirrhosis	1.21 (0.84–1.75)	0.3	1.85 (1.06–3.22)	0.03
Microvascular invasion				
Mild	2.16 (1.4–3.31)	<0.001	2.78 (1.29–5.98)	0.009
Severe	2.92 (1.9–4.51)	<0.001	6.61 (3.32–13.16)	<0.001
Intrahepatic micrometastasis				
Present	1.98 (1.27–3.07)	0.002	3.47 (1.91–6.30)	<0.001
Capsular formation				
Present	0.87 (0.6–1.27)	0.482	1.09 (0.61–1.94)	0.771
Type of surgical resection				
Minor	1.18 (0.82–1.69)	0.38	1.64 (0.94–2.86)	0.081

HR hazard ratio, *CI* confidence interval, *HCV* hepatitis C virus, *HBV* hepatitis B virus, *CH* chronic hepatitis, *AST* aspartate aminotransferase, *AFP* alpha-fetoprotein, *DCP* des-gamma-carboxy prothrombin, *well* well differentiated, *moderate* moderately differentiated, *poorly* poorly differentiated

short term.[5–8] Nevertheless, because MVI encompasses many recurrence patterns ranging from curative to fatal, the differences in recurrence patterns are suggested to be associated with a wide range of outcomes with respect to long-term survival. Therefore, we classified patients into two groups (mild and severe MVI) and evaluated the significance of MVI classification.

In the present study, we showed that both mild and severe MVI were significant independent risk factors affecting recurrence-free survival in HCC patients after curative resection. Moreover, our results showed that both patients with mild and severe MVI had a high frequency of micrometastasis in resected liver specimens. Cancer cell spreading via the portal vein has been generally thought to be the main mechanism for such intrahepatic micrometastasis.[25] Micrometastasis is an important cause of early intrahepatic recurrence after liver resection.[26] Consequently, the identification of MVI as a risk factor for early recurrence after curative resection regardless of MVI grade in this study is very relevant.

In addition, both mild and severe MVI were identified as significant independent risk factors affecting survival in HCC patients after curative resection. These results suggest that a high frequency of early recurrence was the primary contributor to poor survival in patients with mild MVI. Early recurrence of HCC is known to be the major risk factor affecting survival following liver resection.[27,28] Moreover, liver function was also identified as an independent risk factor of survival in the present study. Thus, in patients with mild MVI, repeated recurrence and treatment are thought to decrease liver function, thereby contributing

TABLE 3 Multivariate analyses of recurrence-free survival and disease-specific survival for hepatocellular carcinoma

	HR (95 % CI)	*P* value
Recurrence-free survival		
Microvascular invasion		
Mild	1.93 (1.25–2.98)	0.003
Severe	2.87 (1.85–4.46)	<0.001
Age (year)		
>65	1.84 (1.27–2.65)	0.001
Number of tumors		
2–3	1.68 (1.13–2.51)	0.011
Disease-specific survival		
Microvascular invasion		
Mild	2.4 (1.09–5.26)	0.029
Severe	6.06 (2.93–12.53)	<0.001
Background liver		
Cirrhosis	2.54 (1.42–4.55)	0.002
Tumor size (mm)		
>30	2.41 (1.36–4.27)	0.003

HR hazard ratio, *CI* confidence interval

to poor long-term survival.[28] In contrast, although no significant difference in the frequency of recurrence was observed between patients with mild versus severe MVI, patients with severe MVI experienced significantly shorter survival compared with patients with mild MVI. Thus, this observed difference in survival was likely associated with recurrence pattern and not frequency of recurrence. In this study, patients with severe MVI experienced a higher frequency of fatal recurrence, associated with multiple intrahepatic tumors, macroscopic VI, and extrahepatic metastasis. Such fatal recurrence limits additional attempts at curative therapies in HCC patients with severe MVI.[10] As a result, patients with severe MVI experienced poorer survival compared to those with mild MVI. Consequently, we have shown that MVI classification based on the number of invaded vessels can be used to stratify patients into three distinct groups (without MVI, with mild MVI, and with severe MVI) with different risks of survival after curative resection.

Extrahepatic metastasis contributes to poor survival following liver resection in HCC patients.[4,29] Previous studies proposed that MVI was an independent risk factor affecting extrahepatic metastasis in HCC patients after curative resection.[29,30] In agreement with this, the present results revealed that extrahepatic metastasis occurred in approximately 31 % of HCC patients with severe MVI. Liver transplantation is widely accepted as a therapeutic option in HCC patients, particularly for those with cirrhosis and who fulfill the Milan criteria. Recently, MVI has been proposed as a significant risk factor for recurrence and survival in HCC patients after liver transplantation as well as liver resection.[20,21] Because total hepatectomy is performed in the recipient, extrahepatic metastasis is the primary site of recurrence in HCC patients following liver transplantation. Consequently, the present results suggest that severe MVI is a risk factor for liver transplantation in HCC patients, even if they fulfill the Milan criteria.

Prevention of early recurrence of HCC with MVI is the most important strategy for improving long-term survival in HCC patients after curative resection; however, no adjuvant systemic treatment has previously been reported to show a survival benefit. Sorafenib is an oral multikinase inhibitor that has recently become available for advanced HCC. Randomized phase III placebo-controlled trials demonstrated that sorafenib treatment resulted in a significant survival benefit in patients with advanced HCC and maintained liver function; as a result, sorafenib has become the only standard systemic treatment for advanced HCC.[31,32] Consequently, a prospective trial is required to

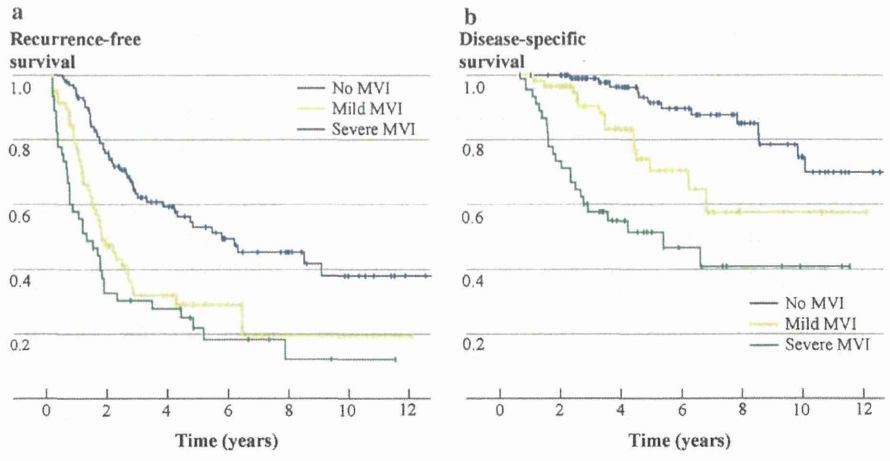

FIG. 2 Recurrence-free survival and disease-specific survival curves of patients stratified by grade of microvascular invasion (MVI). **a** Recurrence-free survival rates at 2 years were 75.9 % in patients without MVI, 47.2 % in patients with mild MVI, and 32.7 % in patients with severe MVI. **b** Disease-specific survival rates at 5 years were 91.5 % in patients without MVI, 70.4 % in patients with mild MVI, and 51.4 % in patients with severe MVI

assess the utility of sorafenib as adjuvant treatment for HCC patients with MVI, particularly because patients with severe MVI experience a high frequency of fatal recurrence after curative resection.

CONCLUSIONS

The present results demonstrated that MVI classification based on number of invaded vessels could stratify different recurrence patterns and risk of survival after curative resection in HCC patients within the Milan criteria. In particular, the presence of severe MVI was found to be associated with high malignant potential of HCC. Therefore, the results of this study suggest that it is important to histologically evaluate the presence of severe MVI after liver resection for determination of strict observation and adjuvant treatment.

DISCLOSURE No commercial interest.

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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

FIB-4 index for assessing the prognosis of hepatocellular carcinoma in patients with Child-Pugh class A liver function

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Abstract
Purpose We evaluated the prognosis of hepatocellular carcinoma (HCC) patients with Child-Pugh (C-P) class A based on FIB-4 index, which is a liver fibrosis marker.
Patients and methods A total of 915 HCC patients with C-P class A were investigated. We assessed the prognosis using FIB-4 index, and factors associated with survival rates were analyzed in these patients.
Results When patients were categorized according to FIB-4 index as <2.0 ($n = 93$), ≥2.0 and <4.0 ($n = 311$), and ≥4.0 ($n = 511$), survival rates at 5 years were 70.5 % [95 % confidence interval (CI) 59.0–79.9], 56.4 % (95 % CI 50.1–62.5), and 47.1 % (95 % CI 42.2–52.1), respectively. Patients with FIB-4 index <2.0 had a higher survival rate than the other groups (≥4.0 vs ≥2.0 and <4.0, $p = 0.010$; ≥2.0 and <4.0 vs <2.0, $p = 0.028$). We were able to predict prognosis in patients with C-P score 5 by FIB-4 index, but survival rate did not significantly differ in patients with C-P score 6. Multivariate analysis identified C-P score, FIB-4 index [≥2.0 and <4.0; hazard ratios (HRs) 1.638 (95 % CI 1.084–2.474); $p = 0.019$/≥4.0; HR 1.828 (95 % CI 1.217–2.744); $p = 0.004$], *Lens culinaris* agglutinin-reactive α-fetoprotein, tumor size, number, vascular invasion, antiviral therapy, and hepatectomy as independent predictive factors for survival.
Conclusions The FIB-4 index is useful for assessing prognosis in HCC patients with C-P class A, especially those with C-P score 5.

