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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

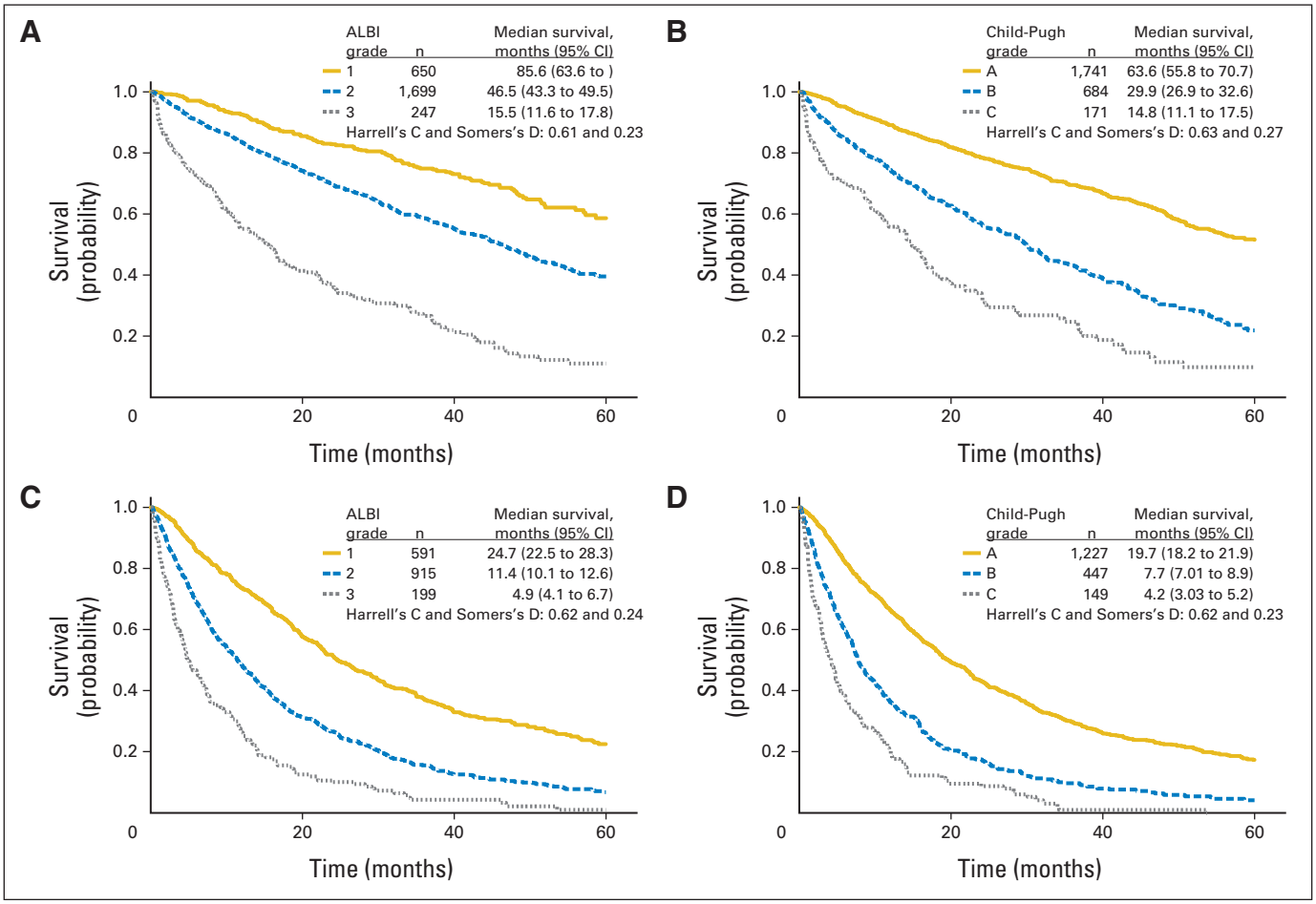

Fig 1. Application of the Albumin-Bilirubin (ALBI) model and comparison with Child-Pugh (C-P) grade. Kaplan-Meier curves depict survival according to (A, C, E, and G) ALBI and (B, D, F, and H) C-P class in (A and B) Japanese, (C and D) European, (E and F) Chinese, and (G and H) US cohorts. Associated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

