Table 3 Characteristics of patients who developed HCC after SVR ($n = 18$)

Age at SVR24 (years)	58.7 ± 5.6
Age at HCC development (years)	65.5 ± 5.2
Sex (female/male)	3 (16.7)/15 (83.3)
Habitual alcohol intake (no/yes)	11 (61.1)/7 (38.9)
Diabetes mellitus (no/yes)	10 (55.6)/8 (44.4)
Treatment when SVR was achieved (naïve/retreatment)	13 (72.2)/5 (27.8)
Ribavirin use (no/yes)	12 (66.7)/6 (33.3)
Peginterferon use (no/yes)	11 (61.1)/7 (38.9)
HCV genotype (1b/2a or 2b)	7 (38.9)/11 (61.1)
Pretreatment HCV-RNA levels (log_{10}IU/mL)	4.61 ± 1.52
Pretreatment AFP (ng/dL)	4.17 ± 2.02
AFP at HCC development (ng/dL)	44.3 ± 79.0
Pretreatment liver fibrosis (F0/F1/F2/F3/F4)	1 (5.5)/5 (27.8)/7 (38.9)/5 (27.8)/0
Liver fibrosis at HCC development (F0/F1/F2/F3/F4)†	0/ 1 (6.7)/3 (20.0)/5 (33.3)/6 (40.0)
FIB-4 index at SVR24	4.01 ± 2.98
FIB-4 index at HCC development	3.57 ± 2.73
APRI at SVR24	1.02 ± 1.04
APRI at HCC development	0.76 ± 0.69
Interval between SVR24 and HCC development (years)	6.76 ± 4.19

†Among 15 patients who underwent surgical resection and liver specimen was available.

AFP, alpha fetoprotein; APRI, aspartate aminotransferase to platelet count ratio index; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; SVR, sustained virologic response.

index at SVR24 were identified as risk factors independently associated with HCC development in multivariate analysis. Previous study reported the association between diabetes mellitus and HCC development in patients with chronic hepatitis C after SVR.[38] More recent study reported patient age, severity of liver disease, and diabetes mellitus as risk factors of HCC development after SVR.[39] Because FIB-4 index is a laboratory index for severity of liver disease (liver fibrosis) and includes age as a factor, our results were consistent with previous reports.

Liver fibrosis is an important risk factor for the development of HCC in patients with HCV infection,[12] and liver biopsy is the gold standard for assessing liver fibrosis.[40] However, it is associated with rare but lethal complications such as hemorrhage,[41] and it is impractical to perform serial liver biopsies after the achievement of SVR. Several laboratory indices of liver fibrosis have been reported.[28,29,42] Vallet-Pichard *et al.* reported that the FIB-4 index is concordant with liver fibrosis based on pathological evaluation of liver biopsy specimens in patients with persistent HCV infection.[43] The results of the present study showed that the FIB-4 index could predict the likelihood of HCC development focusing on patients who achieved SVR, reflecting the degree of liver fibrosis before antiviral therapy. In addition, needle biopsy has a risk of sampling error;[25] pathological assessment is not always objective and does not necessarily reflect the fibrosis status of the entire liver when based on needle-biopsied specimens. In addition, one recent study reported poor association between histological liver fibrosis and laboratory indices of liver fibrosis in HCV-infected patients after SVR.[44] These might be why pretreatment histological liver fibrosis based on the biopsied liver tissue was not identified as a factor associated with HCC development after SVR in multivariate analysis. In contrast, FIB-4 index was associated with HCC development after SVR, including risk factors for HCC after SVR as factors for calculation.

APRI, another laboratory index of liver fibrosis had a less predictive ability of HCC development after SVR, showing superiority of FIB-4 index as a laboratory predictive index of HCC development after SVR. In patients who achieved SVR, AST and ALT usually normalized because of the eradication of HCV. Whereas FIB-4 index includes AST/ALT$^{1/2}$ ratio, APRI includes only AST. In addition, APRI does not include patient age, an important risk factor of HCC development. These may be reasons of the lower ability of APRI to predict HCC development after SVR in comparison to FIB-4 index.

There are several issues that should be further studied in the future. This study is retrospective based on the laboratory data and medical records, although study patients underwent regular follow-up prospectively after the achievement of SVR. Therefore, the prospective validation of this result will be necessary. It is reported that imaging techniques to assess liver fibrosis, such as transient elastography, have the ability to predict the risk of HCC development in patients with persistent HCV infection.[45] It is necessary to clarify whether these imaging techniques can predict the risk of HCC also in patients after SVR, comparing the ability with laboratory fibrosis indices. The eradication of HCV was achieved with IFN-based antiviral therapy using IFN or PEG-IFN with or without ribavirin in all patients in the present study. Although the use of PEG-IFN, ribavirin, or both was not associated with the incidence of HCC after SVR, it should be reevaluated in patients who achieve SVR with newly emerging IFN-free DAAs, with a very high rate of SVR.[21–24] The risk of HCC after SVR may depend on the kind of antiviral drugs used to induce SVR when DAAs are included in the analysis. In addition, genotype 2 was the most common genotype among patients in the present study. With the use of DAAs, it is presumed that there will be more patients with genotype 1 infection resistant to IFN-based antiviral therapy who achieve SVR, including those bearing an unfavorable interleukin-28B polymorphisms genotype,[46,47] HCV with histidine at residue 70 of the HCV core region,[48] and liver steatosis, all of which have reportedly been also associated with a higher likelihood of HCC development.[49,50] Reappraisal of the predictive value of the FIB-4 index for HCC after SVR will be necessary as patients with factors associated with resistance to IFN-based antiviral therapy and a higher likelihood of developing HCC achieve SVR through DAAs in the future.

In conclusion, the incidence of HCC was 1.2% at 5 years and 4.3% at 10 years in non-cirrhotic patients with chronic HCV infection who achieved the eradication of HCV with IFN-based antiviral therapy in Japan. The risk of HCC after SVR was not associated with the antiviral treatment regimen that eradicated HCV. The presence of diabetes mellitus and the elevation of FIB-4 index at SVR24 are at risk factors of HCC after SVR.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 Summary of patients who developed hepatocellular carcinoma after the eradication of hepatitis C virus by antiviral therapy.

A laboratory marker, FIB-4 index, as a predictor for long-term outcomes of hepatocellular carcinoma patients after curative hepatic resection

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Background. *Liver fibrosis is associated with the prognosis of patients with hepatocellular carcinoma (HCC) after treatment. The laboratory marker for liver fibrosis, the FIB-4 index, is reportedly correlated with the degree of liver fibrosis. We evaluated the predictive value of FIB-4 index on the recurrence and survival of HCC patients who underwent curative hepatectomy.*

Methods. *A total of 431 consecutive patients who underwent hepatectomy for primary, nonrecurrent HCC were analyzed. The FIB-4 index was calculated from the patient's age, serum alanine aminotransferase and aspartate aminotransferase levels, and platelet count at the time of HCC diagnosis. Postoperative recurrence and survival rates were compared according to tumor characteristics, tumor markers, Child-Pugh class, and the FIB-4 index.*

Results. *The pretreatment FIB-4 index was associated with recurrence and survival rates, independent of HCC progression or tumor marker levels in a multivariate analysis. Recurrence rates after hepatectomy were higher in patients with a FIB-4 index >3.25 versus ≤3.25 (5-year recurrence rates 69.6% vs 54.8%; P = .0049). Survival was also worse in patients with a FIB-4 index >3.25 than those with a FIB-4 index ≤3.25 (5-year survival rates 67.1% vs 72.2%; P = .0030).*

Conclusion. *The FIB-4 index is a predictive marker for long-term outcomes in patients with HCC treated with curative hepatic resection. (Surgery 2015;157:699-707.)*

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Hepatocellular carcinoma (HCC) is among the most prevalent cancers worldwide,[1] and its incidence is predicted to increase.[2,3] In Japan, HCC is the third and fifth most common cause of death from cancer in men and women, respectively.[4] Hepatectomy is usually a curative treatment for HCC that results in a better prognosis than other treatment modalities, such as percutaneous locoregional therapies, transcatheter arterial chemoembolization, or sorafenib. However, the outcome of patients treated with hepatectomy varies, despite its curative intent. This is partly owing to the high incidence of HCC recurrence, even after curative treatment.

