

**Keywords:** hepatocellular carcinoma; curative therapy; ALBI; indocyanine green (ICG)

# Long-term impact of liver function on curative therapy for hepatocellular carcinoma: application of the ALBI grade

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**Background:** Application of curative therapy for hepatocellular carcinoma is crucially dependent on underlying liver function. Using the recently described ALBI grade we examined the long-term impact of liver dysfunction on survival of early-stage hepatocellular carcinoma (HCC) patients.

**Methods:** This cohort study comprised 2559 HCC patients from different geographic regions, all treated with curative intent. We also examined the relation between indocyanine green (ICG) clearance and ALBI score. Survival was measured from the date of treatment to the date of death or last follow-up.

**Results:** The ALBI score correlated well with ICG clearance. Among those undergoing surgical resection, patients with ALBI grade-1 (good liver function) survived approximately twice as long as those with ALBI grade-2 (less good liver function), although more than 90% of these patients were classified as Child–Pugh (C-P) grade A. In the cohort receiving ablative therapies, there was a similar difference in survival between ALBI grade-1 and grade-2. Cox regression analysis confirmed that the ALBI score along with age, gender, aetiology and tumour factors (AFP, tumour size/number and vascular invasion) independently influenced survival in HCC patients receiving curative treatments.

**Conclusions:** The ALBI score represents a simple approach to the assessment of liver function in patients with HCC. After potentially curative therapy, those with ALBI grade-1 survived approximately twice as long as those with ALBI grade-2. These data suggest that ALBI grade-1 patients are appropriately treated with surgical resection whereas ALBI grade-2 patients may, where the option exists, be more suitable for liver transplantation or the less invasive curative ablative therapies.

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Revised 17 December 2015; accepted 18 January 2016

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The prognosis of patients with hepatocellular carcinoma (HCC) is influenced by several factors, the primary ones being related to the tumour itself and the underlying liver function, the latter usually being characterised by the Child–Pugh (C-P) score (Bruix and Sherman, 2005; European Association For The Study Of The Liver-European Organisation For Research And Treatment Of Cancer, 2012). Although potentially curative therapies for HCC are usually reserved for patients with C-P grade ‘A’ chronic liver disease (Bruix and Sherman, 2005; European Association For The Study Of The Liver-European Organisation For Research And Treatment Of Cancer, 2012), it is recognised that, within this single grade, there is a wide variation in the degree of hepatic reserve (Schneider, 2004; Seyama and Kokudo, 2009; Fan, 2010; Vauthey *et al*, 2010). For this reason, additional more sophisticated quantitative measures of liver function such as indocyanine green (ICG) clearance (Hemming *et al*, 1992) and hepatic venous pressure gradient (HVPG) measurements (Bruix *et al*, 1996; Thalheimer *et al*, 2004; Berzigotti *et al*, 2015) have been advocated. Such tests have been used predominantly to identify those patients in whom liver resection can be safely undertaken (i.e., to avoid periprocedural, ‘short-term’ mortality because of post-hepatectomy liver failure).

We have recently suggested that a new model, known as ‘ALBI’, can accurately assess liver (dys)function in patients with HCC and identify two distinct prognostic categories among C-P ‘A’ patients (Johnson *et al*, 2014). A simple formula, involving only albumin and bilirubin, generates an ‘ALBI score’ (ranging from  $-5$  to  $0.5$ , with higher scores representing worse liver function) and defined ranges are then applied to calculate a grade, from 1 to 3, with ‘one’ representing the best liver function and ‘three’ the worst (Johnson *et al*, 2014). In the first part, we provide evidence that the ALBI score can identify two distinct prognostic groups among C-P ‘A’ patients undergoing surgical resection or ablative therapies with curative intent and that can significantly affect *long-term* survival. In the second part of the present study, we examine how ICG clearance and HVPG correlate with the ALBI score. Such observations may have significant implications for surgical practice, specifically the choice between transplantation and surgical resection in circumstances under which both such options are available.

## MATERIALS AND METHODS

The study is based on large individual patient cohorts recruited from major HCC centres as part of an international collaboration. Centres were chosen so as to generate a data set that reflected typical patients who undergo treatment with curative intent both in terms of the therapeutic options applied and the aetiology of the associated liver diseases.

Treatments were considered potentially curative if patients underwent surgical resection, radiofrequency ablation (RFA), microwave ablation (MWA) or, as in Western cohorts, liver transplantation. The latter was not offered at the Japanese and Hong Kong centres. The cohorts comprised 1072 patients from Japan where the aetiology was mainly chronic HCV infection, 738 from Hong Kong, where the aetiology was mainly chronic HBV infection, and 749 from the United Kingdom, Spain and Germany, merged under ‘Europe’, where the aetiology was mainly chronic HCV or alcohol abuse. Aetiology, treatment and other clinical characteristics of the cohorts are shown in Table 1. Aetiology is classified as HCV, HBV, HCV/HBV co-infection and ‘other’. The latter comprises alcoholic and fatty-liver disease, primary biliary cirrhosis, haemochromatosis and cryptogenic cirrhosis.

