Modified Fibrosis-4 index stratifies the risk of hepatocellular carcinoma in Asian patients with chronic hepatitis B treated with entecavir

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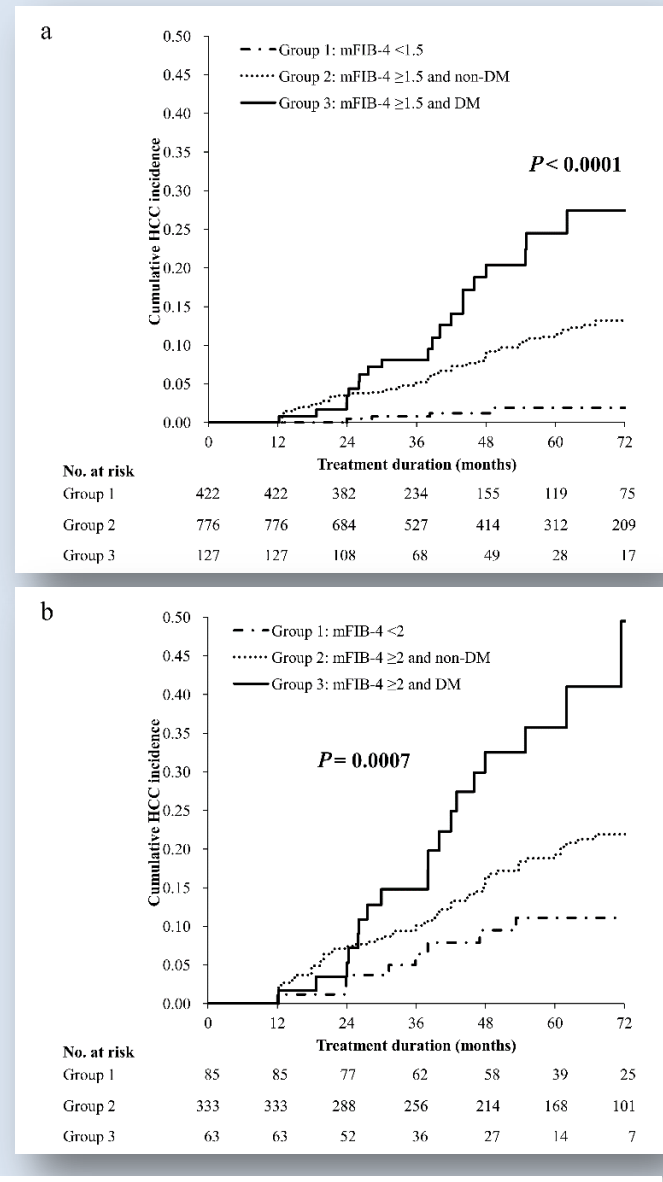
Objectives: Nucleos(t)ide analogues (NAs) have been widely used for HBV treatment in patients with chronic hepatitis B (CHB). Although NA therapy reduces the incidence of hepatocellular carcinoma (HCC), it does not completely eliminate its occurrence. Noninvasive fibrosis indices could predict the risk of HCC in patients with CHB. We investigated the predictive accuracy of several extant noninvasive fibrosis indices, including APRI, FIB-4 and mFIB-4, for HCC incidence at baseline in CHB patients receiving entecavir therapy.

Methods: We enrolled 1325 NA-naïve CHB patients (noncirrhotic: 844; cirrhotic: 481) treated with entecavir from January 2007 to August 2012. Baseline clinical features and fibrosis indices were collected and evaluated for predicting HCC risk by univariate and multivariate Cox regression analyses. The predictive accuracy of each predictor was evaluated by receiver operating characteristic (ROC) curves.

Results: Of 1325 patients, 105 patients (7.9%) developed HCC during a median follow-up period of 4.1 years. The cumulative incidences of HCC at 3, 5, and 6 years were 4.1%, 9.9%, and 11.4%, respectively. The predictive accuracy of mFIB-4 for HCC incidence within 5 years of entecavir treatment was significantly superior to those of other indices (AUROCs: APRI, 0.4216; FIB-4, 0.6773; and mFIB-4, 0.7316). Age (hazard ratio [HR]: 1.039; 95% confidence interval [CI]: 1.020–1.059; $P < 0.0001$), diabetes mellitus (DM) (HR: 1.902; 95% CI, 1.185–3.052; $P = 0.0077$), and modified Fibrosis-4 (mFIB-4) (HR: 4.619; 95% CI, 1.810–11.789; $P = 0.0014$) were independent predictors of HCC in all patients (mFIB-4 ≥1.5 for the noncirrhotic cohort; DM and mFIB-4 ≥2.0 for the cirrhotic cohort). A combination of mFIB-4 and the status of DM stratified the cumulative risk of HCC into three subgroups in all patients (high: mFIB-4 ≥1.5/DM; intermediate: mFIB-4 ≥1.5/non-DM; low: mFIB-4 <1.5/±DM, $P < 0.0001$) and in the cirrhotic cohort (high: mFIB-4 ≥2.0/DM; intermediate: mFIB-4 ≥2.0/non-DM; low: mFIB-4 <2.0/±DM, $P = 0.0007$). An mFIB-4 cutoff value of 1.5 stratified the cumulative risk of HCC in the noncirrhotic cohort ($P = 0.015$).

Conclusions: The mFIB-4 index alone or in combination with DM is the optimal noninvasive predictor of HCC risks at baseline in CHB patients undergoing long-term entecavir therapy.

Figure 1. Combination of mFIB-4 and DM stratifies patients into subgroups of different HCC risks. (a) All patients. (b) Cirrhotic patients.



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