Role of Fibrosis-4 Score in Predicting Risk of Hepatocellular Carcinoma in Patients with Cirrhosis due to Nonalcoholic Steatohepatitis

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Introduction

Hepatocellular carcinoma (HCC) represents the main cause of death in patients with nonalcoholic steatohepatitis (NASH) cirrhosis and is a leading indication for liver transplantation. Identification of high-risk patients for HCC is essential for long term monitoring of disease progression, early detection, and effective intervention. Fibrosis-4 (FIB-4) is a noninvasive index of readily available laboratory measurements and is widely validated for predicting cirrhosis and HCC.

Aim

We sought to determine if FIB-4 score is predictive of HCC risk among patients with NASH cirrhosis.

Methods and Materials

We conducted a retrospective cohort study of adult patients with NASH cirrhosis (n= 1,338) who were evaluated at our medical center between 2005 and 2015. Those who developed HCC were identified via ICD codes until the end of September 2021. At day of index NASH cirrhosis diagnosis, clinical and biochemical measurements were recorded on each patient. Descriptive statistics were calculated for all factors. Kaplan-Meier analysis was performed to evaluate time to HCC event. Cox regression models were used to evaluate associations between HCC and factors of interest. Models were adjusted for age, sex, number of comorbidities, and laboratory values.

Results I

During a median follow-up time of 3.7 years, 157 (11.7%) patients with NASH cirrhosis developed HCC. At index visit, the study population had a median age 57 years, 43% males, 78.8% White, median BMI 31.9 kg/m2, 26.2% had diabetes mellitus, 9.9% current smokers, mean FIB-4 score 4.2, and mean MELD score 8.2. Multivariable Cox regression models revealed that male sex, BMI 25-29.9 kg/m2, and FIB-4 >3.25 were independent factors associated with development of HCC in patients with NASH cirrhosis.

Results II

Compared to patients with FIB-4 < 1.45, patients with FIB-4 between 1.45-3.25 had a similar risk of HCC (HR 1.15, 95% CI: 0.58-2.28, p=0.686), whereas patients with FIB-4 >3.25 had a 2.84 (95% CI: 1.57-5.11, p=0.001) increased hazard of HCC.

Table 1. Factors Associated with HCC in NASH Cirrhosis: Univariate and Multivariable Analyses.

Factors	Univariate		Multivariable	
	Unadjusted Hazard Ratio (95% Confidence Interval)	p-value	Adjusted Hazard Ratio (95% Confidence Interval)	p-value
Age group, yrs				
≤49	1 [reference]			
>49-59	1.21 (0.79-1.85)	0.374		
>59-69	1.46 (0.96-2.24)	0.078		
>69	2.23 (1.26-3.97)	0.006		
Sex				
Female	1 [reference]		1 [reference]	
Male	2.35 (1.70-3.24)	0.000	2.56 (1.59-4.11)	0.000
Race and ethnicity				
Hispanic	0.93 (0.34-2.50)	0.878	0.47 (0.07-3.45)	0.461
Non-Hispanic				
White	1 [reference]		1 [reference]	
Black	0.78 (0.50-1.20)	0.254	0.96 (0.55-1.70)	0.896
Other*	0.28 (0.04-2.02)	0.208	0.55 (0.07-3.99)	0.552
BMI category, Kg/m2				
<18.5	1.27 (0.16-10.15)	0.822	1.38 (0.17-11.3)	0.762
18.5–24.9	1 [reference]		1 [reference]	
25.0–29.9	2.90 (1.36-6.19)	0.006	2.86 (1.30-6.27)	0.009
30.0–34.9	2.18 (1.05-4.51)	0.036	1.63 (0.69-3.84)	0.263
35.0–39.9	1.70 (0.74-3.88)	0.208	1.59 (0.67-3.77)	0.298
≥40	0.90 (0.36-2.28)	0.827	0.97 (0.34-2.73)	0.948
Albumin, g/dL	0.602 (0.48-0.75)	0.000		
INR	1.40 (1.02-1.92)	0.038		
Total Bilirubin, mg/dL	1.03 (1.00-1.07)	0.031		
Platelet count, x10⁹/L	0.996 (0.994-0.998)	0.000		
FIB-4 score				
<1.45	1 [reference]		1 [reference]	
1.45-3.25	1.31 (0.79-2.18)	0.296	1.15 (0.58-2.28)	0.686
>3.25	2.65 (1.71-4.13)	0.000	2.84 (1.57-5.11)	0.001

Kaplan–Meier survival estimates

Number at risk

fib4_cat = <=1.45	267	218	202	181	0
fib4_cat = 1.45-3.25	335	246	215	184	0
fib4_cat = >3.25	545	337	260	204	0

