Potential role of fibrosis-4 score in hepatocellular carcinoma screening

Original Article

Potential role of Fibrosis-4 Score in Hepatocellular Carcinoma Screening: The Kangbuk Samsung Health Study

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CONFLICT OF INTEREST STATEMENT

Authors declare no Conflict of Interests for this article.

DATA AVAILABILITY STATEMENT

The data are not publicly available outside the hospital because of institutional review board restrictions (the data were not collected in a manner that could be widely distributed). However, the analytical methods are available from the corresponding author upon request.

ETHICS STATEMENT

Approval of the research protocol by an Institutional Reviewer Board: The study protocol was approved by the Institutional Review Board of Kangbuk Samsung Hospital (No: KBSMC 2022-12-019), which waived the requirement for informed consent because we used a de-identified data routinely collected as part of health-screening examinations for the analyses and implemented according to the Declaration of Helsinki.

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ABSTRACT

Aim: Hepatocellular carcinoma (HCC) is a major cause of cancer-related death, with low survival rates worldwide. Fatty liver disease (FLD) significantly contributes to HCC. We studied the screening performance of different methods for identifying HCC in patients with FLD or with metabolic risk factors for FLD.

Methods: Korean adults (n=340,825) without a prior HCC diagnosis were categorized into four groups: normal (G1), ≥2 metabolic risk factors (G2), FLD (G3), and viral liver disease or liver cirrhosis (G4). The National Cancer Registry data were used to identify HCC cases within 12 months. We assessed the area under the receiver operating characteristic curve (AUROC), sensitivity, specificity, and positive and negative predictive values of individual or combined screening methods.

Results: In 93 HCC cases, 71 were identified in G4, while 20 cases (21.5%) in G2 and G3 combined where ultrasound and fibrosis-4 performed similarly to alpha-fetoprotein and ultrasound. In G2, fibrosis-4 and ultrasound had the highest AUROC (0.93 [0.87–0.99]), whereas in G3, the combined screening methods had the highest AUROC (0.98 [0.95–1.00]). The positive predictive value was lower in G2 and G3 than in G4 but was >5% when restricted to a high fibrosis-4 score.

Conclusions: More than 21% of HCC cases were observed in patients with diagnosed FLD or at risk of FLD with metabolic risk factors. Nevertheless, screening for HCC in individuals without cirrhosis or viral hepatitis yielded very low results, despite the potential value of the fibrosis-4 score in identifying individuals at high risk of HCC.

KEYWORDS: alpha-fetoprotein, fatty liver disease, fibrosis-4, hepatocellular carcinoma, liver ultrasound

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AFP, alpha-fetoprotein; AUROC, area under the receiver operating characteristic curve; BP, blood pressure; CI, confidence interval; EASL, European Association for the Study of the Liver; FIB-4, fibrosis-4; FLD, Fatty liver disease; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HOMA-IR, homeostatic model assessment of insulin resistance; LC, liver cirrhosis; NCR, National Cancer Registry; NPVs, negative predictive values; OR, odds ratio; PPVs, positive predictive values; SEER, Surveillance, Epidemiology, and End Results; USG, ultrasonography.

INTRODUCTION

Hepatocellular carcinoma (HCC) is a major cause of cancer mortality globally, with low survival rates.[1-4] Nonalcoholic or metabolic-associated fatty liver disease (FLD) has emerged as a significant contributor to HCC, alongside viral hepatitis, and alcoholic liver disease.[5-8] The Korean National Liver Cancer Screening Program only targets high-risk patients (e.g., those with viral hepatitis or cirrhosis), neglecting those with FLD.[9] The exclusion of FLD has led to an underestimation of HCC risk and delayed treatment.[10] It is crucial to target populations who are not currently included in the screening program but are at high-risk of HCC, especially because FLD affects over a third of the global population.[9,11-13]

High-risk patients are recommended to undergo liver ultrasonography (USG), sometimes combined with alpha-fetoprotein (AFP) tests.[14-17] However, there is limited data on the screening efficacy for HCC among patients with FLD, coupled with inadequate surveillance and suboptimal screening in this group that contributes to a poor prognosis in subjects who are diagnosed with HCC in this group.[10] Several meta-analyses have reported that fibrosis-4 (FIB-4) score, derived from routine blood tests, can serve as a predictor and prognostic factor for HCC in patients with viral liver disease or FLD.[15,18,19] However, whether the FIB-4 score is a reliable predictor of HCC in a screening setting remains uncertain.[15,20]

This study aimed to evaluate the screening performance of the conventional methods, USG and AFP, as well as the FIB-4 score in detecting HCC in patients with FLD and those with metabolic risk factors, but without FLD, who are not currently considered high-risk groups in a cohort of relatively healthy adults participating in a regular screening program. This information will help identify appropriate approaches to improve early detection and prognosis of HCC in at-risk individuals.

METHODS

Study Population

We analyzed data from the Kangbuk Samsung Health Study, which included men and women aged >18 years who underwent regular health examinations at the Kangbuk Samsung Hospital Total Healthcare Screening Center in South Korea.[21] De-identified data from 350,800 participants who agreed to be included in the National Cancer Registry (NCR) between January 2011 and December 2019 were used. After excluding 9,577 participants owing to missing data on AFP, USG, hepatitis B/C virus (HBV/HCV) serology (hepatitis B surface antigen [HBsAg], hepatitis B surface antibody, hepatitis B core antibody, hepatitis C antibody), FIB-4 score, or metabolic syndrome components (n=9,833); a self-reported history of liver cancer (n=47); or malignant neoplasms of the liver or intrahepatic bile ducts (n=95) that were registered before the baseline data; the final analysis included 340,825 participants without a previous HCC diagnosis. The study protocol was approved by the Institutional Review Board of Kangbuk Samsung Hospital (No: KBSMC 2022-12-019), which waived the requirement for informed consent because we used a de-identified data routinely collected as part of health-screening examinations for the analyses and implemented according to the Declaration of Helsinki.

Measurements

A standardized self-administered questionnaire was used to evaluate patient demographic and behavioral characteristics, medical history, and medication use. Smoking status was categorized as never, past, or current smoker. Daily alcohol consumption was calculated based on the weekly frequency and number of drinks consumed per drinking day and categorized as <20 g/day or ≥20 g/day.[22] Additionally, we categorized alcohol intake in accordance with the recently proposed American Association for the Study of Liver Diseases (AASLD) and

European Association for the Study of the Liver (EASL) guidelines as follows: for males, <30 g/day, 30-60 g/day, and ≥60 g/day, and for females, <20 g/day, 20-50 g/day, and ≥50 g/day.[23]

Since it has been reported that the hepatocarcinogenesis in patients with fatty liver increases when alcohol consumption exceeds 40g/day, additional analyses based on this specific alcohol intake were conducted in Group 3.[24,25] Trained nurses performed the sitting blood pressure (BP) and anthropometric measurements. Obesity was defined as a body mass index ≥25 kg/m^2 according to the Asian-specific cutoff value.[26]

Fasting blood measurements included lipid profiles, glucose, albumin, liver enzymes, and insulin levels, platelets, and HBV/HCV serology.[21] The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as fasting blood insulin (μU/mL) × fasting blood glucose (mmol/L) / 22.5. Diabetes mellitus was defined as a fasting serum glucose level ≥126 mg/dL or the use of insulin or glucose-lowering medication.

AFP, hepatitis B serological markers, and HCV antibodies were measured using an electrochemiluminescence immunoassay Modular E170 (Roche Diagnostics, Tokyo, Japan) until April 12, 2015; Cobas 8000 e602 (Roche Diagnostics) until February 8, 2018; and Cobas 8000 e802 (Roche Diagnostics) thereafter.[27] Chronic HBV infection was indicated by the presence of HBsAg, whereas chronic HCV infection was indicated by the presence of HCV antibodies. Viral liver disease was defined as having either chronic HBV or HCV infection.

USG was performed by experienced radiologists who were blinded to the study. A series of images of both lobes of the liver were acquired for the evaluation of focal lesions, steatosis, and parenchymal echotexture. Hepatic steatosis and focal hepatic lesions (nodular, hyper/hypoechoic, mass, suspected tumor, and metastatic) on ultrasound were diagnosed according to the standard criteria.[28,29] Lesions were considered hyper- or hypoechoic when their echogenicity was higher or lower than that of the adjacent parenchyma, respectively. Suspected

hepatic hemangiomas and calcified nodules were excluded from suspected liver nodules and tumors.[30]

The metabolic risk factor group were defined as those having two or more of the following: waist circumference ≥90 cm (men) or ≥85 cm (women), serum triglycerides ≥150 mg/dL or receiving treatment, serum high-density lipoprotein <40 mg/dL (men) or <50 mg/dL (women), BP ≥130/85 mmHg or taking BP-lowering drugs, prediabetes (fasting glucose 100–125 mg/dL [5.6–6.9 mmol/L] or HbA1c 5.7–6.4% [39–46 mmol/mol]), or HOMA-IR index ≥2.5. [31] Although USG is commonly used to detect fatty liver, its accuracy can be reduced in cases with low-level fatty infiltration.[32] Therefore, patients in the metabolic risk factor group were considered at risk of FLD as it is plausible that this group had fatty liver below the limits of detect of liver ultrasound.

Participants were categorized into the following four groups based on metabolic risk factor or diagnosed FLD and traditional high-risk group as follows: normal group (G1), metabolic risk factor group (G2, two or more metabolic risk factors and without FLD on ultrasound), FLD on ultrasound group (G3), and viral liver disease (HBV/HCV infection) or liver cirrhosis (LC) group (G4; both conditions are currently recognized high risk group for HCC and covered by national HCC screening program). For the sensitivity analysis, G4 was further divided into G4A (viral liver disease or LC only) and G4B (viral liver disease and diagnosed FLD or two or more metabolic risk factors]). FIB-4 score was used to define the risk of advanced fibrosis as follows: <1.30 ("low risk"), 1.30–2.67 ("intermediate risk"), and ≥2.67 ("high-risk").[33] Additionally, based on previous research findings enhanced HCC diagnostic performance with increasing FIB-4 scores, we conducted an investigation to assess the results based on varying FIB-4 score cutoff values.[34-37]

Identification of HCC and non-HCC Cancer Cases

The NCR data (available until December 2020) were used to identify HCC cases. HCC was defined as International Classification of Diseases, Tenth Revision, code C22.0.[38] To evaluate the screening performance of USG, AFP, and FIB-4 score for HCC, the study outcome was defined as the presence or absence of a diagnosis of HCC within 12 months of the initial screening. The stage of HCC at diagnosis was obtained from the Korean Central Cancer Registry and categorized as localized, regional, or distant, according to categories used in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) staging.[39] Neoplasms without adequate information to assign a stage were classified as "unknown."

Initial treatment within four months of diagnosis was categorized as surgical (surgery alone, surgery with chemotherapy, surgery with radiotherapy, or surgery with chemotherapy and radiotherapy), non-surgical (chemotherapy alone, radiotherapy alone, or chemotherapy and radiotherapy), and no active treatment information. Transcatheter arterial chemoembolization was included into the non-surgical group.[40,41]

Furthermore, given prior research that reported the predictive utility of the FIB-4 score for non-HCC cancers,[42-44] we also conducted further investigations to assess the ability of the FIB-4 in predicting breast cancer and colorectal cancer.

Statistical Analysis

Demographic and clinical characteristics were divided into four groups according to traditional high-risk status and the risk of FLD: normal group (G1), metabolic risk factor group (G2), FLD on ultrasound group (G3), and viral liver disease or LC group (G4).

The performance of USG, AFP, and FIB-4 score in detecting HCC diagnosed within 12 months of screening in patients without a previous diagnosis of HCC at baseline was compared among the four groups. Screening performance was evaluated using sensitivity,

specificity, and positive and negative predictive values (PPVs/NPVs). The area under the receiver operating characteristic curve (AUROC) was used to assess diagnostic accuracy, and 95% confidence intervals were calculated. The cutoff value was determined using the Youden index, which identifies the threshold that maximizes both sensitivity and 1-specificity for predicting HCC. All statistical analyses were conducted using the Stata (version 17.0; StataCorp LP, College Station, TX, USA) and R package "pROC".[45] $P<0.05$ was considered statistically significant.