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Keywords FIB-4 index · Noninvasive fibrosis marker · Prognosis · Hepatocellular carcinoma · Child-Pugh classification

Abbreviations

HCC	Hepatocellular carcinoma
C-P	Child-Pugh
SVR	Sustained virological response
HCV	Hepatitis C virus
HBV	Hepatitis B virus
EASL	European Association for the Study of the Liver
AFP	α-Fetoprotein
AFP-L3	*Lens culinaris* agglutinin-reactive α-fetoprotein
DCP	Des-γ-carboxy prothrombin
US	Ultrasonography
CT	Computed tomography
MRI	Magnetic resonance imaging
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
HR	Hazard ratio
LAT	Locoregional ablative therapy
RFA	Radiofrequency ablation
TACE	Transcatheter arterial chemoembolization
CI	Confidence interval

Introduction

The incidence of hepatocellular carcinoma (HCC) has rapidly increased worldwide. HCC is the sixth most common malignancy and the third most common cause of cancer-related death (El-Serag and Rudolph 2007; Jemal et al. 2011). Since HCC usually develops in a damaged liver, the prognosis of HCC depends not only on tumor progression

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but also on the degree of liver dysfunction (de Lope et al. 2012; Izumi et al. 1994).

The Child-Pugh (C-P) classification, also known as the Child-Turcotte-Pugh score, is commonly used to evaluate liver function in the context of chronic liver disease, mainly cirrhosis (Pugh et al. 1973). The C-P score is based on 5 factors, which are each assigned 1–3 points: serum bilirubin and serum albumin levels, prothrombin time, ascites, and encephalopathy. The total number of points can range from 5 to 15. In multivariate analysis, the C-P class is associated with mortality in liver cirrhosis patients (Merkel et al. 2000; Fernández-Esparrach et al. 2001).

The percentage of patients who had C-P class A liver function at the initial diagnosis of HCC is increasing in Japan (Toyoda et al. 2011) because of the development of surveillance systems for HCC. In addition, the increase in the average age of HCC patients results in the increase of HCC patients with C-P class A; HCC is likely to develop without the progressed liver disease in elderly patients (Umemura et al. 2009; Kumada et al. 2013a).

Furthermore, the treatment for viral hepatitis has been undergoing rapid change. All-oral drug combination therapy will be replaced by peginterferon and ribavirin in the near future in patients with chronic hepatitis C, which will achieve the eradication of HCV sustained virological response (SVR) (Lok et al. 2012; Afdhal et al. 2014a, b; Jacobson et al. 2013).

On the other hand, peginterferon and nucleos(t)ide analogue therapy has been reported to improve liver function among HBV-related chronic hepatitis and cirrhosis patients (Buster et al. 2007; Kumada et al. 2013b; Schiff et al. 2008; Shim et al. 2010).

With these progresses in treatments and managements of viral hepatitis, the number of HCC patients with C-P class A will be expected to increase.

Given the expected increase in the number of patients with C-P class A liver function at the diagnosis of HCC, it will be necessary to further discriminate the prognosis of HCC patients with C-P class A from the aspect of liver function. In the present study, we attempted to incorporate the liver fibrosis factors for the evaluation of the prognosis of HCC patients with C-P class A.

Several noninvasive biomarkers of liver fibrosis that may replace liver biopsy in the diagnosis of fibrosis have been reported (Leroy et al. 2007; Wai et al. 2003; Sebastiani et al. 2006). The FIB-4 index is a noninvasive liver fibrosis evaluation method calculated by using age, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet count is one noninvasive liver fibrosis evaluation method. Vallet-Pichard et al. (2007) reported that the FIB-4 index is concordant with FibroTest results.

The aim of this study was to assess the utility of the FIB-4 index in assessing the prognosis of HCC patients with C-P class A.

Methods

Patients and HCC follow-up protocol

Between 1992 and 2012, a total of consecutive 1,340 patients were diagnosed with HCC at the Department of Gastroenterology of Ogaki Municipal Hospital, Japan. Patients with C-P class B ($n = 334$) and C ($n = 91$) were excluded from this analysis. Therefore, we investigated 915 HCC patients with C-P class A disease in the present study.

HCC was diagnosed on the basis of histological examination of tumor tissue in 423 patients (46.2 %) including 401 patients who underwent hepatectomy and 22 patients who underwent percutaneous liver biopsy. In the remaining 492 patients, the diagnosis was confirmed by typical radiological findings according to the guidelines of the European Association for the Study of the Liver (EASL) guidelines (2012).

All laboratory data were measured at the time of HCC diagnosis, including tumor markers for HCC [i.e., α-fetoprotein (AFP), *Lens culinaris* agglutinin-reactive α-fetoprotein (AFP-L3), des-γ-carboxy prothrombin (DCP)].

All patients received regular follow-up examinations at three-month intervals at our institution, which consisted of imaging studies, either ultrasonography (US), contrast-enhanced computed tomography (CT), or magnetic resonance imaging (MRI), and measurement of HCC tumor markers. We selected the treatment strategies for HCC according to the clinical practice guidelines of the Japan Society of Hepatology (2009). The study protocol was approved by the institutional review board and was conducted in compliance with the Helsinki Declaration.

Calculation of the FIB-4 index

The FIB-4 index was calculated at the time of HCC diagnosis using the following formula: FIB-4 index = AST [IU/L] × age [years]/platelet count [10^9/L] × ALT [IU/L]$^{1/2}$. The optimal FIB-4 index cutoff point was determined using a Cox proportional hazards model and the distribution of patients. Patients were grouped according to their FIB-4 index score as follows: <2.0 ($n = 93$), ≥2.0 and <4.0 ($n = 311$), and ≥4.0 ($n = 511$). Patients with a C-P score 5 and 6 were grouped according to their FIB-4 index score as follows: <2.0 ($n = 79$ and 14, respectively), ≥2.0 and <4.0 ($n = 245$ and 66, respectively), and ≥4.0

($n = 282$ and 229, respectively). Patients who underwent hepatectomy/locoregional ablative therapy [LAT, which included radiofrequency ablation (RFA) and ethanol injection] were grouped according to their FIB-4 index score as follows: <2.0 ($n = 70$), ≥2.0 and <4.0 ($n = 222$), and ≥4.0 ($n = 357$).

Statistical analysis

The SPSS software package, version 15.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. Continuous variables are expressed as medians (first quartile–third quartile points). An actuarial analysis of the cumulative survival and recurrence rates was performed using the Kaplan–Meier method, and differences across groups were compared using the log-rank test. Cox proportional hazards modeling with forward selection was used to estimate the hazard ratios (HRs) for the survival rate associated with the following parameters: etiology (viral or non-viral hepatitis), C-P score (5 or 6 points), AFP (≤20 or >20 ng/mL), AFP-L3 (≤10 or >10 %), DCP (≤40 or >40 mAU/mL), FIB-4 index (<2.0, ≥2.0 and <4.0, or ≥4.0), tumor size (<3 or ≥3 cm), number of tumors (single or multiple), vascular invasion (absent or present), and hepatectomy as initial treatment for HCC. We used the lower or upper limit of the reference values at our institute as cutoff values for laboratory data. Statistical significance was defined as $p < 0.05$.

Results

Patient characteristics

The characteristics of the study patients are shown in Table 1. The median age was 69 years, and there was a predominance of men (73.3 %). The majority of patients were infected with HCV (69.9 %). HBV infection was observed in 15.6 % of patients. Alcohol abuse was defined as ≥60 g/day intake. One hundred and fifteen patients with HCV infection underwent interferon (IFN)-based antiviral therapy. Of these, 30 patients (21.6 %) achieved sustained virological response (SVR). SVR was defined by the absence of serum HCV RNA 24 weeks after the end of the treatment. Of 153 patients with HBV infection, 89 (58.2 %) received nucleos(t)ide analogue therapy.

There were 606 (66.2 %) patients with C-P score of 5 and 309 (33.8 %) with C-P score of 6. The median of FIB-4 of whole patients' index was 4.4. It was 3.7 in patients with C-P score 5, and 6.3 in those with C-P score 6, respectively. The median follow-up period was 3.0 years. Of the 915 patients, 401 underwent hepatectomy, 248 were treated with LAT, and 170 were initially treated with transcatheter arterial chemoembolization (TACE).

Overall survival rate of entire patients based on Child-Pugh score

The overall survival rates of entire patients at 5 and 10 years were 52.7 % [95 % confidence interval (CI) 48.8–56.2] and 29.7 % (95 % CI 25.7–34.1), respectively (Fig. 1). The overall survival rate for patients with C-P score 5 was 60.5 % (95 % CI 55.7–64.5) at 5 years and 33.9 % (95 % CI 28.9–39.3) at 10 years, compared to 36.3 % (95 % CI 30.1–42.9) at 5 years and 20.8 % (95 % CI 14.4–29.0) at 10 years in patients with C-P score 6. The group with C-P score 5 had a significantly better prognosis than the group with C-P score 6 ($p < 0.001$) (Fig. 2).