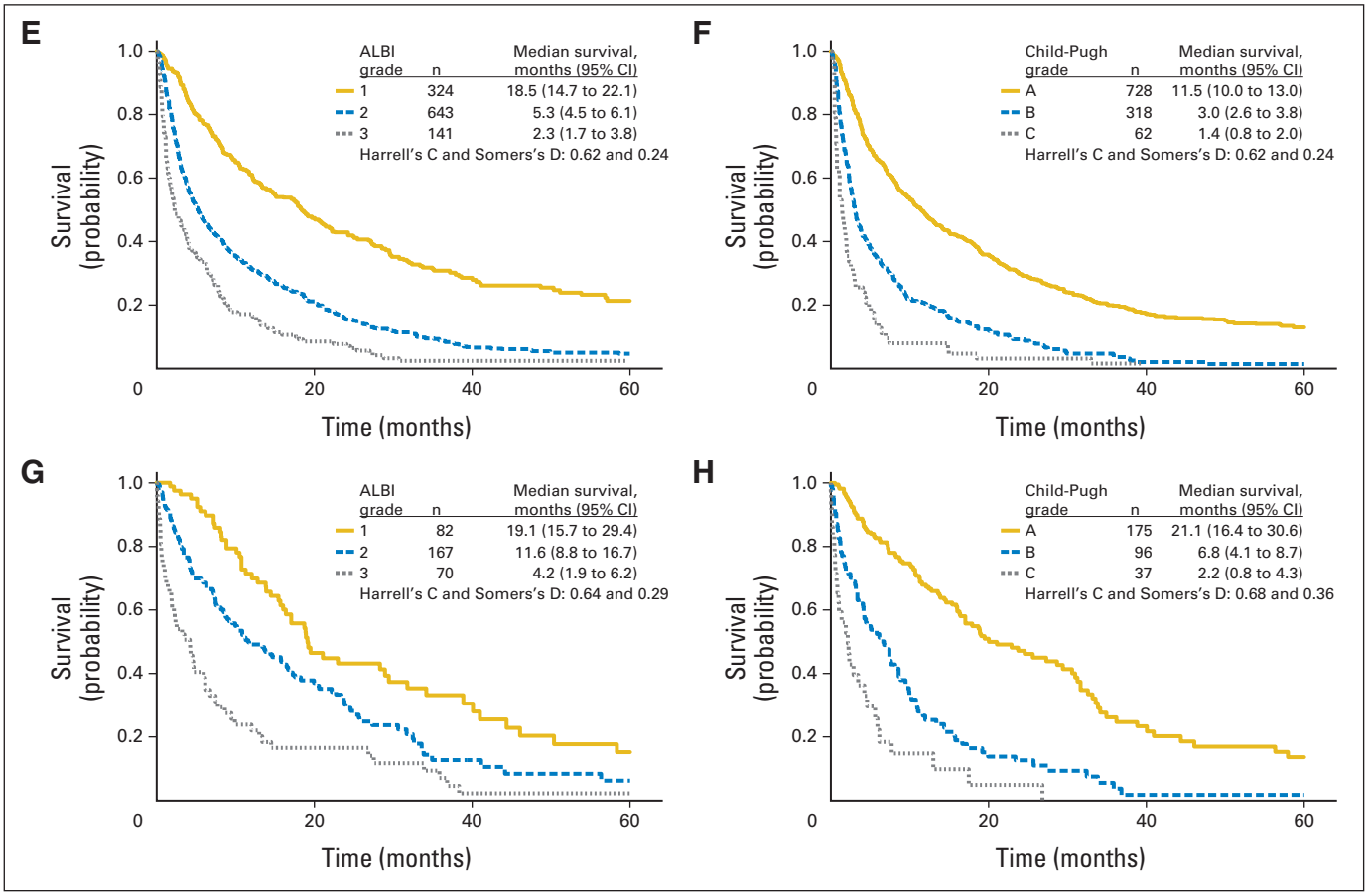

Fig 1. (Continued).

