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Development and Internal Validation of a Model for Early Detection of Hepatocellular Carcinoma in Patients with Cirrhosis

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Abstract

Background—Surveillance for hepatocellular carcinoma (HCC) is recommended in patients with cirrhosis; however, early detection efforts are limited by suboptimal effectiveness.

Aim—To derive and validate a model to accurately distinguish cirrhotic patients with and without HCC and compare the accuracy of the model to that of AFP alone

Methods—We conducted a case-control study of cirrhotic patients with and without HCC seen at a large urban hospital system between January 2005 and June 2012. We derived multivariate logistic regression models for the presence of HCC and early stage HCC. Discriminatory power was evaluated using receiver operating characteristic curve analysis in derivation and validation cohorts using a 10-fold cross-validation approach.

Results—We identified 1356 patients with cirrhosis, with (n=455; 147 early stage) and without (n=901) HCC. We found AFP >20ng/mL and FIB-4, a non-invasive marker of fibrosis, were significantly associated with the presence of HCC (OR 10.5, 95%CI 7.9-13.9 and OR 1.05, 95%CI 1.03-1.07 respectively) and early stage HCC (OR 4.4, 95%CI 2.9-6.5 and OR 1.06, 95%CI 1.03-1.09 respectively). Models incorporating AFP and FIB-4 had good discriminatory power,

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with c-statistics of approximately 0.80, in both derivation and validation cohorts. The model for early stage HCC had higher discriminatory power than AFP alone (c-statistic 0.73, 95%CI 0.69-0.78) in derivation and validation cohorts (p=0.02 and p=0.15 respectively).

Conclusion—Models including AFP and FIB-4 can accurately discriminate cirrhotic patients with early stage HCC from those without HCC.

Keywords

liver cancer; cirrhosis; risk factors; alpha fetoprotein; FIB-4

Introduction

Hepatocellular carcinoma (HCC) is the 5th most common cause of cancer and 3rd leading cause of cancer-related death worldwide. HCC primarily occurs in patients with cirrhosis and is the leading cause of death among those with cirrhosis. HCC incidence doubled over the past two decades and will continue to increase over the next 20 years(1). Prognosis for patients with HCC depends on tumor stage, with curative options only available for patients diagnosed at an early stage(2).

Surveillance using ultrasound is recommended in patients with cirrhosis to detect HCC at an early stage(2). HCC surveillance is efficacious for early detection and is associated with improved survival in cohort studies(3). Unfortunately, there is a gap between its efficacy and effectiveness due to underutilization and ultrasound's operator dependent nature(4-6). An analysis of the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial found poor surveillance sensitivity is the most common reason for late HCC detection among patients followed at academic centers(7).

Alpha fetoprotein (AFP), the best studied serologic biomarker, is often used as an adjunct HCC surveillance test but was removed from the American Association for the Study of Liver Diseases (AASLD) guidelines given insufficient sensitivity and specificity. At the recommended cut-off of 20 ng/mL, AFP has 90% specificity but only 53% sensitivity for early HCC(8). Although novel biomarkers are being evaluated for HCC surveillance, none are currently available for use in clinical practice. Studies to improve the accuracy of AFP through different cut-offs based on cirrhosis etiology or incorporation of longitudinal data have yielded insufficient benefit(9, 10). Other studies have suggested it may be possible to create “AFP-adjusted algorithms” with higher accuracy through incorporation of other clinical variables(11). The aim of our study was to i) derive and validate an AFP-based model to accurately distinguish cirrhotic patients with and without HCC and ii) compare the accuracy of our model to that of AFP alone.

Methods

Study Population

We conducted a retrospective case-control study of cirrhotic patients with and without HCC at Parkland Health and Hospital System, the safety-net health system for Dallas County. With 11 primary care clinics in nearby neighborhoods, Parkland cares for a large proportion

of patients with cirrhosis and HCC in Dallas County. Parkland is also one of the few safety-net health systems with an integrated electronic medical record for the hospital and clinics. We chose a case-control design based on the five phases of biomarker development(12), in which the second phase uses a case-control design and ROC curve analysis to determine diagnostic accuracy of proposed biomarkers.