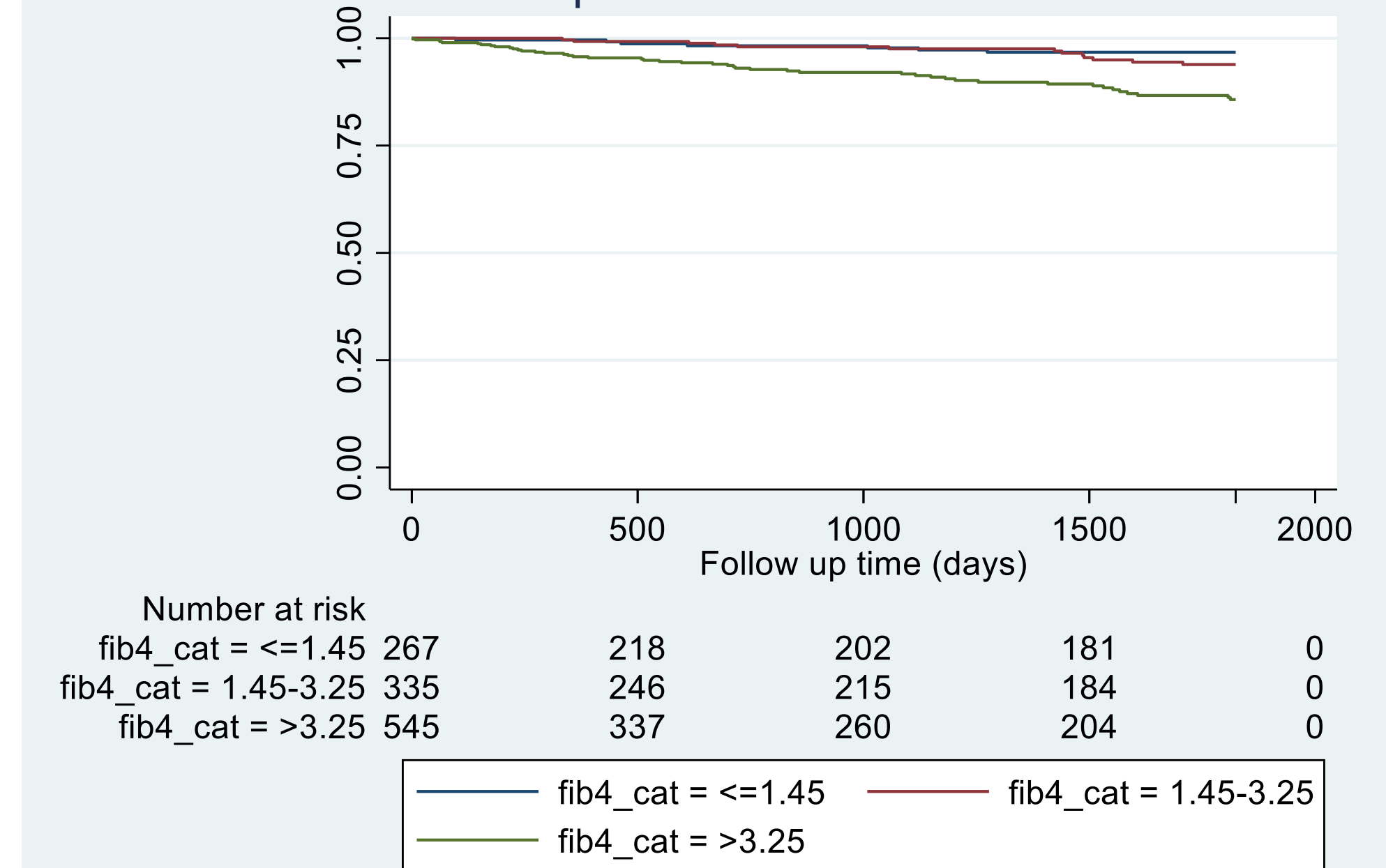fib4_cat = <=1.45   fib4_cat = 1.45-3.25
fib4_cat = >3.25

Figure 1. Kaplan-Meier estimates of developing HCC in patients with NASH cirrhosis by FIB-4 score within 5 years of follow up.

Discussion

Our main findings were (1) Age > 69 years, male sex, BMI 25-29.9 kg/m2, and FIB-4 > 3.25 were independent factors associated with development of HCC in patients with NASH cirrhosis; (2) high FIB-4 score (>3.25) was a significant independent predictor and one of the strongest independent predictors of progression to HCC in patients with NASH cirrhosis, after controlling for important clinical risk factors. Our observations are in line with previous studies. FIB-4 can be used as a noninvasive tool to identify patients at risk of developing HCC and to stratify those at high risk who could benefit from intensive treatment.

Conclusions

FIB-4 > 3.25 was an independent predictor of HCC risk in NASH cirrhosis. Providers should pay attention to FIB-4 for long term monitoring of disease progression. FIB-4 is a promising tool for identification of high-risk patients and may be used in routine clinical practice as a simple screening strategy for HCC risk in patients with NASH cirrhosis.

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