RESULTS

Participant Characteristics

The characteristics of the study participants by the diagnosis of HCC are shown in **Table 1**. The mean age was 43.1±9.8 years, and 54.7% were male. The proportion of people with HCC in each group was as follows: G1, 2.2%; G2, 10.8%; G3, 10.8%; and G4, 76.3%. Ninety-three HCC cases were identified within 12 months of screening. G4 had the highest number of HCC cases (n=71; 76.3%). Particularly, 69 (74.2%) of the HCC cases were identified in patients with HBV infection. However, 22 (23.7%) were identified in patients without viral liver disease or LC. Among them, 90.9% were detected in G2 and G3 combined. Patients with HCC were more likely to be older, male, drink alcohol (with an average alcohol intake of 10g/day) and have a higher prevalence of FLD and other metabolic risk factors, including diabetes and hypertension. The lipid profiles of patients with HCC were lower than those of patients without HCC. The characteristics of the study participants across the four groups are presented in **Table S1**.

HCC Characteristics

The age distribution, SEER stage at diagnosis, and initial treatment course of patients with

HCC are shown in **Table 2**. Patients with HCC in G2 and G3 were more likely to be older than those in G4. The highest number of HCC cases in G2 and G3 was observed in the >60 years age group, whereas the highest number of cases in G4 was observed in the 50–59 years age group. The SEER stage at diagnosis was localized, regional, and distant in 71,0%, 19.4%, and 2.2% of cases, respectively. The remaining 7.5% of cases had an "unknown" SEER stage at diagnosis. HCC cases in G3 were less likely to be diagnosed at the localized stage than those in other groups.

Screening Performance of USG and AFP Stratified by FIB-4 score

The performance of combined conventional screening methods (USG and AFP) is shown in **Table 3**. A positive test was defined as either a liver nodule/tumor on ultrasound or AFP ≥ 20 ng/mL. The AUROC of each group ranged from 0.73 to 0.88. However, the PPV was lower in G2 (0.14%) and G3 (0.17%) than in G4 (6.8%) but was similar to G4 when G2 and G3 were restricted to a high FIB-4 score (G2, 5.1%; G3, 5.6%). The PPV increased as FIB-4 score increased in G2, G3 and G4. Although we performed an additional analysis for the performance of combined conventional screening methods (USG and AFP) among the group 3 with and without excessive alcohol consumption stratified by FIB-4 score, the cases of HCC with advanced fibrosis were too small to evaluate a dose– response relationship between incident HCC and excessive alcohol consumption in patients with FLD (**Table S3**). Nevertheless, it is worth noting that the overall screening performance tends to be more favorable in Group 3 individuals who consume less than 40 grams of alcohol per day compared to those who exceed this threshold.

G4 was further divided into those with and without FLD or metabolic risk factors (**Table 4**). Among 71 HCC cases in G4, 60 had concomitant FLD or metabolic risk factors.

Screening performance was better in patients with combined FLD or with metabolic risk factors than in those without. The PPV increased and the NPV decreased as FIB-4 score increased in G4 patients with and without FLD or metabolic risk factors.

AUROC Based on USG, AFP, and FIB-4 score in HCC screening

Table S2 demonstrates that when comparing screening modalities among groups, USG and AFP performed the best in G4 (AUROC, 0.92), although this was not significantly different from that of USG and FIB-4 score. In G3, the combination of USG, AFP, and FIB-4 score had the highest AUROC (0.98 [0.96–1.00]), although this was not significantly different from those of the other three combinations (USG and AFP, USG and FIB-4 score, and AFP and FIB-4 score). In G1 and G2, FIB-4 score had the highest AUROC (G1, 0.91 [0.77–1.00]; G2, 0.9 [0.81–0.98]) among the individual screening methods, and the FIB-4 score did not differ significantly from the combination methods. The cutoff values for predicting HCC using the FIB-4 score, both in the total population and within each group, were determined using the Youden index, and all of these determined values were lower than the cutoff values for predicting advanced fibrosis (**Table S4, S5**). Following the categorization of alcohol intake in accordance with the recently proposed AASLD/EASL guidelines, the AUROC values remained consistently high across different alcohol consumption categories, with all three groups showing values ranging from 0.899 to 0.931 (**Table S6**).

AUROC Based on FIB-4 score in non-HCC cancer screening

In the study cohort, there were 392 cases of breast cancer and 149 cases of colorectal cancer. For breast and colorectal cancers, the AUROC of the FIB-4 score was 0.60 (0.58-0.63) and 0.67 (0.61-0.74), respectively (**Table S7, S8**). **Table S9** shows the age-adjusted odds ratios (OR) of breast and colorectal cancer based on FIB-4 score quartiles. Compared with FIB-4 quartile

1 as the reference, FIB-4 quartiles 2, 3, and 4 were associated with a higher risk of breast cancer, with age-adjusted ORs (95% CIs) of 1.97 (1.34-2.83), 2.02 (1.40-2.92). and 1.59 (1.04-2.41), respectively. In the case of colorectal cancer, no statistically significant association were observed in both men and women.

DISCUSSION

The present study investigated the screening performance of conventional methods (USG and AFP) and the FIB-4 score for diagnosing HCC. Among 93 HCC cases, the highest proportion was detected in G4. The majority of HCC cases in G4 were patients with concomitant FLD or with metabolic risk factors. Approximately one quarter of the HCC cases were detected in patients without viral liver disease or cirrhosis, with most of them (90.9%) occurring in G2 and G3. The FIB-4 score had comparable screening ability to other individual methods. When combined with either AFP or USG, the FIB-4 score showed comparable discrimination ability to other individual and combined screening methods. Although the proportion of HCC cases was very low in G2 and G3, conventional screening methods demonstrated a PPV >5% when restricted to a high FIB-4 score. The PPV was similar to that of the screening methods in G4, which is the traditional target population for HCC surveillance.[46-49]

Several studies and meta-analyses have shown that patients with FLD have a significantly higher risk of HCC and HCC-related mortality.[50,51] FLD is a major indication for liver transplantation, with a rapidly increasing incidence.[52] As the incidence of FLD continues to increase globally, taking proactive measures to address this issue is crucial.[11,52] In this study, >21% of all HCC cases occurred in patients with FLD or metabolic risk factors who are not considered "high-risk" according to current surveillance guidelines, but the frequency was lower compared to the group currently defined as high-risk for HCC. However, even within the existing high-risk group for HCC, which includes patients with viral liver disease or LC, we

demonstrated a 2.6 times higher rate of HCC diagnosis when accompanied by FLD or metabolic risk factors. Our findings suggest that patients with FLD or with metabolic risk factors, particularly those belonging to the "high-risk subgroup" with a high FIB-4 score, may benefit from screening, and this groups needs to be studied further in other studies.

Currently, USG is the primary screening method for HCC surveillance, with AFP sometimes used in some regions.[12,14-17] According to a previous study, the sensitivity of USG alone as an early screening tool for HCC is 45%; however, the sensitivity increases to 63% when it is used in combination with AFP.[53] The South Korean National Liver Cancer Screening Program recommends USG and AFP every 6 months for high-risk groups of HCC.[54,55] Despite early HCC screening in high-risk groups, the survival rate of HCC is less than 20%, which is similar to that observed in South Korea.[12,56] This suggests that the effect of early HCC screening is limited and suboptimal, indicating the need for developing more effective surveillance strategies. Current HCC screening strategies face challenges such as risk stratification and cost-effectiveness.[12,15] These issues have been addressed in several studies and clinical guidelines, emphasizing the need for improved HCC screening methods.[12,15]

Previous meta-analyses have reported that the FIB-4 score can serve as a non-invasive and simple predictive and prognostic factor for HCC in patients with FLD or viral liver disease.[15,18,19] However, few studies have reported the screening efficacy of FIB-4 score for detecting HCC. In our study, FIB-4 score had the highest AUROC among the individual screening methods in G1 and G2. Moreover, the FIB-4 score and USG had comparable or better screening performance than USG and AFP in patients with FLD or metabolic risk factors, who are not considered "high-risk" according to current surveillance guidelines. A PPV >5% that is restricted to a high FIB-4 score in patients with FLD or with metabolic risk factors is considered a meaningful result when compared to other studies that proposed PPV thresholds of 2–5% for evaluating individual cancer types in primary care settings or cancer screening programs.[46-49]

However, while the FIB-4 score shows potential in identifying individuals who may benefit from HCC screening, it is important to exercise caution, as screening for HCC in individuals without cirrhosis or viral hepatitis may yield very low results, possibly leading to unnecessary further testing in the general population.

This study had several limitations. First, there was no histological evaluation of hepatic steatosis and fibrosis, due to the invasive nature of liver biopsy. Because the study population were participating in a health screening program and were not patients in a Hepatology secondary care service, alternative methods such as USG and laboratory testing were used to characterize fatty liver. Although the accuracy of USG is poor in subjects with low-level fatty infiltration (e.g. <20%),[32] USG is commonly used to detect fatty liver and screen for HCC, which reflects the common practice in real-world settings. Second, the identification of HCC relied on the NCR data, which included the SEER stage rather than the TNM stage. Despite this limitation, the NCR has a high completion rate and covers the entire South Korean population, providing reliable information for HCC diagnosis. Third, owing to the retrospective nature of the study, we could not rule out the possibility of unmeasured factors that might have influenced the diagnosis of HCC. Our data were based on annual or biannual health screening rather than the recommended 6-month screening for high-risk groups of HCC, which might limit the evaluation of each screening method and its optimal interval. Additionally, some patients with viral liver disease or LC may have undergone additional work-up (e.g., Computed Tomography or Magnetic Resonance Imaging), which could not be fully captured in this study. Finally, our cohort comprised individuals undergoing health screening, resulting in a relatively small number of patients with significant fibrosis or cirrhosis. Therefore, our study included a large number of relatively healthy young, employed adults. Further research is needed to generalize these results to other populations and races with different characteristics.

In conclusion, over 21% of HCC cases were observed in patients with FLD or two or more metabolic risk factors, who are not typically considered "high-risk" according to current HCC surveillance guidelines. Our study suggests the potential role of the FIB-4 score as a screening strategy for HCC, but its yield is relatively low in the low-risk population. Further studies are needed to validate our findings in other ethnic groups and establish effective screening strategies for HCC in patients with FLD or metabolic risk factors.

CONFLICT OF INTEREST STATEMENT

Authors declare no Conflict of Interests for this article.

DATA AVAILABILITY STATEMENT

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Appendices/Supplementary information

Table S1. Baseline characteristics of the population strata of the four groups

Table S2. Comparison of receiver operating characteristic curves of individual and combination methods based on liver ultrasound, AFP, and FIB-4

Table S3. Comparison of the screening performance of liver ultrasound and AFP† in detecting HCC stratified by FIB-4 score‡ among the group 3§ with and without excessive alcohol consumption

Table S4. Screening performance of fibrosis-4 score cutoff-value determined using the Youden index both overall and within each group

Table S5. Determining the optimal fibrosis-4 score cutoff value for predicting hepatocellular carcinoma in the study population

Supplementary Table R1. The screening performance of the previously documented fibrosis-4 score cutoff value of 3.25

Table S6. Receiver operating characteristic curves of fibrosis-4 score according to the alcohol drinking status

Table S7. Receiver operating characteristic curves of fibrosis-4 score for predicting breast cancer or colorectal cancer

Table S8. Screening performance of fibrosis-4 score cutoff-value determined using the Youden index for predicting breast cancer and colorectal cancer

Table S9. Breast cancer and colorectal cancer according to the fibrosis-4 score

Tables

TABLE 1 Baseline characteristics according to HCC diagnosis

Characteristic	No HCC (*n* = 340,732)	HCC (*n* = 93)	*p*-value
Age (years), n (%)	43.1 (9.8)	53.1 (9.3)	<0.001
Male (%)	54.7	80.6	<0.001
Current smoker (%)	16.7	41.4	<0.001
Average alcohol grams per day	4 (1-14)	10 (3-29)	<0.001
Alcohol intake ≥ 20 g/d (%)	20.7	37.2	<0.001
Alcohol intake ≥ 40 g/d (%)	9.0	19.8	<0.001
Diabetes mellitus (%)	6.1	25.8	<0.001
Prediabetes (%)	42.0	57.7	<0.001
Elevated BP (%)	18.2	37.6	<0.001
Lipid-lowering medication (%)	5.5	5.4	0.955
Obesity (%)	32.7	50.5	<0.001
BMI (kg/m^2)	23.8 (3.5)	25.1 (3.0)	<0.001
Waist circumference (cm)	82.1 (9.9)	87.9 (9.3)	<0.001
Fasting glucose (mg/dL)	98.1 (16.4)	112.2 (30.2)	<0.001
HbA1c (%)	5.6 (0.6)	6.0 (1.3)	0.001
HOMA-IR	1.8 (1.5)	3.0 (2.2)	<0.001
Total cholesterol (mg/dL)	191.5 (34.7)	176.0 (31.3)	<0.001
LDL-C (mg/dL)	126.4 (33.4)	111.3 (26.4)	<0.001
Triglycerides (mg/dL)	97 (68–144)	93 (65–126)	0.175
HDL-C (mg/dL)	59.5 (16.0)	54.9 (16.3)	0.005
Systolic BP (mmHg)	110.4 (12.8)	112.7 (13.3)	0.079
Diastolic BP (mmHg)	71.1 (9.8)	72.6 (9.9)	0.144
ALT (IU/L)	19 (13–29)	33 (24–51)	<0.001
AFP (ng/mL)	2.5 (1.8–3.5)	7.4 (3.8–70.6)	<0.001
HBV infection (%)	2.8	74.2	<0.001
HCV infection (%)	0.1	1.1	0.006

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Liver nodule/tumor on USG (%)	4.4	52.7	<0.001
Liver cirrhosis on USG (%)	0.04	21.5	<0.001
FIB-4 score[†] (%)			<0.001
Low	88.7	25.8	
Intermediate	10.7	36.6	
High	0.6	37.6	
Group[‡] (%)			<0.001
G1	33.4	2.2	
G2	31.0	10.8	
G3	32.7	10.8	
G4	2.9	76.3	

Data are expressed as mean (SD), median (interquartile range), or percentage.

