Comparison of twelve liver functional reserve models for outcome prediction in patients with hepatocellular carcinoma undergoing surgical resection

Shu-Yein Ho1,3, Po-Hong Liu3,6, Chia-Yang Hsu3,7, Cheng-Yuan Hsia2,3, Chien-Wei Su1,3, Yun-Hsuan Lee1, Yi-Hsiang Huang1,3,4, Fa-Yauh Lee1,3, Ming-Chih Hou1,3 & Teh-Ia Huo1,3,5

Various noninvasive liver functional reserve models have been proposed, but their prognostic ability in patients with hepatocellular carcinoma (HCC) is unclear. We aimed to investigate the performance of twelve noninvasive liver reserve models in HCC patients undergoing surgical resection. A total of 645 patients undergoing resection were prospectively identified and retrospectively analyzed. Tumor recurrence, overall survival, and independent prognostic factors were evaluated by the Cox proportional hazards model. Of the twelve models, the King’s score showed the highest homogeneity and lowest corrected Akaike information criterion (AICc) value, suggesting a better predictive ability for tumor recurrence. In multivariate Cox analysis, we confirmed that King’s score, tumor size and serum alpha-fetoprotein level were independent predictors associated with recurrence. In survival prediction, albumin-bilirubin (ALBI) revealed the highest homogeneity and lowest value among twelve invasive models, indicating a better prognostic performance. In the Cox model, ALBI grade, tumor burden, alpha-fetoprotein, vascular invasion, diabetes mellitus and performance status were independent predictors linked with overall survival. In summary, the currently used liver function models have differential predictive ability for HCC patients undergoing surgical resection. The King’s score is a feasible tool to predict tumor recurrence, whereas ALBI grade is a more robust model for prognostic prediction.

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, accounting for more than 700,000 deaths each year. Chronic hepatitis B and C virus (HBV, HCV) infection and alcoholism are the major risk factors for HCC. HCC develops in the background of chronic liver disease or cirrhosis in 70–90% of patients, and various degrees of liver dysfunction are usually present at the time of diagnosis. Surgical resection is the curative treatment option for patients with early stage HCC with well preserved liver function, and provides 5-year survival rate up to 70%–90%. However, tumor recurrence after surgery is common and is associated with a decreased overall survival.

The prognosis and management of HCC is typically influenced by tumor burden, liver functional reserve and performance status. The Child-Turcotte-Pugh (CTP) classification has been widely used for decades in assessing the severity of liver dysfunction. Many HCC staging systems, including the Barcelona Clinic Liver Cancer (BCLC) staging system, utilize CTP classification as an indicator of liver disease severity. However, the CTP classification is not an evidence-based practice. The model for end-stage liver disease (MELD) has been a prevailing system to prioritize cirrhotic patients awaiting liver transplantation, and is used in assessing liver functional reserve and...
outcome for HCC patients. Another important marker, indocyanine green retention rate at 15 minutes (ICG-15) test, has also been widely used to evaluate liver reserve in surgical HCC patients.

Alternatively, the albumin-bilirubin (ALBI) and the platelet-albumin-bilirubin (PALBI) grade were recently proposed to assess liver functional reserve in HCC. In addition, serum sodium concentration was found to inversely correlate with the severity of cirrhosis, and has been used to assess the degree of portal hypertension. Other tools to evaluate liver functional reserve include aspartate aminotransferase-to-platelet ratio (APRI), fibrosis index based on 4 factors (FIB-4), King's score, cirrhosis discriminate index (CDS), Lok index and the Göteborg University Cirrhosis Index (GUCI). These models incorporate different clinical parameters such as age and serum biochemistries. Up to date, twelve noninvasive liver reserve models are used to assess the degree of liver dysfunction, but the prognostic role of these models in HCC patients remains unclear. This study aimed to investigate the correlation of these noninvasive models and their prognostic impact on tumor recurrence and overall survival in HCC patients undergoing surgical resection.