Table 1 Clinical background of the study patients ($n = 915$)

Age (years)	69 (62–75)
Sex (female/male)	244 (26.7 %)/671 (73.3 %)
Etiology (HBV/HCV/HBV + HCV/non-HBV and non-HCV)	143 (15.6 %)/640 (69.9 %)/10 (1.1 %)/122 (13.3 %)
Alcohol abuse (negative/positive)	666 (72.8 %)/249 (27.2 %)
Ascites (absent/present)	902 (98.6 %)/13 (1.4 %)
Encephalopathy (absent/present)	909 (99.3 %)/6 (0.7 %)
AST (IU/mL)	53 (36–79)
ALT (IU/mL)	45 (28–73)
Platelet count ($\times 10^4/m^3$)	12.6 (9.0–17.4)
Prothrombin time (%)	90 (88–99)
Total bilirubin (mg/dL)	0.7 (0.5–1.0)
Albumin (g/dL)	3.8 (3.5–4.1)
Child-Pugh score (5/6)	606 (66.2 %)/309 (33.8 %)
AFP (ng/mL)	19 (6–144)
AFP-L3 (%)	0.5 (0–11.6)
DCP (mAU/mL)	49 (20–389)
FIB-4 index	4.4 (2.8–6.8)
Tumor size (cm)	2.5 (1.7–4.3)
Tumor number (single/multiple)	570 (62.3 %)/345 (37.7 %)
Vascular invasion (absent/present)	801 (87.5 %)/114 (12.5 %)
Initial treatment	
No treatment/hepatectomy/LAT	48 (5.2 %)/401(43.8 %)/248 (27.1 %)
TACE/other[a]	170 (18.6 %)/48 (5.2 %)
Observation period (years)	3.0 (1.3–5.7)

Values are expressed as medians (first quartile, third quartile points)

HBV hepatitis B virus, *HCV* hepatitis C virus, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *AFP* α-fetoprotein, *AFP-L3 Lens culinaris* agglutinin-reactive α-fetoprotein, *DCP* des-γ-carboxy prothrombin, *LAT* locoregional ablative therapy, *TACE* transcatheter arterial chemoembolization

[a] Includes repeated arterial infusion chemotherapy, systemic chemotherapy, and radiation therapy

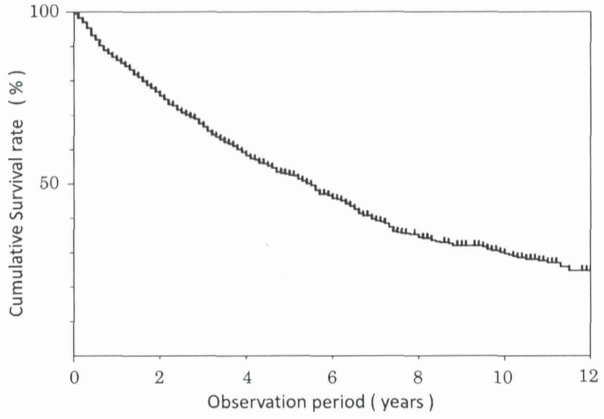

Fig. 1 Overall survival rates of entire patients at 5 and 10 years were 52.7 and 29.7 %, respectively

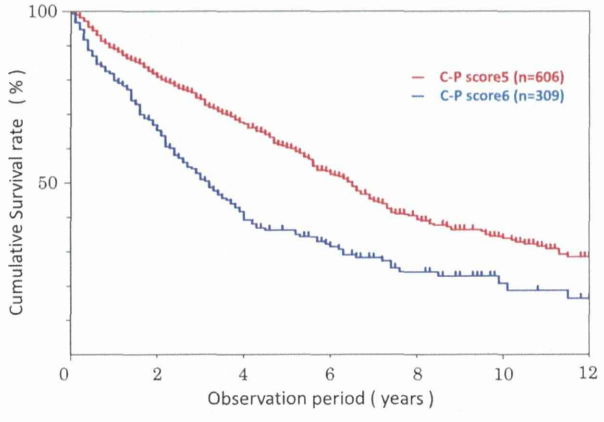

Fig. 2 Prognosis of the Child-Pugh score 5 group was significantly better compared to the Child-Pugh score 6 group

Overall survival rate of entire patient based on the FIB-4 index

When patients were categorized according to the FIB-4 index as <2.0 ($n = 93$), ≥2.0 and <4.0 ($n = 311$), and ≥4.0 ($n = 511$), the survival rates at were 70.5 % (95 % CI 59.0–79.9), 56.4 % (95 % CI 50.1–62.5), and 47.1 % (95 % CI 42.2–52.1) at 5 years, respectively, and 55.3 % (95 % CI 42.2–67.7), 32.2 % (95 % CI 25.5–39.6), and 23.7 % (95 % CI 18.6–29.7) at 10 years, respectively (Fig. 3). The FIB-4 index <2.0 group had a significantly better prognosis than the FIB-4 index ≥2.0 and <4.0 group ($p = 0.028$). The FIB-4 index ≥2.0 and <4.0 group had a significantly better prognosis than the FIB-4 index ≥4.0 group ($p = 0.010$).

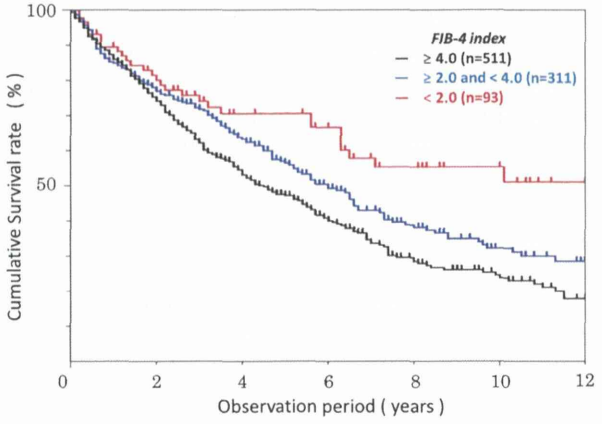

Fig. 3 Overall survival rate based on the FIB-4 index. The FIB-4 index of patients with Child-Pugh class A predicts outcomes with good discriminative ability

Overall survival and recurrence rate of patients who underwent hepatectomy/LAT based on the FIB-4 index

When focusing on HCC patients who underwent hepatectomy/LAT, FIB-4 index was <2.0 in 70 patients (10.8 %), ≥2.0 and <4.0 in 222 patients (34.2 %), and ≥4.0 in 357 patients (55.0 %). Figure 4a shows the overall survival rates of these three groups. The survival rates of the FIB-4 index <2.0, ≥2.0 and <4.0, and ≥4.0 groups were 80.0 % (95 % CI 67.1–88.7), 68.9 % (95 % CI 61.7–75.2), and 59.1 % (95 % CI 53.2–64.7) at 5 years, respectively, and 65.2 % (95 % CI 49.4–78.1), 40.9 % (95 % CI 32.6–49.9), and 28.6 % (95 % CI 22.1–36.1) at 10 years, respectively. The FIB-4 index <2.0 group had a significantly better prognosis than the FIB-4 index ≥2.0 and <4.0 group ($p = 0.047$). The FIB-4 index ≥2.0 and <4.0 group had a significantly better prognosis than the FIB-4 index ≥4.0 group ($p = 0.005$).

Figure 4b shows overall intrahepatic recurrence rates following the initial treatment in these three groups. The recurrence rates of patients with FIB-4 index <2.0, ≥2.0 and <4.0, and ≥4.0 were 54.3 % (95 % CI 52.4–79.5), 63.6 % (95 % CI 56.1–70.5) and 79.6 % (95 % CI 74.5–89.0), respectively, at 5 years and 67.4 % (95 % CI 52.4–79.5), 79.0 % (95 % CI 70.6–85.5) and 89.7 % (95 % CI 84.2–93.4), respectively, at 10 years. The FIB-4 index ≥4.0 group had a significantly higher recurrence rate than the other groups (FIB-4 index ≥4.0 vs ≥2.0 and <4.0, $p < 0.001$; ≥4.0 vs <2.0, $p = 0.001$). There were no significant differences in recurrence rate between the FIB-4 index <2.0 and ≥2.0 and <4.0 groups ($p = 0.465$).

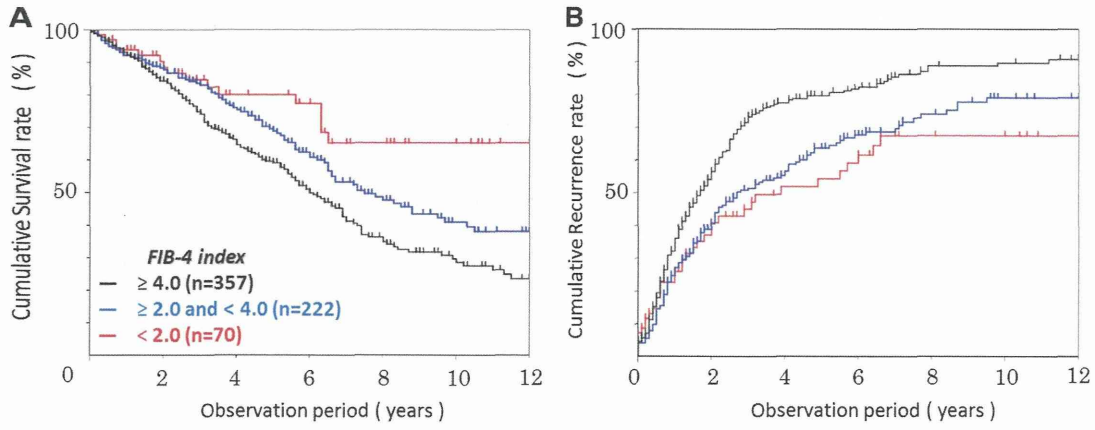

Fig. 4 Overall survival (**a**) and recurrence rate (**b**) based on the FIB-4 index in patients who underwent hepatectomy/LAT. The FIB-4 index <2.0 group had a significantly better prognosis than the other groups, and the recurrence rate of FIB-4 index ≥4.0 group was higher than that of the other groups

