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BRIEF REPORT: ACCURACY OF FIB-4 FOR CIRRHOSIS IN PEOPLE LIVING WITH HIV AND HEPATOCELLULAR CARCINOMA

Jessie Torgersen, MD, MHS, MSCE[1,2], **Michael J. Kallan, MS**[2], **Dena M. Carbonari, MS**[2], **Lesley S. Park, PhD, MPH**[3], **Rajni L. Mehta, MPH**[4,5], **Kathryn D'Addeo**[4,5], **Janet P. Tate, MPH, ScD**[4,5], **Joseph K. Lim, MD**[4,5], **Matthew Bidwell Goetz, MD**[6], **Maria C. Rodriguez-Barradas, MD**[7], **Norbert Bräu, MD, MBA**[8], **Sheldon T. Brown, MD**[8], **Tamar H. Taddei, MD**[4,5], **Amy C. Justice, MD, PhD**[4,5], **Vincent Lo Re III, MD, MSCE**[1,2]

[1]Division of Infectious Diseases, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

[2]Department of Biostatistics, Epidemiology, and Informatics, Center for Clinical Epidemiology and Biostatistics, Center for Pharmacoepidemiology Research and Training, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

[3]Stanford Center for Population Health Sciences, Stanford University School of Medicine, Stanford, CA

[4]Department of Medicine, Yale School of Medicine, New Haven, CT

[5]VA Connecticut Healthcare System, West Haven, CT

[6]VA Greater Los Angeles Healthcare System and David Geffen School of Medicine at UCLA, Los Angeles, CA

[7]Infectious Diseases Section, Michael E. DeBakey VA Medical Center and Department of Medicine, Baylor College of Medicine, Houston, TX

[8]Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA and James J. Peters VA Medical Center, Bronx, NY

Abstract

Background: Hepatocellular carcinoma (HCC) may develop in the absence of cirrhosis in HIV, and determining how often this occurs can provide insights into mechanisms of carcinogenesis. Studies evaluating the prevalence of cirrhosis in the setting of HCC among people living with HIV (PLWH) often rely on non-invasive markers, such as the Fibrosis-4 Index for Hepatic Fibrosis (FIB-4). However, the accuracy of FIB-4 for cirrhosis in the setting of HCC has not been determined among PLWH.

Corresponding Author: Jessie Torgersen, MD, MHS, MSCE, Division of Infectious Diseases, University of Pennsylvania School of Medicine, Penn Presbyterian Medical Center, 51 N. 38th Street, Medical Arts Building, Suite 103B, Philadelphia, PA 19104, USA, Fax: 215-243-3272, jessie.torgersen@pennmedicine.upenn.edu.

Methods: We conducted a cross-sectional study among PLWH in the Veterans Aging Cohort Study with VA cancer registry-confirmed HCC diagnosed between 1999 and 2015. FIB-4 was calculated using the age, alanine aminotransferase, aspartate aminotransferase, and platelet count obtained closest, but within one year prior, to HCC diagnosis. Medical records were reviewed within one year prior to HCC diagnosis to determine cirrhosis status. We evaluated the area under the receiver-operating characteristic curve (AUROC) and performance characteristics of FIB-4 for confirmed cirrhosis

Results: Incident HCC was diagnosed in 302 PLWH. After medical record review, 203 (67.2%, 95% [confidence interval] CI, 61.6–72.5%) had evidence of cirrhosis. FIB-4 identified patients with cirrhosis with an AUROC of 0.67 (95% CI, 0.60–0.73). FIB-4 scores >5.0 had a positive predictive value >80% and specificity of >77%, negative predictive value <41% and sensitivity of <45%.

Conclusion: The accuracy of FIB-4 for cirrhosis in the setting of HIV and HCC is modest and may result in misclassification of cirrhosis in this population.

Keywords

FIB-4; cirrhosis; HIV; hepatocellular carcinoma

INTRODUCTION

Hepatocellular carcinoma (HCC) incidence is increasing among people living with HIV (PLWH), and the risk of HCC is four-fold higher among PLWH compared to uninfected persons.[1,2] Cirrhosis remains the strongest risk factor for the development of HCC, regardless of HIV status.[3] However, HCC can also develop in the absence of cirrhosis, particularly with chronic hepatitis B virus (HBV) infection and nonalcoholic fatty liver disease, and up to 13% of people in the general population develop HCC in the absence of cirrhosis.[4–6] Determining which PLWH develop HCC in the absence of cirrhosis is important as this may provide insights into mechanisms of hepatocarcinogenesis in this population.