Of those undergoing surgical resection, 94.3% were graded as C-P ‘A’ by local investigators. The criteria for surgical resection in Eastern patients (Hong Kong and Japan) were: a 15-min ICG retention rate of  $<30\%$ ; single HCC, or not more than 3 HCCs, located in the same segment;  $<85$  years of age; and absence of

extrahepatic metastasis. The European centres in Spain, Germany, Birmingham and Newcastle followed BCLC guidelines for resection. The extent of surgical resection (major or minor) was available for the Hong Kong cohort only (Strasberg, 2005). Transplantation was undertaken according to the modified Milan Criteria. Within the guidelines listed above, the final treatment decision was based on a multidisciplinary team consensus in all regions. In the Japanese and Hong Kong cohorts, data were collected to permit assessment of changes in the ALBI score at 1, 3 and 6 months following resection and the degree of fibrosis (graded F0–F4) (Knodel *et al*, 1981) was available in all.

For patients undergoing surgical resection or liver transplantation, all patients had histological confirmation of the diagnosis; for those undergoing ablative therapies the diagnosis was based on internationally recommended criteria (Bruix and Sherman, 2005; European Association For The Study Of The Liver-European Organisation For Research And Treatment Of Cancer, 2012). Recurrence was assessed by serial imaging and AFP assessment, confirmed by biopsy in cases of doubt.

Correlation of the ALBI score with ICG clearance and HVPG was studied. Indocyanine green was presented as percentage retention at 15 min. Hepatic venous pressure gradient was measured in the 53 UK patients using a balloon occlusion catheter positioned in the right hepatic vein according to the technique described by Bosch *et al* (2009).

**Post treatment antiviral therapies.** After curative therapy, those Japanese HCV patients without specific contraindications (35% of the total HCV cohort) received conventional interferon-based antiviral therapy. Among those with HBV-related disease, 87% received a nucleoside analogue (lamivudine or, since 2102, entecavir). In Hong Kong, 15% of patients with HBV-related HCC received lamivudine. Very few ( $<5\%$ ) of the European patients received any form of antiviral therapy treatment. The cohorts were recruited before the availability of directly acting antivirals (DAAs) and there were few HBV-related cases.

**The ALBI score.** The ALBI score is a simple and objective measure of liver function and is applicable to HCC at all stages of chronic liver disease unlike the C-P score that is conventionally restricted to patients with cirrhosis. It is based on serum bilirubin and albumin and was derived from, and subsequently validated by, rigorous statistical analysis of over 6000 patients with HCC (Johnson *et al*, 2014).

The score is calculated from the formula,

$$\text{ALBI score} = (\log_{10} \text{bilirubin} \times 0.66) (\text{Albumin} \times 0.085)$$

Where bilirubin is in  $\mu\text{mol l}^{-1}$  and albumin in  $\text{g l}^{-1}$ .

Specific cutoffs are then applied to generate three prognostic groups: ALBI score  $\leq -2.60$  (ALBI grade-1),  $> -2.60$  to  $\leq -1.39$  (ALBI grade-2) and ALBI score  $> -1.39$  (ALBI grade-3).

The score and grade can be readily calculated from a ‘heat map’ given in the original publication (Johnson *et al*, 2014).

**Statistical methods.** All statistical analyses were undertaken using Stata IC 12 (StataCorp., TX, USA). Survival was measured from the time of treatment that was typically within 1 month of diagnosis. For continuous variables with extreme skewness, an appropriate transformation was applied. Correlations between the ALBI score and each of HVPG and ICG were analysed using the pairwise correlation coefficient ( $r$ ). The ALBI score and grade was calculated for each cohort according to Johnson *et al* (2014) and discrimination between the grades was assessed by fitting Kaplan–Meier (KM) curves. The log-rank test was used to compare the survival distributions between the different grades. Cox regression models were fitted to derive hazard ratios and for testing the effect of ALBI on survival after adjusting for other factors in a multivariable model.