We included patients diagnosed with cirrhosis and HCC at Parkland between January 2005 and June 2012. As previously described, patients were identified by a combination of ICD-9 codes (155.0 or 155.2), a list of patients seen in a multidisciplinary HCC clinic(13), and tumor conference presentation lists(14). Two authors (A.S. and A.Y.) adjudicated HCC cases to confirm they met diagnostic criteria based on AASLD guidelines. Our control population consisted of patients with cirrhosis seen at Parkland between January 2010 and July 2011. Patients were identified using a validated combination of ICD-9 codes and confirmed to have cirrhosis through chart review(15).. Cirrhosis was defined by histology in some cases but most cases were defined clinically, with a cirrhotic-appearing shrunken nodular liver with signs of portal hypertension (ascites, esophageal or intra-abdominal varices, and/or splenomegaly with thrombocytopenia). We excluded patients with any suspicious liver mass on imaging. Patients were required to have at least six months of clinical follow-up to confirm the absence of HCC. The study was approved by the Institutional Review Board of UT Southwestern Medical Center.

Data Collection

Patient demographics, clinical history, laboratory data and imaging results were obtained through review of computerized and paper medical records. Two investigators (A.S. and A.Y.) independently extracted information regarding HCC patients using standardized forms, with discrepancies resolved through consensus. Similarly, two investigators (J.P. and A.S.) extracted information regarding non-HCC patients using standardized forms. Age, gender, race/ethnicity, and lifetime alcohol and smoking history were recorded. Data regarding liver disease included underlying etiology and presence of decompensation (ascites or encephalopathy). We classified patients according to etiology of liver disease, including HCV, hepatitis B virus (HBV), alcohol-related liver disease, non-alcoholic steatohepatitis (NASH), and other. NASH was defined as cirrhosis in those with components of the metabolic syndrome (e.g. obesity, diabetes, and dyslipidemia) but no other known underlying liver disease. Patients with HCV and history of alcohol abuse were classified as HCV, as this was thought to be primary driver of cirrhosis. Laboratory data of interest included platelet count, sodium, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, bilirubin, albumin, international normalized ratio (INR), and AFP. AFP was dichotomized at 20 ng/mL, the most commonly used cut-off used for HCC surveillance. Laboratory data was abstracted from first clinic visit for non-HCC cirrhosis patients and from time of diagnosis for HCC patients. The non-invasive marker of fibrosis, FIB-4, was calculated as $(\text{age} * \text{AST}) / (\text{platelets} * \text{ALT}^{1/2})$. We included a non-invasive marker of fibrosis given it may differentiate degree of fibrosis and HCC risk among patients with cirrhosis. FIB-4 was selected because it could be derived from available clinical data and did not require specialized testing. Tumor characteristics were determined by imaging studies, which had all been interpreted by radiologists at our institution. Early

stage HCC was defined using the Milan criteria (one tumor less than 5 cm or 2-3 tumors, each less than 3 cm in diameter, without vascular invasion or distant metastases).

Statistical Analysis

Demographics and clinical features were compared between patients with and without HCC using Chi-square and Wilcoxon rank-sum tests for categorical and continuous variables, respectively. Missing data was imputed using missForest, which uses flexible random forest models to impute missing values(16). We developed and compared logistic regression models to identify a) patients with HCC and b) patients with early stage HCC. Regression models (Model 1 for HCC and Model 2 for early stage HCC) were developed using variables identified by Wilcoxon rank sum tests, Chi-square tests, and univariate logistic regression. All variables with p-value < 0.05 on univariate analysis, as well as those determined to be clinically relevant *a priori* (e.g. gender and AFP level) were selected for multivariate logistic regression analysis, in which p< 0.05 was considered statistically significant. Multicollinearity was assessed using variable inflation factor (VIF), with variables greater than 10 suggesting multicollinearity.