Liver fibrosis is an important risk factor for the development of HCC.[5] Patients with progressive liver fibrosis or cirrhosis have a high likelihood of developing HCC. In addition, several previous studies have reported that liver fibrosis is also a risk factor for HCC recurrence after curative hepatectomy.[6-8]

Recently, several biomarkers of liver fibrosis calculated based on routine laboratory data have been described.[9-11] The FIB-4 index is a surrogate biomarker of liver fibrosis[9] that has been demonstrated to be correlated with liver fibrosis in patients with chronic liver diseases with various etiologies without HCC.[12-14] However, it remains unclear whether this laboratory marker of liver fibrosis can also serve as a biomarker that can predict outcomes in patients with HCC who undergo curative hepatectomy. In this study, we evaluated the ability of the FIB-4 index, a laboratory marker of liver fibrosis, to predict recurrence and survival rates in patients with HCC after hepatectomy with curative intent.

There is no conflict of interest on this study. There is no grant or other financial supports on this study.

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METHODS

Patients. Between January 1995 and June 2013, 1,413 patients were diagnosed with primary, nonrecurrent HCC at Ogaki Municipal Hospital. Of these 1,413 patients, 431 underwent hepatectomy; we included all 431 consecutive patients in the present study. Decisions regarding individual treatment were made based on the treatment guidelines for HCC in Japan.[15] In all patients, HCC was resected as an anatomic hepatectomy with ample margins; enucleation of tumors without surgical margins was not performed. A diagnosis of HCC was confirmed by pathologic examination of the resected tissue.

After hepatectomy, all patients were followed for a median duration of 69.6 months (range, 8.1–213.6) with ultrasonography and CT or MRI performed every 3–6 months at our institution through the end of 2013. Regular monitoring of serum tumor markers (alpha-fetoprotein [AFP], *lens culinaris* agglutinin-reactive AFP [AFP-L3], and des-gamma-carboxy prothrombin [DCP]) was performed every 3 months. An increased tumor marker prompted additional imaging (usually CT or MRI) to check for HCC recurrence. If recurrence was confirmed, patients underwent treatment for recurrent HCC based on treatment guidelines.[15]

The entire study protocol was approved by the hospital's institutional review board and conducted in compliance with the Declaration of Helsinki. Written, informed consent was obtained from all patients.

Calculation of the FIB-4 index. The FIB-4 index was calculated based on laboratory data at the time of HCC diagnosis,[10] which was within 2 weeks of hepatectomy, as:

$$\frac{\text{AST [IU/L]} \times \text{age [years]}}{\text{platelet count } [10^9/\text{L}] \times \text{ALT[IU/L]}^{1/2}}$$

Measurement of tumor markers for HCC. Measurements of AFP, AFP-L3, and DCP were performed on serum samples collected at the time of HCC diagnosis. Serum AFP levels were determined by enzyme-linked immunosorbent assay using a commercially available kit (ELISA-AFP; International Reagents, Kobe, Japan). A cutoff of 20 ng/mL was used to define AFP positivity, as proposed by Oka et al.[16] Serum AFP-L3, expressed as a percentage of total AFP (AFP-L3/total AFP × 100), was measured by lectin-affinity electrophoresis followed by antibody-affinity blotting (AFP Differentiation Kit L; Wako Pure Chemical Industries, Ltd., Osaka, Japan). The cutoff for AFP-L3 positivity was 10%, as proposed by Shimizu et al.[17] The serum DCP level was determined by a specific enzyme immunoassay (Eitest PIVKA-II kit; Eisai Laboratory, Tokyo, Japan) according to the manufacturer's instructions. The cutoff for DCP positivity was 40 mAU/mL, as proposed by Okuda et al.[18]

Statistical analysis. Differences in percentages between groups were analyzed using the Chi-square test. Differences in means of quantitative values were analyzed using the Mann–Whitney *U* test. Changes in quantitative values with the progression of liver fibrosis were analyzed with the Jonckheere–Terpstra test. The date of treatment (hepatectomy) was defined as time zero for calculations of recurrence and survival rates. For recurrence rates, patients in whom HCC recurred were noncensored, and patients with no HCC recurrence were censored. In the analysis of cancer-specific survival rates, patients who died from HCC-related causes were not censored, whereas all other patients were censored. In the analysis of overall survival, all patients who died were not censored; surviving patients were censored. The Kaplan–Meier method[19] was used to calculate recurrence and survival rates, and the log-rank test[20] was used to analyze differences in recurrence and survival.

The Cox proportional hazards model[21] was used for univariate and multivariate analysis of factors related to recurrence and survival. Variables analyzed included patient age and sex, Child-Pugh class (A/B), tumor size (≤2, >2 and ≤5, or >5 cm), number of tumors (single/multiple), portal vein invasion based on the preoperative imaging studies (absent/present), pretreatment serum AFP level (<20 or ≥20 ng/mL), pretreatment AFP-L3 percentage (<10 or ≥10%), pretreatment serum DCP level (<40 or ≥40 mAU/mL), degree of liver fibrosis of resected noncancerous tissue (F1-2, F3, or F4) according METAVIR liver fibrosis score,[22] and pretreatment FIB-4 index. Statistical analysis was performed using JMP statistical software, version 6.0 (Macintosh version; SAS Institute, Cary, NC). All *P* values were derived from 2-tailed tests.

RESULTS

Patient characteristics and FIB-4 index. Table I summarizes the pretreatment characteristics of the study patients. This population was comprised of 335 males and 96 females with a mean age of 66.6 ± 9.2 years. HCC was detected during surveillance at our institution in 47.1% of patients, with 95.6% of patients in Child-Pugh class A.[23] Multiple tumors were present in 16.0% of patients at the diagnosis. Based on preoperative imaging studies,

Table I. Characteristics of the study patients (n = 431)