**Table 1. Characteristics of the cohorts (all patients undergoing curative treatments)**

	Europe (Germany, Spain and UK)	Japan	Hong Kong, China
Number of patients	749	1072	738
Accrual period	1994–2014	1990–2013	2004–2014
% Ethnicity	92.3 (Caucasian)	> 99% (Oriental)	> 99% (Oriental)
<b>Age (years)</b>			
Median (IQR)	63.2 (56–70)	67 (61–73)	58 (52–65)
Mean ( $\pm$ s.d.)	62.7 ( $\pm$ 10.8)	66.6 ( $\pm$ 8.9)	58.7 ( $\pm$ 10.2)
% Male	80.6	71.6	83.1
	n = 712	n = 1072	n = 738
<b>Child grade (A/B/C)</b>			
n	515/144/52	864/180/27	700/36/02
%	73/20/7%	81/17/2%	95/05/00
N	N = 711	N = 1071	N = 738
<b>Fibrosis stage (F0/F1/F2/F3/F4)</b>			
n		11/19/78/140/268	30/62/81/54/180
%	75.3% (F3 and F4)	2.1/3.7/15.1/27.1/51.9%	7.4/15.2/19.9/13.3/44.2%
N	N = 749	N = 516	N = 407
Solitary tumours (%)	66.8	69.7	80.1
	n = 662	n = 1065	n = 738
Tumour size (cm), median (IQR)	3 (2.3–4.3)	2.2 (1.6–3.4)	3 (2.2–5)
	n = 651	n = 1061	n = 738
% Macroscopic vascular invasion (presence)	5.6	4.7	4.9
	n = 667	n = 1066	n = 738
AFP (>200 ng ml <sup>-1</sup> ), %	13.6	16.3	28.5
AFP (ng ml <sup>-1</sup> ), median (IQR)	8.7 (4–51)	16 (6.2–80)	26 (5–289)
N	N = 655	N = 1050	N = 738
<b>ALBI grade (1/2/3)</b>			
n	316/317/74	424/591/50	501/231/6
%	45/45/10	40/55/5	68/31/01
N	N = 707	N = 1065	N = 738
<b>Crude 90-day mortality rate per 100 patients</b>			
(ALBI 1/2/3)	1.45/2.62/2.74	1.42/1.69/0	0.2/2.6/NA
N	276/305/73	424/591/50	501/231/6
ICG R15, median (IQR)	7.5 (4.1–11.2)	16.3 (10.7–26.0)	4.1 (2.4–6.9)
	n = 34	n = 969	n = 344
<b>Treatment</b>			
Transplantation %	42.6 (n = 712)	0 (n = 1072)	0 (n = 738)
Resection %	30.6 (n = 749)	53.8 (n = 1072)	62.7 (n = 738)
RFA %	24.2 (n = 712)	24.9 (n = 1072)	37.3 (n = 738)
PEI %	5.2 (n = 712)	19.5 (n = 1072)	0
Aetiology %	N = 698	N = 1072	N = 738
HCV	29.4	70.8	7.9
HBV	10.3	14.7	81.3
HCV + HBV	4.2	1.1	0
Other	56.2	13.3	10.8
<b>Median survival (months)</b>			
Resection (Child–Pugh A), months (95% CI)	67.5 (55.4, 72.3), n = 179	89.3 (80.1, 104.7), n = 591	Not reached, 5-year survival = 68.2% (62.5–73.3%), n = 463
Ablative (PEI, MWA and RFA), months (95% CI)	34.3 (30.8, 39.1), n = 216	54.8 (48.5, 63.3), n = 495	64.1 (56.6, 81.0), n = 275
Transplantation, months (95% CI)	135.4 (100.6), n = 302	NA	NA
Overall median survival, months (95% CI)	69.5 (58.9, 75.4)	72.5 (67.3, 78.6)	103.1 (82.2)
	n = 708	n = 1072	n = 738

Abbreviations: AFP =  $\alpha$ -fetoprotein; HBV = hepatitis B virus; HCV = hepatitis C virus; ICG R15 = indocyanine green retention rate at 15 min; IQR = interquartile range; MWA = microware ablation; NA = not available; PEI = percutaneous ethanol injection; RFA = radiofrequency ablation.

## RESULTS

Overall (Hong Kong, Japan and Europe), the 90-day mortality was < 3% (breakdown of this result according to ALBI grade is shown

in Table 1). Based on histological examination of resected HCC cases, 51.9% of Japanese and 44.2% of Hong Kong cases had fibrosis stage 4 (cirrhosis); the figures for 'severe' fibrosis (stage  $\geq$  3) were 79% and 57.5% respectively (Table 1). Of the patients in the European cohort, 75% had stage 3 and 4 fibrosis. In a

multivariable Cox regression model that included age, gender, tumour size, tumour number, AFP and vascular invasion, the ALBI score remained a strong predictor of survival ( $P < 0.0001$ ), even after adjusting for tumour-related factors (Supplementary Table 1). Within the entire group of 2559 patients, classification according to ALBI resulted in three clear and non-overlapping groups with median survival figures of 106.3 (95% CI 96.3, 122.7), 53.7 (95% CI 48.2, 58.6) and 26.9 (95% CI 20.4, 33.4) months in ALBI grade-1, -2 and -3 respectively (Figure 1).

