The Ishak scoring system has been used to stage liver fibrosis. Ten noninvasive liver reserve models were proposed to assess the severity of liver fibrosis, but their performance in hepatocellular carcinoma (HCC) is unknown. We aimed to evaluate the correlation between these models and severity of fibrosis in patients with HCC. A total of 464 patients with HCC undergoing surgical resection were retrospectively analyzed. Multivariate logistic regression analysis was performed to determine independent factors associated with advanced fibrosis (Ishak score 4 or higher). There were no significant correlations between all noninvasive models and severity of fibrosis in HCC (p for trend all >0.1). In subgroup analysis, cirrhosis discriminant index (CDS) and Lok’s index in hepatitis B-, and fibrosis index based on 4 factors (FIB-4), CDS and Lok’s index in hepatitis C-associated HCC, best correlated with the severity of liver fibrosis. Low platelet count, prolonged prothrombin time, hepatitis C and multiple tumors were independently associated with advanced fibrosis. Among the 10 models, CDS was the best model to predict cirrhosis. Currently used noninvasive liver reserve models do not well correlate with severity of histological fibrosis in HCC. New noninvasive models are required to improve the predictive accuracy of liver fibrosis in HCC.
fibrosis include model for end-stage liver disease (MELD) score, aspartate aminotransferase-to-platelet ratio (APRI), fibrosis index based on 4 factors (FIB-4), cirrhosis discriminate score (CDS), Göteborg University Cirrhosis Index (GUCI), Lok’s index and King’s score16–29. More recently, albumin-bilirubin (ALBI) grade and the platelet-albumin-bilirubin (PABLI) grade were proposed to evaluate the severity of liver fibrosis in HCC30,31. However, with all these choices, no study to date has specifically evaluated the relationship and accuracy between noninvasive liver reserve models and the severity of liver fibrosis in HCC. We aimed to investigate the correlation of the currently used noninvasive liver function models and histological fibrosis in HCC patients undergoing surgical resection.

Material and Methods

Patients. Patients with newly diagnosed HCC in our hospital during the period from 2009 to 2016 were prospectively identified and retrospectively analyzed. A total 464 patients undergoing surgical resection were enrolled in this study. Their baseline information, including patient’s demographics, etiology of liver disease, performance status, tumoral status, liver functions and serum biochemistry, were comprehensively recorded at the times of diagnosis. The inclusion criteria of surgery were (1) tumor involving no more than three Couinaud segments, (2) CTP class A or B, (3) no main portal vein trunk involvement or distant metastases, and (4) absence of other major diseases that contradict surgical resection32. Patients were followed every 3–4 months until death or dropout from follow-up. 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 before analysis.

Diagnosis and definition. The pre-operative diagnosis of HCC was based on the findings of typical four-phase multidetector contrast-enhanced dynamic computed tomography (CT) scan or magnetic resonance imaging (MRI)6,33, and as all histologically confirmed post-operatively. Patients who were seropositive for hepatitis B antigen (HBsAg), seronegative for anti-HCV antibody, and without a history of alcoholism were classified as HBV-related HCC. HCV-related HCC was defined as seropositive for anti-HCV, seronegative for HBsAg and no history of alcoholism. Dual HBV- and HCV-related HCC was defined as seropositive for HBsAg and anti-HCV34. The performance status was assessed by using the Eastern Cooperative Oncology Group Performance scale ranging from 0 (asymptomatic) to 4 (confined to bed).

Surgical resection. After the diagnosis was confirmed, patients were reviewed at our multi-disciplinary HCC team for treatment discussion. Share-decisions regarding treatment modalities were made by patients and physicians after individual counseling. Written informed consent was obtained prior to definite treatment. The operative procedures have been previously described in detail34,35. 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.

Histological analysis. Histology slides of all eligible patients were retrieved and carefully reviewed for tumoral part and non-tumoral part by the pathologists who were blinded to clinical information. The degree of hepatic inflammation and stage of fibrosis in non-tumoral part of the specimen were graded according to the Ishak scoring system. The Ishak staging was defined as the following: 0, no fibrosis; 1, fibrous expansion of some portal area, with or without of short fibrous septa; 2, fibrous expansion of most portal area, with or without short fibrous septa; 3, fibrous expansion of most portal area, with occasional portal to portal bridging; 4, fibrous expansion of portal area with marked bridging as well as portal-central; 5, marked bridging with occasional nodules (incomplete cirrhosis); 6, cirrhosis, probable or definite36.