Characteristic	n *(%)**
Age (y)	
Mean ± SD	66.6 ± 9.2
Median (range)	68 (21–85)
Sex	
Female	96 (22.3)
Male	335 (77.7)
Surveillance status at the time of HCC diagnosis	
Our institution	203 (47.1)
Other	164 (38.1)
None†	64 (14.8)
Etiology	
HBV	81 (18.8)
HCV	270 (62.7)
HBV+HCV	4 (0.9)
Non-HBV, non-HCV	76 (17.6)
Child-Pugh class‡	
A	412 (95.6)
B	19 (4.4)
Albumin, g/dL (mean ± SD)	3.98 ± 0.45
Total bilirubin, mg/dL (mean ± SD)	0.75 ± 0.33
ICG 15-minute retention rate, % (mean ± SD)	14.8 ± 7.6
Prothrombin, % (mean ± SD)	92.4 ± 15.0
Platelet count, ×1,000/mL (mean ± SD)	149 ± 70
Tumor size (cm)	
Mean ± SD (range)	3.35 ± 2.54 (0.6–11.7)
≤2	167 (38.7)
>2 and ≤5	184 (42.7)
>5	80 (18.6)
No. of tumors (single/multiple)	
1	137 (84.0)
≥1	26 (16.0)
Portal vein invasion§	
Absent	404 (93.7)
Present	27 (6.3)
Extrahepatic metastasis	
Absent	431 (100)
Present	0
BCLC staging	
0	147 (34.1)
A	284 (65.9)
AFP (ng/mL)	
Median (range)	11.3 (0.8–69,300)
<20	251 (58.2)
≥20	180 (41.8)
AFP-L3 (%)	
Median (range)	0.5 (0–88.1)
<10	338 (78.4)
≥10	93 (21.6)
DCP (mAU/mL)	
Median (range)	40.0 (5–65,856)
<40	217 (50.3)
≥40	214 (49.7)
Liver fibrosis of noncancerous tissue‖	
F1-2	93 (21.6)
F3	114 (26.4)
F4	224 (52.0)
FIB-4 index	
Mean ± SD	4.15 ± 2.68
Median (range)	3.5 (0.3–19.3)
≤3.25	202 (46.7)
>3.25	229 (53.1)
Extent of hepatic resection	
Subsegmentectomy	145 (33.6)
Segmentectomy or lobectomy	286 (66.4)
Blood loss (mL)¶	
Mean ± SD	483 ± 604
Median (range)	330 (0–5,140)
Blood transfusion¶	40 (9.3)
Perioperative complications	33 (7.7)
Perioperative death	8 (1.9)

*Unless otherwise specified.
†Our institution, under surveillance at our institution before the detection of HCC; other, under surveillance by a family physician prior to the detection of HCC; none, not under surveillance and admitted to our institution with symptoms.
‡Child-Pugh class A includes patients without cirrhosis.
§Based on preoperative imaging studies.
‖According to METAVIR fibrosis score.
¶During hepatic resection.
AFP, Alpha-fetoprotein; *AFP-L3*, *lens culinaris* agglutinin-reactive AFP; *BCLC*, Barcelona-Clinic Liver Cancer; *DCP*, des-gamma-carboxy prothrombin; *HBV*, hepatitis B virus; *HCC*, hepatocellular carcinoma; *HCV*, hepatitis C virus; *ICG*, indocyanine green.

portal vein invasion was observed in 6.3% of patients. No extrahepatic metastasis was observed because hepatectomy was not considered as a treatment option in patients with extrahepatic metastasis according to Japanese guidelines.[15] Pretreatment AFP, AFP-L3, and DCP levels were above the specified cutoffs in 41.8%, 21.6%, and 49.7% of patients, respectively. The METAVIR fibrosis score based on histologic examination of the noncancerous liver tissue adjacent to the resected HCC was F1-2 in 21.6%, F3 in 26.4%, and F4 (ie, cirrhosis) in 48.0% of patients. The pretreatment FIB-4 index was 4.15 ± 2.68. The pretreatment FIB-4 index was 3.09 ± 1.94 in patients with F1-2, 3.74 ± 2.08 in F3, and 4.95 ± 3.08 in F4. There was a gradual increase in the FIB-4 index

as the severity of liver fibrosis increased ($P < .0001$). Median blood loss during hepatic resection was 330 mL (range, 0–5,140) and 40 patients (9.3%) received blood transfusion during surgery. Thirty-three patients (7.7%) experienced perioperative complications. Perioperative mortality was 1.9%. Preoperative FIB-4 index was not associated with perioperative morbidity or mortality (data not shown).

Factors associated with the HCC recurrence rate after hepatectomy. We investigated factors associated with the recurrence rate of HCC in patients with curative hepatectomy. Univariate analysis identified patient age, tumor size (>2 and ≤5 and 5 cm), multiple tumors, portal vein invasion, FIB-4 index, blood loss during hepatectomy, and blood transfusion during hepatectomy as factors significantly associated with recurrence after hepatic resection. According to the multivariate analysis, all of these factors except for patient age were independent factors associated with higher recurrence rates (Table II). When we compared the preoperative FIB-4 index between patients in whom HCC recurred (n = 252) and those in whom HCC did not recur (n = 179), the FIB-4 index was significantly greater in patients with recurrence of HCC (4.44 ± 2.70 in patients with recurrence vs 3.75 ± 2.61 in patients without recurrence; P = .0010; Supplementary Fig 1). When postoperative recurrence rates were compared using the FIB-4 index cutoff of 3.25, which indicated severe fibrosis based on a previous report,[12] the 5- and 10-year recurrence rates were 54.8% and 71.4%, respectively, in patients with a pretreatment FIB-4 index of ≤3.25, compared with 69.9% and 84.7%, respectively, in patients with a pretreatment FIB-4 index of >3.25. The recurrence rate was significantly higher in patients with a pretreatment FIB-4 index of >3.25 than those with a pretreatment FIB-4 index of ≤3.25 (P = .0049; Fig 1). When patients were categorized based in the FIB-4 index cutoff of 3.25, hazard ratio of FIB-4 index of >3.25 was 1.66 (95% CI, 1.28–2.17; P = .0002) on multivariate analysis. We further categorized patients with FIB-4 index of ≤3.25 into patients with FIB-4 index of ≤1.45 and those with FIB-4 index of 1.45–3.25 to analyze the influence the moderate fibrosis[12] on the recurrence after hepatectomy. The recurrence rate was lowest in patients with FIB-4 index of ≤1.45 and increased in those with FIB-4 index of 1.45–3.25, and >3.25, in this order (FIB-4 index ≤1.45 vs 1.45–3.25 [P = .1936]; FIB-4 index 1.45–3.25 vs > 3.25 [P = .0192]; and FIB-4 index ≤1.45 vs > 3.25 [P = .0206]; Supplementary Fig 2).

Factors associated with cancer-specific and overall survival rates after hepatectomy. During the follow-up period, 160 patients died and the remaining 271 patients survived. Among 160 patients who died, 134 patients died from HCC-related causes. Twenty-six patients who died from non–HCC-related causes were censored in the analysis of cancer-specific survival rates but were not censored in the analysis of overall survival rates. We investigated factors that were associated with cancer-specific survival in HCC patients after curative hepatectomy. Univariate analysis identified patient age, tumor size (>5 cm), multiple tumors, portal vein invasion, pretreatment AFP (≥20 ng/mL) and AFP-L3 (≥10%) levels, FIB-4 index, blood loss during hepatectomy, and blood transfusion during hepatectomy as factors that are significantly associated with the survival rate after hepatic resection. According to the multivariate analysis, all of these factors, except for pretreatment AFP and AFP-L3 levels, were also independent factors associated with lower survival rates (Supplementary Table). When we investigated factors that were associated with overall survival in HCC patients after curative hepatectomy, univariate analysis identified patient age, tumor size (>5 cm), multiple tumors, portal vein invasion, pretreatment AFP-L3 levels (≥10%), FIB-4 index, blood loss during hepatectomy, and blood transfusion during hepatectomy as factors significantly associated with the survival rate after hepatectomy. According to the multivariate analysis, all of these factors except for pretreatment AFP-L3 level were also independent factors associated with lower survival rates (Table III). When postoperative survival rates were compared using the FIB-4 index cutoff of 3.25, the 5- and 10-year survival rates were 72.2% and 55.2%, respectively, in patients with a pretreatment FIB-4 index of ≤3.25, compared with 67.1% and 33.0%, respectively, in patients with a pretreatment FIB-4 index of >3.25. The survival rate was significantly lower in patients with a pretreatment FIB-4 index of >3.25 than those with a pretreatment FIB-4 index of ≤3.25 (P = .0030; Fig 2). When patients were categorized based on the FIB-4 index cutoff of 3.25, the hazard ratio for an FIB-4 index of >3.25 was 1.72 (95% CI, 1.20–2.51; P = .0034) on multivariate analysis. We further categorized patients with an FIB-4 index of ≤3.25 into patients with an FIB-4 index of ≤1.45 and those with an FIB-4 index of 1.45–3.25. The survival rate was highest in patients with an FIB-4 index of ≤1.45 and decreased in those with an FIB-4 index of 1.45–3.25, and >3.25, in this order (FIB-4 index ≤1.45 vs