**Patients undergoing orthotopic liver transplantation.** There was no significant difference in survival between the three ALBI grades after liver transplantation (log-rank test,  $P = 0.68$ ). At 5 years, survival for ALBI grade-1, -2 and -3 were 73.4% (95% CI 59.9, 83.1%), 67.3% (95% CI 58.1, 74.9%) and 73.3% (95% CI 58.0, 83.8%) respectively (Supplementary Figure 1).

**Patients undergoing hepatic resection.** Among the C-P grade A patients, two clear and non-overlapping ALBI subgroups emerged in each of the Japanese (log-rank test,  $P < 0.0001$ ), Hong Kong (log-rank test,  $P < 0.0001$ ) and European (log-rank test,  $P = 0.0477$ ) cohorts respectively (Figure 2). Survival was approximately twice as long in the ALBI grade-1 patients as in the ALBI grade-2 patients (Figure 2). For instance, ALBI grade-1 patients had median survival of 122.7 (95% CI 96.3, 148.7), not reached (or 5-year survival at 72.8%, 95% CI 66.5, 78.0) and 71.1 months (95% CI 59.0, 120.4) in the Japanese, Hong Kong and European patients respectively, whereas ALBI grade-2 survival was 71.2 (95% CI 56.2, 82.4), 44.5 (95% CI 28.6) and 42.3 months (95% CI 25.0, 69.5) in the same cohorts. The hazard ratio in ALBI grade-2 was twice that of ALBI grade-1 (Table 2). The better survival in ALBI grade-1 patients persisted in the subgroup of patients without tumour recurrence (Supplementary Figures 2a and b).

Among the Hong Kong patients, we assessed the impact of the ALBI grade according to the extent of resection. From those who underwent surgical resection ( $n = 463$ ), 263 and 200 received minor and major (three hepatic segments or more) resections respectively (Strasberg, 2005). In these patients, a clear distinction between ALBI grade-1 and grade-2 persisted (log-rank test,  $P = 0.0002$  and  $0.0236$  respectively) (Supplementary Figures 3a and b). Following resection, in both Japan and Hong Kong, there was a modest decrease in liver function (as assessed by ALBI) at 1 month followed by a return towards the preoperative score at 3 and 6 months (Supplementary Figure 4).

**Patients undergoing RFA or MWA.** Among those undergoing curative ablative therapies, ALBI grade-1 patients survived significantly longer than ALBI grade-2 in the Japanese, Hong Kong and

European cohorts (log-rank test,  $P = 0.0222$ ,  $0.0068$  and  $0.0011$  respectively). In those cohorts, ALBI grade-1 median survivals were 84.2 (95% CI 63.8), 89.3 (95% CI 66.7, 115.8) and 56.5 months (95% CI 36.0, 69.2), whereas for ALBI grade-2 these were 56.1 (95% CI 48.6, 72.4), 59.2 (95% CI 47.2, 64.1) and 30.2 months (95% CI 27.4, 34.3) (Figure 3). The corresponding hazard ratios are also shown in Table 2. Patients with ALBI grade-3 showed the least survival in all three cohorts.

**Survival by aetiology in patients undergoing curative treatment.** When patients undergoing curative treatment were classified

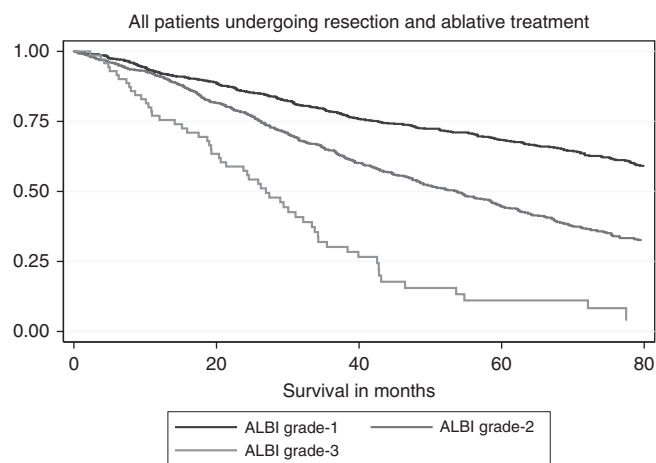


Figure 1. Survival according to ALBI grade in all patients undergoing resection and ablative treatment.