Patients and Methods

Patients and follow-up. During a 12-year period between 2003 to 2015, patients with newly diagnosed HCC and admitted to Taipei Veterans General Hospital were prospectively identified and retrospectively analyzed. A total 645 patients undergoing surgical resection were enrolled in this study. The baseline demographics, etiology of liver disease, tumor status and serum biochemistries were collected at the time of diagnosis. Tumor recurrence, subsequent anti-cancer therapy, and overall survival were recorded. The inclusion criteria of surgery were (1) tumor involving no more than three Couinaud segments, (2) CTP class A or B and data for ICG-15, (3) no main portal vein trunk involvement or distant metastases, and (4) absence of other major diseases that may complicate resection.

After surgery, the patients were followed up with imaging studies and serum a-fetoprotein (AFP) level every 3 to 6 months until death or dropout from the follow-up program. This study complies with the standard of the Declaration of Helsinki and current ethical guidelines, and has been approved by the Institutional Review Board of Taipei Veterans General Hospital. Waiver of consent was obtained, and patient records/information was anonymized and de-identified prior to analysis.

Diagnosis and definition. The pre-operative diagnosis of HCC was histologically confirmed or based on the findings of typical four-phase multidetector contrast-enhanced dynamic computed tomography (CT) scan or magnetic resonance imaging (MRI). The performance status was assessed by using the Eastern Cooperative Oncology Group Performance scaling ranging from 0 (asymptomatic) to 4 (confined to bed). Intrahepatic recurrence was defined as residual disease within or adjacent to the previously treated tumor site, whereas extrahepatic recurrence was defined as emergence of the tumor elsewhere in or outside the liver.

Treatment. Surgical resection was performed by our experienced surgical team. The operative procedures have been previously described in detail. The resected liver tissue was sent for gross and microscopic examinations, and the recorded tumor size was based on the largest dimension of the resected specimen. The treatment of recurrence HCC included re-resection, local ablative treatment, transarterial chemoembolization, targeted therapy, chemotherapy, radiotherapy and best supportive care.

Grading of 12 models. The calculation of 12 noninvasive liver functional reserve models was based on clinical variables and serum biochemistries at the time of diagnosis. The grading of these liver functional reserve models was according to published studies. Grade 1 indicates adequate liver functions, and grade 3 is associated with poor liver reserve (Table 1).

Statistical Analysis. All statistical analyses were conducted using the SPSS for Windows version 21 release (SPSS Inc., Chicago, IL, USA). The X2 test or Fisher’s exact test was used to analyze categorical variables and the Mann-Whitney ranked sum test for continuous variables. The recurrence-free survival and overall survival were estimated by the Kaplan-Meier method and compared by a log-rank test. Independent prognostic factors that were possibly linked to recurrence-free survival and overall survival were analyzed. Factors that were significant in the univariate analysis were entered into the adjusted multivariate Cox proportional hazards model to determine adjusted hazard ratio (HR) and 95% confidence interval (CI).

The discriminatory ability of different models association with tumor recurrence and overall survival was examined by using the Cox proportional hazards model, and the consequences of the Cox model were expressed with the corrected Akaike information criterion (AICc), which reveals how the model affects the dependent variable and represents an overall assessment of the model. The lower the AIC, the more explanatory and informative the model is. We also examined the correlation of ICG-15 and other 11 noninvasive liver functional reserve models. For all tests, a p < 0.05 was considered statistically significant.

Results

Baseline characteristics. A prospective data set of 645 patients who received surgical resection as curative treatment were enrolled during the study period. Baseline demographics and clinical information of these patients are shown in Table 2. The median age was 61 years with the majority being male (80%). Three hundred and twenty-seven (51%) patients had HBV infection, and 131 (20%) had a history of diabetes mellitus. Two hundred and thirty (36%) patients had tumor size ≤3 cm and 633 (98%) of had ≤3 nodules at initial presentation. In these patients, 254 (39%) and 232 (36%) received lobectomy and bi-segmentectomy respectively, while 133 (21%) and 26 (4%) patients received segmentectomy and sub-segmentectomy respectively. All patients were histologically confirmed HCC and were free of surgical margin.
### Table 1. Formula and grading of 12 noninvasive liver functional reserve models.