We compared discriminatory power of the models using receiver operating characteristic (ROC) curve analysis. C-statistics in ROC analysis range from 0.5 to 1.0, with c-statistic exceeding 0.70 considered reasonable and strong if greater than 0.80. Given model accuracy can be lower in validation than derivation cohorts(17), we compared performance of the models using a 10-fold cross-validation approach. All analyses were conducted using STATA statistical software 13.1 (College Station, TX) and R statistical package 2.15.

Results

Patient Characteristics

Between January 2005 and June 2012, 455 cirrhotic patients were diagnosed with HCC. Between January 2010 and July 2011, 901 patients with cirrhosis were seen in an outpatient setting at Parkland. Baseline characteristics of the 1356 patients are shown in Table 1. Median age of patients was 56 years, and the majority (69%) was male, with a higher proportion of males among HCC patients (78% vs. 65%, p<0.001). Our population was racially diverse, with 32% Caucasians, 37% Hispanics, and 26% African Americans. Non-HCC patients were significantly more likely to be non-Hispanic Caucasian than those with HCC (36% vs. 26%, p<0.001). The most common etiologies of cirrhosis were HCV (58%), alcohol-induced (23%), and NASH (12%). HCV cirrhosis was significantly more common among HCC patients than non-HCC patients (67% vs. 53%, p<0.001). Our cohort was diverse with respect to liver function, with 567 (42%) Child A cirrhosis, 525 (39%) Child B cirrhosis, and 264 (19%) Child C cirrhosis. Of patients in the HCC cohort, 147 (32%) had early stage tumors per Milan criteria.

Factors Associated with HCC

We compared 455 cirrhotic patients with HCC to 901 non-HCC patients to identify factors associated with the presence of HCC. The multivariate model (Model 1) included male gender, Black race, viral etiology, alkaline phosphatase greater than 1.5 times upper limit

normal, FIB-4, and AFP >20ng/mL (Table 2). Smoking status and Child Pugh class were significant on univariate analysis but no longer significant on multivariate analysis. Components of Child Pugh (ascites, encephalopathy, albumin, and bilirubin) and components of FIB-4 (age and AST) were significant on univariate analyses but not included in multivariate analysis given clinical multicollinearity. The model accurately distinguished presence of HCC with c-statistics of 0.84 (95%CI 0.81-0.86) and 0.83 (95%CI 0.80-0.85) in derivation and validation cohorts (Figure 1), respectively. The discriminatory power of the model was similar to AFP alone (c-statistic 0.83, 95%CI 0.81-0.86) in the derivation (p=0.91) and validation (p=0.70) cohorts.

Factors Associated with Early Stage HCC

When including 147 patients with early HCC and 901 non-HCC patients, variables significantly associated with early HCC in univariate analysis included male gender, race, smoking status, etiology of cirrhosis, platelet count, albumin, AST, FIB-4, and AFP. Platelet count and AST (components of FIB-4) were not included in the multivariate model given clinically collinear. Other variables with significance in univariate analysis were entered into a multivariate logistic regression model (Model 2). In multivariate analysis, male gender, viral etiology, active smoking status, FIB-4, and AFP >20ng/mL were associated with early HCC (Table 3). The model was highly accurate for the early HCC with c-statistics of 0.78 (95%CI 0.74-0.82) and 0.76 (95%CI 0.72-0.81) in derivation and validation cohorts (Figure 2). The model's discriminatory power was significantly higher for AFP alone (c-statistic 0.73, 95%CI 0.69-0.78) in the derivation cohort (p=0.02). Although discriminatory power was higher than AFP alone in the validation cohort, this did not reach statistical significance (p=0.15).