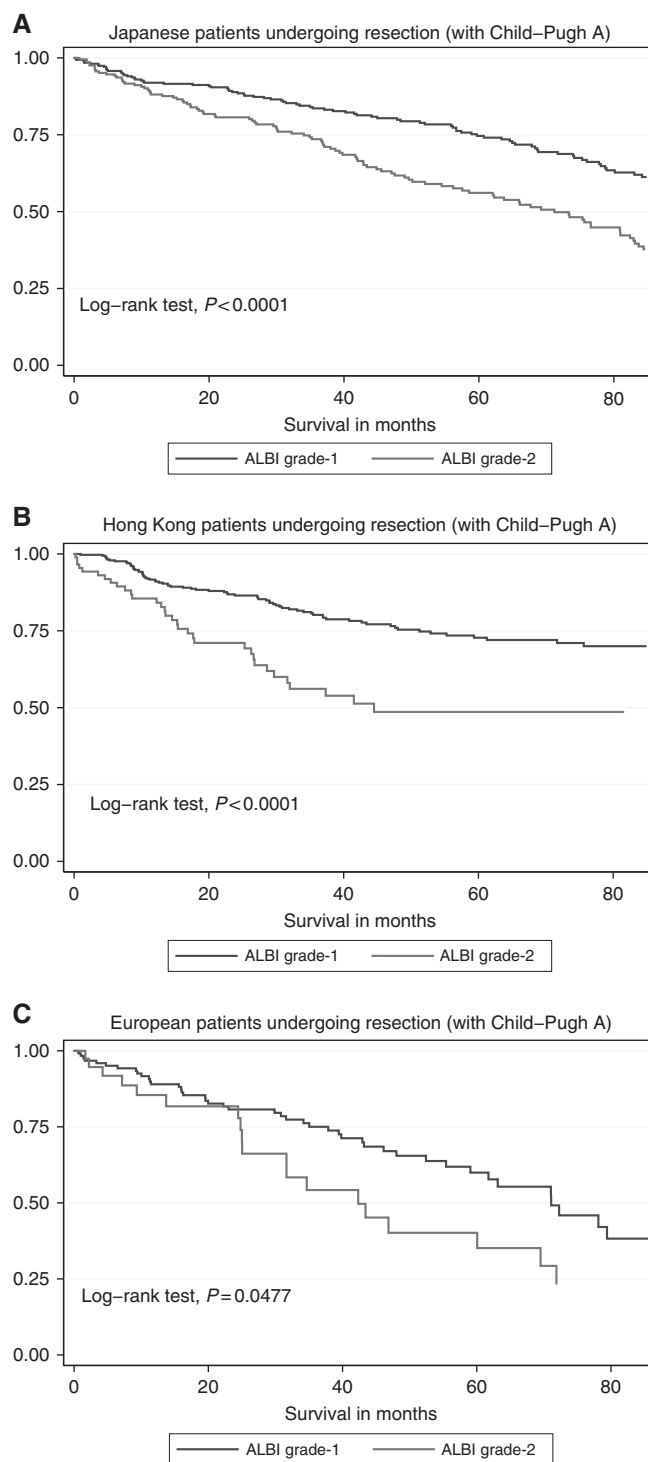


Figure 2. Survival according to ALBI grade in C-P grade A patients undergoing resection in (A) Japan, (B) Hong Kong and (C) Europe.



**Table 2. Median survival in the cohorts according to ALBI grade within each treatment**

Treatment	Cohort	ALBI grade	N	Median survival in months (95% CI)	5-year survival, % (95% CI)	Hazard ratio (95% CI), P-value
All patients undergoing resection and ablative treatments	All	1	1124	106.3 (96.3, 122.7)	68.4 (65.0, 71.5)	1
		2	983	53.7 (48.2, 58.6)	44.7 (40.9, 48.4)	2.0 (1.8, 2.3), $P < 0.0001$
		3	71	26.9 (20.4, 33.4)	11.1 (4.3, 21.6)	5.0 (3.8, 6.7), $P < 0.0001$
Patients undergoing resection (Child, Pugh A)	Japan	1	325	122.7 (96.3, 148.7)	74.6 (68.5, 79.7)	1
		2	211	71.2 (56.2, 82.4)	56.1 (48.1, 63.3)	1.9 (1.5, 2.5), $P < 0.0001$
	Hong Kong	1	359	Not reached	72.8 (66.5, 78.0)	1
		2	91	44.5 (28.6)	48.6 (34.9, 61.1)	2.4 (1.6, 3.7), $P < 0.0001$
	Europe	1	123	71.1 (59.0, 120.4)	60.0 (48.3, 69.8)	1
		2	39	42.3 (25.0, 69.5)	35.1 (16.9, 54.0)	1.7 (1.0, 2.9), $P = 0.05$
Patients undergoing RFA	Japan	1	65	84.2 (63.8)	67.0 (51.5, 78.5)	1
		2	189	56.1 (48.6, 72.4)	48.0 (38.7, 56.7)	1.7 (1.1, 2.6), $P = 0.024$
		3	13	23.8 (10.1)	0%	5.1 (2.2, 11.7), $P < 0.0001$
	Hong Kong	1	141	89.3 (66.7, 115.8)	61.6 (51.2, 70.5)	1
		2	129	59.2 (47.2, 64.1)	45.7 (34.7, 56.1)	1.7 (1.1, 2.4), $P = 0.003$
		3	5	7.4 (2.3)	0%	9.4 (3.3, 26.6), $P < 0.0001$
	Europe	1	61	56.5 (36.0, 69.2)	43.7 (27.4, 58.9)	1
		2	89	30.2 (27.4, 34.3)	16.2 (8.4, 26.1)	2.0 (1.3, 3.0), $P = 0.002$
		3	12	19.3 (7.8, 34.2)	13.8 (0.8, 44.3)	2.9 (1.4, 6.2), $P = 0.005$

