Screening for hepatocellular carcinoma (HCC) is clinically important given that its early detection has remarkable survival benefits. We investigated the possible role of FIB-4, a recently developed noninvasive marker for liver fibrosis based on routine laboratory tests, as a clinical indicator for predicting future HCC among hepatitis B surface antigen (HBsAg) carriers. Our retrospective cohort study involved 986 Korean HBsAg carriers 40 years of age or older who visited Seoul National University Hospital for a health checkup. National medical service claims data were used to determine HCC incidence. Median follow-up time was 5.4 years (interquartile range: 4.4 years). Adjusted for age, sex, body mass index, smoking, alcohol, and antiviral medication for hepatitis B, compared to subjects with FIB-4 < 1.25, subjects with 1.7 ≤ FIB-4 < 2.4 showed an adjusted hazard ratio (aHR) of 4.57 (95% confidence interval [CI]: 1.50-13.92) and subjects with FIB-4 ≥ 2.4 showed an aHR of 21.34 (95% CI: 7.73-58.92) for HCC incidence. FIB-4 was shown to have incremental predictive value to ultrasonographic liver cirrhosis for HCC incidence (C-index: 0.701 vs. 0.831; P = 0.001). FIB-4 was also better predictive of HCC incidence, compared to that of ultrasonographic liver cirrhosis (C-index: 0.775 vs. 0.701; P = 0.040). Conclusion: High FIB-4 is a highly predictive risk factor for HCC incidence among Korean HBsAg carriers. FIB-4 is a promising, easily applicable, and cost-effective clinical tool in identifying a subpopulation of HBsAg carriers who are at heightened risk. Our study needs to be replicated in larger future studies on various ethnic groups; nonetheless, our study suggests that FIB-4 may play a valuable role in HCC screening among HBsAg carriers. (HEPATOLOGY 2015;61:1261-1268)
cases, particularly high in CHB, as hepatitis B surface antigen (HBsAg) was found in 68.8%-78.6% of patients with hepatocellular carcinoma (HCC).  

Screening for HCC is clinically important given that its early detection brings remarkable survival benefits. However, screening rate for HCC has been low, only 23% among high-risk groups in Korea, despite the establishment of national screening programs in the past two decades. Beyond political measures to improve screening behavior, improvement in the screening strategy in terms of cost-effectiveness by risk stratification will most likely be highly beneficial. Investigation of clinical factors or markers that effectively stratify subjects with differing risk is warranted.

In recent years, various noninvasive markers of liver fibrosis (LF) have been developed to stage liver fibrosis, as an alternative to liver biopsy, the invasive gold standard for LF. These indices are based on serological markers derived from blood tests reflecting liver function, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), or platelet (PLT), and/or markers of extracellular matrix metabolism. These markers, shown to be accurate for LF in subjects with hepatitis C, hepatitis B, alcoholic hepatitis, and nonalcoholic fatty liver, predict liver-related mortality in subjects with chronic liver disease. In a particular study, FIB-4, an index calculated from age, AST, ALT, and PLT, was reported to be a strong risk factor for HCC in human immunodeficiency virus infected subjects. This is not surprising given that age, elevated aminotransferases, and low PLT have all been associated with HCC risk.

FIB-4 is remarkable for its high predictive value to LF, as well as clinical applicability, owing to the fact that it can be easily determined by routine laboratory tests. We evaluated the association of FIB-4 with HCC incidence in HBsAg carriers in order to investigate the potential role of FIB-4 as a clinical marker capable of effectively differentiating those at high risk.

Patients and Methods

Study Population. We retrospectively enrolled 1,043 consecutive Korean individuals at least 40 years of age with positive HBsAg who received a general health evaluation at Seoul National University Hospital (SNUH; Seoul, Korea) from January 1, 2003 to December 31, 2010. Subjects with a history of cancer (n = 14), those positive for hepatitis C antibody (n = 8), those sonographically diagnosed with HCC at baseline (n = 5), and those with missing laboratory results or insufficient medical records (n = 30) were excluded for a total study population of 986. This retrospective study was approved by the SNUH Institutional Review Board, and the requirement for informed consent was waived.