Since a minority of people undergo tissue sampling for the diagnosis of HCC,[7] studies evaluating the prevalence of cirrhosis in HCC must consider alternative methods to liver biopsy to classify cirrhosis status at HCC diagnosis. The gold standard for defining the presence of cirrhosis is through liver histopathology; however, prior work has shown only 36% of HCC diagnoses in the US are made by liver tissue sampling.[7] Moreover, even if a liver biopsy is performed, there may not be sufficient background hepatic parenchyma to determine presence of cirrhosis. One method to classify advanced hepatic fibrosis/cirrhosis status in epidemiologic studies is the Fibrosis-4 Index for Hepatic Fibrosis (FIB-4), a non-invasive measure of hepatic fibrosis that yields a calculable score based on age, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and platelet count.[5,8,9] In absence of HCC, FIB-4 has been shown to be an accurate index of advanced hepatic fibrosis/cirrhosis (METAVIR stage F3 or F4) compared to liver biopsy in people with viral hepatitis (area under the receiver-operating characteristic curve [AUROC], 0.91–0.93),[10] HIV/viral hepatitis coinfection (AUROC, 0.77),[11] and alcoholic liver disease (AUROC, 0.70–0.80).[12]

However, FIB-4 has not been validated in the setting of HIV and HCC.[13,14] HIV and HCC may be associated with systemic inflammation that could affect platelet count, and HCC might alter the hepatic parenchyma, resulting in elevations in liver aminotransferase levels. Thus, HCC might lead to inaccuracies in FIB-4 that could misclassify cirrhosis status among PLWH.[15]

To address this issue, we determined the accuracy of FIB-4 to identify cirrhosis among PLWH with HCC. We determined the discriminative ability of FIB-4 for medical record-confirmed cirrhosis and evaluated the performance characteristics (i.e., sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV]) of different cut-offs.

METHODS

We conducted a cross-sectional study among PLWH in the Veterans Aging Cohort Study (VACS) with incident HCC diagnosis. PLWH were included if they had: 1) HIV RNA and CD4+ cell count measured between October 1, 1999 and September 30, 2015, 2) ≥180 days of care in the Veterans Health Administration (VHA), and 3) incident diagnosis of HCC. HCC diagnoses were determined from the VHA national cancer registry, which records cancers diagnosed or treated within VHA. HCC diagnoses were determined by topography codes (C22.0 [liver]) and histology codes (8170–8180 [HCC]) from the International Classification of Diseases for Oncology, Third Edition (ICD-O-3).[16] To account for lags in reporting diagnoses and minimize the likelihood of missing HCC events, we supplemented HCC case finding with hospital or outpatient International Classification of Diseases, Ninth Revision (ICD-9) diagnoses for HCC (155.0, 155.1, and 155.2) within the VHA electronic medical record, which were further confirmed by medical record review by trained adjudicators.

For all confirmed HCC cases, we determined the presence of cirrhosis by medical record review. A single trained abstractor reviewed the records of all people with HCC within one year prior to the HCC diagnosis date. Data were abstracted onto structured forms and reviewed by a clinician with expertise in classifying cirrhosis (J.T.). Cirrhosis was confirmed if: 1) liver histopathology report indicated cirrhosis (METAVIR stage F4 or Ishak fibrosis score ≥5); 2) abdominal imaging indicated cirrhosis (nodular contour of liver, splenomegaly with ascites, or esophageal varices); 3) esophagogastroduodenoscopy identified varices or portal gastropathy; 4) paracentesis was performed; or 5) clinician note indicated history or examination consistent with of ascites, spontaneous bacterial peritonitis, variceal hemorrhage, or hepatic encephalopathy (indicative of decompensated cirrhosis)[17]. The prevalence of cirrhosis and 95% confidence intervals (CI) were calculated.