Grading of 10 noninvasive liver reserve models. The calculation of the 10 noninvasive liver reserve models was based on clinical variables and serum biochemistry at the time of diagnosis. The grading of these models was determined according to published studies15–18,20–22,24,25,30,31. Generally, grade 1 indicates no or mild liver fibrosis, and grade 3 shows advanced liver fibrosis or cirrhosis (Table 1).

Statistical analysis. The χ² test or Fisher’s exact test was used to analyze categorical variables, and the Mann-Whitney ranked sum test was used for continuous variables. Factors that showed significant difference in univariate analysis were subjected to multivariate analysis by forward logistic regression to identify independent predictors and determination of odds ratio (OR) and 95% confidence interval (CI). The predictive accuracy of noninvasive models for cirrhosis was determined by calculating the area under receiver operating curve (AUC-ROC)37. Spearman’s correlation analysis was used to estimate the correlation between noninvasive liver reserve models and Ishak fibrosis stage in HBV- and HCV-related HCC patients. For all tests, a p < 0.05 was considered statistically significant. All statistical analyses were conducted using the SPSS for Windows version 21 release (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics. As shown in Table 2, the median age of the study patients was 63 years and 77% were male. The most frequent cause of chronic liver disease was hepatitis B (55%), followed by hepatitis C (16%). Approximately 65% of patients were classified as performance status 0, and 26% had diabetes mellitus. The majority (83%) of patients had single tumor, and 63% of patients had main tumor size larger than 3 cm. In these patients, 118 (26%) and 177 (38%) received lobectomy and bi-segmentectomy, respectively. Another 149 (32%) and 20 (4%) patients received segmentectomy and sub-segmentectomy, respectively. All patients had histologically confirmed HCC and the resected tumors were free of surgical margin. The numbers of patients in each grade in different noninvasive liver reserve models are described in Table 2.
Correlation of noninvasive liver functional reserve models and Ishak fibrosis score in HCC. The distributions of Ishak fibrosis scores were as follows: score 0, 18 (4%) patients; score 1, 85 (18%) patients; score 2, 60 (13%) patients; score 3, 55 (12%) patients; score 4, 65 (14%) patients; score 5, 71 (15%) patients and score 6, 110 (24%) of patients (Table 2). The relationship of these models and Ishak fibrosis score were assessed. There were no significant correlations between the Ishak score and all 10 (ALBI, APRI, CTP, FIB-4, GUCI, King’s score, MELD, PALBI, CDS and Lok index) models (Figs 1 and 2; p values for trend all >0.1).

Factors associated with advanced fibrosis in HCC. Two hundred and eighteen (47%) patients with Ishak fibrosis score of 0 to 3 were classified as mild fibrosis group, and 246 (53%) patients with Ishak fibrosis score of 4 to 6 were classified as advanced fibrosis group (Table 3). In comparison with those with mild fibrosis, advanced fibrosis group had a significantly higher prevalence of HCV infection; these patients also had significantly lower platelet count, prolonged international normalized ratio (INR) of prothrombin time and serum bilirubin level >1mg/dl. With regard to tumor factors, tumor number of 2 or more and tumor size larger than 2 cm were significantly associated with advanced fibrosis. In multivariate logistic regression analysis, anti-HCV-positivity (OR, 1.842; 95% CI, 1.444–2.35) [(AST/upper limit of normal)/Platelet Count (10^9/l)] ≥−2.53 and INR ≤−2.53, and platelet count less than 150 (x1,000/uL) (OR, 3.397; 95% CI, 2.258–5.111; p < 0.001), INR > 1 (OR, 2.405; 95% CI, 1.444–4.007; p < 0.001), and smaller serum AFP levels tended to be lower with lower scores of APRI, CDS, FIB-4, King’s score, Lok index and MELD (all p < 0.05).

Noninvasive liver reserve models to predict cirrhosis. The predictive accuracy of the 10 models for cirrhosis (Ishak score of 5 or 6) was assessed by estimating their AUROCs (Table 4). Among these models, CDS had the highest AUROC (0.729), followed by GUCI (AUROC = 0.711) and King’s score (AUROC = 0.709; all p < 0.05).