Table II. Univariate and multivariate analysis of factors associated with postoperative recurrence of HCC in patients treated with curative hepatectomy (n = 431)

Factor	*Univariate analysis*	*Multivariate analysis*	*Hazard ratio (95% CI)*
Age	0.0049	0.3518	1.01 (0.99–1.03)
Sex			
Male			
Female	0.6496	—	
Child-Pugh class*			
A			
B	0.4953	—	
Tumor size (cm)			
≤2			1
>2 and ≤5	0.0303	0.2710	1.23 (0.85–1.76)
>5	<0.0001	0.0022	2.27 (1.35–3.75)
No. of tumors			
1			1
≥1	0.0310	0.0109	1.72 (1.14–2.51)
Portal vein invasion†			
Absent			1
Present	<0.0001	0.0011	2.83 (1.55–4.93)
Pretreatment AFP (ng/mL)			
<20			
≥20	0.2982	—	
Pretreatment AFP-L3 (%)			
<10			
≥10	0.1169	—	
Pretreatment DCP (mAU/mL)			
<40			
≥40	0.1158	—	
Liver fibrosis of noncancerous tissue‡			
F1-2			
F3	0.4691	—	
F4	0.2850	—	
FIB-4 index	0.0030	<0.0001	1.14 (1.07–1.20)
Blood loss§	<0.0001	0.1463	1.00 (0.99–1.01)
Blood transfusion§			
No			
Yes	0.0384	0.3049	0.67 (0.31–1.41)
Perioperative complications			
No			
Yes	0.9366	—	
Extent of hepatic resection			
Subsegmentectomy			
Segmentectomy or lobectomy	0.2365	—	

*Child-Pugh class A includes patients without cirrhosis.
†Based on preoperative imaging studies.
‡According to METAVIR fibrosis score.
§During hepatic resection.
AFP, Alpha-fetoprotein; *AFP-L3*, *lens culinaris* agglutinin-reactive AFP; *DCP*, des-gamma-carboxy prothrombin; *HCC*, hepatocellular carcinoma.

1.45–3.25 [P = .3956]; FIB-4 index 1.45–3.25 vs > 3.25 [P = .0093]; FIB-4 index ≤1.45 vs > 3.25 [P = .0401]; Supplementary Fig 3).

DISCUSSION

Child-Pugh class that reflects the liver function is among the important factors that influence the prognosis for patients with HCC.[24,25] However, the percentage of patients with better liver function at diagnosis of initial HCC continues increase in Japan,[26] partly owing to improved surveillance.[27] Most HCC patients who underwent curative hepatectomy have Child-Pugh class A liver function. Therefore, it would be difficult to discriminate

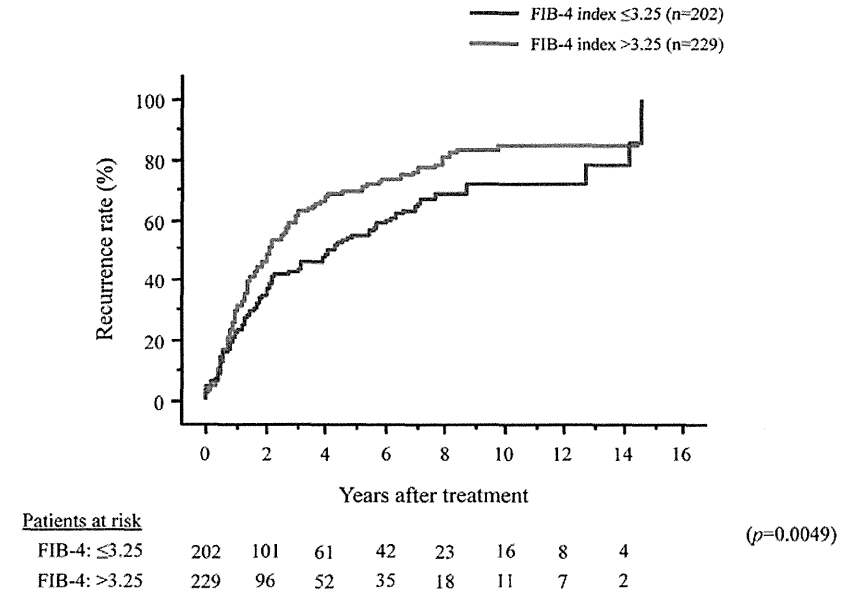

Fig 1. Recurrence rates after hepatectomy in patients with a pretreatment FIB-4 index of ≤3.25 (*blue line*) or >3.25 (*red line*). Recurrence rates were significantly higher in patients with a pretreatment FIB-4 index of >3.25 than those with a pretreatment FIB-4 index of ≤3.25 ($P = .0049$). (Color illustration of figure appears online.)

the prognosis of HCC patients treated with curative hepatectomy regarding liver function based on Child-Pugh class.

In the present study, we attempted to incorporate liver fibrosis as a factor of the background liver to predict the outcome of patients treated with curative hepatic resection, using a laboratory liver fibrosis marker, the FIB-4 index. The FIB-4 index was originally developed as a surrogate marker of liver fibrosis.[9] It has been found to be highly correlated with histologic evaluation of liver fibrosis in liver biopsy specimens.[12] The present study demonstrated that the FIB-4 index at the time of HCC diagnosis correlated with the degree of liver fibrosis in adjacent, noncancerous liver tissue. A previous study reported that a FIB-4 index cutoff of 3.25 showed an excellent discrimination between F0–F2 liver fibrosis and F3–F4 liver fibrosis.[12]

This study demonstrated that the FIB-4 index is strongly associated with recurrence and survival rates in patients with HCC who undergo hepatectomy with curative intent. Univariate and multivariate analyses identified the FIB-4 index as one of the strongest factors associated with higher recurrence and lower survival rates after hepatectomy, in addition to large tumor size (>5 cm) and portal vein invasion. Thus, the FIB-4 index is an independent predictor of prognosis in patients with HCC treated with hepatectomy with curative intent; it is unrelated to tumor factors, reflecting the risk of recurrence in the remnant liver. In contrast with the FIB-4 index, the degree of liver fibrosis was not associated with postoperative recurrence or survival rates in the present study. The reasons are unknown for this discrepancy between the FIB-4 index and the histologic liver fibrosis of the resected specimen observed in the present study, despite the significant increase in the FIB-4 index in association with the increase of fibrosis grade of the resected specimen. Because histologic assessment of liver fibrosis was based on noncancerous liver tissue adjacent to the resected HCC, it may have been influenced by the presence and growth of the liver tumor and might not always have reflected the degree of fibrosis in the entire liver. However, further studies are needed to clarify this discrepancy and determine whether the FIB-4 index or histologic grade of the resected specimen is a stronger indicator of recurrence and survival of HCC patients who underwent hepatectomy.