Data Collection. Korean National Health Insurance (KNHI) medical service claims data that covers virtually all Koreans except for Medicaid beneficiaries (approximately 3% of the population) were used, which include registered diagnosis data coded using the International Classification of Diseases, 10th revision (ICD-10), as well as KNHI claims data on radiation therapy, surgical operations for cancer, and claims for chemotherapeutic agents within 1 year since the first diagnosed date (as cancer, i.e., ICD-10 C00-C97) to determine previous history of cancer, if the claims data were registered before the baseline date (i.e., day of first visitation). HCC incidence was determined using diagnosis registration data (ICD-10 C22) that matched claims data for surgical operations, nonsurgical treatments for HCC (including radiofrequency ablation [RFA], transarterial chemoembolization [TACE], and percutaneous ethanol injection [PEI]), and chemotherapeutic agents. Subjects with HCC that occurred before the baseline date were excluded.

Antiviral medication for hepatitis B was determined by extracting prescription claims for various antiviral drugs for hepatitis B, including adefovir, clevudine, emtricitabine, entecavir, interferon-alpha-2a, lamivudine, rebivudine, and tenofovir.
Alcohol drinking and smoking status were inquired by self-reported questionnaire. Serum AST, ALT, and PLT levels were measured on the same day of the study. Weight and height were measured at the clinic upon examination using a standardized protocol. Body mass index (BMI) was calculated and categorized according to the World Health Organization Asia-Pacific criteria. Current alcohol drinkers were asked about the frequency and amount of alcohol consumption, and average alcohol consumption in grams per day was estimated by multiplying grams per serving of the specific alcohol beverage per serving.

Hepatic ultrasound (US) examinations were performed and interpreted in consensus by experienced radiologists. Semiquantitative grading of fatty liver (FL) was done by widely accepted criteria for subjective visual steatosis evaluation of bright liver with increased liver-kidney contrast, blurring of intrahepatic vessels and diaphragm, and loss of echoes of posterior hepatic segments, as previously described. Presence of liver cirrhosis (LC) was assessed by surface nodularity, liver edge, and parenchymal echotexture, as previously described.

Statistical Analysis. FIB-4 was defined as (age × AST [U/L])/(PLT [10^9/L] × ALT [U/L]^{1/2}), as previously described. Participants were categorized into four groups according to their FIB-4 levels: 1.25 < FIB-4 (representing the median value); 1.25 ≤ FIB-4 < 1.7 (representing the 75th percentile value); 1.7 ≤ FIB-4 < 2.4 (representing the 90th percentile value); and FIB-4 ≥ 2.4.

Descriptive statistics were used to determine the basic characteristics of the study population. Cox's proportional hazards regression models were employed to determine the association of high FIB-4 with HCC, adjusted for age, sex, and previously known risk factors for HCC, including BMI, smoking, amount of alcohol consumption, as well as antiviral medication for hepatitis B at baseline and antiviral medication for hepatitis B after baseline (and before HCC event for those with HCC incidence, and before last date of follow-up for those without HCC incidence). The association was compared in different subpopulations: subjects with normal ALT levels (<40 IU/L); absence of ultrasonographic cirrhosis, absence of ultrasonographic FL, and subjects with none or light alcohol consumption (i.e., daily alcohol consumption <20 g/day). Kaplan-Meier's curves were used to portray the cumulative incidence of HCC by FIB-4 levels. Incremental predictive value of FIB-4 for HCC incidence was determined by comparing Harrell's C-index of different Cox's proportional hazards regression models.

All statistical analysis was performed by STATA (version 12.1; StataCorp LP, College Station, TX), and results with P values less than 0.05 were considered significant.

Results

Characteristics of Study Population. Baseline clinical characteristics of the study population are shown in Table 1. Mean age was 52.6 ± 8.1 years, 55.2% were male, 20.6% were current smokers, and 36.9% were obese. Subjects with moderately high FIB-4 levels (1.7 ≤ FIB-4 < 2.4) consisted of 17.8%, and subjects with severely high FIB-4 levels (≥ 2.4) consisted of 10.5% of the study population. US revealed 9.9% to have LC and 24.3% to have FL (of any degree). A total of 4.4% took antiviral medication for hepatitis B within 1 year of baseline, and 10.6% took antiviral medication for hepatitis B after baseline. Median follow-up time for HCC incidence was 5.4 years (interquartile range: 4.4 years).

FIB-4 Levels Associated With HCC Incidence. Compared to subjects with FIB-4 < 1.25, subjects with 1.7 ≤ FIB-4 < 2.4 showed a hazard ratio (HR) of 3.51 (95% confidence interval [CI]: 1.22-10.12) and subjects with FIB-4 ≥ 2.4 showed an HR of 15.24 (95% CI: 6.08-38.17) for HCC incidence (Table 2; Fig. 1). Adjusted for age, sex, BMI, smoking, amount of alcohol consumption, antiviral medication for hepatitis B at baseline, and antiviral medication for hepatitis B after baseline, subjects with 1.7 ≤ FIB-4 < 2.4 showed an adjusted HR (aHR) of 4.57 (95% CI: 1.50-13.92) and subjects with FIB-4 ≥ 2.4 showed an aHR of 21.34 (95% CI: 7.73-58.92) for HCC incidence, compared to subjects with FIB-4 < 1.25.