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

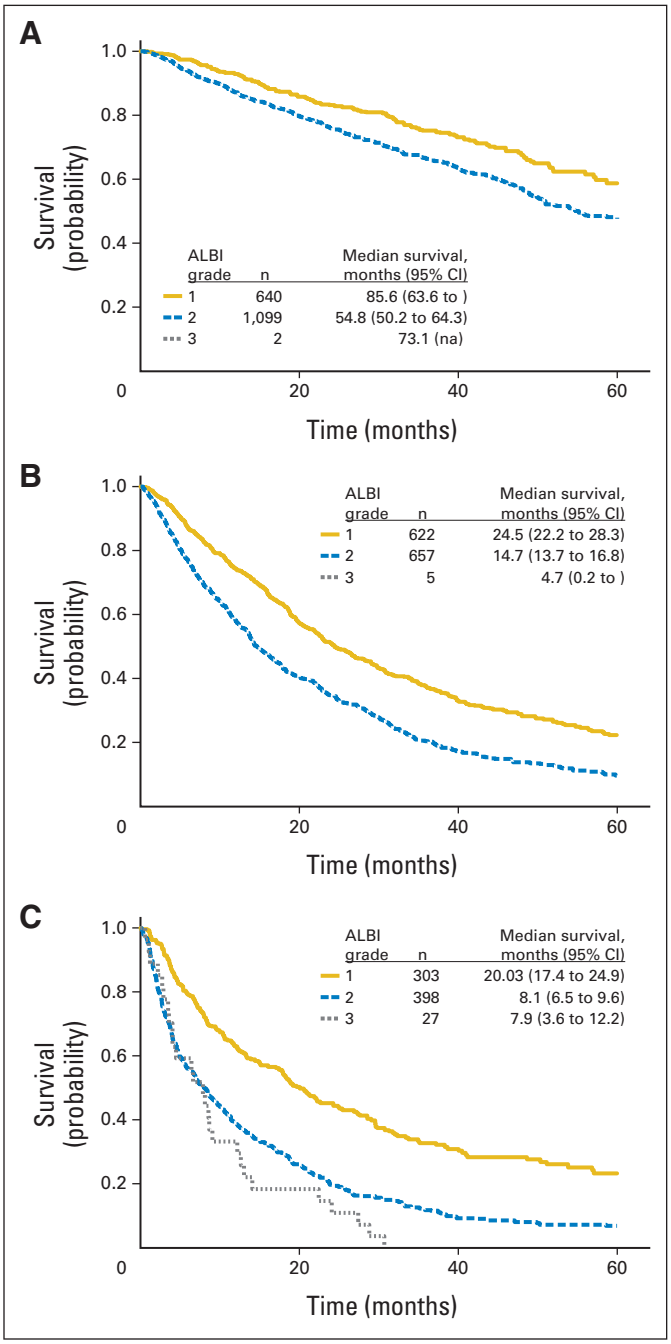

Fig 2. Performance of the Albumin-Bilirubin (ALBI) model in patients with hepatocellular carcinoma with Child-Pugh (C-P) grade A. Kaplan-Meier curves depict survival according to ALBI grades within C-P grade A patients of the (A) Japanese, (B) European/US, and (C) Chinese cohorts. Associated tables display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