Pretreatment elevations of HCC tumor markers, especially AFP-L3 and DCP, have been reported to indicate a more aggressive potential in HCC tumors, which is associated with higher recurrence rates and lower survival rates.[28,29] In this study, however, we were unable to identify differences in recurrence or survival based on pretreatment elevations in tumor markers, except for a mild association between AFP-L3 elevation and decreased survival rates. This may be owing to our study's focus on patients who underwent hepatectomy

Table III. Univariate and multivariate analysis of factors associated with postoperative overall survival in HCC patients treated with curative hepatectomy (n = 431)

Factor	*Univariate analysis*	*Multivariate analysis*	*Hazard ratio (95% CI)*
Age	<0.0001	0.0908	1.02 (0.99–1.05)
Sex			
Male			
Female	0.4470	—	
Child-Pugh class*			
A			
B	0.9994	—	
Tumor size (cm)			
≤2			1
>2 and ≤5	0.0860	—	
>5	<0.0001	0.0004	3.18 (1.71–5.68)
No. of tumors			
1			1
≥1	0.0006	0.0324	1.75 (1.05–2.81)
Portal vein invasion†			
Absent			1
Present	<0.0001	0.0263	2.26 (1.11–4.38)
Pretreatment AFP (ng/mL)			
<20			
≥20	0.0503	—	
Pretreatment AFP-L3 (%)			
<10			1
≥10	0.0073	0.0415	1.63 (1.02–2.55)
Pretreatment DCP (mAU/mL)			
<40			
≥40	0.3553	—	
Liver fibrosis of noncancerous tissue‡			
F1-2			
F3	0.7061	—	
F4	0.2651	—	
FIB-4 index	0.0010	<0.0001	1.21 (1.13–1.29)
Blood loss§	<0.0001	0.7366	1.00 (0.99–1.01)
Blood transfusion§			
No			
Yes	0.0254	0.4576	1.47 (0.52–3.84)
Perioperative complications			
No			
Yes	0.4011	—	
Extent of hepatic resection			
Subsegmentectomy			
Segmentectomy or lobectomy	0.6050	—	

*Child-Pugh class A includes patients without cirrhosis.
†Based on preoperative imaging studies.
‡According to METAVIR fibrosis score.
§During hepatic resection.
AFP, Alpha-fetoprotein; *AFP-L3*, *lens culinaris* agglutinin-reactive AFP; *DCP*, des-gamma-carboxy prothrombin; *HCC*, hepatocellular carcinoma.

with curative intent, which excludes patients who underwent nonoperative management or no treatment. Hepatectomy may have a more significant impact on recurrence or survival than the aggressiveness in HCC tumors as reflected by a pretreatment elevation of tumor markers.

A comparison of the recurrence curve between patients with a pretreatment FIB-4 index of >3.25 and those with a pretreatment FIB-4 index of ≤3.25 (Fig 1) revealed that the difference in recurrence rates became marked at 1–2 years after hepatectomy. Previous studies reported that liver fibrosis and the FIB-4 index were associated with hepatocarcinogenesis,[5,30] which may account for the relation between the FIB-4 index and late recurrence after hepatectomy. Also, the difference

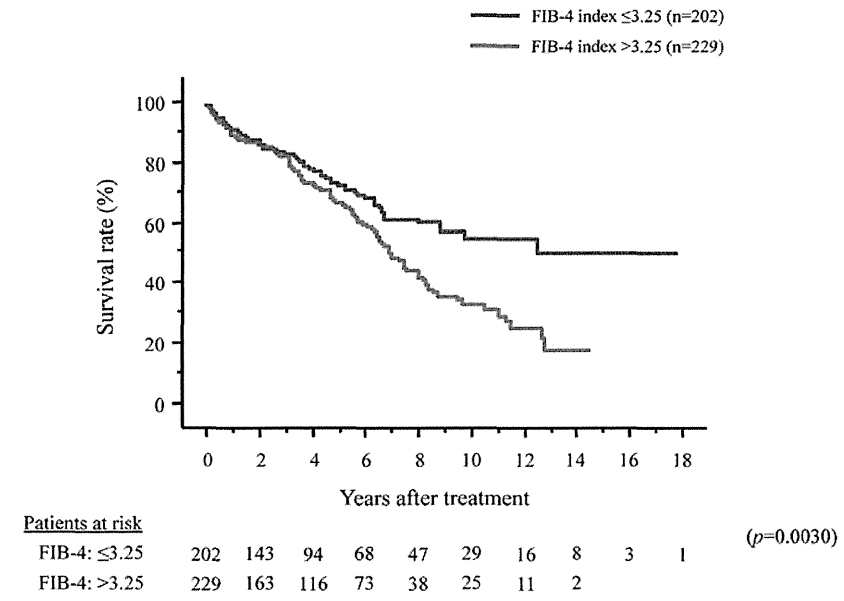

Fig 2. Overall survival rates after hepatectomy in patients with a pretreatment FIB-4 index of ≤3.25 (*blue line*) or >3.25 (*red line*). Overall survival rates were significantly lower in patients with a pretreatment FIB-4 index of >3.25 than those with a pretreatment FIB-4 index of ≤3.25 ($P = .0030$). (Color illustration of figure appears online.)

in survival rates between patients with a pretreatment FIB-4 index of >3.25 and those with a pretreatment FIB-4 index of ≤3.25 became marked 3 years after hepatectomy. Thus, the impact of the FIB-4 index that reflects the degree of fibrosis of the remnant liver seems to be stronger when predicting long-term outcomes. A previous study also reported that the degree of liver fibrosis was an important factor associated with recurrence and survival of HCC patients after 10 years of disease-free survival after curative hepatectomy.[8]

There are several limitations to this study. All patients were ethnically Japanese and the predominant etiology of liver fibrosis was hepatitis C virus infection. To generalize our findings, these results should be evaluated in other ethnicities with a different distribution of liver fibrosis etiology. In addition, the proportion of study patients with portal vein invasion was lower than the proportion in HCC patients from the Japanese general population,[31] likely owing to the high rate of early detection of HCC under surveillance at our liver center in the present study.[27] Furthermore, because none of our patients were treated with liver transplantation, we have no data on whether the FIB-4 index reflects the degree of fibrosis in the explanted liver and how this might influence recurrence or survival.

In conclusion, our examination of 431 consecutive patients treated with hepatectomy with curative intent revealed that the pretreatment FIB-4 index was associated with recurrence and survival after hepatectomy; patients with a higher pretreatment FIB-4 index had higher recurrence and lower survival rates. Further studies are needed in other populations to confirm whether the FIB-4 index is a clinically useful biomarker for predicting long-term outcomes in patients with HCC who undergo curative hepatectomy.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.surg.2014.10.022.

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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

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).