| Noninvasive blood testing for liver serve makers | Formula |
|-----------------------------------------------|---------|
| ALBI, Grade 1/2/3 (<−2.6/−2.6−1.39/−1.39) | (log(Bilirubin[umol/L]) × 0.66) + (Albumin[g/L] × −0.085) |
| APRI, Grade 1/2/3 (<0.5/0.5–1.5>/1.5) | ([AST/upper limit of normal]/Platelet Count (10^9/L)) × 100 |
| CTP, A/B/C, grade 1/2/3 (<5–6/7–9/10–15) | Encephalopathy: none = 1, grade 1 or 2 = 2, grade 3 or 4 = 3 Ascites: none = 1, mild to moderate = 2, severe = 3 Bilirubin(mg/dl): <2 = 1, 2–3 = 2, >3 = 3 Albumin(g/dl): <3.5 = 1, 2.8–3.5 = 2, <2.8 = 3 PT sec (INR): <4 (1.7) = 1, 4–6 (2.3) = 2, >6 (2.3) = 3 |
| CDS, Grade 1/2/3 (<4/4–7>/7) | Platelet count (< × 10^10/L); >340 = 0; 280–339 = 1; 220–279 = 2; 160–219 = 3; 100–159 = 4; 40–99 = 5; <40 = 6 |
| | ALT/AST ratio: >1.7 = 0; 1.7–1.4 = 1; 1.1–1.4 = 2; <0.6 = 3 |
| FIB-4 index, Grade 1/2/3 (<1.45/1.45–3.25>/3.25) | (Age[years] × AST[U/L])/(platelet (10^9/L) × PALBI (10^9/L)^2) |
| GUCl, Grade 1/2/3 (<0.5/0.5–1.56>/1.56) | [AST/TOPNORMAL AST] × INR × 100/(Platelets × 10^9) |
| Lok index, Grade 1/2/3 (<0.5/0.5–0.8>/0.8) | Lok Index = e^(log10b[rubin](umol/L) × (0.378 × ln(Bilirubin)) + (0.12 × ln(INR))) + 6.43 |
| MELD, Grade 1/2/3 (<8/8–12>/12) | 10 × ((0.957 × ln(Creatinine)) + (0.378 × ln(Bilirubin)) + (1.12 × ln(INR))) + 6.43 |
| PALBI, Grade1/2/3 (<−2.53, −2.53 and −2.09, <−2.09) | (2.02 × log10 bilirubin) − (0.37 × log10 bilirubin/Albumin) − 0.04 × albumin (g/L) − 3.48 × log10 platelets(10^10/L) + 1.01 × log10 platelets(10^10/L)^2 |
| King's score (<7.6/7.6–16.7)/67.6 | Age × AST × INR/(platelets (10^9/L)] |
| Serum sodium (≥135>/135 mmole/L) | |
| ICG-15 test (%) (10/10–20>/20) | |

### Tumor recurrence.

The median recurrence-free survival was 23 months, and 413 (64%) patients had tumor recurrence during the follow-up. The estimated 1-, 3-, and 5-year recurrence-free survival rates were 73%, 43% and 33%, respectively. The predictive role of 12 noninvasive liver functional reserve models on recurrence-free survival was evaluated according to their grading (Figs 1 and 2). A significant difference in recurrence-free survival were found only in APRI, FIB-4, GUCl, King's score, Lok index and PALBI (all p < 0.05). Pairwise comparison showed that there was no significant difference between APRI grade 2 vs 3 (p = 0.995), GUCl grade 2 vs 3 (p = 0.984), Lok index grade 2 vs 3 (p = 0.267) and PALBI grade 1 and grade 2 (p = 0.593). Comparison of prognostic performance in terms of tumor recurrence prediction among 12 models reveals that the King's score had the highest homogeneity and lowest AICc value (Table 3).

In univariate analysis, positive HBsAg, alcoholism, high AFP, tumor number > 3 nodules, tumor size > 3 cm, presence of vascular invasion and King's score grade 3 were associated with increased risk of recurrence (all p < 0.05; Table 4). In the Cox model, 4 independent predictors of tumor recurrence were identified: alcoholism (HR: 1.443; 95% CI: 1.062–1.960, p = 0.019), high AFP level (HR: 1.499; 95% CI: 1.185–1.897, p = 0.001), tumor size > 3 cm (HR: 1.562, 95% CI: 1.219–2.001, p < 0.001) and King's score grade 3 (HR: 1.770, 95% CI: 1.318–2.378, p < 0.001).