Discussion

Although surveillance is recommended in patients with cirrhosis to detect HCC at an early stage, risk of HCC is likely not uniform among all patients. We developed models for discrimination of cirrhotic patients with and without HCC and those with and without early HCC using readily available clinical variables. Our models had strong discriminatory power, with c-statistics of approximately 0.80, in derivation and validation cohorts. Our model significantly improved discrimination for early HCC among cirrhotic patients compared to AFP alone.

Since release of the AASLD guidelines, there has been debate regarding the utility of AFP in clinical practice(2, 5, 9, 18). Although AFP has imperfect sensitivity and specificity, its accuracy can be improved using different cut-offs based on cirrhosis etiology, incorporation of longitudinal data, and incorporation of other clinical data(9-11). El-Serag and colleagues found a predictive model using AFP, ALT, platelet count, and age accurately discriminated HCV-positive patients with and without HCC(11). In our study, addition of clinical variables to AFP significantly improved discrimination of patients with cirrhosis (viral and non-viral etiology) with and without HCC. More importantly, our AFP-modified algorithms were able to distinguish the presence of cirrhosis alone from early stage HCC. Detection of HCC at an early stage is of utmost importance given selective availability of curative

treatments for those with early tumors. Our study suggests an AFP-modified model can serve an important role to optimize early HCC detection among patients with cirrhosis.

In addition to well-described HCC risk factors such as male gender and AFP, we found FIB-4, a non-invasive marker of fibrosis(19), is an independent risk factor for HCC in patients with cirrhosis. FIB-4 was analyzed as a continuous variable to parallel the nature of fibrosis progression, meaning the odds of early stage HCC increases by 6% for every one-point increase in FIB-4. Although a prior study found FIB-4 is a risk factor for HCC in HIV-infected patients, this was an unselected group of patients and FIB-4 may have simply been a marker for presence of cirrhosis(20). Other studies suggest liver stiffness, assessed by transient elastography, may be associated with HCC in patients with cirrhosis(21). Non-invasive markers, such as FIB-4 and transient elastography, have an advantage over liver biopsy as they are able to assess a wider range in fibrosis – including potentially among those with cirrhosis – and therefore further differentiate HCC risk among patients.

Accurate HCC early detection models may facilitate targeted application of CT or MRI in patient subgroups to optimize early detection in a cost-effective manner. However prior models have been limited by suboptimal accuracy, particularly when tested in validation cohorts(22, 23). There are several well-accepted risk factors for HCC but the optimal set of variables for an accurate model, and how best to identify these variables, is unclear(24-26). Our study suggests AFP and FIB-4 are important risk factors for HCC and may serve as important variables for future early detection and/or predictive models. Inclusion of longitudinal data and/or genetic risk factors may also further improve the accuracy of risk stratification, but studies in this area are still needed(10, 27-29).

It is important to note our study has limitations. Given its retrospective nature, our study was limited by possible unmeasured confounders and missing data. Furthermore, our study is prone to verification bias, as some patients with cirrhosis may have had unrecognized HCC. Although it is possible some patients were diagnosed with HCC at outside institutions, this is unlikely given that Parkland is the safety-net health system for Dallas County and the only option for indigent patients. We also required six months of follow-up to verify absence of subclinical HCC. Another limitation of our study is we only assessed variables in a cross-sectional manner, and longitudinal assessment of variables may alter performance characteristics of our models. Further, our study may not be generalized to groups not represented in this study, including patients with non-cirrhotic HBV infection. Finally, we assessed diagnostic accuracy of our model using a case-control design. Validation using longitudinal cohort data, in which HCC prevalence is 3-5% as seen in clinical practice, are still needed. Overall, we believe our study's limitations are outweighed by its strengths, including its well-characterized cohort who all had cirrhosis, its racially diverse population, and its large sample size with over 1000 patients.