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

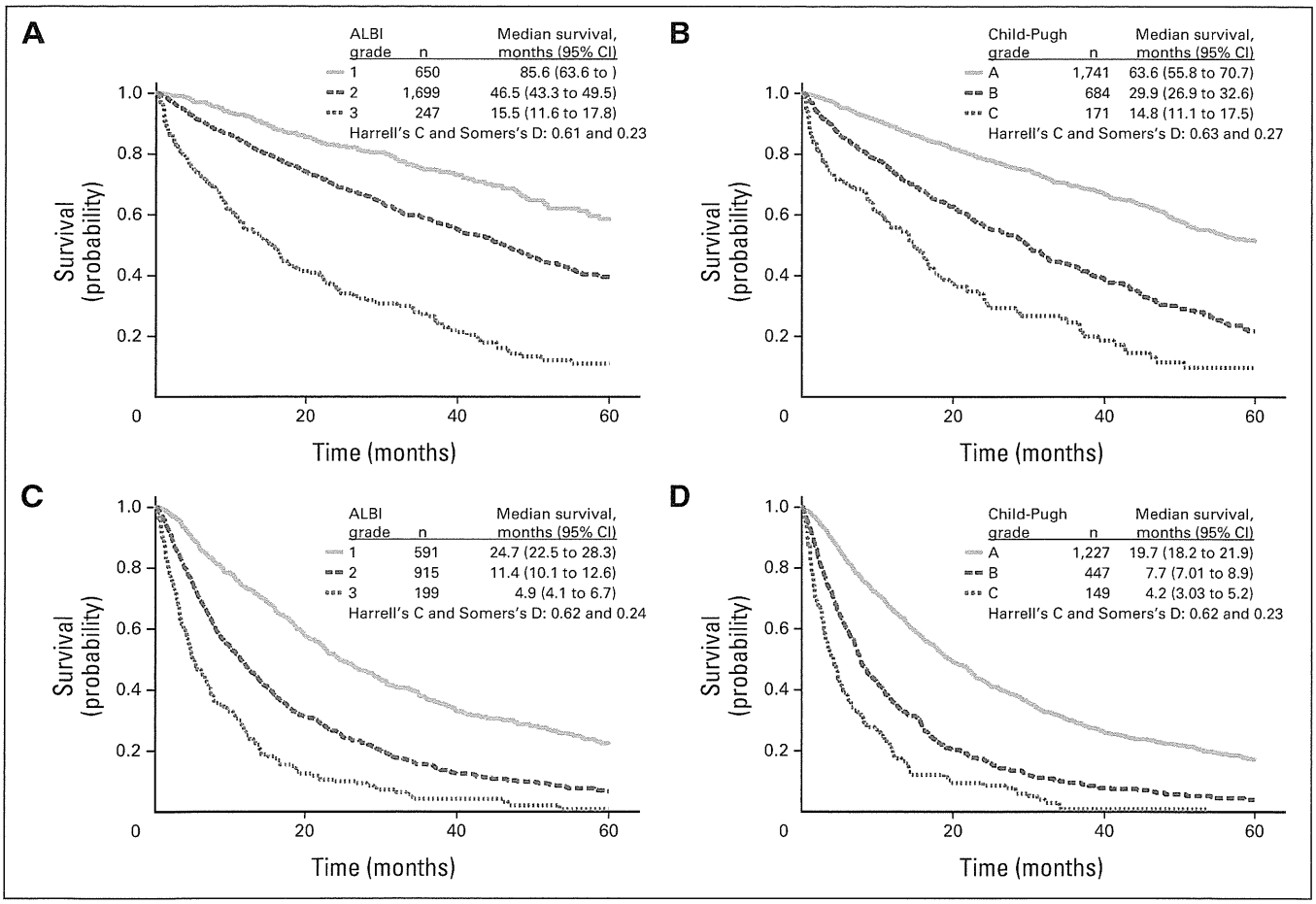

Fig 1. Application of the Albumin-Bilirubin (ALBI) model and comparison with Child-Pugh (C-P) grade. Kaplan-Meier curves depict survival according to (A, C, E, and G) ALBI and (B, D, F, and H) C-P class in (A and B) Japanese, (C and D) European, (E and F) Chinese, and (G and H) US cohorts. Associated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

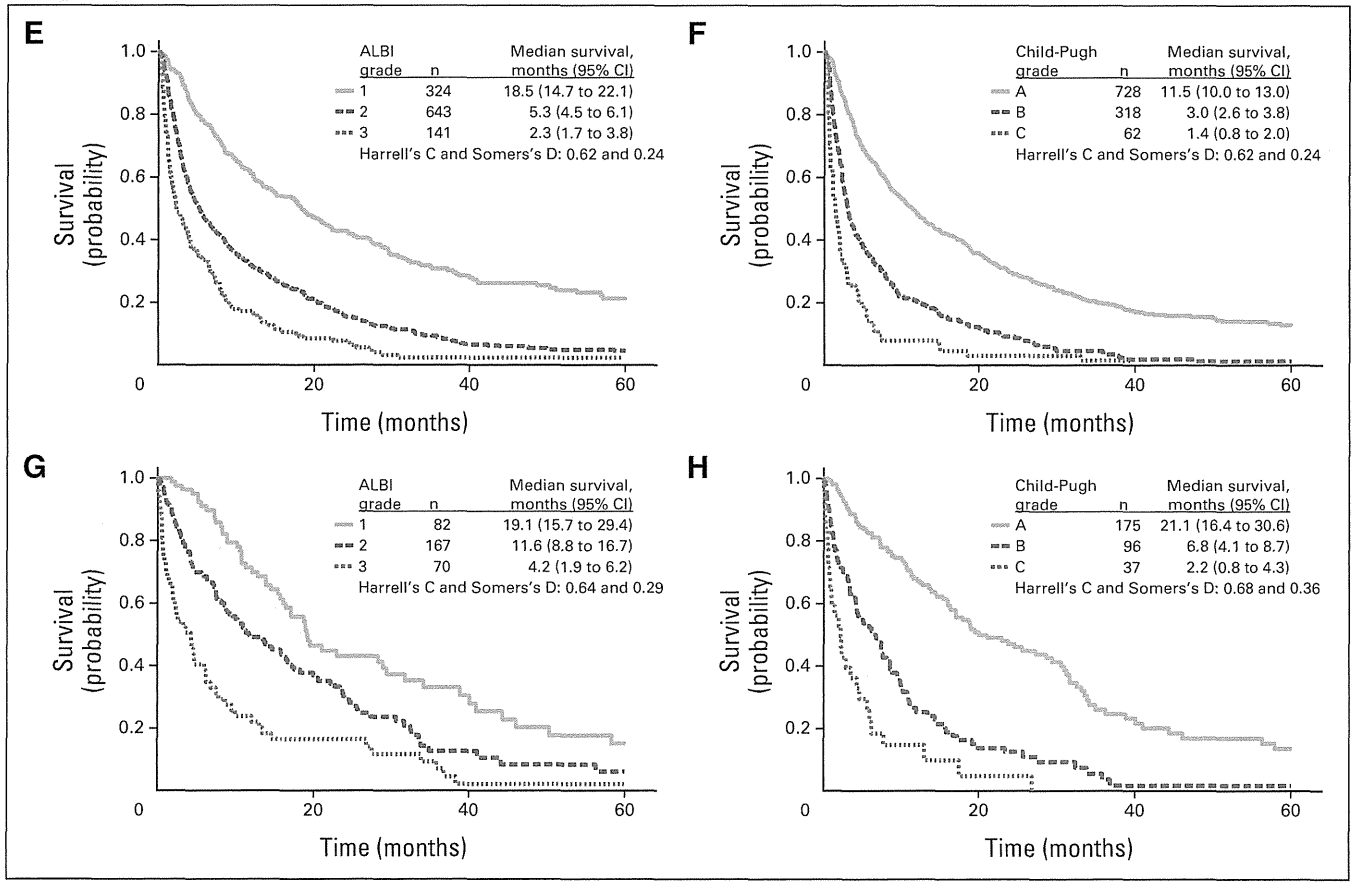

Fig 1. (Continued).