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; BMI, body mass index; BP, blood pressure; FIB-4, fibrosis-4; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; LDL-C, low-density lipoprotein cholesterol; USG, ultrasound.

[†]FIB-4 score cutoff values: <1.30 ("low risk"), 1.30–2.67 ("intermediate risk"), and ≥2.67 ("high risk").

[‡]Participants were categorized into four groups: normal group (G1), metabolic risk factor group without fatty liver disease on ultrasound (G2), fatty liver disease on ultrasound group (G3), and viral liver disease or liver cirrhosis group (G4). Metabolic risk factor group were defined as those having two or more of the following condition: waist circumference ≥90 cm (men) or ≥85 cm (women), serum triglycerides ≥150 mg/dL or receiving treatment, serum high-density lipoprotein <40 mg/dL (men) or <50 mg/dL (women), BP ≥130/85 mmHg or taking BP-lowering drugs, prediabetes (fasting glucose 100–125 mg/dL [5.6–6.9 mmol/L] or HbA1c 5.7–6.4% [39–46 mmol/mol]), or HOMA-IR ≥2.5.

TABLE 2 Characteristics of HCC cases (C22.0) in the four groups[†]

Characteristic	Total (*n* = 93)	G1 (*n* = 2)	G2 (*n* = 10)	G3 (*n* = 10)	G4 (*n* = 71)
Age (years)					
< 40	6.5	0.0	0.0	10.0	7.0
40–49	33.3	50.0	20.0	10.0	38.0
50–59	39.8	0.0	20.0	40.0	43.7
≥ 60	20.4	50.0	60.0	40.0	11.3
Sex					
Female	19.4	50.0	30.0	20.0	16.9
Male	80.7	50.0	70.0	80.0	83.1
AFP (ng/mL)	7.5 (3.8–70.6)	1.9 (1.3–7.5)	4.3 (2.2–7.5)	5.1 (4.4–378.5)	9.5 (3.9–78.0)
Liver nodule/tumor (%)	52.7	50.0	50.0	70.0	50.7
Liver cirrhosis (%)	21.5	0.0	0.0	0.0	28.2
FIB-4 score[‡] (%)					
Low	25.8	50.0	40.0	40.0	21.1
Intermediate	36.6	50.0	30.0	40.0	36.6
High	37.6	0.0	30.0	20.0	42.3
SEER stage (HCC)					
Localized	71.0	100.0	80.0	60.0	70.4
Regional	19.4	–	0.0	30.0	21.1
Distant	2.2	–	0.0	0.0	2.8
Unknow	7.5	–	20.0	10.0	5.6
Initial treatment course[§]					
Surgical	52.7	50.0	40.0	60.0	53.5

Non-surgical	30.1	0.0	20.0	30.0	32.4
No active treatment	17.2	50.0	40.0	10.0	14.1

Data are expressed as median (interquartile range) or percentage.

Abbreviations: AFP, alpha-fetoprotein; BP, blood pressure; FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; HOMA-IR, homeostatic model assessment for insulin resistance; SEER, Surveillance, Epidemiology, and End Results.

[†]Participants were categorized into four groups: normal group (G1), metabolic risk factor group without fatty liver disease on ultrasound (G2), fatty liver disease on ultrasound group (G3), and viral liver disease or liver cirrhosis group (G4). Metabolic risk factor group were defined as those having two or more of the following condition: waist circumference $\geq$90 cm (men) or $\geq$85 cm (women), serum triglycerides $\geq$150 mg/dL or receiving treatment, serum high-density lipoprotein <40 mg/dL (men) or <50 mg/dL (women), BP $\geq$130/85 mmHg or taking BP-lowering drugs, prediabetes (fasting glucose 100–125 mg/dL [5.6–6.9 mmol/L] or HbA1c 5.7–6.4% [39–46 mmol/mol]), or HOMA-IR $\geq$2.5.

[‡]FIB-4 score cutoff values: <1.30 ("low risk"), 1.30–2.67 ("intermediate risk"), and $\geq$2.67 ("high risk").

[§]Initial treatment within 4 months of diagnosis was categorized as surgical (surgery alone, surgery with chemotherapy, surgery with radiotherapy, or surgery with chemotherapy and radiotherapy), non-surgical (chemotherapy alone, radiotherapy alone, or chemotherapy and radiotherapy), and no active treatment (no surgical or non-surgical treatment)

TABLE 3 Comparison of the screening performance of liver ultrasound and AFP[†] in detecting HCC stratified by FIB-4 score[‡] among the four groups[§]

	Overall	Low FIB-4	Intermediate FIB-4	High FIB-4
G1				
Participants (n)	113,656	103,452	9,852	0
HCC cases (n)	2	1	1	0
Sensitivity (95% CI)	50.0 (1.3–98.7)	0.0 (0.0–97.5)	100.0 (2.5–100)	–
Specificity (95% CI)	95.2 (95.1–95.3)	95.3 (95.2–95.4)	94.3 (93.9–94.8)	–
AUROC (95% CI)	0.73 (0.24–0.97)	0.48 (NA–1.00)	0.97 (NA–1.00)	–
PPV (95% CI)	0.02 (0.00–0.10)	0.00 (0.00–0.08)	0.18 (0.01–0.99)	–
NPV (95% CI)	100.0 (100–100)	100.0 (100–100)	100.0 (100–100)	–
G2				
Participants (n)	105,804	92,065	13,069	670
HCC cases (n)	10	4	3	3
Sensitivity (95% CI)	60.0 (26.2–87.8)	50.0 (6.8–93.2)	66.7 (9.4–99.2)	66.7 (9.4–99.2)
Specificity (95% CI)	95.8 (95.7–95.9)	95.8 (95.7–96.0)	95.7 (95.3–96.0)	94.5 (92.4–96.1)
AUROC (95% CI)	0.78 (0.62–0.94)	0.73 (0.45–1.00)	0.81 (0.49–1.00)	0.81 (0.48–1.00)
PPV (95% CI)	0.14 (0.05–0.29)	0.05 (0.01–0.19)	0.35 (0.04–1.26)	5.10 (0.60–17.3)

NPV (95% CI)	100.0 (100–100)	100.0 (100–100)	100.0 (100–100)	99.8 (99.1–100)
G3				
Participants (n)	111,383	99,325	11,317	741
HCC cases (n)	10	4	4	2
Sensitivity (95% CI)	80.0 (44.4–97.5)	100.0 (39.8–100)	50.0 (6.8–93.2)	100.0 (15.8–100)
Specificity (95% CI)	95.8 (95.7–95.9)	95.7 (95.6–95.9)	96.4 (96.1–96.8)	95.4 (93.6–96.8)
AUROC (95% CI)	0.88 (0.75–1.00)	0.98 (0.98–0.98)	0.73 (0.45–1.00)	0.98 (0.97–0.99)
PPV (95% CI)	0.17 (0.07–0.34)	0.09 (0.03–0.24)	0.49 (0.06–1.76)	5.60 (0.7–18.7)
NPV (95% CI)	100 (100–100)	100 (100–100)	100.0 (100-100)	100 (99.5–100)
G4				
Participants (n)	9,982	7,503	2,197	282
HCC cases (n)	71	15	26	30
Sensitivity (95% CI)	70.4 (58.4–80.7)	53.3 (26.6–78.7)	80.8 (60.6–93.4)	70.0 (50.6–85.3)
Specificity (95% CI)	93.1 (92.6–93.6)	94.1 (93.5–94.6)	91.1 (89.8–92.2)	80.6 (75.1–85.3)
AUROC (95% CI)	0.82 (0.76–0.87)	0.74 (0.61–0.87)	0.86 (0.78–0.94)	0.75 (0.67–0.84)
PPV (95% CI)	6.80 (5.10–8.90)	1.80 (0.77–3.47)	9.77 (6.15–14.5)	28.3 (17.5–41.4)
NPV (95% CI)	99.8 (99.7–99.9)	99.9 (99.8–100)	99.7 (99.4–99.9)	95.6 (91.1–98.2)

Abbreviations: AFP, alpha-fetoprotein; AUROC, area under the receiver operating characteristic curve; BP, blood pressure; CI, confidence interval; FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; HOMA-IR, homeostatic model assessment for insulin resistance; NPV, negative predictive value; PPV, positive predictive value.

†AFP cutoff value: 20 ng/mL.

‡FIB-4 score cutoff values: <1.30 ("low risk"), 1.30–2.67 ("intermediate risk"), and ≥2.67 ("high risk").

§Participants were categorized into four groups: normal group (G1), metabolic risk factor group without fatty liver disease on ultrasound (G2), fatty liver disease on ultrasound group (G3), and viral liver disease or liver cirrhosis group (G4). Metabolic risk factor group were defined as those having two or more of the following condition: waist circumference ≥90 cm (men) or ≥85 cm (women), serum triglycerides ≥150 mg/dL or receiving treatment, serum high-density lipoprotein <40 mg/dL (men) or <50 mg/dL (women), BP ≥130/85 mmHg or taking BP-lowering drugs, prediabetes (fasting glucose 100–125 mg/dL [5.6–6.9 mmol/L] or HbA1c 5.7–6.4% [39–46 mmol/mol]), or HOMA-IR ≥2.5.

TABLE 4 Comparison of the screening performance of liver ultrasound and AFP[†] in detecting HCC stratified by FIB-4 score[‡] in G4 patients[§] with and without FLD or metabolic risk factors

	Overall	Low FIB-4	Intermediate FIB-4	High FIB-4
G4A				
Participants (n)	3,124	2,402	661	61
HCC cases (n)	11	3	5	3
Sensitivity (95% CI)	63.6 (30.8–89.1)	66.7 (9.4–99.2)	60.0 (14.7–94.7)	66.7 (9.4–99.2)
Specificity (95% CI)	92.9 (91.9–93.7)	94.0 (92.9–94.9)	89.9 (87.4–92.1)	81.0 (68.6–90.1)
AUROC (95% CI)	0.78 (0.63–0.93)	0.80 (0.48–1.00)	0.75 (0.51–0.99)	0.74 (0.41–1.00)
PPV (95% CI)	3.10 (1.20–6.20)	1.40 (0.17–4.83)	4.35 (0.91–12.20)	15.40 (1.92–45.40)
NPV (95% CI)	99.9 (99.6–100.0)	100.0 (99.8–100.0)	99.7 (98.8–100.0)	97.9 (88.9–99.9)
G4B				
Participants (n)	6,858	5,101	1,536	221
HCC cases (n)	60	12	21	27
Sensitivity (95% CI)	71.7 (58.6–82.5)	50.0 (21.1–78.9)	85.7 (63.7–97.0)	70.4 (49.8–86.2)
Specificity (95% CI)	93.2 (92.5–93.8)	94.1 (93.5–94.8)	91.6 (90.0–92.9)	80.4 (74.1–85.8)
AUROC (95% CI)	0.82 (0.77–0.88)	0.72 (0.57–0.87)	0.89 (0.81–0.96)	0.75 (0.66–0.85)

PPV (95% CI)	8.50 (6.20–11.30)	2.00 (0.73–4.25)	12.30 (7.47–18.80)	33.30 (21.40–47.10)
NPV (95% CI)	99.7 (99.6–99.8)	99.9 (99.7–100.0)	99.8 (99.4–100.0)	95.1 (90.6–97.9)

AFP, alpha-fetoprotein; AUROC, area under the receiver operating characteristic curve; BP, blood pressure; CI, confidence interval; FIB-4, fibrosis-4; FLD, fatty liver disease; HCC, hepatocellular carcinoma; HOMA-IR, homeostatic model assessment for insulin resistance; NPV, negative predictive value; PPV, positive predictive value.