Association of FIB-4 With HCC Incidence in Different Subpopulations. The association of FIB-4 with HCC incidence was heightened in subjects with normal-range ALT (aHR, 34.58; 95% CI: 6.39-187.03), whereas the association was shown to be modestly attenuated in subjects without sonographically detected cirrhosis (aHR, 14.12; 95% CI: 3.43-58.14 for subjects with FIB-4 ≥ 2.4), with statistically significant interaction (P = 0.004). The association was only slightly or not attenuated in subjects with either none or light alcohol consumption or subjects without sonographically detected FL, without significant interaction (Table 2).

Incremental Predictive Value of FIB-4 for HCC Incidence. When FIB-4 was added to the basic regression model for HCC incidence, the model's Harrell's C-index was significantly greater than that of the
model when ultrasonographic LC was added (0.775 vs. 0.701; \( P = 0.040 \)), as shown in Table 3. FIB-4 also was shown to have incremental predictive value to the model with LC (0.701 vs. 0.831; \( P = 0.001 \)). LC and high FIB-4 were independently associated with HCC incidence, although the aHR for each were attenuated when they were added together to the basic regression model. The predictive value for HCC incidence was significantly highest when both LC and FIB-4 were added to the basic regression model (C-index: 0.831).

**Discussion**

In our relatively large retrospective cohort study of Korean HBsAg carriers, we have identified a subpopulation of subjects with high LF index (FIB-4) who are at high risk for future HCC incidence. Given that high FIB-4 reflects underlying LF,\(^2\) our result is not particularly surprising, owing to the fact that LC has been associated with increased risk for HCC in subjects with chronic hepatitis.\(^2^4,3^2\) A previous study that compared hepatitis B virus (HBV) genotype, core promoter and precore mutations, hepatitis B envelope antigen (HBeAg)/hepatitis B envelope antibody status, HBV-DNA levels, and presence of cirrhosis as risk factors for HCC development among HBsAg carriers partially incorporated the AST to PLT ratio index, an LF index similar to FIB-4 (but without age included) in defining those with cirrhosis, and reported presence of cirrhosis to be the most important independent risk factor for HCC development.\(^3^2\) However, this study did not directly investigate the role of using LF index in detecting subjects at risk for HCC development among HBsAg carriers.

Our study shows high FIB-4 is a risk factor for HCC independent of ultrasonographic LC or FL (Fig. 1; Table 2), but more important, our study shows high FIB-4 is better predictive of HCC incidence, compared to that of ultrasonographically detected LC (which is a common way LC is first detected, especially in early stages): The model with FIB-4 showed a Harrell’s C-index of 0.775 whereas the model with ultrasonographic LC showed a Harrell’s C-index of 0.701 with \( P = 0.040 \) (Table 3). There are two main biological explanations for this. First, HBsAg carriers with high FIB-4 without ultrasonographic LC may represent subclinical LC/LF undetected by US, reflecting the moderate accuracy of US at best when evaluating LC (with sensitivity reported to be
approximately 82%-88%). This is probably the most plausible explanation given that high FIB-4 represents underlying LF. Second, HBsAg carriers with high FIB-4 without ultrasonographic LC may reflect those at risk for HCC without LC. In fact, previous studies have reported on a subpopulation of HBsAg carriers diagnosed with HCC without LC, and LF without cirrhosis was found in patients with HCC. A notable possibility is that HBsAg carriers with high FIB-4 may reflect active hepatitis B (with elevated serum ALT and/or high HBV-DNA levels), which is a risk factor for HCC development itself. It is also noteworthy to mention that elevated ALT was not an absolute prerequisite for the association of high FIB-4 with HCC, as shown in Table 2, although a larger number of HCC events occurred in subjects with elevated ALT. We have also evaluated the involvement of FL and heavy alcohol drinking in the association of high FIB-4 with HCC, given that both alcoholic hepatitis and nonalcoholic steatohepatitis have been associated with risk for HCC. Our results showed a nonsignificant