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.

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

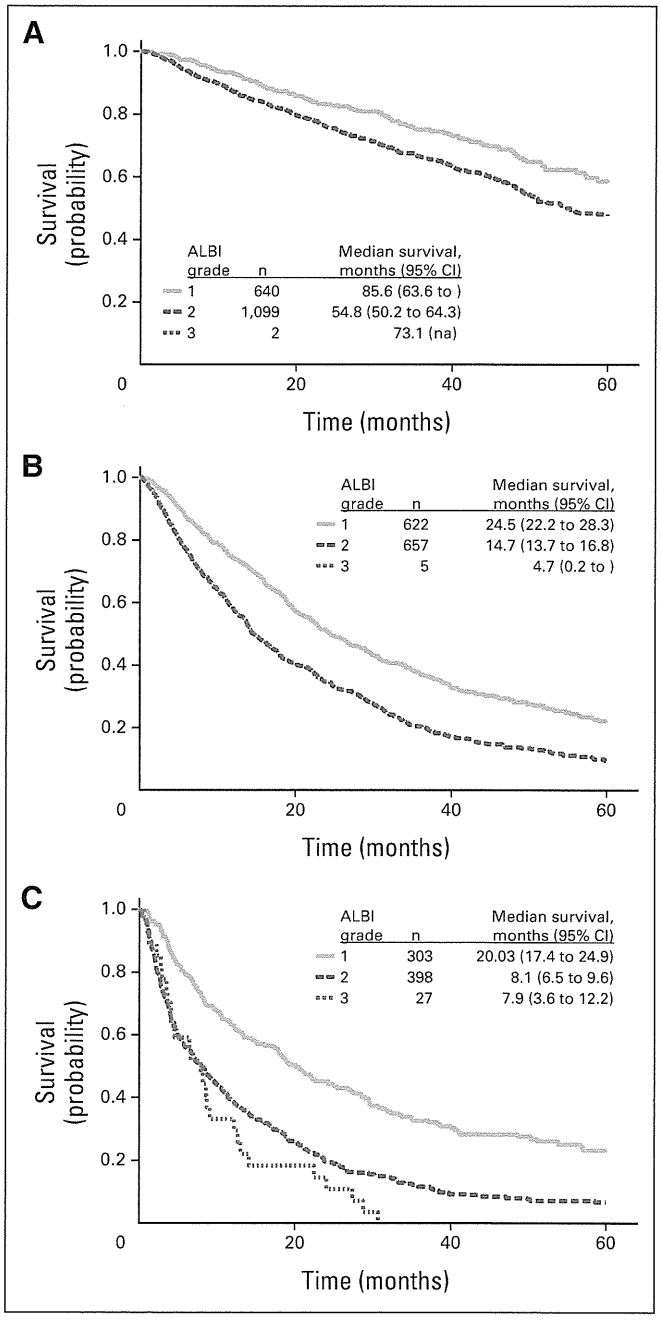

Fig 2. Performance of the Albumin-Bilirubin (ALBI) model in patients with hepatocellular carcinoma with Child-Pugh (C-P) grade A. Kaplan-Meier curves depict survival according to ALBI grades within C-P grade A patients of the (A) Japanese, (B) European/US, and (C) Chinese cohorts. Associated tables display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

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

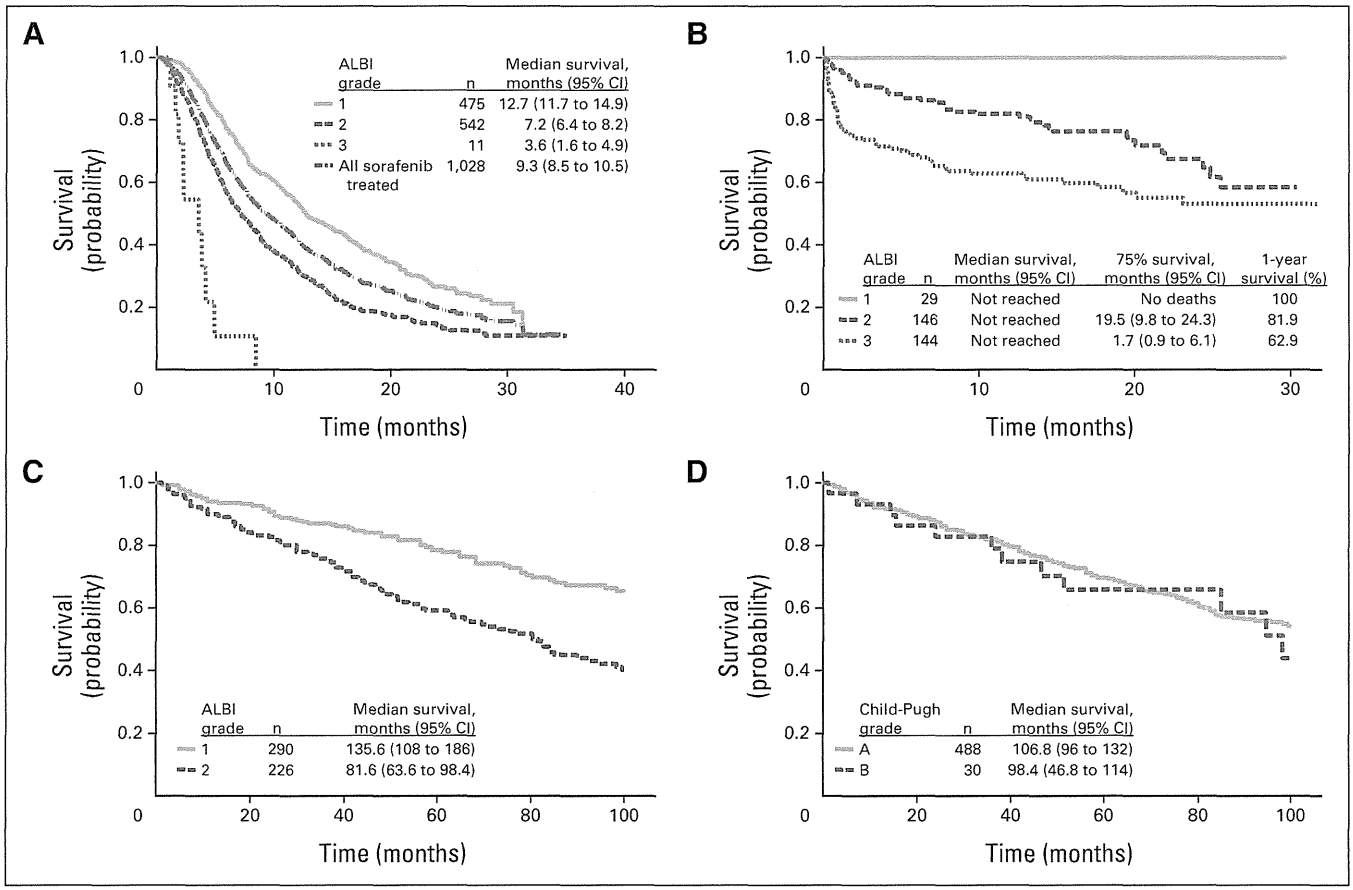

Fig 3. Performance of the Albumin-Bilirubin (ALBI) model in patients undergoing sorafenib treatment, those undergoing resection, and those with cirrhosis (without hepatocellular carcinoma). Kaplan-Meier curves illustrate survival according to ALBI grades in patients (A) treated with sorafenib as part 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.