### Treatment after tumor recurrence.

During the follow-up period, 377 (58%) patients had intrahepatic recurrence and 36 (9%) had extrahepatic recurrence. Treatment of recurrent HCC included re-resection (n = 35), local ablative therapy (n = 131), transarterial chemoembolization (n = 187), sorafenib (n = 6), chemotherapy (n = 16), radiotherapy (n = 10) and best supportive care (n = 27).

### Overall survival.

The median overall survival was 55 months and 343 (53%) of patient died during follow-up. The cause of death was tumor recurrence in 213 (62.2%) patients. Another 73 (20.2%) patients died of liver failure or complications of portal hypertension with (66 patients) or without (7 patients) tumor recurrence, and the remaining 57 (16.6%) died of non-liver related causes.

The estimated 1-, 3-, and 5-year survival rates were 88%, 74% and 56%, respectively. The survival distribution according to the grading of 12 noninvasive liver reserve models are shown in Figs 3 and 4. Significant differences in overall survival were found only in ALBI, FIB-4, King's core and PALBI (all p < 0.05). Pairwise comparison showed that there were no significant differences in FIB-4 grade 1 vs 3 (p = 0.145), King's grade 1 vs 3 (p = 0.545), PALBI grade 1 vs grade 3 (p = 0.084) and grade 2 vs grade 3 (p = 0.083). The prognostic role of these 12 models for survival analysis showed that the ALBI grade had the highest homogeneity and lowest AICc value (Table 3).

In univariate analysis of overall survival among surgical patients, older age (≥ 65 years), alcoholism, presence of diabetes mellitus, presence of ascites, high AFP level, larger tumor (> 3 cm) and multi-nodularity (> 3 nodules),
poor performance status, presence of vascular invasion and ALBI grade 2–3 were associated with decreased survival (all p < 0.05, Table 4). In the Cox model, seven independent adverse prognostic predictors were found: diabetes mellitus (HR: 1.489, 95% CI: 1.152–1.925, p = 0.002), AFP ≥ 20 ng/ml (HR: 1.513; 95% CI: 1.211–1.891, p < 0.001), >3 tumor nodules (HR: 2.599, 95% CI: 1.372–4.924, p = 0.003), main tumor size > 3 cm (HR: 1.747, 95% CI: 1.365–2.236, p < 0.001), poor performance status (HR: 1.311, 95% CI: 1.006–1.710, p = 0.045), vascular invasion (HR: 2.334; 95% CI: 1.723–3.162, p < 0.001), and ALBI grade 2–3 (HR: 1.439, 95% CI: 1.158–1.790, p < 0.001).

Table 2. Baseline characteristics of hepatocellular carcinoma undergoing surgical resection. ALBI, Albumin-bilirubin; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; APRI, Aspartate transaminase-to-Platelet ratio; CDS, Cirrhosis discriminant index; CTP, Child-Turcotte-Pugh score; FIB-4, Fibrosis-4 score; ICG, Indocyanine green; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, Model for End-stage liver disease; GUCI, Göteborg University Cirrhosis Index; PALBI, platelet-albumin-bilirubin; SD, standard deviation; IQR, interquartile range.
Figure 1. Comparison of recurrence-free survival distribution according to (A) ALBI, (B) APRI, (C) CDS, (D) CTP, and (E) FIB-4, (F) GUCI grading. Significant survival differences are found in APRI, FIB-4 and GUCI (p < 0.05).

Figure 2. Comparison of recurrence-free survival distributions according to (A) ICG, (B) King's score, (C) Lok index, (D) MELD, and (E) Serum sodium, (F) PALBI grading. Significant survival differences are found in King's score, Lok index and PALBI (p < 0.05).
Correlation analysis. Except for serum sodium, the scores of other 10 noninvasive liver functional reserve models all significantly increased with higher ICG-15 value (Table 5).