Table 2. Cox's Proportional Hazards Models for HCC Incidence

| All subjects (n = 986) | Person-Years | Event (n) | Rate* | HR (95% CI) | aHR† (95% CI) |
|----------------------|--------------|-----------|-------|-------------|--------------|
| FIB-4 < 1.25         | 2,436.7      | 6         | 2.5   | 1           | 1            |
| 1.25 ≤ FIB-4 < 1.7   | 1,502.4      | 4         | 2.7   | 1.08 (0.30-3.82) | 1.31 (0.36-4.77) |
| FIB-4 ≥ 2.4          | 477.4        | 19        | 39.8  | 15.24 (6.08-38.17) | 21.34 (7.73-58.92) |

| Subjects with ALT < 40 IU/L (n=762) | Person-Years | Event (n) | Rate* | HR (95% CI) | aHR† (95% CI) |
|------------------------------------|--------------|-----------|-------|-------------|--------------|
| FIB-4 < 1.25                       | 2,026.8      | 3         | 1.5   | 1           | 1            |
| 1.25 ≤ FIB-4 < 1.7                 | 1,292.5      | 4         | 2.3   | 1.89 (0.37-9.72) | 1.92 (0.37-10.13) |
| FIB-4 ≥ 2.4                        | 660.4        | 4         | 6.1   | 5.18 (1.09-24.56) | 5.68 (1.15-28.05) |

| Subjects without LC‡ (n = 888) | Person-Years | Event (n) | Rate* | HR (95% CI) | aHR† (95% CI) |
|---------------------------------|--------------|-----------|-------|-------------|--------------|
| FIB-4 < 1.25                    | 2,309.1      | 4         | 1.7   | 1           | 1            |
| 1.25 ≤ FIB-4 < 1.7              | 1,408.1      | 4         | 2.8   | 1.63 (0.41-6.50) | 1.60 (0.38-6.81) |
| FIB-4 ≥ 2.4                     | 345.4        | 7         | 20.3  | 11.23 (3.29-38.37) | 14.12 (4.35-58.14) |

| Subjects without FL‡ (n = 746) | Person-Years | Event (n) | Rate* | HR (95% CI) | aHR† (95% CI) |
|--------------------------------|--------------|-----------|-------|-------------|--------------|
| FIB-4 < 1.25                    | 1,756.7      | 4         | 2.3   | 1           | 1            |
| 1.25 ≤ FIB-4 < 1.7              | 1,132.0      | 3         | 2.7   | 1.15 (0.26-5.13) | 1.40 (0.31-6.36) |
| FIB-4 ≥ 2.4                     | 705.6        | 7         | 9.9   | 4.20 (1.23-14.36) | 6.04 (1.67-21.86) |

| Subjects with none or light alcohol drinking§ (n = 864) | Person-Years | Event (n) | Rate* | HR (95% CI) | aHR† (95% CI) |
|--------------------------------------------------------|--------------|-----------|-------|-------------|--------------|
| FIB-4 < 1.25                                           | 2,079.3      | 6         | 2.9   | 1           | 1            |
| 1.25 ≤ FIB-4 < 1.7                                      | 1,339.9      | 2         | 1.5   | 0.52 (0.10-2.56) | 0.60 (0.12-3.03) |
| FIB-4 ≥ 2.4                                            | 779.5        | 7         | 9.0   | 3.02 (1.02-9.00) | 3.84 (1.22-12.12) |

*Rate per 1,000 person-years.  
†Adjusted for age, sex, BMI, current smoking, amount of alcohol consumption, antiviral medication for hepatitis B at baseline (within 1 year), and antiviral medication for hepatitis B after baseline.  
‡Determined by US.  
§Daily alcohol consumption <20 g/day.

Fig. 1. Kaplan-Meier’s curve for HCC incidence by FIB-4 levels. Compared to subjects with FIB-4 < 1.25, subjects with 1.7 ≤ FIB-4 < 2.4 showed an aHR of 4.57 (95% CI: 1.50-13.92) and subjects with FIB-4 ≥ 2.4 showed an aHR of 21.34 (95% CI: 7.73-58.92) for HCC incidence, adjusted for age, sex, BMI, current smoking, amount of alcohol consumption, antiviral medication for hepatitis B at baseline, and antiviral medication for hepatitis B after baseline (Table 2). Log-rank test: $P < 0.0001$.  

Log-rank test: $P < 0.0001$.
interaction between FIB-4 and FL or alcohol drinking. Therefore, it is likely that the association of FIB-4 with HCC is independent of (ultrasonographic) FL and heavy alcohol drinking.