We collected age, sex, race/ethnicity, body mass index, tobacco use,[18] alcohol dependence/abuse,[19] diabetes (defined by random glucose ≥200 mg/dL, hemoglobin A1c ≥6.5%, or anti-diabetic drug use[20]), HBV coinfection (ever positive HBV surface antigen), and hepatitis C virus (HCV) coinfection (ever detectable HCV RNA or genotype), HIV RNA, CD4+ T lymphocyte count and use of antiretroviral therapy (ART) within one year prior to HCC diagnosis. ALT, AST, and platelet count were collected from dates closest, but within one

year prior, to HCC diagnosis. FIB-4 was calculated by: (age [years] x AST [U/L])/(platelet count [10^9/L]) x (ALT [U/L])$^{1/2}$).[21]

To define the discriminative ability of FIB-4 to distinguish between the presence and absence of medical record-confirmed cirrhosis, we calculated the AUROC of FIB-4. We then evaluated the sensitivity, specificity, PPV, and NPV of a variety of cut-offs of FIB-4 for confirmed cirrhosis, including: 1) traditional threshold for advanced hepatic fibrosis/cirrhosis (FIB-4 >3.25),[21] 2) cirrhosis threshold identified among the Electronically Retrieved Cohort of HCV-Infected Veterans (FIB-4 >3.50),[13] and 3) threshold for cirrhosis determined by the Chronic Hepatitis B and C Cohort Study (FIB-4 >5.88).[14] In sensitivity analyses, we evaluated performance characteristics stratified by alcohol dependence/abuse, and limited to people with histopathology and/or radiographic evaluation. Statistical analyses were performed with STATA 14.1 (Stata Corporation; College Station, TX).

RESULTS

Among 35,659 PLWH in VACS who met eligibility criteria between October 1, 1999 and September 30, 2015, 302 (0.8%) were confirmed to have an incident HCC diagnosis. Those included were predominantly male, 52.6% black race with median age of 56.4 years (interquartile range [IQR], 51.3–61.1) at time of HCC diagnosis. Underlying liver disease was common: including 250 (82.8%) people with chronic HCV infection, 57 (18.9%) with chronic HBV, and 191 (63.2%) with alcohol dependence/abuse (Table 1). Less than 3% had no evidence of chronic viral hepatitis or alcohol dependence/abuse. After review of medical records, 203 (67.2%, [95% CI, 61.6–72.5%]) had cirrhosis, while 99 (32.8% [95% CI, 27.5%−38.4%] had no evidence of cirrhosis within one year prior to their HCC diagnosis. Liver histopathology and/or radiographic studies were available in 295 of the 302 PLWH and HCC. Of the 203 people with cirrhosis, evidence of cirrhosis was most commonly reported by radiology (63.1%) and histopathology (28.1%). Of those people with cirrhosis defined by other means, history of prior liver biopsy with cirrhosis, clinical history of decompensated cirrhosis, or esophagogastroduodenoscopy findings of varices or portal gastropathy were found in 5.4%, 2.5%, and 1%, respectively (Supplemental Figure 1).

The median FIB-4 at HCC diagnosis was higher for those with cirrhosis compared to without (4.37 [IQR, 2.42–7.71] versus 2.87 [IQR, 1.66–4.83]; p<0.001). FIB-4 had only moderate discriminatory ability for cirrhosis (AUROC, 0.67 [95% CI, 0.60–0.73]). At cut-offs previously reported for the identification of cirrhosis, FIB-4 >3.25, FIB-4 >3.50, and FIB-4 >5.88 had PPVs of 75.7%, 77.1%, and 83.5%, respectively, with overall low sensitivity and NPV (Table 2). A FIB-4 cutoff >5.00 achieved a PPV greater than 80%; however, sensitivity was less than 45%. When stratified by alcohol dependence/abuse, PPV and sensitivity were similar; however, NPV and specificity were decreased compared to the primary analysis (Supplemental Table 1). When limited to people with histopathology and/or radiographic assessments (Supplemental Table 2), all performance characteristics remained similar to those in the primary analysis.