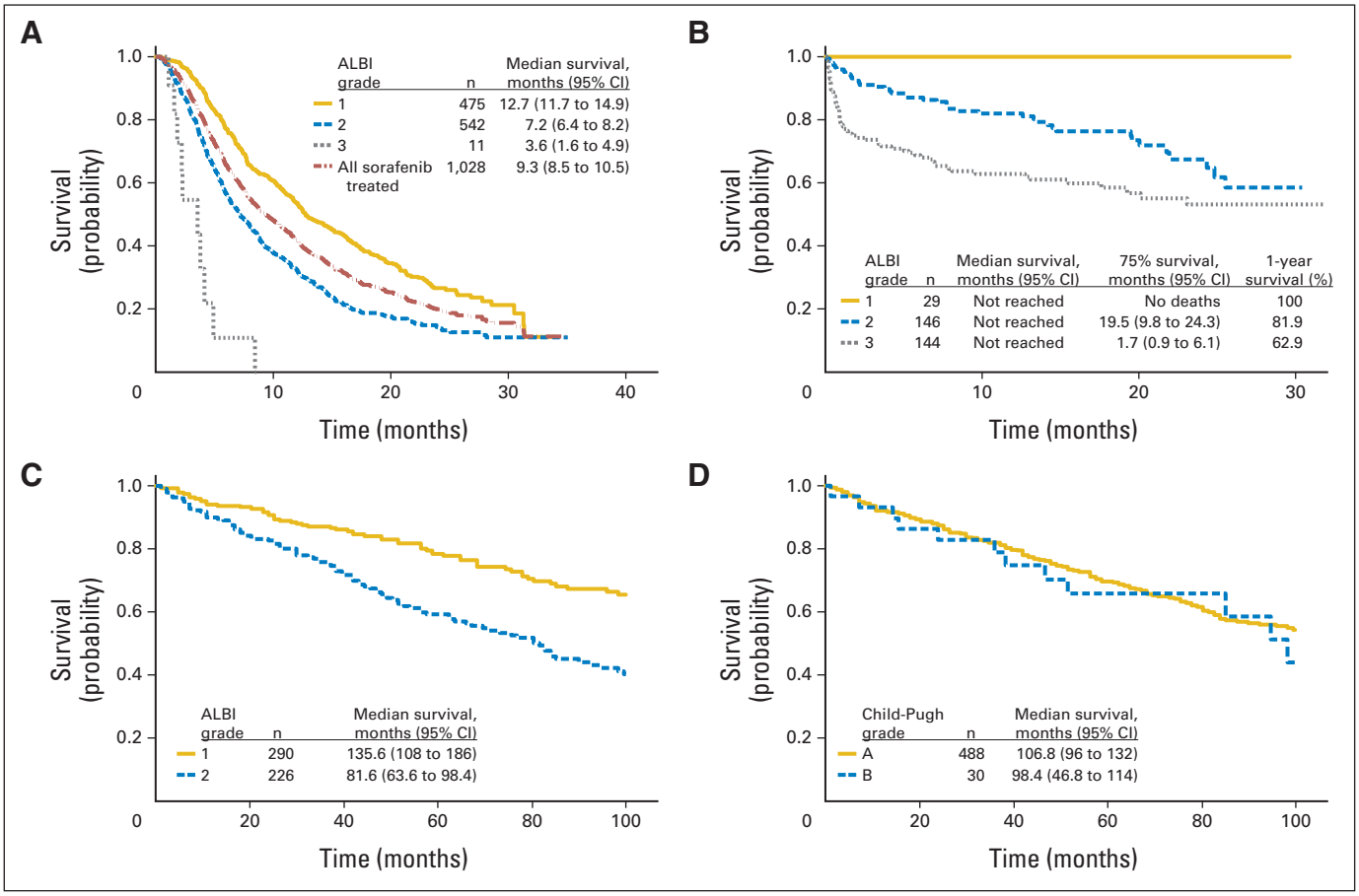

Fig 3. Performance of the Albumin-Bilirubin (ALBI) model in patients undergoing sorafenib treatment, those undergoing resection, and those with cirrhosis (without hepatocellular carcinoma). Kaplan-Meier curves illustrate survival according to ALBI grades in patients (A) treated with sorafenib as part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