Early detection of HCC is crucial but effectiveness is limited in clinical practice by suboptimal surveillance tools. Our study suggests AFP can serve an important role in HCC surveillance, particularly if interpreted in the setting of other readily available clinical data. Specifically, FIB-4 is an independent risk factor for HCC and may be useful to incorporate in models to improve the accuracy of AFP for early HCC detection. Further studies are

needed to evaluate if models using these variables can prospectively and effectively discriminate cirrhotic patients with and without early stage HCC.

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Figure 1. Receiver operator characteristic curve for Discrimination of HCC in Validation Cohort

Figure 2. Receiver operator characteristic curve for Discrimination of Early HCC in Validation Cohort

Table 1
Patient characteristics

Variable	Patients with HCC (n=455)	Patients without HCC (n=901)	p-value
Age (years)	57.1 ± 8.4	55.2 ± 9.5	< 0.001
Gender (% male)	357 (78.5%)	585 (64.9%)	< 0.001
Race			0.05
Caucasian	117 (25.8%)	321 (35.6%)	
Black	163 (35.9%)	192 (21.3%)	
Hispanic	135 (29.7%)	363 (40.3%)	
Etiology of Liver Disease			< 0.001
Chronic Hepatitis C	306 (67.3%)	477 (52.9%)	
Chronic Hepatitis B	40 (8.8%)	27 (3.0%)	
Alcohol-related	55 (12.1%)	251 (27.9%)	
Nonalcoholic steatohepatitis	42 (9.2%)	120 (13.3%)	
Other	12 (2.6%)	26 (2.9%)	
Smoking status (% active)	224 (49.5%)	312 (35.4%)	< 0.001
Platelet count (*1000/mm ³)	154 ± 104	114 ± 66	< 0.001
Albumin (g/dL)	3.1 ± 0.6	3.4 ± 0.7	< 0.001
AST (U/L)	154 ± 210	75 ± 54	< 0.001
Alkaline phosphatase (IU/L)	201 ± 162	144 ± 92	< 0.001
Bilirubin (mg/dL)	2.9 ± 4.6	1.8 ± 2.4	< 0.001
FIB-4	9.9 ± 10.9	6.9 ± 5.8	< 0.001
AFP (ng/dL)	25324 ± 117889	720 ± 6134	< 0.001
Presence of ascites	210 (46.2%)	358 (39.7%)	0.03
Presence of encephalopathy	70 (15.4%)	188 (20.9%)	0.02
Child Pugh class			
Child Pugh A	168 (36.9%)	399 (44.3%)	0.01
Child Pugh B	189 (41.5%)	336 (37.3%)	
Child Pugh C	98 (21.6%)	166 (18.4%)	

AFP – alpha fetoprotein; AST – aspartate aminotransferase

Table 2
Factors Associated with HCC in Patients with Cirrhosis

Variable	Multivariate analysis	
	Adjusted Odds Ratio	95% CI
Male gender	1.94	1.41 – 2.67
Black race	1.18	1.01 – 1.39
Viral etiology of cirrhosis	1.65	1.19 – 2.27
Alkaline phosphatase > 1.5 upper limit of normal	2.06	1.47 – 2.88
FIB-4	1.05	1.03 – 1.07
AFP > 20 ng/mL	10.5	7.86 – 13.9

* Adjusted for smoking status and Child Pugh class (significant on univariate analysis)

AFP – alpha fetoprotein; HCC – hepatocellular carcinoma

Table 3
Factors Associated with Early HCC in Patients with Cirrhosis

Variable	Multivariate analysis	
	Adjusted Odds Ratio	95% CI
Male gender	2.01	1.28 – 3.18
Viral etiology of cirrhosis	2.30	1.43 – 3.72
Active smoking status	1.65	1.12 – 2.43
FIB-4	1.06	1.03 – 1.09
AFP > 20 ng/mL	4.36	2.94 – 6.45

* Adjusted for black race and albumin level (significant on univariate analysis)

AFP – alpha fetoprotein; HCC – hepatocellular carcinoma