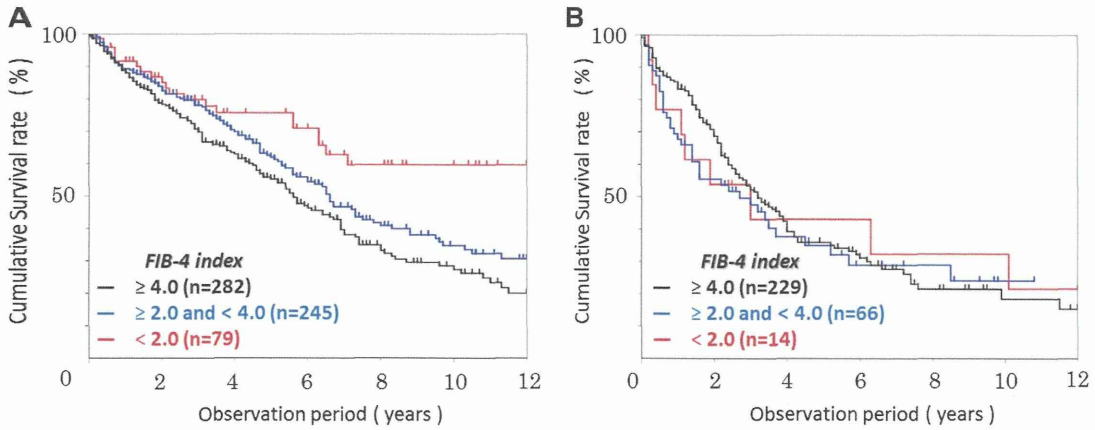

Fig. 5 Overall survival rates of patients with a Child-Pugh score of 5 (**a**) and 6 (**b**) based on the FIB-4 index. The FIB-4 index was useful for assessing mortality among patients with a Child-Pugh score of 5, but there were no significant difference among patients with a Child-Pugh score of 6

Overall survival rate of patients with C-P score 5 or 6 based on the FIB-4 index

When focusing on HCC patients with C-P score 5, FIB-4 index was <2.0 in 79 patients (13.0 %), ≥2.0 and <4.0 in 245 patients (40.4 %), and ≥4.0 in 282 patients (46.5 %). Figure 5a shows the overall survival rates of these three groups. The survival rates of the FIB-4 index <2.0, ≥2.0 and <4.0, and ≥4.0 groups were 75.7 % (95 % CI 63.2–84.9), 61.9 % (95 % CI 54.8–68.5), and 55.2 % (95 % CI 48.6–61.5) at 5 years, respectively, and 59.7 % (95 % CI 44.9–72.9), 34.7 % (95 % CI 27.1–43.2), and 27.3 % (95 % CI 20.6–35.3) at 10 years, respectively. The survival rate was highest in patients with FIB-4 index <2.0, followed by those with FIB-4 index ≥2.0 and <4.0, and those with FIB-4 index ≥4.0, although the difference between patients with FIB-4 index ≥2.0 and <4.0 and those with FIB-4 index ≥4.0 was not significant statistically (FIB-4 index <2.0 vs ≥2.0 and <4.0, $p = 0.028$, FIB-4 index <2.0 vs ≥4.0, $p < 0.001$, and FIB-4 index ≥2.0 and <4.0 vs ≥4.0, $p = 0.052$).

When focusing on HCC patients with C-P score 6, FIB-4 index was <2.0 in 14 patients (4.5 %), ≥2.0 and <4.0 in 66 patients (21.4 %), and ≥4.0 in 229 patients (74.1 %). Figure 5b shows overall survival rate of these three groups. The survival rate of patients with FIB-4 index <2.0, ≥2.0 and <4.0, and ≥4.0 were 43.1 % (95 % CI 19.0–71.0), 35.0 % (95 % CI 22.9–49.4) and 36.0 % (95 % CI 28.8–43.8), respectively, at 5 years and 32.3 % (95 % CI 11.6–63.5), 24.1 % (95 % CI 12.7–40.8) and 18.4 % (95 % CI

Table 2 Factors associated with patient survival (univariate analysis)

Factor	Hazard ratio	95 % CI	*p* value
Age (years)			
<65	1		
≥65	1.335	1.095–1.628	0.004
Sex			
Female	1		
Male	1.156	0.605–1.422	0.172
AST (IU/mL)			
≤40	1		
>40	1.518	1.235–1.860	0.001
ALT (IU/mL)			
≤35	1		
>35	1.158	0.954–1.407	0.139
Platelet count ($\times 10^4/m^3$)			
≥15	1		
<15	1.026	0.804–1.181	0.792
Total bilirubin (mg/dL)			
≤1.2	1		
>1.2	1.195	0.888–1.608	0.239
Albumin (g/dL)			
>3.5	1		
≤3.5	1.912	1.549–2.360	<0.001
Prothrombin time (%)			
>70	1		
≤70	1.086	0.519–1.634	0.921
Etiology (viral hepatitis)			
Present	1		
Absent	1.356	1.041–1.761	0.024
Child-Pugh score			
5	1		
6	1.845	1.528–2.227	<0.001
Alcohol abuse			
Absent	1		
Present	1.033	0.844-1.264	0.756
AFP (ng/mL)			
≤20	1		
>20	1.449	1.207–1.739	<0.001
AFP-L3 (%)			
≤10	1		
>10	1.904	1.549–2.342	<0.001
DCP (mAU/mL)			
≤40	1		
>40	1.614	1.339–1.945	<0.001
FIB-4 index			
<2.0	1		
≥2.0 and <4.0	1.550	1.048–2.292	0.028
≥4.0	2.001	5.761–2.917	<0.001
Tumor size (cm)			
<3	1		
≥3	2.220	1.849–2.665	<0.001
Tumor number			
Single	1		
Multiple	2.350	1.953–2.824	<0.001
Vascular invasion			
Absent	1		
Present	4.989	3.883–6.410	<0.001
Antiviral therapy			
−	1		
+	0.501	0.393–0.639	<0.001
Initial treatment			
Hepatectomy			
−	1		
+	0.438	0.368–0.531	<0.001
LAT			
−	1		
+	0.880	0.717–1.071	0.218

CI confidence interval, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *AFP* α-fetoprotein, *AFP-L3 Lens culinaris* agglutinin-reactive α-fetoprotein, *DCP* des-γ-carboxy prothrombin, *LAT* locoregional ablative therapy

11.1–28.9), respectively, at 10 years. There were no significant differences in survival rates among these three groups (FIB-4 index <2.0 vs ≥2.0 and <4.0, $p = 0.812$; FIB-4 index <2.0 vs ≥4.0, $p = 0.743$; FIB-4 index ≥2.0 and <4.0 vs ≥4.0, $p = 0.393$).

Factors associated with patient survival

Factors significantly associated with overall survival in the univariate analysis are listed in Table 2. The following associations were statistically significant: age, AST, albumin, HCC etiology, C-P score, AFP, AFP-L3, DCP, FIB-4 index, tumor size, number of tumors, vascular invasion, antiviral therapy, and hepatectomy/LAT as initial treatment. Factors that were significantly associated with overall survival in the multivariate analysis were C-P score 6 [HR 1.564 (95 % CI 1.257–1.946); $p < 0.001$], FIB-4 index ≥2.0 and <4.0 [HR 1.638 (95 % CI 1.084–2.474); $p = 0.019$] and FIB-4 index ≥4.0 [HR 1.828 (95 % CI 1.217–2.744); $p = 0.004$], AFP-L3 >10 % [HR 1.458 (95 % CI 1.163–1.829); $p = 0.001$], tumor size ≥3 cm [HR 1.718 (95 % CI 1.382–2.136); $p < 0.001$], number of tumors (multiple) [HR 1.464 (95 % CI 1.172–1.828); $p = 0.001$], vascular invasion (present) [HR 2.884 (95 % CI 2.102–3.957); $p < 0.001$], antiviral therapy [HR 0.761 (95 % CI 0.585–0.989); $p = 0.041$], and hepatectomy as initial treatment [HR 0.625 (95 % CI 0.497–0.786); $p < 0.001$] (Table 3).

Table 3 Factors associated with patient survival based on multivariable Cox proportional hazards modeling with forward selection

Factor	Hazard ratio	95 % CI	*p* value
Child-Pugh score			
5	1		
6	1.564	1.257–1.946	<0.001
FIB-4 index			
<2.0	1		
≥2.0 and <4.0	1.638	1.084–2.474	0.019
≥4.0	1.828	1.217–2.744	0.004
AFP-L3 (%)			
≤10	1		
>10	1.458	1.163–1.829	0.001
Tumor size (cm)			
<3	1		
≥3	1.718	1.382–2.136	<0.001
Tumor number			
Single	1		
Multiple	1.464	1.172–1.828	0.001
Vascular invasion			
Absent	1		
Present	2.884	2.102–3.957	<0.001
Antiviral therapy			
−	1		
+	0.761	0.585–0.989	0.041
Initial treatment			
Hepatectomy			
−	1		
+	0.625	0.497–0.786	<0.001

CI confidence interval, *AFP-L3 Lens culinaris* agglutinin-reactive α-fetoprotein

Discussion

C-P classification and tumor staging are both important factors for predicting mortality in HCC patients. Therefore, we have to assess both tumor factors and residual liver function when choosing the type of treatment for HCC. Recently, proposed staging system for HCC combined tumor factors and liver functional markers has been reported (the Cancer of the Liver Italian Program (CLIP) investigators 1998; Llovet et al. 1999; Kudo et al. 2004).