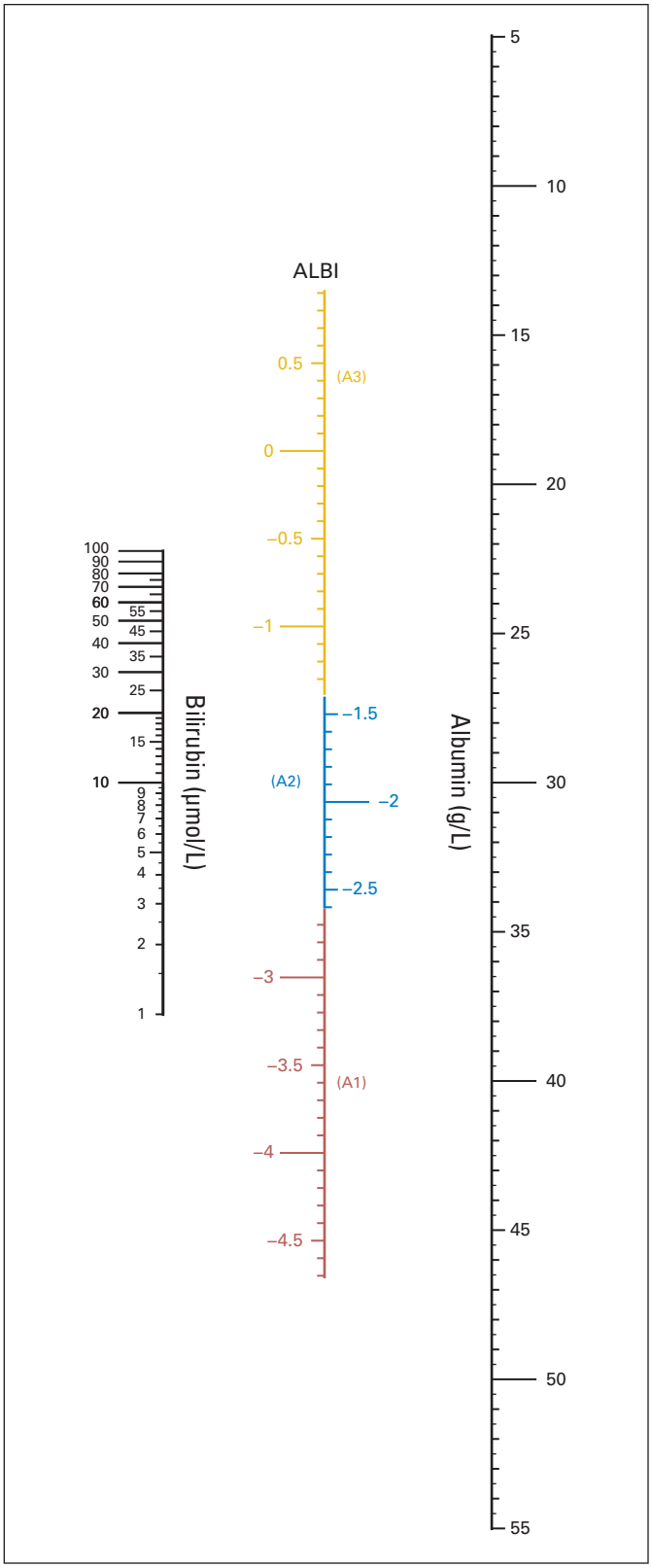

Fig 4. Nomogram for rapid assessment of the Albumin-Bilirubin (ALBI) score. Colors refer to ALBI grades A1, A2, and A3.

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.