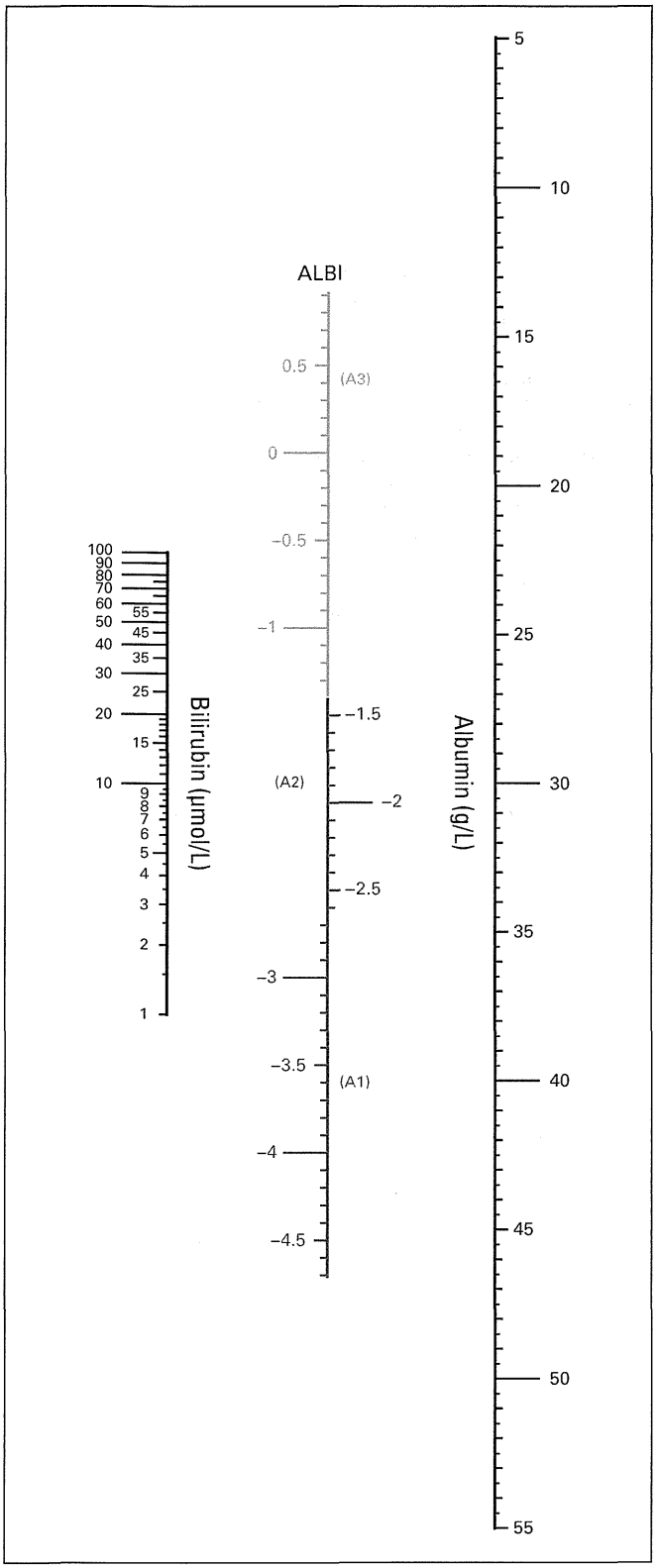

Fig 4. Nomogram for rapid assessment of the Albumin-Bilirubin (ALBI) score. Colors refer to ALBI grades A1, A2, and A3.

regions. In Europe and the United States, for example, when C-P grade A patients were reclassified into ALBI grade 1 or 2, there was a 10-month difference in survival between the two ALBI grades. Our analysis has focused on the impact of liver function on survival, and not on liver disease–related events or deaths, because in practice, it is difficult to specifically attribute the cause of death to the HCC or the underlying liver disease.

Assessment of liver function is particularly important in clinical trials because it is perceived that cirrhosis is a competing cause of death. To isolate the impact of a specific HCC treatment on survival, many HCC treatment studies are limited to patients with C-P grade A. However, our findings suggest that not all C-P grade A patients are the same and that this heterogeneity may have an impact on survival findings. Among C-P grade A patients in clinical trials who received the standard care, sorafenib, the model distinguishes between a good risk group (ALBI grade 1) and a relatively poorer risk group (ALBI grade 2), with a median survival difference of nearly 6 months. Such refinement of liver function assessment might permit retrospective assessment of sorafenib efficacy and survival in these subgroups and determine the most appropriate group for this type of treatment in the future.

One of the strengths of this study is the large number of patients and the generalizability of the results because we have considered high-, medium-, and low-incidence HCC areas and a broad spectrum of etiologies. We specifically excluded patients who underwent liver transplantation because, in these patients, underlying (dys)function is effectively abrogated by the procedure.

The fact that both serum bilirubin and albumin are part of the battery of tests widely referred to as liver function tests suggests that our model is, indeed, measuring liver function, a contention that is supported by our demonstration that the model showed discrimination in patients with uncomplicated cirrhosis. We have examined this group specifically for the aforementioned reason, not to suggest that it would have a role outside the area of HCC and chronic liver disease. Interestingly, in a systematic review of prognostic indicators in cirrhosis, serum albumin and bilirubin were the two most prominent individual prognostic variables in good studies.[23]

It might seem surprising that survival in particular ALBI stages varied across geographical regions, but overall median survival is different across geographical regions and the variation is just as striking in the case of the C-P grades. This may be partly attributable to lead-time bias because it is likely that some countries where extensive public health measures have been implemented, such as Japan, will have apparent survival times greater than those seen in countries such as Hong Kong, where there is less access to primary care. Using sophisticated approaches, our model could be recalibrated for each region, as we have previously shown.[24]

We have previously reported and validated[13,24] an objective serology-based model for survival prediction in HCC. This model, known as BALAD-2, combines bilirubin and albumin with three serum biomarkers (α-fetoprotein [AFP], AFP-L3%, and DCP). This study adds to the plausibility of the BALAD-2 model because bilirubin and albumin seem to represent the impact of the underlying liver function on survival (as shown here), whereas the three biomarkers may represent the impact of the tumor itself on survival.

The Model for End-Stage Liver Disease score might be considered an alternative to C-P grade. However, this system is specifically designed for patients with end-stage cirrhosis,[25-28] and as shown here,

this is not the case in most patients with HCC. Furthermore, serum creatinine is one of the parameters in the Model for End-Stage Liver Disease score and may be less reliable in patients with cancer because of cancer-related cachexia (creatinine levels are related to muscle mass).[29] Although the performance of ALBI is similar to that of C-P, the fact that it is evidence based, much simpler (using the proposed nomogram or heat map), and entirely objective will make it easier to implement. Furthermore, relying on fewer variables, it may be more readily applicable in large-scale international studies. For example, in a recent US study based on the GIDEON registry (a global, prospective, noninterventional study of patients with unresectable HCC undergoing sorafenib treatment),[30] 27% of patients were not evaluable for C-P assessment, largely because of missing international normalized ratio values (a constituent of the C-P grade). A limitation of this study is that we did not have access to the C-P score, only the C-P grade, as classified by investigators at the individual centers. Hence, we can draw no conclusions as to the performance of the ALBI system in relation to specific C-P scores, for example, C-P score 5 to 6.

The ALBI approach will avoid interobserver variation and may highlight distinct prognostic subgroups within C-P grade A. All these advantages are important considerations in the clinical trial setting.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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