In patients with HCC who have C-P class A liver function at diagnosis, in the present study, there were significant differences in the survival rates between C-P score 5 and 6 groups. However, we are not able to further stratify HCC patients with C-P score 5 in terms of liver function, because the minimum score of C-P is 5 points.

It has been reported that the FIB-4 index is well correlated with liver fibrosis (Sterling et al. 2006; Vallet-Pichard et al. 2007; Shah et al. 2009). Although liver fibrosis is reportedly intertwined with hepatocarcinogenesis and the prognosis of chronic hepatitis C (Tamaki et al. 2013; Vergniol et al. 2014), there have been few reports on whether the FIB-4 index is associated with mortality in HCC patients. In this study, we investigated the impact of the FIB-4 index on prognosis of HCC with C-P class A.

When patients were categorized as <2.0, ≥2.0 and <4.0, and ≥4.0 by FIB-4 index, patients with FIB-4 index <2.0 had a highest survival rate, followed by those with FIB-4 index ≥2.0 and <4.0, and those with FIB-4 index ≥4.0. In addition, the FIB-4 index was also useful for predicting prognosis in patients who underwent curative treatment (hepatectomy/LAT), and the recurrence rate of FIB-4 index ≥4.0 group was higher than that of the other groups in this analysis. These results indicate that the calculation of the FIB-4 index at the start of follow-up is useful for predicting the outcome of HCC patients with C-P class A.

Whereas we found a significant difference in survival rates based on the FIB-4 index in patients with C-P score 5, we did not find a difference in survival rates in patients with C-P score 6. The C-P scoring system is considered to reflect remnant liver function. In contrast, the FIB-4 index is a marker of liver fibrosis. Although liver fibrosis is partly linked to remnant liver function, these are not completely coincident. Patients with C-P class A can have various degrees of liver fibrosis. Therefore, we were able to further stratify the prognosis of HCC patients with C-P score 5 using the FIB-4 index, a quantitative marker of liver fibrosis.

Both the FIB-4 index and C-P score were identified as independent risk factors for predicting the outcome of HCC along with tumor factors such as tumor size, number, and tumor marker levels, and initial treatment in the multivariate analysis. In addition, the hazard ratio of the FIB-4 index was higher than the HR for the C-P score. Therefore, FIB-4 index has a strong impact on the prognosis of patients with HCC when they have C-P class A liver function.

The utility of FIB-4 index is enhanced by the fact that it is calculated using age and general laboratory data, in terms of low cost, easy to calculate. In addition, the index can be monitored easily with repeated calculation. Nevertheless, the FIB-4 index has several limitations. The formula for the FIB-4 index includes platelet count. Therefore, caution is needed when a patient's platelet count is low due to extrahepatic causes, for example, idiopathic thrombocytopenic purpura and post-splenectomy.

There are several issues that should be further studied in the future. The FIB-4 index has been developed as a noninvasive marker of fibrosis in patients with chronic hepatitis C and non-alcoholic fatty liver disease (Sterling et al. 2006; Vallet-Pichard et al. 2007; Shah et al. 2009). Since the predominant etiology of HCC in the present study was HCV,

further studies are required for assessing the prognosis of HCC due to other etiologies (HBV and non-HBV + HCV). Additionally, we did not investigate other serum liver fibrosis markers including hyaluronic acid and type IV collagen 7s. Hence, it is necessary to assess the utility of these values for the prediction of prognosis in HCC patients and their relationship to the FIB-4.

In conclusion, the FIB-4 index was closely associated with mortality in HCC patients with C-P class A, especially those with C-P score 5. The FIB-4 index was identified as an independent predictive factor for HCC prognosis from a set of tumor and therapy-related factors. Therefore, the FIB-4 index is very useful to clinicians when predicting mortality and determining treatment strategies for HCC patients with C-P score 5.

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Conflict of interest The authors declare no conflicts of interests.

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ORIGINAL REPORT

Assessment of Liver Function in Patients With Hepatocellular Carcinoma: A New Evidence-Based Approach—The ALBI Grade

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ABSTRACT

Purpose
Most patients with hepatocellular carcinoma (HCC) have associated chronic liver disease, the severity of which is currently assessed by the Child-Pugh (C-P) grade. In this international collaboration, we identify objective measures of liver function/dysfunction that independently influence survival in patients with HCC and then combine these into a model that could be compared with the conventional C-P grade.

Patients and Methods
We developed a simple model to assess liver function, based on 1,313 patients with HCC of all stages from Japan, that involved only serum bilirubin and albumin levels. We then tested the model using similar cohorts from other geographical regions (n = 5,097) and other clinical situations (patients undergoing resection [n = 525] or sorafenib treatment for advanced HCC [n = 1,132]). The specificity of the model for liver (dys)function was tested in patients with chronic liver disease but without HCC (n = 501).

Results
The model, the Albumin-Bilirubin (ALBI) grade, performed at least as well as the C-P grade in all geographic regions. The majority of patients with HCC had C-P grade A disease at presentation, and within this C-P grade, ALBI revealed two classes with clearly different prognoses. Its utility in patients with chronic liver disease alone supported the contention that the ALBI grade was indeed an index of liver (dys)function.

Conclusion
The ALBI grade offers a simple, evidence-based, objective, and discriminatory method of assessing liver function in HCC that has been extensively tested in an international setting. This new model eliminates the need for subjective variables such as ascites and encephalopathy, a requirement in the conventional C-P grade.

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INTRODUCTION

Most patients with hepatocellular carcinoma (HCC) have associated chronic liver disease,[1] usually at the stage of cirrhosis in which HCC development is one of the main causes of liver-related mortality.[2] It is widely perceived that survival in HCC depends on tumor stage, underlying liver function, and perhaps, performance status. Liver function is currently graded according to the Child-Pugh (C-P) system, which was originally developed to assess prognosis in patients with cirrhosis and portal hypertension undergoing surgery for variceal bleeding.[3,4] The C-P grade (which is based on a score derived from five parameters including conventional liver function tests, extent of ascites, and degree of hepatic encephalopathy) has since become widely used, sometimes with modification for different etiologies, in all areas of chronic liver disease.[5,6] Many of its limitations have been described in detail.[7]

It is not clear that the C-P grade is appropriate for assessing liver function/dysfunction in patients with HCC. A variable percentage of patients with HCC do not, in fact, have cirrhosis, but rather a

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range of liver pathology from mild abnormalities to advanced fibrosis,[8] and the degree of liver (dys)function is likely related to the tumor and the state of the nontumorous liver. In addition, some of the variables considered in the C-P grade are interrelated (eg, ascites and serum albumin levels), and the grading of ascites and encephalopathy can be highly subjective. For example, there are no clear guidelines for distinguishing between mild and moderate ascites and/or the impact of diuretic therapy on the scoring of this variable, and the impact of the tumor on the pathogenesis of the ascites is not clear. Finally, the C-P grade does not offer a wide degree of discrimination among patients with HCC, the majority of whom fall into the A grade.[9] In all clinical studies of HCC in which prognosis is considered, the level of liver (dys)function clearly impacts on overall survival. For this reason, the C-P has been widely used for stratification in clinical trials and staging systems, despite the system having been developed arbitrarily based on clinical observation several decades ago and without formal statistical grounding.[10]

The C-P grade relies on individual parameters that are scored based on arbitrarily defined, predetermined cutoff points. The loss of information consequent on categorizing patients into distinct groups has been shown. Dichotomization of continuous data in a multiple regression procedure may be associated with considerable loss of statistical power and introduction of bias.[11,12] The most noticeable impact lies in patients who fall around the cut point (ie, just below or above the value used to define the two levels of the binary variable) who may be classified as having different risk. In the case of the C-P grade, for example, a score based on a serum bilirubin level of 50