DISCUSSION

The accuracy of FIB-4 for cirrhosis detection among PLWH with HCC has remained unclear. This study found that FIB-4 yielded only moderate accuracy for the detection of cirrhosis among PLWH in the year prior to HCC diagnosis, with an AUROC of 0.67. This discriminatory ability of FIB-4 is similar to that previously reported from a single-center HIV-uninfected population with a predominance of chronic HBV.[8] When using previously established FIB-4 thresholds for cirrhosis of >3.25 and >3.50, PPVs, NPVs, and sensitivity were below 80%. A FIB-4 cut-off of >5.88, previously validated in the Chronic Hepatitis Cohort Study,[14] yielded a PPV of 83.5% but low sensitivity (37.4%). These results indicate that FIB-4 is not an ideal measure to use to classify cirrhosis status at any threshold among PLWH with HCC.

Misclassification of cirrhosis status by FIB-4 among PLWH with HCC may occur due to a number of mechanisms. Progressive expansion of HCC with attendant systemic inflammation could result in hepatic parenchymal hypoxia and cellular necrosis, leading to elevated liver transaminases and an increased FIB-4.[21,22] Alternatively, FIB-4 may be decreased in the setting of HCC due to a relative increase in platelet count due to systemic inflammation and increased levels of platelet derived growth factor and proliferation factors associated with thrombocytosis.[15]

Accurate identification of cirrhosis in the setting of HCC in HIV is important to understand the underlying mechanisms of hepatocarcinogenesis as well as prognosis as cirrhosis directly impacts the treatment modalities.[23] While cirrhosis is reportedly present in 80% of HCC in the general population, cirrhosis is not an obligate precursor of HCC.[3] Chronic HBV and nonalcoholic fatty liver disease are common etiologies of liver disease that predispose to noncirrhotic HCC in the general population, yet limited data exist on the risk of HCC in HIV attributable to these disease processes. In addition, treatment modalities for HCC can be influenced by tumor size and characteristics, presence of portal hypertension, and degree of functional hepatic reserve in the presence or absence of cirrhosis: liver transplantation is often considered to offer the best prognosis among people with cirrhosis and localized disease while tumor resection represents best option among people without cirrhosis but with localized HCC.[23] Observational studies describing the natural history of HCC in HIV require accurate assessment of cirrhosis status to define impacts of treatment interventions on survival. Utilizing FIB-4 as a means to define cirrhosis in the setting of HCC and HIV is likely to result in misclassification that may lead to bias in findings. Objective assessment of cirrhosis status through comprehensive medical record review should be used in future epidemiologic studies to elucidate mechanisms of carcinogenesis that may differ by HIV and cirrhosis status and provide accurate estimates of HCC-related survival.

Our study has potential limitations. First, cirrhosis was not uniformly defined by liver histopathology, the gold standard, although prior work has shown only 36% of HCC diagnoses are made by liver tissue sampling in this patient population.[7] Moreover, even if a liver biopsy is performed, there may not be sufficient background hepatic parenchyma to determine if cirrhosis is present. Our evaluation of abdominal imaging and endoscopy

reports for findings of cirrhosis as well as ascertainment of clinically-recorded complications of decompensated cirrhosis within the medical record helped to reduce misclassification of cirrhosis status. This methodology is consistent with prior studies validating medical record review for the identification of cirrhosis.[4,24] Second, evidence of cirrhosis was abstracted by medical record review within the year preceding HCC diagnosis, and it is possible that evidence of cirrhosis was not reported or occurred outside of this time period. However, people with suspected HCC often undergo diagnostic cross-sectional imaging, thus visualizing the extent of the liver by computed tomography and magnetic resonance imaging and allowing for assessment of cirrhosis.[25] Third, our study population included predominantly older men with HIV/HCV coinfection, a population at high risk for HCC. While the traditional FIB-4 thresholds evaluated here have been previously validated in populations with chronic HCV infection, our results may not be generalizable to nonalcoholic fatty liver disease, women with HIV, or people without HIV in the setting of HCC.

The strengths of our study include the large sample size of PLWH with HCC from across the United States. All HCC diagnoses were abstracted using validated cancer registry and diagnostic code data and confirmed by manual chart review. The robust clinical data available within the VACS and the centralized nature of the VHA allow for comprehensive evaluation of all people.

CONCLUSION

Use of FIB-4 to identify cirrhosis in PLWH with HCC may result in misclassification. Future research should employ medical record review to accurately identify cirrhosis among PLWH with HCC in order to elucidate mechanisms of carcinogenesis that may differ by HIV and cirrhosis status.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Characteristics of PLWH with HCC, by medical record-confirmed cirrhosis status.