Correlation of noninvasive models and Ishak fibrosis score according to viral factors. The correlation between liver reserve models and the stage of fibrosis according to viral factors was analyzed (Table 5). There was a relatively high correlation for CDS and Lok index (correlation coefficient, 0.340 and 0.277, respectively, p < 0.001) and the stage of fibrosis specically in HBV-related HCC. In HCV-related HCC, the correlation was more significant for FIB-4, CDS, Lok index, and APRI with Ishak fibrosis (correlation coefficient: 0.591, 0.546, 0.546, and 0.464, respectively, p < 0.001).

Correlation of noninvasive models and tumor burden. We analyzed the correlation between the surrogates of tumor burden (number and size of tumor, serum AFP level) and 10 noninvasive models (Table 6). Single tumor was associated with lower scores of APRI, GUCI, King’s score and PABLI (all p < 0.05), and smaller size of main tumor was linked with lower ALBI, CTP and PABLI score (all p < 0.05). Serum AFP levels tended to be lower with lower scores of APRI, CDS, FIB-4, GUCI, King’s score, Lok index and MELD (all p < 0.05).

Discussion
Although the CTP and MELD scoring system are widely used in patients with liver diseases, these models are not optimal for evaluating liver fibrosis. Alternatively, noninvasive liver reserve models were proposed to assess the severity of liver fibrosis mainly in patients with chronic hepatitis B or C.23,25,28,36–40 However, the correlation between these models and liver fibrosis in HCC patients is unclear. We have recruited a large cohort of patients and analyzed the correlation between these models and Ishak fibrosis scores in HCC patients. This study demonstrated that noninvasive liver reserve models have some correlation with Ishak fibrosis score in HCC patients. Further studies are needed to evaluate the clinical usefulness of these models.

Table 1. Formula and grading of ten 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][μmol/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 = 2, moderate = 3, severe = 4 Alteration of prothrombin index: <1 = 1, 1–2 = 2, >2 = 3 |
| CDS, Grade 1/2/3 (<4/4–7/>7) | Platelet count (×10^9/l); >340 = 0; 280–339 = 1; 220–279 = 2; 160–219 = 3; 100–159 = 4; 40–99 = 5; <40 = 6 |
| FIB-4 index, Grade 1/2/3 (<1.45–3.25/>3.25) | (Age [years] × AST[U/L])/(platelet [10^9] × ALT[U/L]^2) |
| GUCCI, Grade 1/2/3 (<0.5/0.5–1.56/>1.56) | [AST/normal ASTM] × INR × 100/(Platelets × 10^9) |
| Lok's index, Grade 1/2/3 (<0.5/0.5–0.8/>0.8) | Lok Index = e^[LogOddsLok] × (1 + e^[LogOddsLok]) Log Odds Lok = (2.62 × AST/ALT) + (5.27 × INR) − (0.0089 × Platelets) − 5.56 |
| 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, Grade 1/2/3 (<2.5–3.5/>2.5) | (2.02 × log₁₀ bilirubin) − (0.37 × log₁₀ bilirubin[μmol/L])² − 0.04 × albumin [g/L] − 3.48 × log₁₀ platelets (10^11/l) + 1.01 × (log₁₀ platelets (10^11/l))^2 |
| King’s score (<7/6–7.6/16.7/16.7) | Age × AST × INR/(Platelets × 10^9/l)]
patients undergoing surgical resection to evaluate the degree of liver fibrosis and its association with these models. Surprisingly, our data reveal that none of these models significantly correlate with the severity of histological fibrosis in HCC patients. This finding suggests that the performance of currently used liver reserve models in predicting the severity of liver fibrosis is far from satisfaction. The main possible reason is that the etiologies of fibrosis greatly vary in HCC patients, while these models were generated from patients with distinct clinical characteristics.

We further examined the factors associated with advanced fibrosis, defined as an Ishak score of 4 or higher. Consistent with previous studies18,20,27,39–41, low platelet count and prolonged INR, which are known surrogate markers of cirrhosis, are independent predictors of advanced fibrosis. With increasing fibrosis and worsening portal hypertension, there is increased sequestration and destruction of platelets in the enlarged spleen42. In addition, progression of liver fibrosis was linked with decreased production of thrombopoietin by hepatocytes, and hence reduced platelet production43.