Discussion
Liver functional reserve is a crucial prognostic predictor for HCC. In this study, we utilize a prospective HCC cohort to evaluate the prognostic role of these noninvasive models on tumor recurrence and overall survival in HCC patients undergoing surgical resection. We show that among these noninvasive models, the King's score is a more feasible marker to predict tumor recurrence and ALBI is the most accurate model in the discrimination of survival for HCC patients.

In the prediction of tumor recurrence, our results disclose that the King's score, APRI and FIB-4 are the three most accurate models associated with recurrence according to AICc analysis. Among these models, the King's score has the greatest homogeneity of recurrence pattern among HCC patients, indicating it is a more useful tool for recurrence prediction. In multivariate Cox model, King's score grade 3 had 77% increased risk of recurrence as compared with those with grade 1. In addition to King's score, tumor size, high AFP and alcoholism are also independent predictors associated with tumor recurrence. These findings suggest that liver functional reserve and tumor status are closely linked with a more aggressive tumor behavior.

In survival analysis, consistent with previous report 12,13,34, we found that the ALBI and PALBI grade are the best models for discriminating patient survival. We further show that ALBI grade has the highest homogeneity for survival prediction, suggesting that ALBI is a more robust tool for outcome prediction. In multivariate Cox model, ALBI grade 2–3 was associated with 43% increased risk of mortality compared with ALBI grade 1.

Our analyses indicate that tumor size and number are closely related to survival of HCC patients. In addition, in accordance with previous studies 35,36, performance status and vascular invasion are crucial prognostic predictors. Moreover, consistent with published series 37-40, high serum AFP level and diabetes mellitus may strongly impact the outcome of HCC patients. Taken together, the severity of liver reserve, tumor burden and performance status are the hallmarks for survival prediction.

The CTP classification has been used to evaluate the severity of liver function and prognosis of HCC. However, in our study, CTP was not significantly linked with tumor recurrence and overall prognosis. This is probably because the majority (94%) of the patients were CTP class A and hence its prognostic ability is impaired. The MELD score and serum sodium level are used to evaluate the prognosis of end-stage cirrhotic patients in the process of organ allocation in liver transplantation 41,42. However, these two models could not accurately discriminate tumor recurrence and survival because the patients in this study are mostly mildly cirrhotic or non-cirrhotic.

Table 3. Predictive accuracy of tumor recurrence and overall survival in 12 noninvasive liver functional reserve models.
Serum ICG-15 has been a useful adjunct to quantify hepatic reserve in HCC, but its performance is not superior to other markers in this study. Other noninvasive models (CDS, GUCI and Lok index) have not been used to evaluate the prognosis of HCC patients. Importantly, of all models, the ALBI grade, based simply on serum albumin and bilirubin level, is more objective and a readily available marker that can be used for survival discrimination in surgical HCC patients.

Among the 12 liver functional reserve models, APRI, FIB-4 and King's score are principally designated as liver fibrosis models. Previous studies showed that these models could be used to predict the prognosis of HCC. Notably, these models are associated with liver fibrosis which might be associated with an increased risk of tumor recurrence via carcinogenesis pathway. Interestingly, of these models, the King's score is the best in predicting tumor recurrence in HCC patients undergoing surgical resection. Other noninvasive liver reserve models (CDS, GUCI and Lok index) have not been used to assess liver reserve and prognosis in HCC. Alternatively, the PALBI grade, an updated version of ALBI classification, is a new promising prognostic tool for HCC and more studies are required to validate its clinical role.

The correlation between ICG-15 and other noninvasive liver functional reserve models was investigated in this study. Our results show that, except for serum sodium, there is a strong correlation between ICG-15 and other 10 models, indicating that most models are clinically relevant in evaluating the degree of liver injury. Liver functional reserve plays an important role in determining the extent of surgical resection for HCC. The major surgical resection was performed in patients who had good liver functional reserve. However, for those with relatively poor liver reserve, limited surgical resection was done, and these patients might have a higher risk of recurrence after surgery. As a result, liver function may have indirect impact on tumor recurrence via the choice of extent of surgical resection.