Considering that FIB-4 can be easily determined at low cost, FIB-4 may be a very cost-effective test in determining high-risk subpopulations. According to our results, if high FIB-4 is defined by FIB-4 $< 1.7$ (representing the 75th percentile), which covers 28.3% of the study population, the incidence rate of HCC would be 9.7% (27 events of 279 subjects) over a median follow-up period of 5.4 years, meaning a roughly 1.8% annual incidence of HCC. If high FIB-4 is defined by FIB-4 $< 2.4$ (representing the 90th percentile), the annual incidence of HCC would approximate to 3.4%. Noting that surveillance for HCC in HBsAg carriers is said to be cost-effective once the annual incidence of HCC exceeds 0.2%,48 HBsAg carriers with high FIB-4 would merit HCC screening.

It is important to first note ethnical/regional differences in HCC incidence among HBsAg carriers. The incidence of HCC in Asian HBsAg carriers is higher than that noted in Caucasian patients, which is the basis for the American Association for the Study of Liver Diseases and Asian Pacific Association for the Study of the Liver both recommending screening for HCC in Asian men over 40 years,38,39 and in contrast, in Caucasians with HBV with cirrhosis.38 Hence, in the case of HBsAg carriers, Asians over a certain age (40 in the case of Koreans) are recommended to be screened routinely, whereas it is not so in Caucasians. Caucasian HBsAg carriers are recommended to be screened for HCC only if they have cirrhosis, high viral load, or family history of HCC.38

Our study has important potential clinical implications. First, in relation to our Asian study population (with high incidence of HCC in HBsAg carriers), HBsAg carriers with low FIB-4 may be considered to have a “low-risk,” not indicated for regular biannual HCC screening (given that subjects with FIB-4 $< 1.7$ had an annual incidence of HCC approximately 0.26%). Of course, our results would need to be replicated in future larger-scale, prospective studies as well as randomized, clinical trials to implement significant changes to the current guidelines. Nonetheless, our results suggest that FIB-4 may be a very cost-effective intermediate step in stratifying subpopulations into those who would benefit or not benefit from regular biannual HCC screening: HCC screening in Asian HBsAg carriers over 40 may be restricted to those with high FIB-4. Given that many of the Asian regions of high HCC incidence among HBsAg carriers have limited public resource, this potential implication of our study may have significant impact in terms of public health care policy.

Second, in relation to populations with low HCC incidence among HBsAg carriers (e.g., in Caucasians), high FIB-4 may possibly be an indication for initiation of regular biannual screening, synonymous to how Caucasian HBsAg carriers with LC are indicated to receive regular HCC screening according to current guidelines.38 A specific diagnosis for LC would not be necessary, which is clinically significant given that evaluation for LC by US, elastography, and/or liver biopsy, and so on, may not be necessary. Another possibility is that Caucasian HBsAg carriers with high FIB-4 may be indicated to be evaluated for LC and receive regular HCC incidence once LC is diagnosed in accord to current guidelines.38 Noting that LC is not routinely evaluated, which partly explains why so many HBsAg carriers diagnosed with HCC have previously undiagnosed LC (e.g., 56% in a previous study40), routine evaluation of FIB-4 in Caucasian HBsAg carriers may be clinically useful in early detection of LC by functioning as an intermediate step to

| Table 3. Incremental Predictive Value of FIB-4 for HCC Incidence |
|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
|                        | Base Model*             | US Model*                | FIB-4 Model*             | US & FIB-4 Model*       |
|                        | aHR (95% CI)            | aHR (95% CI)             | aHR (95% CI)             | aHR (95% CI)            |
| US LC (-)              | –                       | 1                       | –                       | 1                       |
| US LC (+)              | –                       | 8.58 (4.39-16.76)        | –                       | 3.85 (1.84-8.06)        |
| FIB-4 < 1.25           | –                       | –                       | 1.31 (0.36-4.77)         | 1.18 (0.33-3.40)        |
| 1.25 ≤ FIB-4 < 1.7    | –                       | –                       | 4.57 (1.50-13.92)        | 3.14 (1.02-9.67)        |
| 1.7 ≤ FIB-4 < 2.4     | –                       | 21.34 (7.73-58.92)       | 11.38 (3.85-33.67)       |
| FIB-4 ≥ 2.4           |                          |                          |                          |
| Harrell’s C-index (95% CI) | 0.635 (0.548-0.722)     | 0.701 (0.619-0.782)      | 0.775 (0.685-0.865)      | 0.831 (0.765-0.898)     |
| $P$ value (vs. base model) | –                       | 0.028                    | 0.004                    | <0.001                  |
| $P$ value (vs. US model) | –                       | –                       | 0.040                    | 0.001                   |
| $P$ value (vs. FIB-4 model) | –                       | –                       | –                       | 0.043                   |