Table 1. Characteristics of the Cohorts

Characteristic	United Kingdom		Spain	Japan	China	United States	Cirrhotic Patients (no HCC)	Clinical Trials Cohort	Patients Undergoing Resection
	Birmingham	Newcastle							
Total No. of patients	724	632	834	2,599	1,112	509	501	1,132	525
Accrual period	2007-2012	2000-2010	1994-2012	1994-2004	2003-2012	1996-2012	2006-2008	2008-2011	1990-2012
Race, %						Not available	Not available		
White	82.9	96.3	97.6					24.4	
Asian				> 95	> 95			66.1	> 95
Other								8.5	
Age, years									
Median	64.6	69	63.2	67	60	60.8	54	60	67
IQR	53.3-71.8	61-76	55.1-70.3	61-72	52-69	53.0-71	45-61	52-68	60-73
Mean	64	68	62.4	66.4	60.1	61.3	53.3	59	65.7
SD	11	11	10.9	8.9	12.1	12.2	12.4	12.6	9.3
Male									
%	80.5	80.7	82.9	71.7	85.6	81.7	63.2	84.0	75.8
Total No. with data	724	632	834	2,598	1,112	416	500	1,132	525
Child-Pugh grade									
Total No. with data	710	626	800	2,599	1,112	361	Not available	1,101	522
A									
No.	525	385	495	1,743	730	208		1,055	492
%	74	61.5	62	67	65	57.6		95.8	94.3
B									
No.	153	150	237	684	319	111		46	30
%	21	24.0	30	26	29	30.8		4.2	5.7
C									
No.	32	91	68	172	63	42		0	0
%	5	14.5	8	7	6	11.6		0	0
Presence of macroscopic vascular invasion							Not applicable		
%	22.3	27.3	25.2	14.1	39.3	35.6		29.7	7.8
Total No. with data	701	631	824	2,592	1,112	232		1,117	523
Bilirubin, μmol/L									
Median	17	18	23.9	15.4	20	20.5	44	15.4	12.0
IQR	10-30	11-34	15.4-40.5	10.3-22.2	12-33	12.0-37.6	23-110	10.3-20.5	8.6-15.4
Total No. with data	715	626	772	2,599	1,112	385	501	1,077	523
Albumin, g/L									
Median	39	36	36.3	35	37	35	31	39	39
IQR	34-43	31-40	31-41	31-39	32-40	30-40	27-35	35-42	36-42
Total No. with data	716	623	675	2,599	1,112	376	501	1,074	522
Survival									
Median, months	18.8	10.8	26.0	47.2	7.2	18.6†	Not reached	9.2	106.8
Total No. with data	716*	630	822	2,596	1,108	505†		1,084	519

Abbreviations: HCC, hepatocellular carcinoma; IQR, interquartile range; SD, standard deviation.
*Overall medial survival time in the United Kingdom and Spain cohorts was 17.8 months (n = 2,168); the median survival excluding those undergoing transplantation was 14.3 months (n = 1,876).
†Excluding those undergoing transplantation, the equivalent figure in the US cohort was 14.4 months (n = 442).

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Table 2. Multivariable Cox Regression Analysis Using Stepwise Forward Selection of Variables (Japanese training set)

Variable	HR	SE	z	P > z	95% CI of HR	Coefficient	SE	z	P > z	95% CI of Coefficient
Whole cohort										
Macroscopic vascular invasion	2.79	0.46	6.19	< .001	2.02 to 3.86					
Albumin (g/L)	0.91	0.0093	−8.81	< .001	0.90 to 0.93					
Tumor size (cm)	1.10	0.021	5.01	< .001	1.06 to 1.14					
Log_{10} bilirubin	2.13	0.46	3.51	< .001	1.40 to 3.26					
Tumor number	1.11	0.035	3.34	.001	1.04 to 1.18					
Age	1.01	0.0062	2.17	.030	1.00 to 1.03					
Sex (male)	1.30	0.147	2.34	.019	1.04 to 1.62					
ALBI model parameters (based on the Japanese training set)										
Log_{10} bilirubin	1.94	0.37	3.49	< .001	1.34 to 2.82	0.66	0.19	3.49	< .001	0.29 to 1.04
Albumin (g/L)	0.92	0.0080	−9.84	< .001	0.90 to 0.93	−0.085	0.0087	−9.84	< .001	−0.10 to −0.068

Abbreviations: ALBI, Albumin-Bilirubin; HR, hazard ratio.

μmol/L has the same impact as one with a value of 500 μmol/L. Similarly, a serum albumin of 27 g/L has the same impact as a serum albumin of 10 g/L, and within C-P grade A, a patient with a serum bilirubin level of less than 5 μmol/L may have significantly better hepatic reserve than a patient with a serum bilirubin of 33 μmol/L and yet both will be scored the same within the C-P system.

In this study, we have used data from large international databases to identify objective measures of liver dys(function) that independently influence survival in patients with HCC (albumin and bilirubin) and then combined them into a model that could be compared with the conventional C-P grade. This resultant model, called the Albumin-Bilirubin (ALBI) score, eliminates the need for

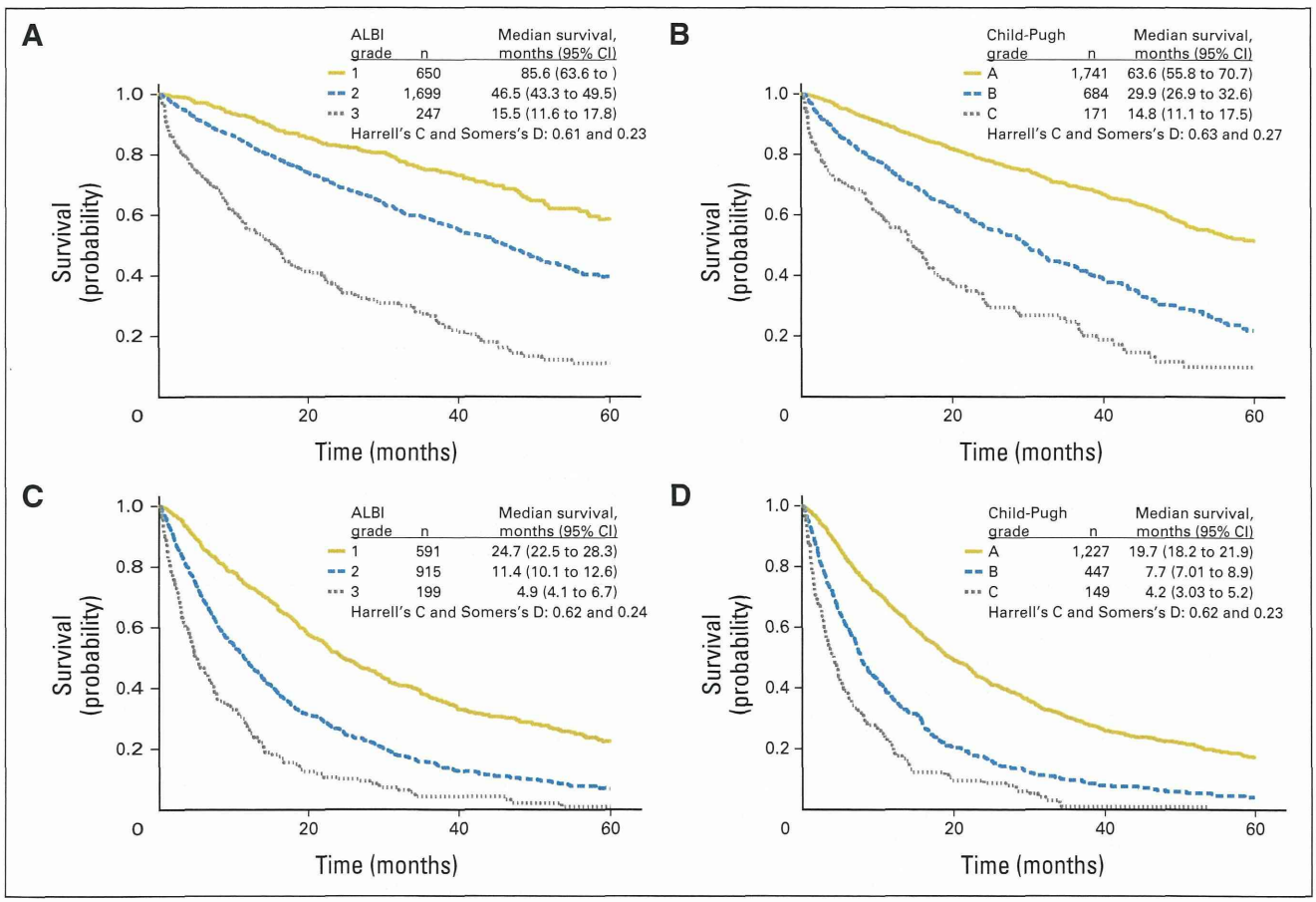

Fig 1. Application of the Albumin-Bilirubin (ALBI) model and comparison with Child-Pugh (C-P) grade. Kaplan-Meier curves depict survival according to (A, C, E, and G) ALBI and (B, D, F, and H) C-P class in (A and B) Japanese, (C and D) European, (E and F) Chinese, and (G and H) US cohorts. Associated tables display the median survival (in months) for each curve as well as Harrell's C and Somers' D scores.