There are some study limitations. This is a single-center study in an HBV endemic area, thus external validation is needed from other study groups. In addition, the results are based on HCC patients undergoing surgical resection, therefore the prognostic accuracy of ALBI and King's score in patients receiving different treatment...
Figure 3. Comparison of overall survival distribution according to (A) ALBI, (B) APRI, (C) CDS, (D) CTP, and (E) FIB-4, (F) GUCI grading. Significant survival differences are found in ALBI and FIB-4 (p < 0.05).

Figure 4. Comparison of overall survival distributions according to (A) ICG, (B) King’s score, (C) Lok index, (D) MELD, and (E) Serum sodium, (F) PALBI grading. Significant survival differences are found in King’s score and PALBI (p < 0.05).
modalities needs further study to establish. Lastly, since our hospital is a tertiary medical center, referral bias cannot be completely avoided.

In conclusion, the currently used liver functional reserve models have differential predictive ability for HCC patients undergoing surgical resection. The King’s score may serve as a feasible model in predicting tumor recurrence, whereas ALBI grade is the best prognostic tool among the 12 noninvasive liver reserve models. Appropriate models should be considered to integrate into cancer staging in future clinical practice.

References
1. Park, J. W. et al. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. Liver Int 35, 2155–2166 (2015).
2. El-Serag, H. B. Hepatocellular carcinoma. N Engl J Med 365, 1118–1127 (2011).
3. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 56, 908–943 (2012).
4. Bruix, J. & Sherman, M. Management of hepatocellular carcinoma: an update. Hepatology 53, 1020–1022 (2011).
5. Inamura, H. et al. Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. J Hepatol 38, 200–207 (2003).
6. El-Serag, H. B., Marrero, J. A., Rudolph, L. & Reddy, K. R. Diagnosis and treatment of hepatocellular carcinoma. Gastroenterology 134, 1752–1763 (2008).
7. Olthoff, K. M. et al. Summary report of a national conference: Evolving concepts in liver allocation in the MELD and PELD era. December 8, 2003, Washington, DC, USA. Liver Transpl 10, A6–22 (2004).
8. Bott, F. et al. MELD scoring system is useful for predicting prognosis in patients with liver cirrhosis and is correlated with residual liver function: a European study. Gut 52, 134–139 (2003).
9. Huo, T. L. et al. The sequential changes of the model for end-stage liver disease score correlate with the severity of liver cirrhosis in patients with hepatocellular carcinoma undergoing locoregional therapy. J Clin Gastroenterol 40, 543–550 (2006).
10. Huo, T. L. et al. Model for end-stage liver disease score to serum sodium ratio index as a prognostic predictor and its correlation with portal pressure in patients with liver cirrhosis. Liver Int 27, 498–506 (2007).
11. Seyer, Y. & Kokudo, N. Assessment of liver function for safe hepatic resection. Hepatol Res 39, 107–116 (2009).
12. Johnson, P. I. et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach—the ALBI grade. J Clin Oncol 33, 550–558 (2015).
13. Liu, P. H. et al. ALBI and PALBI Grade Predict Survival for HCC across Treatment Modalities and BCLC Stages in the MELD Era. J Gastroenterol Hepatol (2016).
14. Kim, W. R. et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med 359, 1018–1026 (2008).
15. Biggs, S. W. et al. Serum sodium predicts mortality in patients listed for liver transplantation. Hepatology 41, 32–39 (2005).
16. Rüf, A. E. et al. Addition of serum sodium into the MELD score predicts waiting list mortality better than MELD alone. Liver Transpl 11, 336–343 (2005).
17. Vallée-Pichard, A. et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. Comparison with liver biopsy and fibrotest. Hepatology 46, 32–36 (2007).
18. Wai, C. T. et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 38, 518–526 (2003).
19. Cross, T. J. et al. King’s Score: an accurate marker of cirrhosis in chronic hepatitis C. Eur J Gastroenterol Hepatol 21, 730–738 (2009).
20. Lok, A. S. et al. Predicting cirrhosis in patients with hepatitis C based on standard laboratory tests: results of the HALT-C cohort. Hepatology 42, 282–292 (2005).
21. Bonacini, M., Hadi, G., Govindarajan, S. & Lindsay, K. L. Utility of a discriminant score for diagnosing advanced fibrosis or cirrhosis in patients with chronic hepatitis C virus infection. Am J Gastroenterol 92, 1302–1304 (1997).
22. Westin, J. et al. A non-invasive fibrosis score predicts treatment outcome in chronic hepatitis C virus infection. Scand J Gastroenterol 43, 73–80 (2008).
23. Chang, W. T. et al. Hepatic resection can provide long-term survival of patients with non-early-stage hepatocellular carcinoma: extending the indication for resection? Surgery 152, 809–820 (2012).
24. N’Konchu, G. et al. Radiofrequency ablation of hepatocellular carcinoma: long-term results and prognostic factors in 235 Western patients with cirrhosis. Hepatology 50, 1475–1483 (2009).
25. Hung, H. H. et al. Fibrosis and AST to platelet ratio index predict post-operative prognosis for solitary small hepatitis B-related hepatocellular carcinoma. Hepatol Int 4, 691–699 (2010).