[†]AFP cutoff value: 20 ng/mL.

[‡]FIB-4 score cutoff values: <1.30 ("low risk"), 1.30–2.67 ("intermediate risk"), and ≥2.67 ("high risk").

[§]G4 patients included those with viral liver disease or cirrhosis. G4 patients were divided into two groups: G4A (viral liver disease or cirrhosis without FLD or metabolic risk factors) and G4B (viral liver disease or cirrhosis with FLD or metabolic risk factors). Metabolic risk factors were defined as those having two or more of the following conditions: waist circumference ≥90 cm (men) or ≥85 cm (women), serum triglycerides ≥150 mg/dL or receiving specific treatment, serum high-density lipoprotein <40 mg/dL (men) or <50 mg/dL (women), BP ≥130/85 mmHg or receiving BP-lowering drugs, prediabetes (fasting glucose 100–125 mg/dL [5.6–6.9 mmol/L] or HbA1c 5.7–6.4% [39–46 mmol/mol]), or HOMA-IR index ≥2.5.

Potential role of Fibrosis-4 (FIB-4) Score in Hepatocellular Carcinoma (HCC) Screening

Participants: Adults who underwent routine health screening exam

N = 340,825 (male 54.7%)
Mean age: 43.1± 9.8 years

Group category

Group 1: Normal (control group)

Group 2: Metabolic risk factors without hepatic steatosis

Group 3: Hepatic steatosis on ultrasound

Group 4: Viral liver disease or liver cirrhosis

Hepatocellular carcinoma (HCC)

: diagnosed from the *National Cancer Registry data*

between 2011 and Dec 2019

Diagnostic accuracy of liver ultrasound + alpha-fetoprotein on HCC

		Low FIB-4 (<1.30)	High FIB-4 (>2.67)
Group 1	AUROC	0.48 (NA-1.00)	-
	PPV	0.00 (0.00-0.08)	-
	NPV	100.0 (100-100)	-
Group 2	AUROC	0.73 (0.45-1.00)	0.81 (0.48-1.00)
	PPV	0.05 (0.01-0.19)	5.10 (0.60-17.3)
	NPV	100.0 (100-100)	99.8 (99.1-100)
Group 3	AUROC	0.98 (0.98-0.98)	0.98 (0.97-0.99)
	PPV	0.09 (0.03-0.24)	5.60 (0.70-18.7)
	NPV	100.0 (100-100)	100.0 (99.5-100)
Group 4	AUROC	0.74 (0.61-0.87)	0.75 (0.67-0.84)
	PPV	1.80 (0.77-3.47)	28.3 (17.5-41.4)
	NPV	99.8 (99.8-100)	95.6 (91.1-98.2)

- **More than 21% of HCC cases** were identified in patients with **cardio-metabolic risk factors with or without hepatic steatosis on ultrasound.**

- **FIB-4 score** may have a **potential role on HCC screening by identifying high risk group** with metabolic risk factors or hepatic steatosis.

Lay Summary

More than 21% of Hepatocellular Carcinoma (HCC) cases were identified in patients with cardio-metabolic risk factors with or without hepatic steatosis on ultrasound. However, screening for HCC in individuals without cirrhosis or viral hepatitis has limited effectiveness and may lead to unnecessary tests. The fibrosis-4 score, a non-invasive index, may have a potential role on HCC screening by identifying high risk group with metabolic risk factors or hepatic steatosis.

Supplementary information

Table S1. Baseline characteristics of the population strata of the four groups[†]

	G1		G2		G3		G4	
	No HCC	HCC	No HCC	HCC	No HCC	HCC	No HCC	HCC
	(n = 113,654)	(n = 2)	(n = 105,794)	(n = 10)	(n = 111,373)	(n = 10)	(n = 9,911)	(n = 71)
Age, years	40.4 (8.8)	58.4 (12.0)	44.0 (10.6)	61.8 (11.2)	44.8 (9.5)	56.4 (12.3)	45.1 (9.1)	51.3 (7.7)
Male (%)	25.8	50.0	60.3	70.0	77.5	80.0	59.7	83.1
Current smoker (%)	8.8	0.0	17.9	40.0	23.5	55.6	19.4	40.3
Alcohol consumption (%)	11.9	50.0	24.2	50.0	26.3	44.4	19.4	33.9
Diabetes mellitus (%)	0.0	0.0	5.7	40.0	12.7	40.0	6.2	22.5
Prediabetes (%)	18.5	50.0	48.2	85.7	61.7	77.8	40.6	51.7
Hypertension (%)	2.0	0.0	14.0	60.0	19.4	50.0	13.4	26.8
Elevated BP (%)	3.3	0.0	21.7	70.0	29.8	50.0	19.9	32.4
Lipid-lowering medication (%)	1.8	0.0	6.2	10.0	8.7	10.0	4.7	4.2
Obesity (%)	0.0	0.0	35.0	40.0	63.9	80.0	34.3	49.3
BMI (kg/m^2)	20.5 (1.6)	21.9 (1.2)	24.4 (2.3)	24.5 (1.2)	26.4 (3.3)	26.2 (2.1)	23.9 (3.4)	25.1 (3.3)

Waist circumference (cm)	72.8 (5.6)	79.4 (5.8)	83.8 (6.6)	87.8 (7.3)	89.8 (8.2)	91.5 (8.2)	83.1 (9.8)	87.7 (9.7)
Fasting glucose (mg/dL)	91.6 (7.2)	94.5 (4.9)	98.5 (14.6)	119.5 (18.8)	104.5 (21.4)	109.8 (17.8)	98.2 (17.7)	112.1 (33.1)
HbA1c (%)	5.4 (0.3)	5.7 (0.1)	5.5 (0.5)	6.1 (0.9)	5.8 (0.8)	6.0 (0.7)	5.5 (0.6)	6.0 (1.4)
HOMA-IR	1.1 (0.7–1.5)	1.0 (0.7–1.3)	1.5 (1.0–2.1)	2.2 (1.3–5.8)	2.2 (1.5–3.2)	2.6 (1.8–3.1)	1.7 (1.1–2.5)	2.4 (1.7–3.6)
Total cholesterol (mg/dL)	184.8 (30.8)	205.0 (31.1)	191.3 (34.2)	162.5 (7.7)	198.8 (37.4)	161.7 (27.6)	186.8 (33.5)	179.0 (32.8)
LDL-C (mg/dL)	116.2 (29.6)	122.5 (29.0)	127.6 (32.6)	105.4 (8.1)	136.0 (34.9)	97.9 (21.8)	123.7 (31.7)	113.7 (28.2)
Triglycerides (mg/dL)	71 (55–93)	74 (64–83)	99 (72–141)	99 (84–120)	141 (102–199)	116 (93–146)	90 (67–128)	91 (64–125)
HDL-C (mg/dL)	69.6 (15.1)	66.5 (4.9)	58.5 (14.4)	50.2 (13.4)	50.3 (12.0)	49.6 (9.3)	58.7 (15.6)	56.0 (17.3)
Systolic BP (mmHg)	102.8 (10.0)	91.5 (3.5)	112.5 (12.2)	121.8 (16.1)	116.1 (12.1)	113.0 (17.6)	110.9 (13.1)	112.0 (11.6)
Diastolic BP (mmHg)	66.1 (8.0)	65 (4.2)	72.0 (9.6)	71.7 (10.8)	75.3 (9.4)	71.3 (9.3)	71.5 (10.1)	73.1 (10.0)
ALT (IU/L)	14 (11–18)	15 (13–17)	18 (14–25)	25 (19–36)	29 (20–43)	36 (26–45)	23 (17–33)	35 (25–59)
AFP (ng/mL)	2.4 (1.7–3.5)	1.9 (1.3–2.6)	2.6 (1.8–3.6)	4.3 (2.2–7.5)	2.6 (1.9–3.5)	5.1 (4.4–378.5)	2.3 (1.7–3.3)	9.5 (3.9–78.0)
Liver nodule/tumor (%)	4.7	50.0	4.1	50.0	4.1	70.0	6.4	50.7
FIB-4 score[‡] (%)								
Low	91.0	50.0	87.0	40.0	89.2	40.0	75.6	21.1

Intermediate	8.7	50.0	12.4	30.0	10.2	40.0	21.9	36.6
High	0.3	0.0	0.6	30.0	0.7	20.0	2.5	42.3

Data are expressed as mean (Standard Deviation), median (interquartile range), or percentage.

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; BP, blood pressure; BMI, body mass index; FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; LDL-C, low-density lipoprotein cholesterol.

[†]Participants were categorized into four groups: normal group (G1), metabolic risk factor group without fatty liver disease on ultrasound (G2), fatty liver disease on ultrasound group (G3), and viral liver disease or liver cirrhosis group (G4). Metabolic risk factor group were defined as those having two or more of the following condition: waist circumference ≥90 cm (men) or ≥85 cm (women), serum triglycerides ≥150 mg/dL or receiving treatment, serum high-density lipoprotein <40 mg/dL (men) or <50 mg/dL (women), BP ≥130/85 mmHg or taking BP-lowering drugs, prediabetes (fasting glucose 100–125 mg/dL [5.6–6.9 mmol/L] or HbA1c 5.7–6.4% [39–46 mmol/mol]), or HOMA-IR ≥2.5.

[‡]FIB-4 score cutoff values: <1.30 ("low risk"), 1.30–2.67 ("intermediate risk"), and ≥2.67 ("high risk").

Table S2. Comparison of receiver operating characteristic curves of individual and combination methods based on liver ultrasound, AFP, and FIB-4

	AUROC	95% CI	*P* value AFP vs other	USG vs other	FIB-4 vs other	AFP+FIB-4 vs other	AFP+USG vs other	FIB-4+USG vs other	FIB-4+USG+FIB-4 vs other
Total population (n = 340,825; HCC cases [n = 93])									
AFP	0.84	0.80–0.89	Ref.	0.002	0.035	<0.001	0.002	0.004	<0.001
USG	0.74	0.69–0.79	0.002	Ref.	<0.001	<0.001	<0.001	<0.001	<0.001
FIB-4	0.90	0.87–0.98	0.035	<0.001	Ref.	<0.001	0.706	0.108	0.001
AFP+FIB-4	0.94	0.92–0.97	<0.001	<0.001	<0.001	Ref.	0.033	0.210	0.318
AFP+USG	0.89	0.85–0.94	0.002	<0.001	0.706	0.033	Ref.	0.199	0.001
FIB-4+USG	0.92	0.90–0.95	0.004	<0.001	0.108	0.210	0.199	Ref.	0.004
AFP+USG+FIB-4	0.95	0.94–0.97	<0.001	<0.001	0.001	0.318	0.001	0.004	Ref.
Normal without metabolic risk factors or fatty liver (n = 113,656; HCC cases [n = 2])									
AFP	0.68	0.25–1.00	Ref.	0.927	0.437	0.137	0.393	0.497	0.338
USG	0.73	0.24–1.00	0.927	Ref.	0.303	0.913	0.319	0.251	0.303
FIB-4	0.91	0.77–1.00	0.437	0.303	Ref.	0.551	0.537	0.709	0.299

	AUC	95% CI	AFP	USG	FIB-4	AFP+FIB-4	AFP+USG	FIB-4+USG	AFP+USG+FIB-4
AFP+FIB-4	0.77	0.45–1.00	0.137	0.913	0.551	Ref.	0.495	0.621	0.420
AFP+USG	0.92	0.81–1.00	0.393	0.319	0.537	0.495	Ref.	0.645	0.190
FIB-4+USG	0.90	0.71–1.00	0.497	0.251	0.709	0.621	0.645	Ref.	0.485
AFP+USG+FIB-4	0.93	0.85–1.00	0.338	0.303	0.299	0.420	0.190	0.485	Ref.