Abbreviations: CI = confidence interval; RFA = radiofrequency ablation.

according to viral status, it was apparent that HBV-positive patients had a significantly better prognosis than HCV-positive patients in the Japanese, Hong Kong and European cohorts (log rank test,  $P < 0.0001$ , 0.0056 and 0.0029 respectively) (Supplementary Figure 5). In the same order of cohorts, HBV-HCC median survival stood at 135.9 (95% CI 82.4, 168.1), 114.7 (95% CI 87.5) and not reached (or 5-year survival at 75.9%, 95% CI 61.7, 85.4), whereas HCV-HCC survival was 67.3 (95% CI 60.4, 74.5), 44.7 (95% CI 34.0, 69.8) and 71.9 months (95% CI 52.8, 90.2). In all, 68% of HBV-HCC patients fell into the ALBI grade-1 category as compared with only 33% of the HCV-HCC patients (Supplementary Table 2). It was notable that the survival curves only separated at between 2 and 3 years. Severe fibrosis or cirrhosis (F3 and F4) was more common in the HCV patients (82.2%) than in the HBV patients (65.2%) (Supplementary Table 3).

Median survival, 5-year survival and hazard ratio figures for all of the above are summarised in Table 2 and Supplementary Table 4).

#### Correlation of ICG clearance and HVPG with ALBI score.

Because of skewness of the ICG distribution, an appropriate transformation was used, in this case, the square root of each value. Among the patients with measured ICG, a strong positive correlation was observed with the ALBI score ( $r = 0.6423$ ,  $n = 1346$ ,  $P < 0.0001$ ; Figure 4A). There was also a positive correlation between HVPG and the ALBI score ( $r = 0.55$ ,  $n = 52$ ,  $P < 0.0001$ ; Figure 4B).

## DISCUSSION

International guidelines suggest that curative treatments, other than liver transplantation, should be confined to those with grade A C-P score in order to avoid the short-term complications associated with poor liver function (Schneider, 2004; Bruix and Sherman, 2005; Seyama and Kokudo, 2009; Fan, 2010; Vauthey *et al*, 2010; European Association For The Study Of The Liver-European Organisation For Research And Treatment Of Cancer, 2012). Such guidelines are refined by estimation of serum bilirubin and HVPG or ICG clearance (Hemming *et al*, 1992; Bruix *et al*, 1996; Thalheimer *et al*, 2004), whereas HVPG is often substituted

for by 'clinical evidence of portal hypertension' (Berzigotti *et al*, 2015; Roayaie *et al*, 2015).

The present data confirm, and greatly extend, our original report that within C-P A grade there are two distinct subgroups as classified by the ALBI score. In all regions, among resected patients, survival was about twice as long among those with ALBI grade-1 than for those with ALBI grade-2. The overall survival results are remarkably consistent across regions. The rather worse survival in the European patients may be attributable to different practices when liver transplantation is an option. As expected, very few patients (<1%) with ALBI grade-3 were subjected to surgical resection. Similar results were obtained for those undergoing ablative therapies with curative intent. The degree of discrimination within C-P A is all the more remarkable for the fact that none of the clinical features related to the tumour itself that are perceived to influence survival (AFP, vascular invasion and tumour size) are taken into account. This implies that a very significant fraction of the mortality in HCC after potentially curative therapies, even in C-P 'A' patients, is attributable to liver dysfunction. The observation that clear separation between survival curves of ALBI grade-1 and ALBI grade-2 persists in those patients without HCC recurrence (Supplementary Figure 2) may be taken to imply that much of the increased mortality in ALBI grade-2 is related to liver failure. There was little change in liver function after resection at 6 months, but we suspect that had more prolonged follow-up been available, separation between ALBI grade-1 and ALBI grade-2 would have become apparent. The observation that surgical resection and ablative therapies, but not transplant, are affected by the ALBI score would be expected if ALBI reflects liver function.