Table 5. Correlation between ICG-15 and different liver functional reserve models. ALBI, Albumin-bilirubin; APRI, Aspartate transaminase-to-Platelet ratio; CDS, Cirrhosis discriminant index; CTP, Child-Turcotte-Pugh score; FIB-4, Fibrosis-4 score; MELD, Model for End-stage liver disease; GUCI, Göteborg University Cirrhosis Index; PALBI, platelet-albumin-bilirubin; SD, standard deviation.

| ICG-15 retention rate (%) | <10 | 10–15 | 15–20 | >20 | p |
|---------------------------|-----|-------|-------|-----|---|
| ALBI (Mean ± SD)          | −3.81 ± 0.45 | −3.69 ± 0.46 | −3.53 ± 0.041 | −3.31 ± 0.57 | <0.001 |
| APRI (Mean ± SD)          | 0.84 ± 1.23  | 1.26 ± 1.90  | 1.45 ± 1.47  | 1.66 ± 1.22  | <0.001 |
| CDS (Mean ± SD)           | 4.78 ± 1.46  | 5.02 ± 1.36  | 5.55 ± 1.65  | 5.98 ± 1.70  | <0.001 |
| FIB-4 (Mean ± SD)         | 2.62 ± 2.36  | 3.85 ± 3.95  | 4.67 ± 2.90  | 5.33 ± 2.80  | <0.001 |
| GUCl (Mean ± SD)          | 0.98 ± 1.50  | 1.44 ± 2.08  | 1.76 ± 1.84  | 2.05 ± 1.71  | <0.001 |
| Lok index (Mean ± SD)     | 0.39 ± 0.21  | 0.42 ± 0.19  | 0.50 ± 0.23  | 0.56 ± 0.24  | <0.001 |
| MELD (Mean ± SD)          | 7.83 ± 2.01  | 8.03 ± 1.73  | 8.49 ± 2.47  | 8.89 ± 2.89  | <0.001 |
| PALBI (Mean ± SD)         | −2.60 ± 0.35 | −2.55 ± 0.32 | −2.52 ± 0.26 | −2.34 ± 0.40 | <0.001 |
| King’s score (Mean ± SD)  | 22.41 ± 31.00 | 36.74 ± 52.79 | 47.91 ± 52.07 | 49.98 ± 39.67 | <0.001 |
| CTP (Mean ± SD)           | 5.25 ± 0.53  | 5.29 ± 0.60  | 5.46 ± 0.68  | 5.80 ± 1.35  | <0.001 |
| Serum sodium (mmole/L, Mean ± SD) | 139.71 ± 2.64 | 139.65 ± 2.81 | 139.40 ± 3.18 | 138.90 ± 2.74 | 0.181 |
26. Lei, H. J. et al. Prognostic value and clinical relevance of the 6th Edition 2002 American Joint Committee on Cancer staging system in patients with resectable hepatocellular carcinoma. *J Am Coll Surg* **203**, 426–435 (2006).
27. Kao, W. Y. et al. A comparison of prognosis between patients with hepatitis B and C virus-related hepatocellular carcinoma undergoing resection surgery. *World J Surg* **35**, 858–867 (2011).
28. Child, C. G. & Turcotte, J. G. Surgery and portal hypertension. *Major Prob Clin Surg* **1**, 1–85 (1964).
29. Lau, H. et al. Evaluation of preoperative hepatic function in patients with hepatocellular carcinoma undergoing hepatectomy. *Br J Surg* **84**, 1255–1259 (1997).
30. Bradburn, M. J., Clark, T. G., Love, S. B. & Altman, D. G. Survival analysis part II: multivariate data analysis—an introduction to concepts and methods. *Br J Cancer* **89**, 431–436 (2003).
31. Feinstein, A. R. Clinical biostatistics. XVI. The process of prognostic stratification. 2. *Clin Pharmacol Ther* **13**, 609–624 (1972).
32. Hosmer, D. W., Hosmer, T., Le Cessie, S. & Lemeshow, S. A comparison of goodness-of-fit tests for the logistic regression model. *Stat Med* **16**, 965–980 (1997).