Two or more metabolic risk factors (n = 105,804; HCC cases [n = 10])

	AUC	95% CI	AFP	USG	FIB-4	AFP+FIB-4	AFP+USG	FIB-4+USG	AFP+USG+FIB-4
AFP	0.68	0.47–0.88	Ref.	0.544	0.011	0.008	0.319	0.003	0.003
USG	0.73	0.57–0.89	0.544	Ref.	0.085	0.088	0.908	0.002	0.002
FIB-4	0.9	0.81–0.98	0.011	0.085	Ref.	0.721	0.138	0.388	0.441
AFP+FIB-4	0.89	0.80–0.98	0.008	0.088	0.721	Ref.	0.139	0.367	0.414
AFP+USG	0.74	0.53–0.94	0.319	0.908	0.138	0.139	Ref.	0.017	0.017
FIB-4+USG	0.93	0.87–0.99	0.003	0.002	0.388	0.367	0.017	Ref.	0.090
AFP+USG+FIB-4	0.93	0.87–0.99	0.003	0.002	0.441	0.414	0.017	0.090	Ref.

Fatty liver on ultrasound (n = 111,383; HCC cases [n = 10])

	AUC	95% CI	AFP	USG	FIB-4	AFP+FIB-4	AFP+USG	FIB-4+USG	AFP+USG+FIB-4
AFP	0.90	0.84–0.97	Ref.	0.297	0.372	0.232	0.079	0.523	0.003
USG	0.83	0.68–0.98	0.297	Ref.	0.879	0.138	0.042	0.051	0.027
FIB-4	0.81	0.64–0.98	0.372	0.879	Ref.	0.034	0.193	0.143	0.065
AFP+FIB-4	0.95	0.89–1.00	0.232	0.138	0.034	Ref.	0.877	0.781	0.353
AFP+USG	0.94	0.87–1.00	0.079	0.042	0.193	0.877	Ref.	0.888	0.154
FIB-4+USG	0.94	0.86–1.00	0.523	0.051	0.143	0.781	0.888	Ref.	0.300

	AUROC	95% CI	AFP	USG	FIB4	AFP+FIB4	AFP+USG	FIB4+USG	AFP+USG+FIB4
AFP+USG+FIB-4	0.98	0.95–1.00	0.003	0.027	0.065	0.353	0.154	0.300	Ref.
Viral liver disease or liver cirrhosis (n = 9,982; HCC cases [n = 71])									
AFP	0.88	0.84–0.97	Ref.	<0.001	0.328	0.337	0.055	0.77	0.176
USG	0.72	0.66–0.78	<0.001	Ref.	<0.001	<0.001	<0.001	<0.001	<0.001
FIB4	0.85	0.81–0.90	0.328	<0.001	Ref.	<0.001	0.039	0.109	<0.001
AFP+FIB4	0.91	0.87–0.94	0.337	<0.001	<0.001	Ref.	0.705	0.100	0.236
AFP+USG	0.92	0.88–0.95	0.055	<0.001	0.039	0.705	Ref.	0.131	0.836
FIB4+USG	0.87	0.83–0.92	0.770	<0.001	0.109	0.100	0.131	Ref.	0.003
AFP+USG+FIB4	0.92	0.89–0.95	0.176	<0.001	<0.001	0.236	0.836	0.003	Ref.

AFP, alpha-fetoprotein; AUROC, area under the receiver operating characteristic curve; FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; Ref., reference; USG, ultrasound.

Table S3. Comparison of the screening performance of liver ultrasound and AFP[†] in detecting HCC stratified by FIB-4 score[‡] among the group 3[§] with and without excessive alcohol consumption

	Overall	Low FIB-4	Intermediate FIB-4	High FIB-4
G3				
Alcohol intake < 40 g/day				
Participants (n)	92,071	83,157	8429	491
HCC cases (n)	6	3	2	1
Sensitivity (95% CI)	100.0 (54.1–100)	100.0 (29.2–100)	100.0 (15.8–100)	100.0 (2.5–100)
Specificity (95% CI)	95.8 (95.7–95.9)	95.8 (95.6–95.9)	96.3 (95.9–96.7)	94.9 (92.6–96.7)
AUROC (95% CI)	0.98 (0.98–0.98)	0.98 (0.98–0.98)	0.98 (0.98–0.98)	0.97 (- –1.0)
PPV (95% CI)	0.16 (0.06–0.34)	0.08 (0.02–0.25)	0.64 (0.08–2.3)	3.9 (0.1–19.6)
NPV (95% CI)	100 (100–100)	100 (100–100)	100.0 (100-100)	100 (99.5–100)
Alcohol intake ≥ 40 g/day				
Participants (n)	12,280	10342	1754	184
HCC cases (n)	3	1	1	1
Sensitivity (95% CI)	66.7 (9.4-99.2)	100.0 (2.5–100)	0 (-–97.5)	100.0 (2.5–100)
Specificity (95% CI)	95.9 (95.6–96.3)	95.9 (95.5–96.2)	96.3 (95.3–97.1)	95.6 (91.6–98.1)
AUROC (95% CI)	0.81 (0.49 –1.0)	0.98 (- –1.0)	0.48 (- –1.0)	0.98 (- –1.0)
PPV (95% CI)	0.40 (0.05–1.43)	0.23 (0.01–1.29)	0 (0–5.5)	11.1 (0.3–48.2)
NPV (95% CI)	100 (100–100)	100 (100–100)	99.9 (99.7–100)	99.9 (97.9–100)

Abbreviations: AFP, alpha-fetoprotein; AUROC, area under the receiver operating characteristic curve; BP, blood pressure; CI, confidence interval; FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; HOMA-IR, homeostatic model assessment for insulin resistance; NPV, negative predictive value; PPV, positive predictive value.

[†]AFP cutoff value: 20 ng/mL.

[‡]FIB-4 score cutoff values: <1.30 ("low risk"), 1.30–2.67 ("intermediate risk"), and ≥2.67 ("high risk").

[§] G3 indicates refers to individuals diagnosed fatty liver disease on ultrasound group (G3).

	Overall	G1	G2	G3	G4
Cutoff-values	1.283	1.114	1.05	1.009	1.291
Participants (n)	340,825	113,656	105,804	111,383	9,982
HCC cases (n)	93	2	10	10	71
Sensitivity (95% CI)	78.5 (68.8–86.3)	100 (15.8-100)	90 (55.5-99.7)	80 (44.4-97.5)	83.1 (72.3-91.0)
Specificity (95% CI)	88.2 (88.1–88.3)	84 (83.8-84.2)	75.3 (75-75.6)	75.5 (75.3-75.8)	75.2 (74.4-76.1)
AUROC (95% CI)	0.83 (0.79–0.88)	0.92 (0.92-0.92)	0.83 (0.73-0.93)	0.78 (0.65-0.91)	0.79 (0.75-0.84)
PPV (95% CI)	0.18 (0.14–0.23)	0.01 (0.01-0.04)	0.03 (0.02-0.07)	0.03 (0.01-0.06)	2.35 (1.79-3.02)
NPV (95% CI)	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)	99.8 (99.7-99.9)

Abbreviations: AUROC, area under the receiver operating characteristic curve; BP, blood pressure; CI, confidence interval; HCC, hepatocellular carcinoma; HOMA-IR, homeostatic model assessment for insulin resistance; NPV, negative predictive value; PPV, positive predictive value.

[†]Participants were categorized into four groups: normal group (G1), metabolic risk factor group without fatty liver disease on ultrasound (G2), fatty liver disease on ultrasound group (G3), and viral liver disease or liver cirrhosis group (G4). Metabolic risk factor group were defined as those having two or more of the following condition: waist circumference ≥90 cm (men) or ≥85 cm (women), serum triglycerides ≥150 mg/dL or receiving treatment, serum high-density lipoprotein <40 mg/dL (men) or <50 mg/dL (women), BP ≥130/85 mmHg or taking BP-lowering drugs, prediabetes (fasting glucose 100–125 mg/dL [5.6–6.9 mmol/L] or HbA1c 5.7–6.4% [39–46 mmol/mol]), or HOMA-IR ≥2.5.

Table S5. Determining the optimal fibrosis-4 score cutoff value for predicting hepatocellular carcinoma in the study population[†]

	Cut-off values of fibrosis-4 score	AUROC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Overall						
	1.30	0.82 (0.77-0.86)	74.2 (64.1-82.7)	88.7 (88.6-88.8)	0.18 (0.14-0.23)	100 (100-100)
	1.77	0.76 (0.71-0.81)	55.9 (45.2-66.2)	96.6 (96.5-96.6)	0.45 (0.33-0.58)	100 (100-100)
	2.50	0.7 (0.65-0.75)	40.9 (30.8-51.5)	99.2 (99.2-99.3)	1.42 (1.01-1.94)	100 (100-100)
	2.67	0.69 (0.64-0.74)	37.6 (27.8-48.3)	99.4 (99.4-99.4)	1.71 (1.19-2.37)	100 (100-100)
	3.25	0.62 (0.58-0.67)	24.7 (16.4-34.8)	99.7 (99.7-99.7)	2.29 (1.46-3.41)	100 (100-100)
G1	1.30	0.71 (0.22-1.00)	50 (1.3-98.7)	91 (90.9-91.2)	0.01 (0.00-0.05)	100 (100-100)
	1.77	0.74 (0.25-1.00)	50 (1.3-98.7)	97.6 (97.5-97.7)	0.04 (0.00-0.21)	100 (100-100)
	2.50	0.50 (0.50-0.50)	0 (0-84.2)	96.6 (96.5-96.6)	0 (0-0.72)	100 (100-100)
	2.67	0.50 (0.50-0.50)	0 (0-84.2)	96.7 (96.7-96.7)	0 (0-1.04)	100 (100-100)
	3.25	0.50 (0.50-0.50)	0 (0-84.2)	96.8 (96.8-96.8)	0 (0-2.07)	100 (100-100)
G2	1.30	0.74 (0.58-0.90)	60 (26.2-87.8)	87 (86.8-87.2)	0.04 (0.02-0.10)	100 (100-100)
	1.77	0.73 (0.57-0.89)	50 (18.7-81.3)	95.9 (95.8-96.1)	0.12 (0.04-0.27)	100 (100-100)
	2.50	0.75 (0.58-0.91)	50 (18.7-81.3)	99.2 (99.1-99.2)	0.56 (0.18-1.29)	100 (100-100)
	2.67	0.65 (0.50-0.80)	30 (6.7-65.2)	99.4 (99.3-99.4)	0.45 (0.09-1.3)	100 (100-100)
	3.25	0.65 (0.50-0.80)	30 (6.7-65.2)	99.7 (99.7-99.7)	0.97 (0.20-2.82)	100 (100-100)
G3	1.30	0.75 (0.59-0.91)	60 (26.2-87.8)	89.2 (89.0-89.4)	0.05 (0.02-0.11)	100 (100-100)
	1.77	0.63 (0.48-0.78)	30.0 (6.7-65.2)	96.7 (96.6-96.8)	0.08 (0.02-0.24)	100 (100-100)
	2.50	0.60 (0.47-0.73)	20.0 (2.5-55.6)	99.2 (99.1-99.2)	0.21 (0.03-0.77)	100 (100-100)
	2.67	0.60 (0.47-0.73)	20.0 (2.5-55.6)	99.3 (99.3-99.4)	0.27 (0.03-0.97)	100 (100-100)
	3.25	0.55 (0.45-0.65)	10.0 (0.3-44.5)	99.7 (99.6-99.7)	0.27 (0.01-1.5)	100 (100-100)
G4	1.30	0.77 (0.73-0.82)	78.9 (67.6-87.7)	75.6 (74.7-76.5)	2.26 (1.71-2.92)	99.8 (99.7-99.9)
	1.77	0.76 (0.70-0.81)	60.6 (48.3-72)	90.5 (89.9-91)	4.35 (3.16-5.81)	99.7 (99.6-99.8)
	2.50	0.79 (0.65-0.76)	43.7 (31.9-56)	97 (96.6-97.3)	9.34 (6.43-13)	99.6 (99.4-99.7)
	2.67	0.70 (0.64-0.76)	42.3 (30.6-54.6)	97.5 (97.1-97.8)	10.6 (7.3-14.8)	99.6 (99.4-99.7)
	3.25	0.63 (0.58-0.68)	26.8 (16.9-38.6)	98.6 (98.4-98.9)	12.4 (7.64-18.7)	99.5 (99.3-99.6)

Abbreviations: AUROC, area under the receiver operating characteristic curve; BP, blood pressure; CI, confidence interval; FIB-4, fibrosis-4 score; HOMA-IR, homeostatic model assessment for insulin resistance; NPV, negative predictive value; PPV, positive predictive value.