An interesting finding in this study is that the factor of multiple tumors was also independently associated with advanced fibrosis. Previous studies showed that non-cirrhotic HCC patients may have larger tumor size than those with cirrhosis; one of the possible explanations is that non-cirrhotic patients were often diagnosed outside the surveillance program44,45. Our earlier study indicated that there was no significant correlation between tumor

| Variables | Patients (n = 464) |
|-----------|------------------|
| Age (years, median [interquartile range]) | 63 [55–71] |
| Male, n (%) | 357 (77) |
| Etiologies of liver disease | |
| HBV, n (%) | 209 (45) |
| HCV, n (%) | 76 (16) |
| HBV + HCV, n (%) | 21 (5) |
| Others, n (%) | 158 (34) |
| Diabetes mellitus, n (%) | 122 (26) |
| Performance status (0/1/2–4), n (%) | 303/128/33 (63/28/7) |
| α-fetoprotein (ng/mL) (median, [interquartile range]) | 18 [4.7–239] |
| Laboratory values (mean ± SD) | |
| Alanine aminotransferase (IU/L) | 58.5 ± 70.4 |
| Aspartate aminotransferase (IU/L) | 56.5 ± 73.5 |
| Albumin (g/dl) | 4.0 ± 0.5 |
| Total bilirubin (μmol/dl) | 0.88 ± 0.71 |
| Creatinine (mg/dl) | 1.18 ± 1.49 |
| Platelets (×10^9/μL) | 171 ± 767 |
| INR of prothrombin time | 1.07 ± 0.9 |
| Ishak score (0/1/2/3/4/5/6/), n (%) | 18/85/60/55/65/71/110 (4/18/13/12/14/15/24) |
| Non-invasive liver reserve markers | |
| ALBI grade (1/2/3), n (%) | 274/181/9 (59/39/2) |
| APRI grade (1/2/3), n (%) | 210/184/70 (45/40/15) |
| CTP classification (A/B–C), n (%) | 431/33 (92/8) |
| CDS grade (1/2/3), n (%) | 139/290/35 (30/62/8) |
| FIB-4 grade (1/2/3), n (%) | 104/204/153 (23/44/33) |
| GUCCI grade (1/2/3), n (%) | 168/206/90 (36/44/20) |
| Lok’s index grade (1/2/3), n (%) | 269/153/42 (58/33/9) |
| MELD score (<8/8–12/>12), n (%) | 276/152/36 (59/33/8) |
| PALBI grade (1/2/3), n (%) | 275/142/47 (59/31/10) |
| King’s score (1/2/3), n (%) | 82/161/221 (17/35/48) |
| Tumor nodules (1/2/>3), n (%) | 384/65/15 (83/14/3) |
| Maximal tumor diameter (<2/2–3/>3 cm), n (%) | 79/96/289 (17/20/63) |
| Extent of hepatic resection | |
| Sub-segmentectomy, n (%) | 20 (4) |
| Segmentectomy, n (%) | 149 (32) |
| Bi-segmentectomy, n (%) | 177 (38) |
| Lobectomy, n (%) | 118 (26) |

Table 2. Baseline characteristics of patients with hepatocellular carcinoma undergoing surgical resection. ALBI, Albumin-bilirubin; APRI, Aspartate transaminase-to-Platelet ratio. CDS, Cirrhosis discriminant index; CTP, Child-Turcotte-Pugh score; FIB-4, Fibrosis-4 score; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, Model for End-stage liver disease; GUCCI, Göteborg University Cirrhosis Index; PALBI, platelet-albumin-bilirubin; SD, standard deviation.
Figure 1. Correlation between (A) ALBI, (B) APRI, (C) CDS, (D) CTP, and (E) FIB-4 index with Ishak fibrosis score. There is no significant correlation between these models and Ishak score (p values for trend all >0.1). Data were expressed as median (horizontal bars) and 25% to 75% percentile of the distribution (lower and upper margin of the square); the upper and lower vertical bars indicate 90% and 10% percentile of the distribution, respectively. *Indicates extreme values.