Our data also demonstrate a further advantage of the ALBI grade over the C-P scoring system in that it is equally applicable to HCC patients without cirrhosis. The ALBI score gave clear discrimination in each grade despite the fact that among patients with HBV-related HCC only 47.2% had cirrhosis (fibrosis stage 4) and even among the HCV patients the figure was only 56.6%. Conventionally, the C-P scoring system is restricted to patients with cirrhosis.

There is controversy concerning how to decide, in an individual patient, whether the most appropriate treatment is transplantation or surgical resection (where that option exists) (Michel *et al*, 1997;

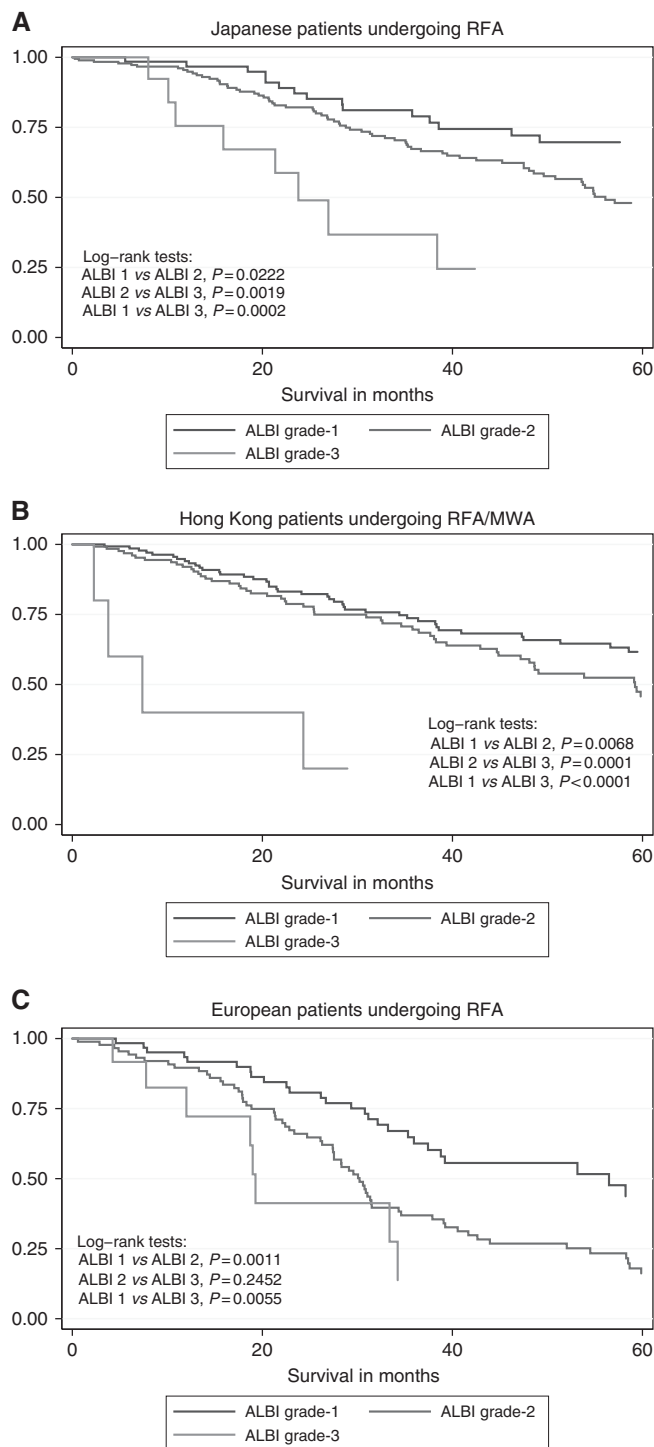


Figure 3. Survival according to ALBI grade in patients undergoing RFA and other ablative therapies in (A) Japanese, (B) Hong Kong and (C) European cohorts.

Sarasin *et al*, 1998; Figueras *et al*, 2000; Schwartz *et al*, 2007). It is widely agreed that transplantation is the preferred choice among patients with C-P B or C because such patients clearly have a higher risk of death from the associated liver disease. However, as noted above, we show that even within C-P 'A' there is a major difference in mortality between ALBI grade-1 and ALBI grade-2. Such information may influence the decision to transplant or resect: resection being, perhaps, more appropriate in ALBI grade-1 and transplantation in ALBI grade-2. We cannot be certain about