†Participants were categorized into four groups: normal group (G1), metabolic risk factor group without fatty liver disease on ultrasound (G2), fatty liver disease on ultrasound group (G3), and viral liver disease or liver cirrhosis group (G4). Metabolic risk factor group were defined as those having two or more of the following condition: waist circumference ≥90 cm (men) or ≥85 cm (women), serum triglycerides ≥150 mg/dL or receiving treatment, serum high-density lipoprotein <40 mg/dL (men) or <50 mg/dL (women), BP ≥130/85 mmHg or taking BP-lowering drugs, prediabetes (fasting glucose 100–125 mg/dL [5.6–6.9 mmol/L] or HbA1c 5.7–6.4% [39–46 mmol/mol]), or HOMA-IR ≥2.5.

	Overall	G1	G2	G3	G4
Cutoff-values	3.25	3.25	3.25	3.25	3.25
Participants[†] (n)	340,825	113,656	105,804	111,383	9,982
HCC cases (n)	93	2	10	10	71
Sensitivity (95% CI)	24.7 (16.4-34.8)	0 (0-84.2)	30 (6.7-65.2)	10 (0.3-44.5)	26.8 (16.9-38.6)
Specificity (95% CI)	99.7 (99.7-99.7)	99.8 (99.8-99.9)	99.7 (99.7-99.7)	99.7 (99.7-99.7)	98.6 (98.4-98.9)
AUROC (95% CI)	0.62 (0.58–0.67)	0.50 (0.50-0.50)	0.65 (0.50–0.80)	0.55 (0.45-0.65)	0.63 (0.58-0.68)
PPV (95% CI)	2.29 (1.46–3.41)	0.0 (0.0-2.07)	0.97 (0.01-2.82)	0.27 (0.01-1.5)	12.4 (7.64-18.7)
NPV (95% CI)	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)	99.5 (99.3-99.6)

Abbreviations: AUROC, area under the receiver operating characteristic curve; BP, blood pressure; CI, confidence interval; HCC, hepatocellular carcinoma; HOMA-IR, homeostatic model assessment for insulin resistance; NPV, negative predictive value; PPV, positive predictive value.

[†]Participants were categorized into four groups: normal group (G1), metabolic risk factor group without fatty liver disease on ultrasound (G2), fatty liver disease on ultrasound group (G3), and viral liver disease or liver cirrhosis group (G4). Metabolic risk factor group were defined as those having two or more of the following condition: waist circumference ≥90 cm (men) or ≥85 cm (women), serum triglycerides ≥150 mg/dL or receiving treatment, serum high-density lipoprotein <40 mg/dL (men) or <50 mg/dL (women), BP ≥130/85 mmHg or taking BP-lowering drugs, prediabetes (fasting glucose 100–125 mg/dL [5.6–6.9 mmol/L] or HbA1c 5.7–6.4% [39–46 mmol/mol]), or HOMA-IR ≥2.5.

Table S6. Receiver operating characteristic curves of fibrosis-4 score according to the alcohol drinking status

Characteristic	AUROC	95% CI
All		
<20 g/day for women; <30 g/day for men	0.899	0.856-0.942
20-<50g/day for women; 30-<60 g/day for men	0.931	0.881-0.982
≥50 g/day for women; ≥60 g/day for men	0.909	0.783-1.000

Abbreviations: AUROC, area under the receiver operating characteristic curve; CI, confidence interval.

Table S7. Receiver operating characteristic curves of fibrosis-4 score for predicting breast cancer or colorectal cancer

Characteristic	AUROC	95% CI
All		
Breast cancer	0.602	0.577-0.627
Colorectal cancer	0.672	0.608-0.737

Abbreviations: AUROC, area under the receiver operating characteristic curve; CI, confidence interval.

Breast cancer was defined as invasive cancer (ICD-10 code C50) or ductal carcinoma in situ (ICD-10 code D05.1). Colorectal cancer was defined as ICD-10 code C18–C20.

	Breast cancer	Colorectal cancer
Cutoff-values	0.694	0.968
Participants (n)	152,317	339,980
Cancer cases (n)	392	149
Sensitivity (95% CI)	72.7 (68.0–77.1)	57.7 (49.4-65.8)
Specificity (95% CI)	44.0 (43.8–44.3)	71.8 (71.7-72)
AUROC (95% CI)	0.58 (0.56–0.61)	0.65 (0.61-0.69)
PPV (95% CI)	0.33 (0.30–0.38)	0.09 (0.07-0.11)
NPV (95% CI)	99.8 (99.8-99.9)	100 (100-100)

Abbreviations: AUROC, area under the receiver operating characteristic curve; NPV, negative predictive value; PPV, positive predictive value.

FIB-4 score categories	Range of FIB-4 score	No of participants	No of cases	Prevalence Per 1000 persons	Crude OR (95% CI)	Age-adjusted OR[†] (95% CI)
Breast cancer in women						
FIB4 quartile 1	0.09-0.57	38577	43	1.12	1.00 (reference)	1.00 (reference)
FIB4 quartile 2	0.57-0.74	38578	100	2.61	2.34 (1.63-3.34)	1.97 (1.37-2.83)
FIB4 quartile 3	0.74-0.98	38576	120	3.15	2.83 (1.99-4.00)	2.02 (1.4-2.92)
FIB4 quartile 4	0.98-27.76	38576	129	3.44	3.08 (2.18-4.35)	1.59 (1.04-2.41)
Colorectal cancer						
Women						
FIB4 quartile 1	0.09-0.57	38,554	5	0.13	1.00 (reference)	1.00 (reference)
FIB4 quartile 2	0.57-0.74	38,538	12	0.31	2.4 (0.85-6.82)	1.67 (0.58-4.78)
FIB4 quartile 3	0.74-0.98	38,489	13	0.34	2.6 (0.93-7.31)	1.25 (0.43-3.66)
FIB4 quartile 4	0.98-27.76	38,428	32	0.83	6.43 (2.5-16.49)	1.47 (0.48-4.49)
Men						
FIB4 quartile 1	0.15-0.59	46,594	13	0.28	1.00 (reference)	1.00 (reference)
FIB4 quartile 2	0.59-0.77	46,543	9	0.19	0.69 (0.3-1.62)	0.43 (0.18-1.01)
FIB4 quartile 3	0.77-1.03	46,523	19	0.41	1.46 (0.72-2.96)	0.56 (0.26-1.18)
FIB4 quartile 4	1.03-44.02	46,311	46	0.99	3.56 (1.92-6.59)	0.56 (0.25-1.27)

Abbreviations: CI, confidence interval; FIB-4 score, fibrosis-4 score; OR, odds ratio.

[†]Estimated from Cox proportional hazard models.

November 15, 2023

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Editor-in-Chief, Hepatology Research

Dear Editor,

We would like to sincerely thank you for considering our manuscript **"Potential role of Fibrosis-4 Score in Hepatocellular Carcinoma Screening: The Kangbuk Samsung Health Study"**. We would also like to thank the reviewer for through review of our manuscript and insightful, constructive comments.

We have addressed all the reviewer's comments. In the pages below, we have provided a detailed description of modifications to the manuscript in response to the reviewer's comments. Changes in the manuscript are highlighted for added sentences in the revised version. We believe that the manuscript has improved substantially in this process, and we hope that it will be acceptable for the Journal.

There are no conflicts of interest to declare, and all authors have participated in this work and have read and approved this manuscript. This paper is an original article that has not been published, and has not been submitted for publication elsewhere.

Thank you for your consideration. We look forward to hearing from you in due course.

Sincerely yours,

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AE COMMENTS:

1.   You are encouraged to include these files below for revision:

- Lay Summary [page 5]

- Graphical Abstract [page 6]

Response. We would like to express our sincere gratitude for the editorial board's interest in our manuscript. Following your recommendation, we have added a Lay Summary and a Graphical Abstract as follows:

"**Lay summary** (page 5)

More than 21% of Hepatocellular Carcinoma (HCC) cases were identified in patients with cardio-metabolic risk factors with or without hepatic steatosis on ultrasound. However, screening for HCC in individuals without cirrhosis or viral hepatitis has limited effectiveness and may lead to unnecessary tests. The fibrosis-4 score, a non-invasive index, may have a potential role on HCC screening by identifying high risk group with metabolic risk factors or hepatic steatosis."

"**Graphical Abstract** (page 6) – *attached separately.*"

Potential role of Fibrosis-4 (FIB-4) Score in Hepatocellular Carcinoma (HCC) Screening

Participants: Adults who underwent routine health screening exam

N = 340,825 (male 54.7%)
Mean age: 43.1± 9.8 years

Group category
- Group 1: Normal (control group)
- Group 2: Metabolic risk factors without hepatic steatosis
- Group 3: Hepatic steatosis on ultrasound
- Group 4: Viral liver disease or liver cirrhosis

Hepatocellular carcinoma (HCC)
: diagnosed from the *National Cancer Registry data* between 2011 and Dec 2019

Diagnostic accuracy of liver ultrasound + alpha-fetoprotein on HCC

		Low FIB-4 (<1.30)	High FIB-4 (>2.67)
Group 1	AUROC	0.48 (NA-1.00)	-
	PPV	0.00 (0.00-0.08)	-
	NPV	100.0 (100-100)	-
Group 2	AUROC	0.73 (0.45-1.00)	0.81 (0.48-1.00)
	PPV	0.05 (0.01-0.19)	5.10 (0.60-17.3)
	NPV	100.0 (100-100)	99.8 (99.1-100)
Group 3	AUROC	0.98 (0.98-0.98)	0.98 (0.97-0.99)
	PPV	0.09 (0.03-0.24)	5.60 (0.70-18.7)
	NPV	100.0 (100-100)	100.0 (99.5-100)
Group 4	AUROC	0.74 (0.61-0.87)	0.75 (0.67-0.84)
	PPV	1.80 (0.77-3.47)	28.3 (17.5-41.4)
	NPV	99.8 (99.8-100)	95.6 (91.1-98.2)

- **More than 21% of HCC cases** were identified in patients with **cardio-metabolic risk factors with or without hepatic steatosis on ultrasound.**
- **FIB-4 score** may have a **potential role on HCC screening by identifying high risk group** with metabolic risk factors or hepatic steatosis.

Reviewer #1:

Comments to the Author

The authors describe "Potential role of Fibrosis-4 Score in Hepatocellular Carcinoma Screening: The Kangbuk Samsung Health Study". The title is impressive, and this study results have potential usefulness in future medicine. However, some concerns should be addressed.

<u>Response.</u> We thank the reviewer for his/her supportive comments and have addressed her/his specific comments and suggestions below.

Major comments

First point: The authors categorize alcohol intake as <20g/day or ≥20g/day in this study. On the other hand, it must be said that this criterion is inadequate when considering the influence of alcohol in carcinogenesis. Other researchers have reported on the factor of alcohol in liver carcinogenesis in the context of fatty liver, and it has been found that the liver carcinogenesis rate tends to increase from an ethanol intake of 40 g/day or more. (for example, the following papers should be referred to and cited, Effects of Alcohol Consumption on Hepatocarcinogenesis in Japanese Patients With Fatty Liver Disease. Clin Gastroenterol Hepatol. 2016 Apr;14(4):597-605.) As it is stated in the methodology that alcohol intake was recorded in more detail in the present study. Therefore the author should analyze the hepatocarcinogenesis rates by alcohol intake in more detail. In other words, the G3 cases should be stratified by ethanol intake in more detail.

<u>Response.</u> We appreciate the reviewer for providing these valuable comments. We have addressed the comments and suggestions provided. First, we have incorporated stratified analysis for group 3 based on alcohol intake (differentiating between ethanol intake of <40 g/day and ≥40 g/day) in Supplementary Table 3 (Table S3). Furthermore, we have included the distribution of alcohol intake in the updated Table 1, along with corresponding adjustments to the methods and results sections to reflect these changes to incorporate the suggested reference. *Methods [page 9, paragraph 1]; Results [page 12, paragraph 2] [page 13, paragraph 2]; Table [page 27, Table 1]; Supplementary Information [page 7, Table S3]*

"Since it has been reported that the hepatocarcinogenesis in patients with fatty liver increases

when alcohol consumption exceeds 40g/day, additional analyses based on this specific alcohol intake were conducted in Group 3.[24,25]"

24.   Kawamura Y, Arase Y, Ikeda K, Akuta N, Kobayashi M, Saitoh S, et al. Effects of alcohol consumption on hepatocarcinogenesis in Japanese patients with fatty liver disease. Clinical Gastroenterology and Hepatology. 2016;14(4):597-605.