33. Forster, M. R. Key Concepts in Model Selection: Performance and Generalizability. *J Math Psychol* **44**, 205–231 (2000).
34. Toyoda, H. et al. Long-term impact of liver function on curative therapy for hepatocellular carcinoma: application of the ALBI grade. *Br J Cancer* **114**, 744–750 (2016).
35. Liu, P. H. et al. Surgical resection versus transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombosis: a propensity score analysis. *Ann Surg Oncol* **21**, 1825–1833 (2014).
36. Hsu, C. Y. et al. Performance status in patients with hepatocellular carcinoma: determinants, prognostic impact, and ability to improve the Barcelona Clinic Liver Cancer system. *Hepatology* **57**, 112–119 (2013).
37. Hsu, C. Y. et al. Using serum alpha-fetoprotein for prognostic prediction in patients with hepatocellular carcinoma: what is the most optimal cutoff? *PLoS One* **10**, e0118825 (2015).
38. Liu, P. H. et al. Prognosis of hepatocellular carcinoma: Assessment of eleven staging systems. *J Hepatol* **64**, 601–608 (2016).
39. Huo, T. I. et al. Diabetes mellitus is a risk factor for hepatic decompensation in patients with hepatocellular carcinoma undergoing resection: a longitudinal study. *Am J Gastroenterol* **98**, 2293–2298 (2003).
40. Huo, T. I. et al. Differential mechanism and prognostic impact of diabetes mellitus on patients with hepatocellular carcinoma undergoing surgical and nonsurgical treatment. *Am J Gastroenterol* **99**, 1479–1487 (2004).
41. Kao, W. Y. et al. Risk factors for long-term prognosis in hepatocellular carcinoma after radiofrequency ablation therapy: the clinical implication of aspartate aminotransferase-platelet ratio index. *Eur J Gastroenterol Hepatol* **23**, 528–536 (2011).
42. Okamura, Y. et al. The FIB-4 index is a significant prognostic factor in patients with non-B non-C hepatocellular carcinoma after curative surgery. *Langenbecks Arch Surg* **401**, 195–203 (2016).
43. Pinato, D. J. et al. The Kings Score refines prognostic prediction in hepatocellular carcinoma: a novel application. *Liver Int* **35**, 2458–2465 (2015).

**Acknowledgements**

This study was supported by the grant from the Center of Excellence for Cancer Research at Taipei Veterans General Hospital (MOHW106-TDU-B-211-144-003), Taiwan, and grants from Taipei Veterans General Hospital (V107A-008, VN107-04, V107C-003), Taipei, Taiwan.

**Author Contributions**

S.-Y. Ho, P.-H. Liu, C.-Y. Hsu and T.-I. Huo performed the research. Y.-H. Lee, C.-W. Su, Y.-H. Huang and C.-Y. Hsia collected and analyzed the data. S.-Y. Ho, P.-H. Liu and T.-I. Huo designed the research study and wrote the paper. M.-C. Hou and F.-Y. Lee contributed to the design of the study. All authors approved the final version of the manuscript.

**Additional Information**

**Competing Interests:** The authors declare no competing interests.

**Publisher’s note:** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.