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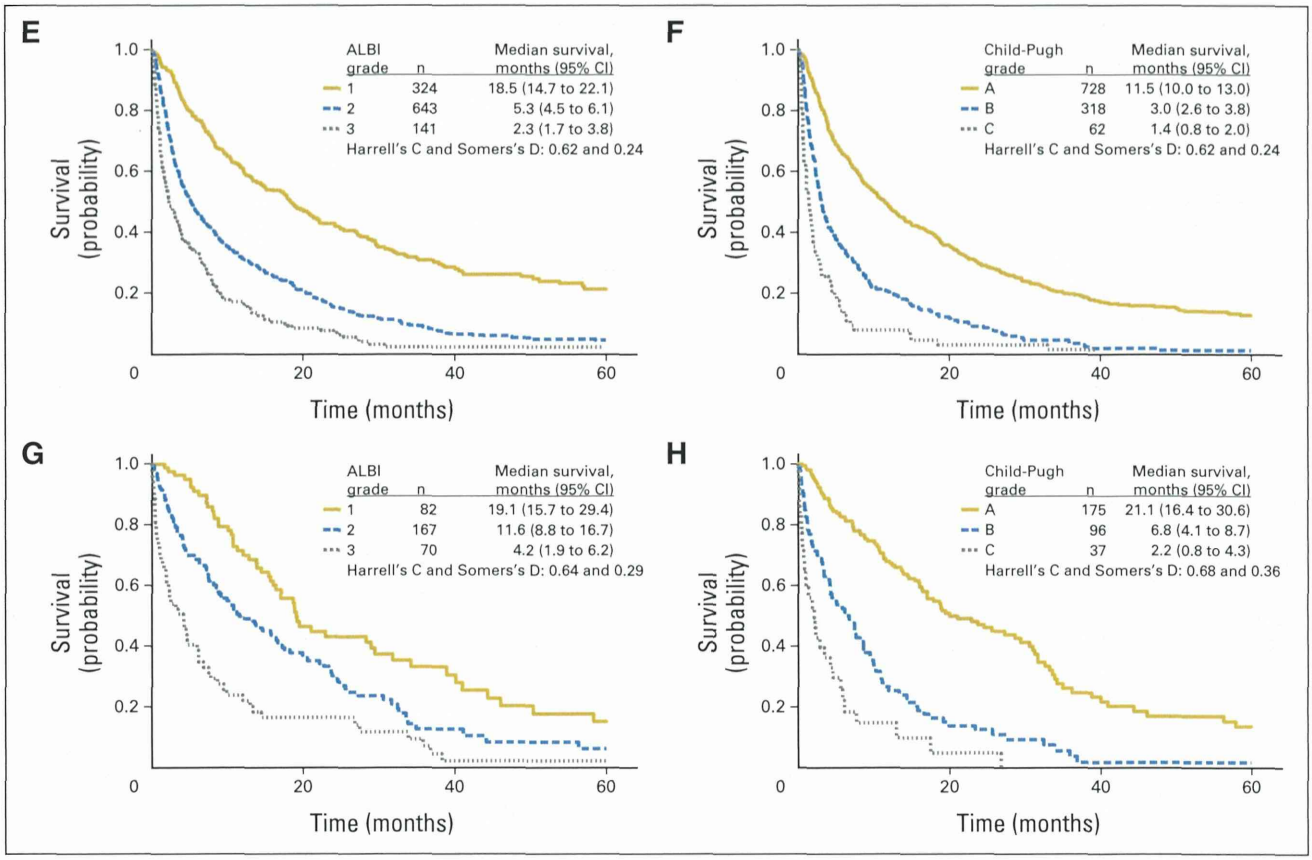

Fig 1. (Continued).

subjective variables such as ascites and encephalopathy, a requirement in the C-P grade.

PATIENTS AND METHODS

We accrued data from major HCC centers and from international HCC clinical trials (Table 1). The centers were chosen to ensure the inclusion of patients of all disease stages and representative of a broad range of etiologies and geographical regions. The patients from clinical trials all had advanced disease and were treated with the current standard of care, sorafenib. The HCC centers comprised two centers from high HCC incidence areas, Japan and Hong Kong (predominant etiologies, chronic hepatitis C virus [HCV] and hepatitis B virus infection, respectively); two from medium-incidence areas, Spain and the United States (predominant etiologies, alcohol and HCV); and the remainder from a low-incidence area, the United Kingdom (mixed etiologies). The United Kingdom and Spanish data were merged into a single European cohort. A cohort of patients with cirrhosis alone was recruited from the Royal Free London National Health Service (NHS) Foundation Trust in London, United Kingdom.

Survival was measured from the date of diagnosis (first presentation with HCC) to date of death or last follow-up. All parameters investigated in the analysis were measured before any treatment and within 6 weeks of diagnosis. In the case of the clinical trials, survival was measured from the date of random assignment. All statistical analysis was undertaken in the United Kingdom. No changes were made to the data presented by the individual centers before the analysis, and the C-P grade for individual patients was, similarly, classified by the investigators at each site before analysis.

Centers

Japan. The Japanese data set (from the Ogaki prefecture) comprised 2,599 patients previously reported by Toyoda et al[13] who were recruited from five institutions in the western part of Japan; the etiology was predominantly HCV. In this area of Japan, cirrhotic patients and noncirrhotic patients with severe fibrosis undergo rigorous screening for HCC every 6 months with ultrasound examinations and serum biomarkers, supported, when appropriate, by computed tomography or dynamic magnetic resonance imaging.[14]

China. This cohort comprised consecutive patients attending the multidisciplinary Joint Hepatoma Clinic at the Prince of Wales Hospital, Hong Kong.[15] As the primary referral clinic for HCC in the New Territories East of Hong Kong, the Prince of Wales Hospital serves a population of approximately two million; the etiology was predominantly hepatitis B virus. There was no formal HCC screening program in place over the period of this study.

Europe. This cohort comprises patients from Spain and the United Kingdom. Spanish patients were diagnosed at, or referred to, the Clinica Universidad de Navarra, Pamplona; the etiology was predominantly HCV or alcohol abuse. United Kingdom patients were those referred to the Queen Elizabeth Hospital, Birmingham, or Newcastle Hospitals NHS Foundation Trust[16]; these patients had various etiologies. Patients undergoing liver transplantation (n = 125 and n = 168 in Spain and United Kingdom, respectively) were excluded from the analysis.

United States. The US cohort was drawn from an institutional database of patients with HCC seen at Beth Israel Deaconess Medical Center in Boston, Massachusetts. The underlying etiology was predominantly HCV or alcohol abuse. Patients undergoing liver transplantation (n = 63) were excluded from the analysis.

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Patients Entered Onto Clinical Trials

We had access to a data set including 1,132 patients receiving sorafenib for unresectable advanced HCC within the control groups of two international clinical trials.[17,18] Of the 1,028 patients with complete data, 96% were classified as C-P grade A. The inclusion criteria are given in the published reports.[17,18]

Patients With Cirrhosis Alone

This cohort comprised 501 consecutive patients with cirrhosis but no HCC admitted to the Royal Free London NHS Foundation Trust for management of complications and/or assessment of liver disease. The intent of this cohort is to provide evidence that the ALBI model is an actual measure of liver function, rather than, in some surrogate manner, a measure of tumor stage.

Patients Undergoing Resection

This cohort consisted of 525 Japanese patients from five institutions in the western part of Japan who had undergone HCC resection between 1990 and 2012.

Statistical Methods

All statistical analysis was undertaken using Stata IC 12 (Stata, College Station, TX). To identify prognostic factors for the future model, exploratory univariable and multivariable Cox regression analyses were undertaken on the entire Japanese cohort because this was the largest and most complete data set. To isolate the impact of liver function on survival (as distinct from that of HCC per se), multivariable Cox regression (with stepwise forward selection) within each disease stage substrata was used to identify predictive patient characteristics common to all strata. Disease stage was described according to tumor size (< 3, 3 to 5, 5.1 to 10, and > 10 cm) or the TNM stage classification of the Liver Cancer Study Group of Japan (stages I to IV).[19] The entire Japanese cohort ($n = 2,599$) was then randomly split into two groups, the training ($n = 1,313$) and validation sets ($n = 1,286$).

Cox regression analysis was performed on the Japanese training set to derive a model. By splitting its linear predictor (xb) at the 25th and 90th percentiles, three groups, according to survival, were generated. Using this classification, patients with HCC were assigned as low, medium, or high risk, describing the lowest 25% of risk, medium risk between the 25th and 90th percentile, and the highest 10% of risk, respectively. Evidence of deviation from proportional hazards assumption was assessed using Stata's phtest and through visual assessment of log-log survival plots.

The discriminatory performance of the ALBI model and C-P grade was calculated and compared using Harrell's C and Somers' D statistics[20-22] and also assessed visually via Kaplan-Meier (KM) plots for each of the Japanese training and validation sets and for the European, Chinese, and US cohorts.

Because patients with HCC predominantly fell into C-P grade A, we used KM plots to investigate the utility of the ALBI grade to detect variation in survival within this C-P grade. The ALBI grade was also applied to patients with advanced disease who received sorafenib and to cirrhotic patients without HCC.

RESULTS

Japanese patients had the highest median survival at 47.2 months, followed by the United States, Europe, and China at 18.6, 17.8, and 7.2 months (including patients undergoing liver transplantation), respectively (Table 1 and Appendix Fig A1, online only). Univariable Cox regression analysis on the Japanese cohort showed that sex (male), $\log_{10}$ bilirubin, albumin, tumor size, tumor number, presence of vascular invasion, and TNM stage were statistically significant prognostic variables (Appendix Table A1, online only). Results of the multivariable Cox regression analysis within each disease stage substrata are shown in Appendix Table A2 (online only).