25.   McGlynn KA, Petrick JL, El-Serag HB. Epidemiology of hepatocellular carcinoma. Hepatology. 2021;73:4-13.

"Patients with HCC were more likely to be older, male, drink alcohol (with an average alcohol intake of 10g/day) and have a higher prevalence of FLD and other metabolic risk factors, including diabetes and hypertension."

TABLE 1 Baseline characteristics according to HCC diagnosis

Characteristic	No HCC (*n* = 340,732)	HCC (*n* = 93)	*p*-value
Average alcohol grams per day	4 (1-14)	10 (3-29)	<0.001
Alcohol intake ≥ 20 g/d (%)	20.7	37.2	<0.001
Alcohol intake ≥ 40 g/d (%)	9.0	19.8	<0.001

"Although we performed an additional analysis for the performance of combined conventional screening methods (USG and AFP) among the group 3 with and without excessive alcohol consumption stratified by FIB-4 score, the cases of HCC with advanced fibrosis were too small to evaluate a dose– response relationship between incident HCC and excessive alcohol consumption in patients with FLD (**Table S3**). Nevertheless, it is worth noting that the overall screening performance tends to be more favorable in Group 3 individuals who consume less than 40 grams of alcohol per day compared to those who exceed this threshold."

Table S3 Comparison of the screening performance of liver ultrasound and AFP[†] in detecting HCC stratified by FIB-4 score[‡] among the group 3 with and without excessive alcohol consumption[§]

	Overall	Low FIB-4	Intermediate FIB-4	High FIB-4
G3				
Alcohol intake < 40 g/day				
Participants (n)	92,071	83,157	8429	491
HCC cases (n)	6	3	2	1
Sensitivity (95% CI)	100.0 (54.1–100)	100.0 (29.2–100)	100.0 (15.8–100)	100.0 (2.5–100)
Specificity (95% CI)	95.8 (95.7–95.9)	95.8 (95.6–95.9)	96.3 (95.9–96.7)	94.9 (92.6–96.7)
AUROC (95% CI)	0.98 (0.98–0.98)	0.98 (0.98–0.98)	0.98 (0.98–0.98)	0.97 (- –1.0)
PPV (95% CI)	0.16 (0.06–0.34)	0.08 (0.02–0.25)	0.64 (0.08–2.3)	3.9 (0.1–19.6)
NPV (95% CI)	100 (100–100)	100 (100–100)	100.0 (100-100)	100 (99.5–100)
Alcohol intake ≥ 40 g/day				
Participants (n)	12,280	10342	1754	184
HCC cases (n)	3	1	1	1
Sensitivity (95% CI)	66.7 (9.4-99.2)	100.0 (2.5–100)	0 (-–97.5)	100.0 (2.5–100)
Specificity (95% CI)	95.9 (95.6–96.3)	95.9 (95.5–96.2)	96.3 (95.3–97.1)	95.6 (91.6–98.1)
AUROC (95% CI)	0.81 (0.49 –1.0)	0.98 (- –1.0)	0.48 (- –1.0)	0.98 (- –1.0)

PPV (95% CI)	0.40 (0.05–1.43)	0.23 (0.01–1.29)	0 (0–5.5)	11.1 (0.3–48.2)
NPV (95% CI)	100 (100–100)	100 (100–100)	99.9 (99.7–100)	99.9 (97.9–100)

Abbreviations: AFP, alpha-fetoprotein; AUROC, area under the receiver operating characteristic curve; BP, blood pressure; CI, confidence interval; FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; HOMA-IR, homeostatic model assessment for insulin resistance; NPV, negative predictive value; PPV, positive predictive value.

[†]AFP cutoff value: 20 ng/mL.

[‡]FIB-4 score cutoff values: <1.30 ("low risk"), 1.30–2.67 ("intermediate risk"), and ≥2.67 ("high risk").

[§]G3 indicates refers to individuals diagnosed fatty liver disease on ultrasound group (G3).

Comments to the Author

This manuscript indicated the usefulness of the Fib4 index for HCC diagnosis in a large cohort.

Advantages: large cohort study, AFP+US performed in all patients

Disadvantages: lack of fibrosis markers/elastography/biopsy data, short observation period of 12 months

1.   It has been reported that changing the cutoff value of Fib4 index was beneficial for the diagnosis of HCC (Cancers (Basel). 2019 Feb 10;11(2):203.). In the present study, does increasing the cutoff value of Fib4 index also increase the diagnostic ability of HCC?

Response. We appreciate the reviewer for providing these valuable comments. In the original manuscript, we initially employed a cutoff value for FIB4 to define the risk of advanced fibrosis as follows: <1.30 ("low risk"), 1.30–2.67 ("intermediate risk"), and ≥2.67 ("high-risk"), which aligns with the approach taken in most prior studies [1,2]. In response to the reviewer's insightful suggestion, we conducted an evaluation of the screening performance of FIB4 using a higher cutoff value in accordance with the reference [3,4]. Furthermore, we calculated cutoff values for predicting HCC both overall and within each group. The cutoff value was determined using the Youden index, which identifies the threshold that maximizes both sensitivity and 1-specificity for predicting HCC. In overall, all cutoff-values in both total and each group were lower than the cutoff-values for predicting advanced fibrosis. Our analysis determined a cutoff value of 1.28 for the FIB4 score in predicting HCC. These findings have been integrated into the method and result sections, as well as the Supplementary Table 4, 5 (Table S4, S5), and Supplementary Table R1 for comprehensive transparency and clarity.

Methods [page 10, paragraph 3] [page 12, paragraph 1]; Results [page 14, paragraph 2]; Supplementary Information [page 9, Table S4] [page 10, Table S5] [page 12, Supplementary Table R1]

"Additionally, based on previous research findings enhanced HCC diagnostic performance with increasing FIB-4 scores, we conducted an investigation to assess the results based on

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varying FIB-4 score cutoff values.[34-37]"

34.   Sumida Y, Yoneda M, Hyogo H, Itoh Y, Ono M, Fujii H, et al. Validation of the FIB4 index in a Japanese nonalcoholic fatty liver disease population. BMC gastroenterology. 2012;12:1-9.

35.   Kariyama K, Nouso K, Toyoda H, Tada T, Hiraoka A, Tsuji K, et al. Utility of FIB4-T as a prognostic factor for hepatocellular carcinoma. Cancers. 2019;11(2):203.

36.   Nouso K, Furubayashi Y, Shiota S, Miyake N, Oonishi A, Wakuta A, et al. Early detection of hepatocellular carcinoma in patients with diabetes mellitus. European Journal of Gastroenterology & Hepatology. 2020;32(7):877-81.

37.   Kim M, Lee Y, Yoon JS, Lee M, Kye SS, Kim SW, et al. The FIB-4 index is a useful predictor for the development of hepatocellular carcinoma in patients with coexisting nonalcoholic fatty liver disease and chronic hepatitis B. Cancers. 2021;13(10):2301.

"The cutoff value was determined using the Youden index, which identifies the threshold that maximizes both sensitivity and 1-specificity for predicting HCC."

"The cutoff values for predicting HCC using the FIB-4 score, both in the total population and within each group, were determined using the Youden index, and all of these determined values were lower than the cutoff values for predicting advanced fibrosis (**Table S4, S5**)."

TABLE S4. Screening performance of fibrosis-4 score cutoff-value determined using the Youden index both overall and within each group[†]

	Overall	G1	G2	G3	G4
Cutoff-values	1.283	1.114	1.05	1.009	1.291
Participants (n)	340,825	113,656	105,804	111,383	9,982
HCC cases (n)	93	2	10	10	71
Sensitivity (95% CI)	78.5 (68.8–86.3)	100 (15.8-100)	90 (55.5-99.7)	80 (44.4-97.5)	83.1 (72.3-91.0)
Specificity (95% CI)	88.2 (88.1–88.3)	84 (83.8-84.2)	75.3 (75-75.6)	75.5 (75.3-75.8)	75.2 (74.4-76.1)
AUROC (95% CI)	0.83 (0.79–0.88)	0.92 (0.92-0.92)	0.83 (0.73-0.93)	0.78 (0.65-0.91)	0.79 (0.75-0.84)
PPV (95% CI)	0.18 (0.14–0.23)	0.01 (0.01-0.04)	0.03 (0.02-0.07)	0.03 (0.01-0.06)	2.35 (1.79-3.02)
NPV (95% CI)	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)	99.8 (99.7-99.9)

Abbreviations: AUROC, area under the receiver operating characteristic curve; BP, blood pressure; CI, confidence interval; HCC, hepatocellular carcinoma; HOMA-IR, homeostatic model assessment for insulin resistance; NPV, negative predictive value; PPV, positive predictive value.

[†]Participants were categorized into four groups: normal group (G1), metabolic risk factor group without fatty liver disease on ultrasound (G2), fatty liver disease on ultrasound group (G3), and viral liver disease or liver cirrhosis group (G4). Metabolic risk factor group were defined as those having two or more of the following condition: waist circumference ≥90 cm (men) or ≥85 cm (women), serum triglycerides ≥150 mg/dL or receiving treatment, serum high-density lipoprotein <40 mg/dL (men) or <50 mg/dL (women), BP ≥130/85 mmHg or taking BP-lowering drugs, prediabetes (fasting glucose 100–125 mg/dL [5.6–6.9 mmol/L] or HbA1c 5.7–6.4% [39–46 mmol/mol]), or HOMA-IR ≥2.5.

TABLE S5. Determining the optimal fibrosis-4 score cutoff value for predicting hepatocellular carcinoma in the study population[†]

	Cut-off values of fibrosis-4 score	AUROC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Overall						
	1.30	0.82 (0.77-0.86)	74.2 (64.1-82.7)	88.7 (88.6-88.8)	0.18 (0.14-0.23)	100 (100-100)
	1.77	0.76 (0.71-0.81)	55.9 (45.2-66.2)	96.6 (96.5-96.6)	0.45 (0.33-0.58)	100 (100-100)
	2.50	0.7 (0.65-0.75)	40.9 (30.8-51.5)	99.2 (99.2-99.3)	1.42 (1.01-1.94)	100 (100-100)
	2.67	0.69 (0.64-0.74)	37.6 (27.8-48.3)	99.4 (99.4-99.4)	1.71 (1.19-2.37)	100 (100-100)
	3.25	0.62 (0.58-0.67)	24.7 (16.4-34.8)	99.7 (99.7-99.7)	2.29 (1.46-3.41)	100 (100-100)
G1	1.30	0.71 (0.22-1.00)	50 (1.3-98.7)	91 (90.9-91.2)	0.01 (0.00-0.05)	100 (100-100)
	1.77	0.74 (0.25-1.00)	50 (1.3-98.7)	97.6 (97.5-97.7)	0.04 (0.00-0.21)	100 (100-100)
	2.50	0.50 (0.50-0.50)	0 (0-84.2)	96.6 (96.5-96.6)	0 (0-0.72)	100 (100-100)
	2.67	0.50 (0.50-0.50)	0 (0-84.2)	96.7 (96.7-96.7)	0 (0-1.04)	100 (100-100)
	3.25	0.50 (0.50-0.50)	0 (0-84.2)	96.8 (96.8-96.8)	0 (0-2.07)	100 (100-100)
G2	1.30	0.74 (0.58-0.90)	60 (26.2-87.8)	87 (86.8-87.2)	0.04 (0.02-0.10)	100 (100-100)
	1.77	0.73 (0.57-0.89)	50 (18.7-81.3)	95.9 (95.8-96.1)	0.12 (0.04-0.27)	100 (100-100)
	2.50	0.75 (0.58-0.91)	50 (18.7-81.3)	99.2 (99.1-99.2)	0.56 (0.18-1.29)	100 (100-100)
	2.67	0.65 (0.50-0.80)	30 (6.7-65.2)	99.4 (99.3-99.4)	0.45 (0.09-1.3)	100 (100-100)
	3.25	0.65 (0.50-0.80)	30 (6.7-65.2)	99.7 (99.7-99.7)	0.97 (0.20-2.82)	100 (100-100)
G3	1.30	0.75 (0.59-0.91)	60 (26.2-87.8)	89.2 (89.0-89.4)	0.05 (0.02-0.11)	100 (100-100)
	1.77	0.63 (0.48-0.78)	30.0 (6.7-65.2)	96.7 (96.6-96.8)	0.08 (0.02-0.24)	100 (100-100)
	2.50	0.60 (0.47-0.73)	20.0 (2.5-55.6)	99.2 (99.1-99.2)	0.21 (0.03-0.77)	100 (100-100)
	2.67	0.60 (0.47-0.73)	20.0 (2.5-55.6)	99.3 (99.3-99.4)	0.27 (0.03-0.97)	100 (100-100)
	3.25	0.55 (0.45-0.65)	10.0 (0.3-44.5)	99.7 (99.6-99.7)	0.27 (0.01-1.5)	100 (100-100)
G4	1.30	0.77 (0.73-0.82)	78.9 (67.6-87.7)	75.6 (74.7-76.5)	2.26 (1.71-2.92)	99.8 (99.7-99.9)
	1.77	0.76 (0.70-0.81)	60.6 (48.3-72)	90.5 (89.9-91)	4.35 (3.16-5.81)	99.7 (99.6-99.8)
	2.50	0.79 (0.65-0.76)	43.7 (31.9-56)	97 (96.6-97.3)	9.34 (6.43-13)	99.6 (99.4-99.7)
	2.67	0.70 (0.64-0.76)	42.3 (30.6-54.6)	97.5 (97.1-97.8)	10.6 (7.3-14.8)	99.6 (99.4-99.7)
	3.25	0.63 (0.58-0.68)	26.8 (16.9-38.6)	98.6 (98.4-98.9)	12.4 (7.64-18.7)	99.5 (99.3-99.6)