AUTHOR CONTRIBUTIONS

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Manuscript writing: All authors
Final approval of manuscript: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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Appendix

Table A1. Univariable Analysis of Whole Japan Cohort

Variable	HR	SE	*z*	$P > z$	95% CI of HR
Sex (male)	1.21	0.085	2.70	.007	1.05 to 1.39
Age	1.00	0.0036	0.17	.865	0.99 to 1.0077
Log_{10} bilirubin	4.91	0.59	13.25	< .001	3.88 to 6.21
INR	1.09	0.055	1.67	.094	0.99 to 1.20
Albumin	0.91	0.0052	−17.39	< .001	0.90 to 0.92
Tumor size, cm	1.14	0.0091	16.53	< .001	1.12 to 1.16
Tumor number	1.32	0.029	12.68	< .001	1.26 to 1.37
Macroscopic vascular invasion	5.40	0.41	22.38	< .001	4.66 to 6.27
TNM stage					
I	1				
II	1.53	0.15	4.26	< .001	1.26 to 1.86
III	2.70	0.27	9.86	< .001	2.22 to 3.29
IV	10.16	1.09	21.55	< .001	8.23 to 12.55

Abbreviations: HR, hazard ratio; INR, international normalized ratio.

Table A2. Multivariable Cox Regression Using Stepwise Forward Selection of Variables (entire Japanese cohort)

Variable	HR	SE	*z*	*P* > *z*	95% CI
Tumor size < 3 cm					
Macroscopic vascular invasion	3.75	1.36	3.64	< .001	1.84 to 7.63
Albumin, g/L	0.90	0.0094	−10.04	< .001	0.88 to 0.92
Tumor number	1.30	0.058	5.89	< .001	1.19 to 1.42
Log_{10} bilirubin	2.74	0.61	4.53	< .001	1.77 to 4.24
Age	1.02	0.0065	3.41	.001	1.01 to 1.03
Sex (male)	1.45	0.16	3.35	.001	1.17 to 1.80
Tumor size 3-5 cm					
Macroscopic vascular invasion	3.43	0.84	5.04	< .001	2.12 to 5.55
Albumin, g/L	0.91	0.013	−6.92	< .001	0.88 to 0.93
Tumor number	1.21	0.057	4.08	< .001	1.10 to 1.33
Log_{10} bilirubin	2.32	0.77	2.55	.011	1.21 to 4.44
Age	1.02	0.0094	2.37	.018	1.0038 to 1.04
Tumor size 5.1-10 cm					
Macroscopic vascular invasion	2.75	0.49	5.67	< .001	1.94 to 3.91
Albumin, g/L	0.96	0.016	−2.63	.009	0.92 to 0.99
Log_{10} bilirubin	2.76	0.92	3.06	.002	1.44 to 5.30
Tumor number	1.13	0.045	2.98	.003	1.04 to 1.22
Tumor size > 10 cm					
Albumin, g/L	0.91	0.022	−4.07	< .001	0.87 to 0.95
Log_{10} bilirubin	10.25	5.52	4.32	< .001	3.56 to 29.48
Stage I					
Log_{10} bilirubin	3.67	1.43	3.34	.001	1.71 to 7.89
Albumin, g/L	0.92	0.016	−5.16	< .001	0.89 to 0.95
Stage II					
Log_{10} bilirubin	2.30	0.51	3.71	< .001	1.48 to 3.56
Albumin, g/L	0.90	0.0097	−9.79	< .001	0.88 to 0.92
Age	1.02	0.0072	2.97	.003	1.01 to 1.04
Sex (male)	1.32	0.16	2.22	.026	1.03 to 1.68
Stage III					
Log_{10} bilirubin	1.76	0.45	2.21	.027	1.07 to 2.91
Albumin, g/L	0.91	0.011	−7.58	< .001	0.89 to 0.94
Stage IV					
Log_{10} bilirubin	3.13	0.76	4.72	< .001	1.95 to 5.02
Albumin, g/L	0.95	0.012	−4.44	< .001	0.92 to 0.97

Abbreviation: HR, hazard ratio.