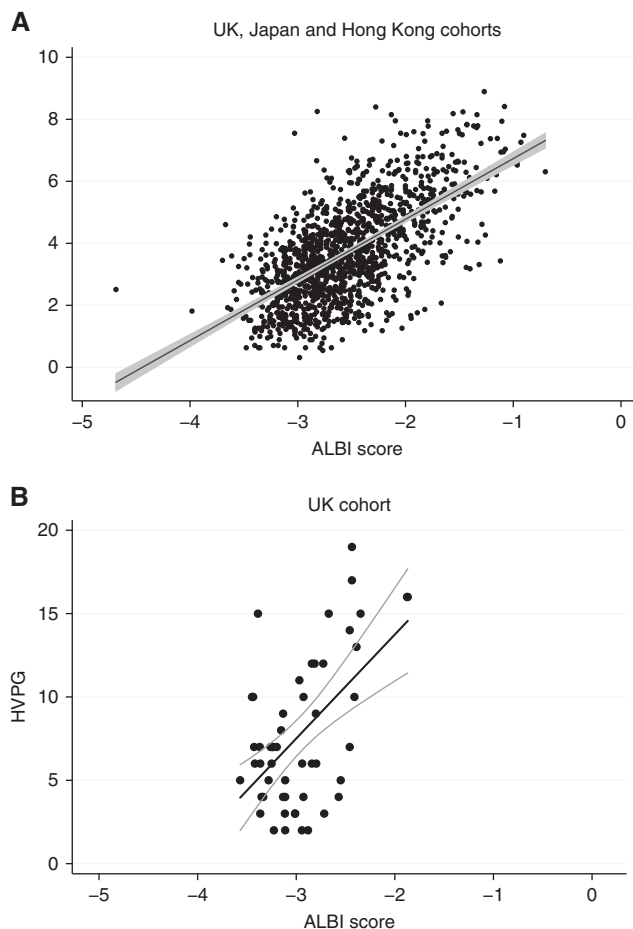


Figure 4. Raw data scatterplots showing with 95% CI correlation between ALBI score and (A) sqrt(ICG) clearance ( $r=0.67$ ,  $n=2190$ ,  $P<0.0001$ ) and (B) WHPG ( $r=0.55$ ,  $n=52$ ,  $P<0.0001$ ). WHPG = wedged hepatic portal hepatic gradient.

the impact of postoperative antiviral therapy on our results. Current evidence suggests that rates of recurrence/development of 'new' tumours are probably decreased but definitive evidence is still awaited (Lok, 2012; Urata *et al*, 2012; Kim and Gores, 2013; Yin *et al*, 2013).

The ability to assess liver dysfunction accurately with the ALBI score before treatment may permit explanation of the findings of Franssen *et al* (2014) that HBV-positive patients survive significantly longer than those who are HCV positive. Analysis of our large international data set confirmed this finding and suggested that this may be attributable to differences in underlying liver function. More patients in the HBV-positive group in all regions were ALBI grade-1. This is consistent with the general consensus (and as shown in our results here; Supplementary Table 3) that HCC arises largely in the cirrhotic (or at least severely fibrotic) liver in HCV-positive patients, whereas it may also arise in the HBV-positive livers before the stage of cirrhosis has been reached (Shiratori *et al*, 1995; Grando-Lemaire *et al*, 1999; Kumar *et al*, 2007; Schuppan and Afdhal, 2008).

All the above interpretations assume that the ALBI score is a valid measure of liver dysfunction. Our initial publication provided circumstantial evidence that this was the case. Here, we adduce three further pieces of supportive evidence. Firstly, there was a positive correlation with ICG clearance, an objective test of liver function widely used in preoperative assessment. Secondly, in a smaller data set, there was also a correlation with HVPg, another parameter used in preoperative assessment. Finally, we hypothesised that in patients undergoing liver transplantation,

preoperative liver function, as defined by the ALBI score, would have no impact on survival and, indeed, this was the case.

We now have objective evidence that the ALBI score assesses liver function in HCC patients. Although it is conventionally considered that assessment of liver function before resection is important to exclude patients who might develop liver failure if too large a resection is undertaken, we show here that the liver function also has a major impact on long-term survival. Such observations may have major implications for decisions as to whether surgery or liver transplantation is undertaken in HCC patients with compromised liver function.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## AUTHOR CONTRIBUTIONS

Study concept and design: PJJ, HT, JO'B, TK and PBSL; acquisition of data: HT, PBSL, CCC, JO'B, SB, HR, WY, TT, MI, AV, NS, SLC, BS and DM; analysis and interpretation of data: SB, HT, PBSL, JO'B, FM and RPF; drafting of the manuscript: PJJ, SB, HT and PBSL; critical revision of the manuscript for important intellectual content: all; statistical analysis: SB, RF and FM; obtained funding: none; administrative, technical or material support: none; study supervision: PJJ.

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Supplementary Information accompanies this paper on British Journal of Cancer website (<http://www.nature.com/bjc>)