Multivariable Cox regression (with forward selection) on the Japanese training set showed that vascular invasion, albumin, tumor size, $\log_{10}$ bilirubin, tumor number, age, and sex were statistically significant prognostic variables (Table 2). When we eliminated the impact of the HCC itself (as measured by tumor size or TMN stage), we discovered that $\log_{10}$ bilirubin and albumin were consistently statistically significant predictors of survival (Appendix Table A2). Although vascular invasion and tumor number had, as expected, an impact on survival in most of the strata, we confined our model to albumin and bilirubin because these, alone, were related to liver function. A Cox regression model based on albumin and $\log_{10}$ bilirubin

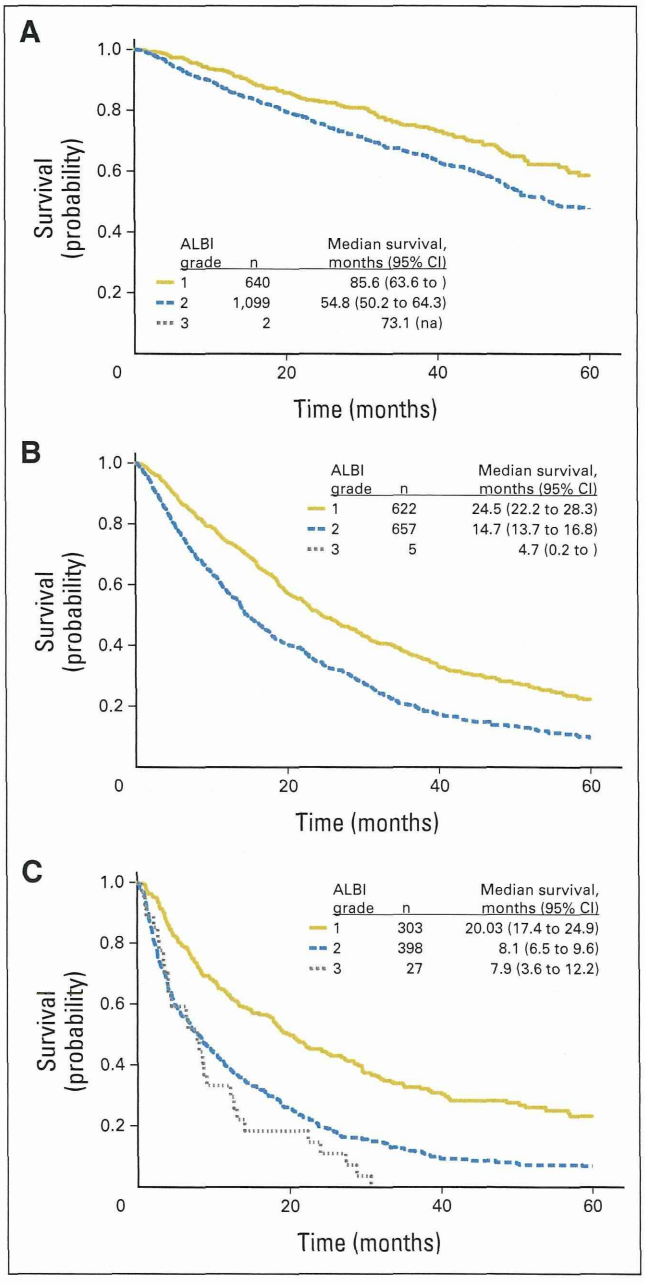

Fig 2. Performance of the Albumin-Bilirubin (ALBI) model in patients with hepatocellular carcinoma with Child-Pugh (C-P) grade A. Kaplan-Meier curves depict survival according to ALBI grades within C-P grade A patients of the (A) Japanese, (B) European/US, and (C) Chinese cohorts. Associated tables display the median survival (in months) for each curve.

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was built on the Japanese training set. The parameters of this model are shown in Table 2; the equation for the linear predictor was as follows: linear predictor = ($\log_{10}$ bilirubin × 0.66) + (albumin × −0.085), where bilirubin is in μmol/L and albumin in g/L.

Calculating the patient-level linear prediction (xb) and applying the cut points assigned each patient to one of three prognostic groups, now named the ALBI grade, 1 to 3. The cut points were as follows: xb ≤ −2.60 (ALBI grade 1), more than −2.60 to ≤ −1.39 (ALBI grade 2), and xb more than −1.39 (ALBI grade 3).

The ALBI model was applied to the training and validation sets of the Japanese cohort and compared with C-P grade for the same data sets (Appendix Fig A2, online only). Visual inspection of the resulting KM curves showed equally good discrimination between the three ALBI prognostic groups and the C-P grade. This is reflected by the Harrell's C and Somers' D scores, which were similar.

Applying the model to the other cohorts, visual inspection of the curves again indicated that the discrimination between the three ALBI groups was as good as that of the C-P grade (Figs 1A to 1H). This is reflected in the Harrell's C and Somers' D scores (Figs 1A to 1H). KM curves showing the ALBI breakdown of C-P grade A patients in the Japanese, European, and US and Chinese cohorts are shown in Figures 2A to 2C and reveal two distinct prognostic groups (mainly falling under ALBI grade 1 or 2).

For C-P grade A patients receiving sorafenib for advanced disease, two clear and nonoverlapping groups were again revealed (Fig 3A). In patients with cirrhosis alone, the ALBI grade revealed three distinct prognostic groups (Fig 3B). In patients undergoing resection, two clear prognostic groups (ALBI grades 1 and 2) were again observed (Fig 3C), whereas for the same cohort, the C-P grades (A and B) overlapped (Fig 3D).

A nomogram that permits calculation of ALBI score directly from serum bilirubin and albumin values in the clinical setting was constructed (Fig 4). An equivalent heat map is also shown in Appendix Figure A3 (online only). There was no evidence to indicate that the ALBI score deviated from the proportional hazards assumption.

DISCUSSION

Our data show that a simple evidence-based model incorporating only serum bilirubin and serum albumin concentrations can stratify patients with HCC into three risk categories. Both formal statistical analysis and visual inspection suggest that the degree of discrimination obtained is at least as good as that achieved by the conventional C-P grade. Across the entire database of 3,887 patients classified as C-P grade A, two distinct prognostic groups could be identified in all

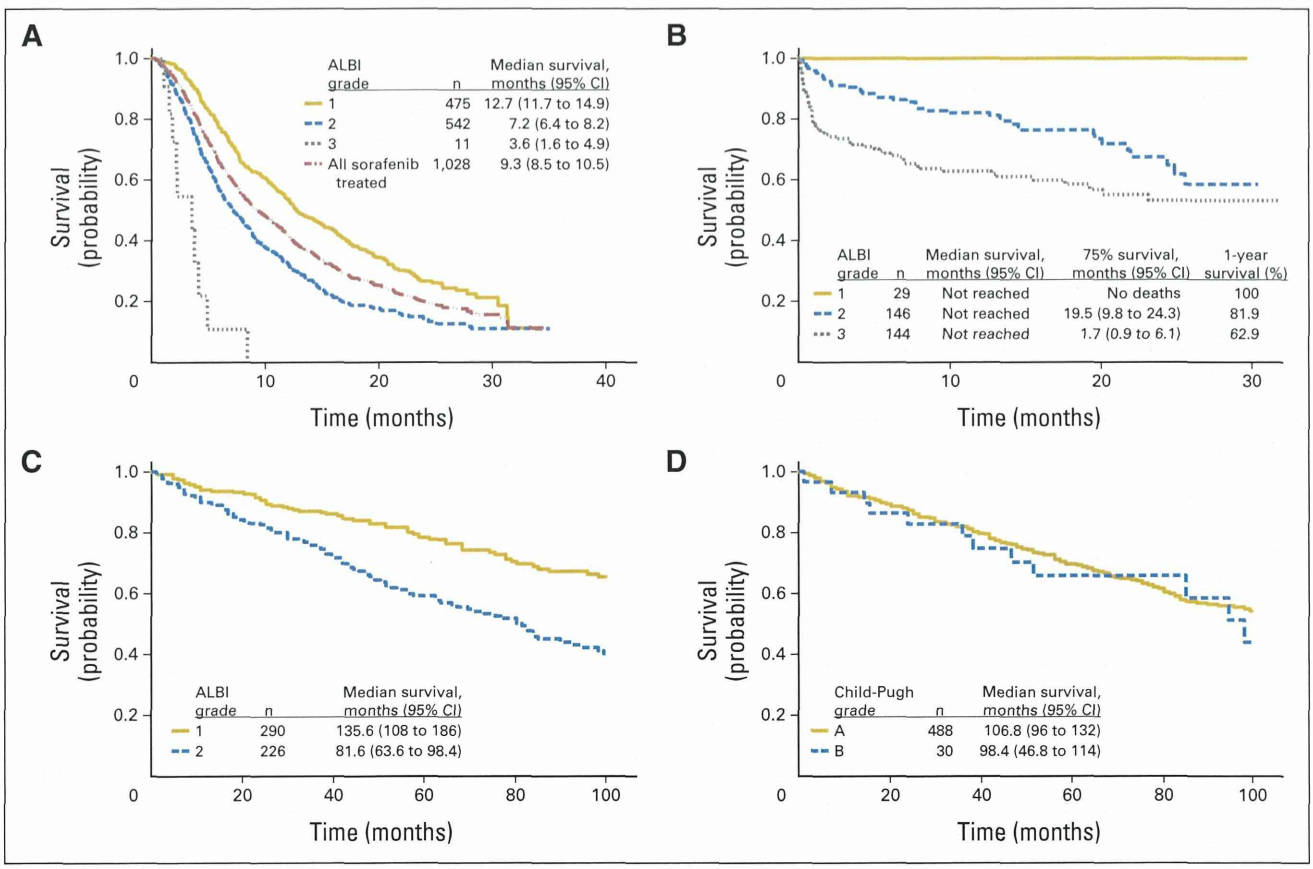

Fig 3. Performance of the Albumin-Bilirubin (ALBI) model in patients undergoing sorafenib treatment, those undergoing resection, and those with cirrhosis (without hepatocellular carcinoma). Kaplan-Meier curves illustrate survival according to ALBI grades in patients (A) treated with sorafenib as part of a clinical trial, (B) with cirrhosis alone, and (C) undergoing resection. (D) Corresponding Child-Pugh grades for the resected patients shown in (C). Associated tables display the median survival (in months) for each curve.

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