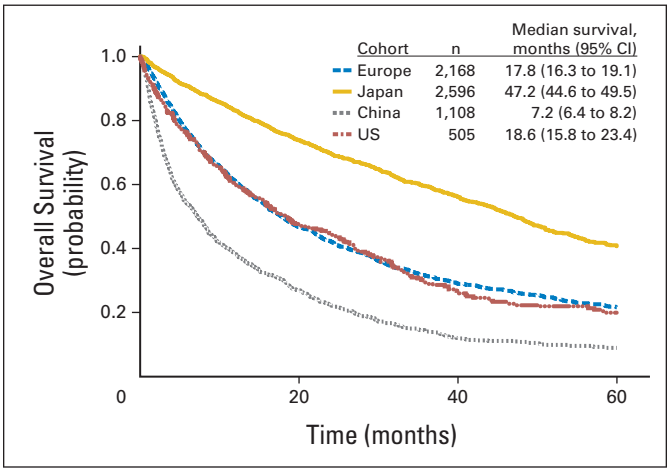

Fig A1. Kaplan-Meier curves showing survival in the Japanese, European, Chinese, and US cohorts.

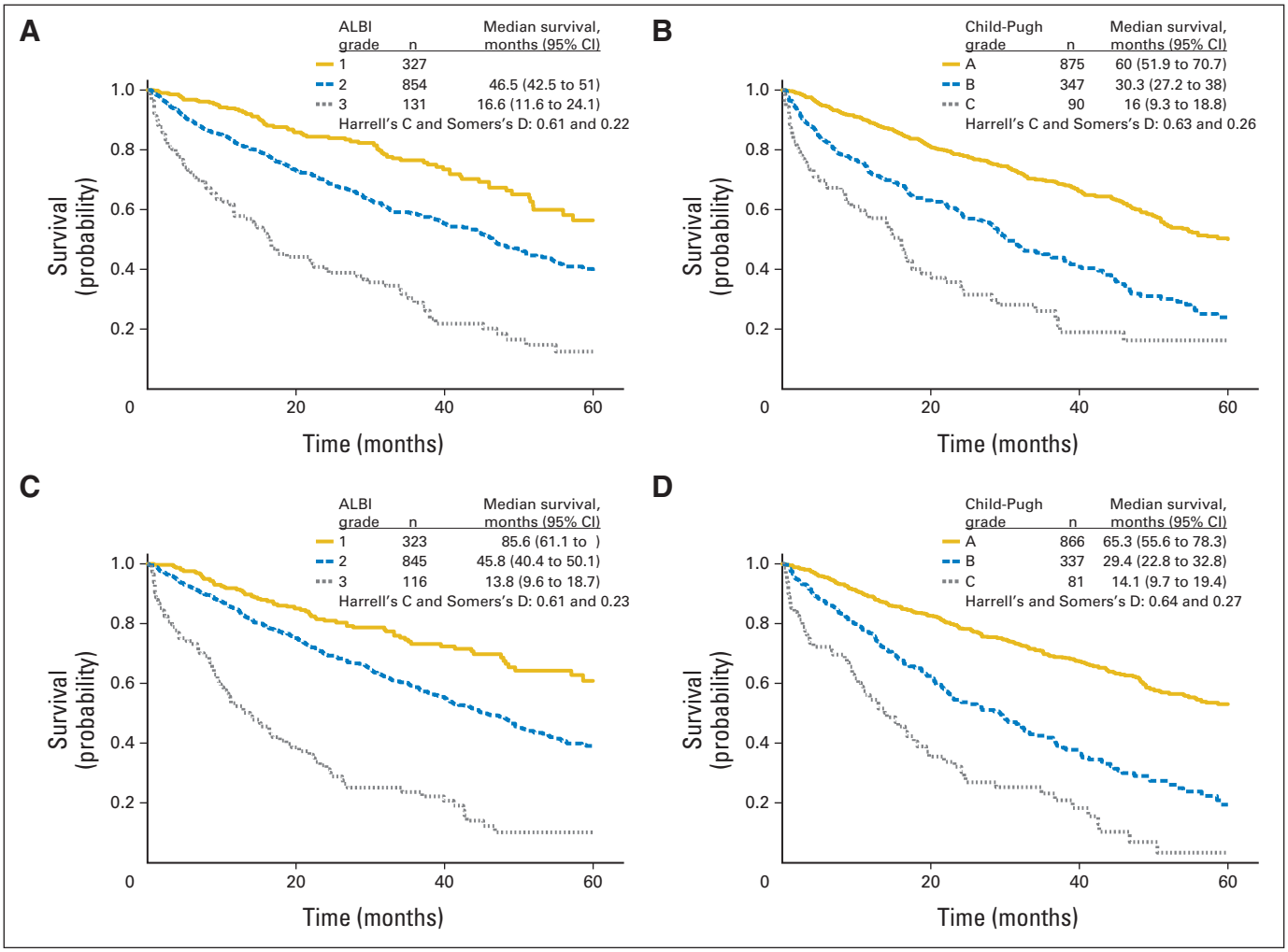

Fig A2. Application of the Albumin-Bilirubin (ALBI) model to the training and validation