Figure 2. Correlation between (A) GUCI, (B) King's score, (C) Lok's index, (D) MELD, and (E) PALBI with Ishak fibrosis score. There is no significant correlation between these models and Ishak score (p values for trend all >0.2). Data were expressed as median (horizontal bars) and 25% to 75% percentile of the distribution (lower and upper margin of the square); the upper and lower vertical bars indicate 90% and 10% percentile of the distribution, respectively. *Indicates extreme values.
burden and CTP score and MELD score. However, in the current study, we found that the surrogates of tumor burden tended to associate with the severity of liver fibrosis. Smaller tumor burden may predict a lower score in most noninvasive models except for the comparison between CDS and tumor size. These findings partly explain why these noninvasive models correlate poorly with histological fibrosis, and suggest that the selection of tools in evaluating liver injury for different clinical entities is crucial. Altogether, not only surrogate markers of cirrhosis, the extent of tumoral involvement should also be taken into consideration in predicting non-tumoral part liver damage in HCC.

Noninvasive models, including APRI, CDS, FIB-4, GUCI, King’s score and Lok’s index, were reported to correlate with the degree of fibrosis in HCV-infected patients. In the current study, we confirm that these 6 models may reflect the severity of liver injury as defined by the Ishak score in HCV-related HCC patients. Additionally, the ALBI score is a new prognostic marker for HCC, and our data indicate that it can also be used to assess liver fibrosis in HCV-related HCC.
### Table 5. Correlation of noninvasive liver reserve models and stage of fibrosis in patients with hepatitis B virus (HBV) and hepatitis C virus (HCV) infection.

| Noninvasive liver reserve models | HBV (n = 209) | HCV (n = 76) |
|-------------------------------|-------------|-------------|
| Coefficient | p | Coefficient | p |
| ALBI | 0.141 | 0.410 | 0.323 | 0.004 |
| APRI | 0.066 | 0.343 | 0.464 | <0.001 |
| CDS | 0.340 | <0.001 | 0.546 | <0.001 |
| CTP | 0.145 | 0.036 | 0.233 | 0.042 |
| FIB-4 | 0.120 | 0.083 | 0.591 | <0.001 |
| GUCl | 0.076 | 0.276 | 0.459 | <0.001 |
| King score | 0.093 | 0.179 | 0.468 | 0.001 |
| Lok’s index | 0.277 | <0.001 | 0.546 | <0.001 |
| MELD | 0.166 | 0.016 | 0.106 | 0.361 |
| PALBI | -0.113 | 0.105 | 0.186 | 0.109 |