*Cox’s proportional regression models adjusted for age, sex, BMI, current smoking, amount of alcohol consumption, antiviral medication for hepatitis B at baseline (within 1 year), and antiviral medication for hepatitis B after baseline, in addition to US LC and/or FIB-4, as indicated.
screen out those with LC who otherwise would not have received necessary regular HCC screening. Nonetheless, given that our results are based on our study population of Asian (Korean) HBsAg carriers, future studies on Caucasian HBsAg carriers are needed to determine the annual incidence of HCC in Caucasian HBsAg carriers with high FIB-4. However, noting that the correlation between high LF indexes and LF has been confirmed to be high, including in Caucasians, there is a high chance that HBsAg carriers with high FIB-4, even in Caucasians, would have a high incidence for HCC, similar to our results.

An emphasis is warranted for the easy clinical applicability of FIB-4. Determined by age, AST, ALT, and PLT only, it can be easily evaluated by routine laboratory tests. This is in contrast to previously reported noninvasive prediction models for HCC among HBsAg carriers, that involve factors that are not readily available in the clinic, such as HBV-DNA level, HBeAg, or liver US, especially in the case of asymptomatic inactive HBsAg carriers. Our results show that, despite its simplicity, FIB-4 has a high predictive value to HCC incidence among HBsAg carriers. Beyond cost-effectiveness, FIB-4 has the clear advantage of easy applicability. Future studies are strongly recommended to validate FIB-4 and explore specific ways to its implementation into current guidelines for HCC screening among HBsAg carriers.

From the perspective of FIB-4 being a readily applicable simple test with high predictive value for HCC incidence, we have comparatively evaluated the predictive values for HCC incidence of each component of FIB-4 (i.e., ALT, AST, and PLT), as shown in Supporting Table 1. Interestingly, all three components had significant incremental predictive value for HCC incidence, where PLT was lowest with a C-index of 0.710, followed by ALT with 0.721 and AST with 0.725 (compared to 0.635 of the base model). As expected, it was when all three were combined (into FIB-4) when the predictive value was highest, with a C-index 0.775.

There are several limitations to our study. First, many of the clinical factors used were based on medical service claims data that may not have been completely accurate. However, we have specified the criterion for cancer diagnosis with comprehensive medical service claims data on specific surgical operations for cancer, radiation therapy, nonsurgical treatments (including RFA, TACE, and PEI in the case of HCC), and prescription for chemotherapeutic agents. By doing so, we have significantly improved the accuracy of cancer diagnosis (including HCC) because these specific claims data are, in fact, very accurate owing to the involvement of actual transaction in payment, in contrast to diagnosis registration being sometimes overcoded by physicians. Second, data on liver biopsy, which is the gold-standard test for LF, was not available for our subjects, which made our analysis of the biology involved in the association of high FIB-4 and HCC incidence inconclusive. Third, our data did not include laboratory tests for hepatitis D virus, HBV DNA, and HBeAg. However, hepatitis D is very rare in Korea (with its prevalence reported to be 0.32% among chronic HBV carriers), and subjects with positive HBeAg and/or elevated HBV DNA would most likely have elevated aminotransferases, leading to high FIB-4. Fourth, our study population was not population based, so our results cannot be generalized. However, when we investigated the prevalence of HBsAg carriers with high FIB-4 in separate population-based nationally representative data, the fifth Korean National Health and Nutritional Examination Survey, we found similar prevalence rate of subjects with high FIB-4: 18.4% had FIB-4 values smaller than 2.4 and greater or equal to 1.7, and 13.5% had FIB-4 values greater or equal to 2.4, as shown in Supporting Table 2. These rates were similar, compared to that of our study population: 18.4% versus 17.8% and 13.5% versus 10.5%, respectively.

Despite the aforementioned limitations, our study has important clinical implications. To our knowledge, we are the first to show that high FIB-4 may be a very useful, easily applicable, and cost-effective clinical indicator associated with HCC incidence. We suggest that FIB-4 may have significant clinical value in stratifying HBsAg carriers into those who would benefit or not from regular HCC screening. Future larger studies on various ethnic groups are needed to consolidate our findings; nonetheless, our study shows that FIB-4 may play a valuable role in HCC screening among HBsAg carriers.

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