sets. Kaplan-Meier curves depicting survival according to ALBI and Child-Pugh (C-P) grade in the (A and B) Japanese training set and (C and D) validation set.

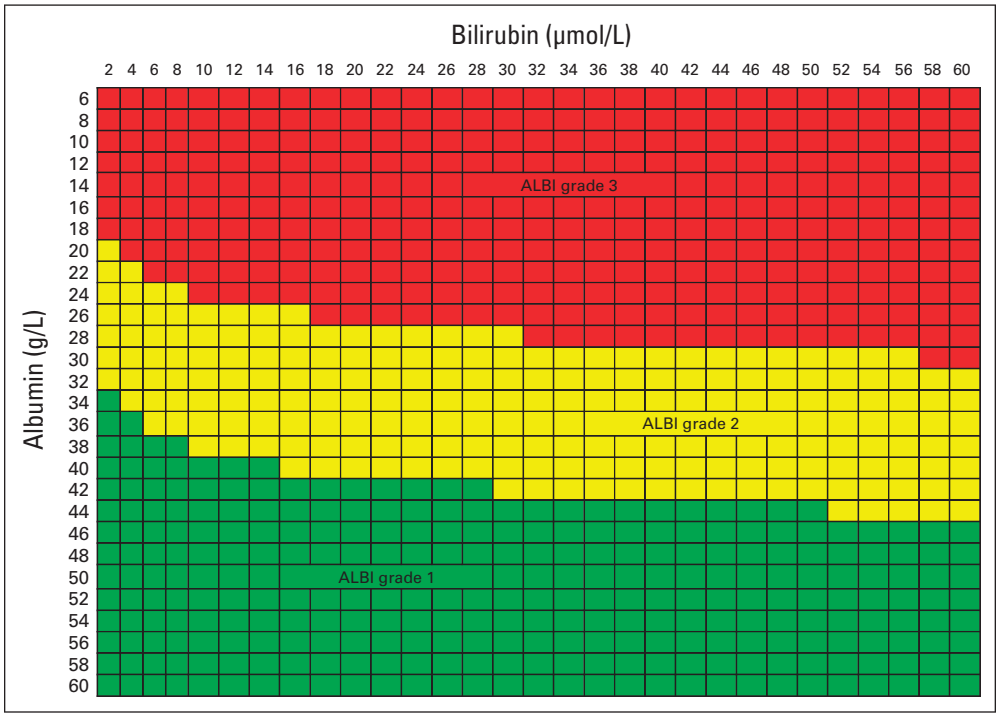

Fig A3. Heat map for rapid assessment of the Albumin-Bilirubin (ALBI) grade.