Characteristic	No cirrhosis (n=99)	Cirrhosis (n=203)
Median age at diagnosis (years, IQR)	57.5 (51.3–61.8)	56.0 (51.3–60.9)
Male sex	99 (100.0)	200 (98.5)
Race/ethnicity		
Black	62 (62.6)	97 (47.8)
Caucasian	24 (24.2)	73 (36.0)
Hispanic	10 (10.1)	27 (13.3)
Other/Unknown	3 (3.0)	6 (3.0)
Obese body mass index	11 (11.1)	31 (15.3)
Diabetes mellitus	24 (24.2)	70 (34.5)
History of alcohol dependence/abuse	61 (61.6)	130 (64.0)
Ever tobacco use	90 (90.9)	172 (84.7)
Hepatitis C virus coinfection		
Detectable HCV RNA or genotype	79 (79.8)	171 (84.2)
HCV antibody+/HCV RNA-	1 (1.0)	4 (2.0)
HCV antibody-	15 (15.2)	24 (11.8)
Never tested	4 (4.0)	4 (2.0)
Hepatitis B virus coinfection		
HBsAg+	17 (17.2)	40 (19.7)
HBsAg-	79 (79.8)	157 (77.3)
Never tested	3 (3.0)	6 (3.0)
Median HIV RNA (log_{10} copies/mL, IQR)	1.7 (1.7–2.6)	1.7 (1.7–2.7)
On antiretroviral therapy	77 (77.8)	152 (74.9)
CD4+ cell percentage		
Median (%, IQR)	26 (14–35)	26 (18–34.3)
<14%	22 (22.2)	25 (12.3)
Median alanine aminotransferase (U/L, IQR) *	52 (35–74)	57 (36–79)
Median aspartate aminotransferase (U/L, IQR) †	61 (38–95)	73 (47–104)
Platelet count <150,000 × 10^6/L	42 (42.4)	130 (64.0)
FIB-4		
Median (IQR)	2.87 (1.66–4.83)	4.37 (2.42–7.71)
<1.45	18 (18.2)	9 (4.4)
1.45–3.25	39 (39.4)	60 (29.6)
>3.25	42 (42.4)	131 (64.5)
Insufficient data to calculate FIB-4	0 (0.0)	3 (1.5)

Abbreviations: HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; IQR, interquartile range; PLWH, people living with HIV.

*Alanine aminotransferase values not available within 360 days preceding HCC diagnosis in two patients with cirrhosis

†Aspartate aminotransferase values not available within 360 days preceding HCC diagnosis in one patient with cirrhosis

Table 2.

Positive predictive value, sensitivity, and specificity of various FIB-4 cut-offs for medical record-confirmed cirrhosis among PLWH with hepatocellular carcinoma in the Veterans Aging Cohort Study (1999–2015).

FIB-4 Cut-Off	No cirrhosis (n=99)	Cirrhosis (n=203)	Positive Predictive Value	Negative Predictive Value	Sensitivity	Specificity
≥1.45	81	194	70.5%	66.7%	95.6%	18.2%
>3.25 *	42	131	75.7%	44.2%	64.5%	57.6%
>3.50 †	36	121	77.1%	43.4%	59.6%	63.6%
>4.00	30	112	78.9%	43.1%	55.2%	69.7%
>4.50	26	96	78.7%	40.6%	47.3%	73.7%
>5.00	22	91	80.5%	40.7%	44.8%	77.8%
>5.50	18	84	82.4%	40.5%	41.4%	81.8%
>5.88 ‡	15	76	83.5%	39.8%	37.4%	84.8%
>6.00	14	75	84.3%	39.9%	36.9%	85.8%
>7.00	8	58	87.9%	38.6%	28.6%	91.9%
>7.50	8	55	87.3%	38.1%	27.1%	91.9%

* Previously established FIB-4 threshold for advanced hepatic fibrosis/cirrhosis in Sterling RK et al.[11]

† Previously established FIB-4 threshold for cirrhosis in Butt AA et al.[13]

‡ Previously established FIB-4 threshold for cirrhosis in Li J et al.[14]