### Table 6. Correlation of tumor burden, serum AFP level and noninvasive liver reserve models.

| Noninvasive liver reserve models (mean ± SD) | |
|------------------------------------------|------------------|------------------|------------------|------------------|------------------|
| Number of tumor | ALBI | APRI | CDS | CTP | FIB-4 | GUCl | King's score | Lok index | MELD | PALBI |
|------------------|------|------|-----|-----|------|------|-------------|----------|------|-------|
| 1 | 1.1 ± 2.2 | 5.19 ± 1.6 | 5.30 ± 0.7 | 5.38 ± 6.5 | 1.31 ± 2.9 | 32 ± 67 | 0.48 ± 0.2 | 8.64 ± 3.4 | -2.55 ± 0.4 |
| 2 | 1.1 ± 1.6 | 5.32 ± 1.6 | 5.43 ± 0.8 | 3.80 ± 4.0 | 1.37 ± 2.0 | 36 ± 54 | 0.50 ± 0.2 | 9.03 ± 4.3 | -2.63 ± 0.4 |
| 3–5 cm | 1.2 ± 1.1 | 5.80 ± 1.1 | 5.47 ± 0.8 | 4.03 ± 2.5 | 1.47 ± 1.3 | 35 ± 30 | 0.59 ± 0.2 | 8.66 ± 2.7 | -2.51 ± 0.3 |
| >5 cm | 0.364 | 0.042 | 0.208 | 0.326 | 0.115 | 0.032 | 0.033 | 0.080 | 0.639 | 0.043 |
| Tumor size | | | | | | | | | | |
| <3 cm | 1.0 ± 1.3 | 5.51 ± 1.5 | 5.28 ± 0.8 | 5.71 ± 3.9 | 1.23 ± 1.6 | 31 ± 42 | 0.50 ± 0.2 | 8.69 ± 3.8 | -2.63 ± 0.3 |
| 3–5 cm | 1.0 ± 2.0 | 5.40 ± 1.6 | 5.23 ± 0.6 | 3.93 ± 7.2 | 1.32 ± 2.9 | 32 ± 64 | 0.50 ± 0.2 | 8.31 ± 2.5 | -2.60 ± 0.3 |
| >5 cm | 1.1 ± 2.8 | 4.78 ± 1.8 | 5.44 ± 0.8 | 3.89 ± 7.1 | 1.32 ± 3.5 | 34 ± 72 | 0.47 ± 0.3 | 9.00 ± 4.0 | -2.45 ± 0.4 |
| p | 0.049 | 0.679 | <0.001 | 0.018 | 0.317 | 0.727 | 0.712 | 0.204 | 0.267 | <0.001 |
| AFP level (ng/ml) | | | | | | | | | | |
| <20 | 0.9 ± 2.3 | 3.27 ± 4.8 | 5.30 ± 0.6 | 3.27 ± 4.8 | 1.13 ± 3.1 | 28 ± 64 | 0.44 ± 0.2 | 8.50 ± 3.4 | -2.59 ± 0.4 |
| 20–200 | 1.4 ± 2.0 | 5.09 ± 8.3 | 5.34 ± 0.7 | 5.10 ± 8.3 | 1.76 ± 2.7 | 43 ± 62 | 0.57 ± 0.2 | 8.85 ± 3.0 | -2.55 ± 0.3 |
| >200 | 1.1 ± 1.6 | 3.88 ± 6.3 | 5.35 ± 0.9 | 3.89 ± 6.3 | 1.33 ± 2.0 | 31 ± 46 | 0.50 ± 0.2 | 8.90 ± 3.5 | -2.51 ± 0.4 |
| p | 0.039 | <0.001 | 0.006 | 0.756 | 0.006 | <0.001 | 0.003 | <0.001 | 0.021 | 0.241 |

Several models, such as APRI, CDS, FIB-4, Lok’s index and King’s score, were also reported to associate with histological fibrosis in HBV-infected patients. In the current study, however, the correlation is apparent only for CDS and Lok’s index. Our result implies that noninvasive models derived from HCV-infected patients may not be necessarily feasible in predicting histological fibrosis in HBV-related HCC. The pathogenesis of liver fibrosis in chronic hepatitis B is distinct and could be different from that of hepatitis C. Activity of hepatitis B can become quiescent after a period of severe activity, such as recurrent hepatitis flares, or resolution of hepatic necroinflammatory activity following HBV e antigen seroconversion after the development of cirrhosis. In contrast, chronic hepatitis C is a slow but progressive disease with persistent inflammation that ultimately leads to cirrhosis. HCC patients due to HBV or HCV are usually at a late stage of infection and may thus have heterogeneous patterns of liver fibrosis that make prediction with noninvasive models much more difficult.

Noninvasive liver reserve models were also adopted as surrogate markers for discriminating cirrhosis from chronic hepatitis. In accordance with previous studies, we found that APRI, CDS, FIB-4, GUCl, Lok’s index and King’s score had moderate power to predict cirrhosis in HCC, with an AUROC between 0.703–0.729. Among these models, CDS was identified as the best model to predict cirrhosis. Given so, the predictive accuracy is considered not satisfactory, and new models are needed to refine the predictive ability for cirrhosis in HCC.

This study has a few limitations. Firstly, in this single-hospital study, the major etiology of HCC is HBV infection. This feature is apparently different from Western counties where HCV infection is the predominant etiology of HCC. Secondly, our hospital is a tertiary medical center. Therefore referral bias cannot be completely avoided. Lastly, since this study is retrospective in nature, external validation from independent patient cohorts is required.

In conclusion, the currently used noninvasive liver reserve models do not well correlate with the severity of histological fibrosis in HCC. Among these models, CDS is more accurate in predicting the presence of cirrhosis. Different models should be used for HCC patients with different viral etiology. In addition to traditional cirrhosis surrogates, the extent of tumoral involvement and viral factor are crucial determinants that contribute to liver injury. We advocate that new models should be explored to enhance the predictive ability for liver fibrosis in the setting of HCC.

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**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 Y.-J. He 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.

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