Abbreviations: AUROC, area under the receiver operating characteristic curve; BP, blood pressure; CI, confidence interval; FIB-4, fibrosis-4 score; HOMA-IR, homeostatic model assessment for insulin resistance; NPV, negative predictive value; PPV, positive predictive value.

[†]Participants were categorized into four groups: normal group (G1), metabolic risk factor group without fatty liver disease on ultrasound (G2), fatty liver disease on ultrasound group (G3), and viral liver disease or liver cirrhosis group (G4). Metabolic risk factor group were defined as those having two or more of the following condition: waist circumference $\geq$90 cm (men) or $\geq$85 cm (women), serum triglycerides $\geq$150 mg/dL or receiving treatment, serum high-density lipoprotein <40 mg/dL (men) or <50 mg/dL (women), BP $\geq$130/85 mmHg or taking BP-lowering drugs, prediabetes (fasting glucose 100–125 mg/dL [5.6–6.9 mmol/L] or HbA1c 5.7–6.4% [39–46 mmol/mol]), or HOMA-IR $\geq$2.5.

Supplementary Table R1. The screening performance of the previously documented fibrosis-4 score cutoff value of 3.25.

	Overall	G1	G2	G3	G4
Cutoff-values	3.25	3.25	3.25	3.25	3.25
Participants[†] (n)	340,825	113,656	105,804	111,383	9,982
HCC cases (n)	93	2	10	10	71
Sensitivity (95% CI)	24.7 (16.4-34.8)	0 (0-84.2)	30 (6.7-65.2)	10 (0.3-44.5)	26.8 (16.9-38.6)
Specificity (95% CI)	99.7 (99.7-99.7)	99.8 (99.8-99.9)	99.7 (99.7-99.7)	99.7 (99.7-99.7)	98.6 (98.4-98.9)
AUROC (95% CI)	0.62 (0.58–0.67)	0.50 (0.50-0.50)	0.65 (0.50–0.80)	0.55 (0.45-0.65)	0.63 (0.58-0.68)
PPV (95% CI)	2.29 (1.46–3.41)	0.0 (0.0-2.07)	0.97 (0.01-2.82)	0.27 (0.01-1.5)	12.4 (7.64-18.7)
NPV (95% CI)	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)	99.5 (99.3-99.6)

Abbreviations: AUROC, area under the receiver operating characteristic curve; BP, blood pressure; CI, confidence interval; HCC, hepatocellular carcinoma; HOMA-IR, homeostatic model assessment for insulin resistance; NPV, negative predictive value; PPV, positive predictive value.

[†]Participants were categorized into four groups: normal group (G1), metabolic risk factor group without fatty liver disease on ultrasound (G2), fatty liver disease on ultrasound group (G3), and viral liver disease or liver cirrhosis group (G4). Metabolic risk factor group were defined as those having two or more of the following condition: waist circumference ≥90 cm (men) or ≥85 cm (women), serum triglycerides ≥150 mg/dL or receiving treatment, serum high-density lipoprotein <40 mg/dL (men) or <50 mg/dL (women), BP ≥130/85 mmHg or taking BP-lowering drugs, prediabetes (fasting glucose 100–125 mg/dL [5.6–6.9 mmol/L] or HbA1c 5.7–6.4% [39–46 mmol/mol]), or HOMA-IR ≥2.5.

2.   The Fib-4 index is affected by AST elevation due to alcohol consumption. That is, Fib4-index does not necessarily reflect fibrosis in a cohort that includes drinkers. Does stratification by alcohol volume change diagnostic performance?

Response. We appreciate the reviewer's valuable input. We've now included a stratified analysis based on alcohol intake (categorizing ethanol intake as <40 g/day and ≥40 g/day) in Supplementary Table 3 (Table S3) (addressed in response to reviewer #1's previous comment). Additionally, another cutoff for alcohol intake was determined in alignment with the recommended cutoff values outlined in the AASLD and EASL guidelines [5]. We have conducted analyses to evaluate the predictive utility of the FIB-4 index according to the alcohol drinking status in Supplementary Table 6 (Table S6). Furthermore, we have made corresponding adjustments to the methods and results sections to ensure that these changes are accurately reflected.

Methods [page 8, paragraph 2 & page 9, paragraph 1]; Results [page 14, paragraph 2]; Supplementary Information [page 13, Table S6]

"Additionally, we categorized alcohol intake in accordance with the recently proposed American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) guidelines as follows: for males, <30 g/day, 30-60 g/day, and >60 g/day, and for females, <20 g/day, 20-50 g/day, and >50 g/day.[23]"

23.   Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, et al. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. Annals of Hepatology. 2023:101133.

"Following the categorization of alcohol intake in accordance with the recently proposed AASLD/EASL guidelines, the AUROC values remained consistently high across different alcohol consumption categories, with all three groups showing values ranging from 0.899 to 0.931 (**Table S6**)."

Table S6. Receiver operating characteristic curves of fibrosis-4 score according to the alcohol drinking status

Characteristic	AUROC	95% CI
All		
<20 g/day for women; <30 g/day for men	0.899	0.856-0.942
20-<50g/day for women; 30-<60 g/day for men	0.931	0.881-0.982
≥50 g/day for women; ≥60 g/day for men	0.909	0.783-1.000

Abbreviations: AUROC, area under the receiver operating characteristic curve; CI, confidence interval.

3. Is the Fib4-index useful in the diagnosis of cancers other than HCC, such as colorectal cancer and breast cancer?

Response. We appreciate the reviewer's insightful comments. We have conducted analyses to evaluate the predictive utility of the FIB4-index for non-HCC cancers, including colorectal and breast cancers in Supplementary Table 7, 8, 9 (Table S7, S8, S9). Corresponding adjustments have been made to the methods and results sections to accurately incorporate these findings.

Methods [page 11, paragraph 3]; Results [page 14, paragraph 3 & page 15, paragraph 1]; Supplementary Information [page 14, Table S7] [page 15, Table S8] [page 16, Table S9]

"Furthermore, given prior research that reported the predictive utility of the FIB-4 score for non-HCC cancers,[42-44] we also conducted further investigations to assess the ability of the FIB-4 in predicting breast cancer and colorectal cancer."

42. Kamada Y, Munekage K, Nakahara T, Fujii H, Sawai Y, Doi Y, et al. The FIB-4 Index Predicts the Development of Liver-Related Events, Extrahepatic Cancers, and Coronary Vascular Disease in Patients with NAFLD. Nutrients. 2022;15(1):66.

43. Kobayashi D, Yamamoto K, Kimura T, Shimbo T. Aspartate aminotransferase/alanine aminotransferase ratio and subsequent cancer development. Cancer medicine. 2022;11(3):798-814.

44. Ito H, Kimura T, Takuro S, Higashitani M, Yamamoto K, Kobayashi D. Liver injury indicators and subsequent cancer development among non-fatty liver population. Cancer Medicine. 2023

"AUROC Based on FIB-4 score in non-HCC cancer screening

In the study cohort, there were 392 cases of breast cancer and 149 cases of colorectal cancer. For breast and colorectal cancers, the AUROC of the FIB-4 score was 0.60 (0.58-0.63) and 0.67 (0.61-0.74), respectively (**Table S7, S8**). **Table S9** shows the age-adjusted odds ratios (OR) of breast and colorectal cancer based on FIB-4 score quartiles. Compared with FIB-4 quartile

1 as the reference, FIB-4 quartiles 2, 3, and 4 were associated with a higher risk of breast cancer, with age-adjusted ORs (95% CIs) of 1.97 (1.34-2.83), 2.02 (1.40-2.92). and 1.59 (1.04-2.41), respectively. In the case of colorectal cancer, no statistically significant association were observed in both men and women."

Table S7. Receiver operating characteristic curves of fibrosis-4 score for predicting breast cancer or colorectal cancer

Characteristic	AUROC	95% CI
All		
Breast cancer	0.602	0.577-0.627
Colorectal cancer	0.672	0.608-0.737

Abbreviations: AUROC, area under the receiver operating characteristic curve; CI, confidence interval.

Breast cancer was defined as invasive cancer (ICD-10 code C50) or ductal carcinoma in situ (ICD-10 code D05.1). Colorectal cancer was defined as ICD-10 code C18–C20.

Table S8. Screening performance of fibrosis-4 score cutoff-value determined using the Youden index for predicting breast cancer and colorectal cancer

	Breast cancer	**Colorectal cancer**
Cutoff-values	0.694	0.968
Participants (n)	152,317	339,980
Cancer cases (n)	392	149
Sensitivity (95% CI)	72.7 (68.0–77.1)	57.7 (49.4-65.8)
Specificity (95% CI)	44.0 (43.8–44.3)	71.8 (71.7-72)
AUROC (95% CI)	0.58 (0.56–0.61)	0.65 (0.61-0.69)
PPV (95% CI)	0.33 (0.30–0.38)	0.09 (0.07-0.11)
NPV (95% CI)	99.8 (99.8-99.9)	100 (100-100)

Abbreviations: AUROC, area under the receiver operating characteristic curve; NPV, negative predictive value; PPV, positive predictive value.

Table S9. Breast cancer and colorectal cancer according to the fibrosis-4 score

FIB-4 score categories	Range of FIB-4 score	No of participants	No of cases	Prevalence Per 1000 persons	Crude OR (95% CI)	Age-adjusted OR[†] (95% CI)
Breast cancer in women						
FIB4 quartile 1	0.09-0.57	38577	43	1.12	1.00 (reference)	1.00 (reference)
FIB4 quartile 2	0.57-0.74	38578	100	2.61	2.34 (1.63-3.34)	1.97 (1.37-2.83)
FIB4 quartile 3	0.74-0.98	38576	120	3.15	2.83 (1.99-4.00)	2.02 (1.4-2.92)
FIB4 quartile 4	0.98-27.76	38576	129	3.44	3.08 (2.18-4.35)	1.59 (1.04-2.41)
Colorectal cancer						
Women						
FIB4 quartile 1	0.09-0.57	38,554	5	0.13	1.00 (reference)	1.00 (reference)
FIB4 quartile 2	0.57-0.74	38,538	12	0.31	2.4 (0.85-6.82)	1.67 (0.58-4.78)
FIB4 quartile 3	0.74-0.98	38,489	13	0.34	2.6 (0.93-7.31)	1.25 (0.43-3.66)
FIB4 quartile 4	0.98-27.76	38,428	32	0.83	6.43 (2.5-16.49)	1.47 (0.48-4.49)
Men						
FIB4 quartile 1	0.15-0.59	46,594	13	0.28	1.00 (reference)	1.00 (reference)
FIB4 quartile 2	0.59-0.77	46,543	9	0.19	0.69 (0.3-1.62)	0.43 (0.18-1.01)
FIB4 quartile 3	0.77-1.03	46,523	19	0.41	1.46 (0.72-2.96)	0.56 (0.26-1.18)
FIB4 quartile 4	1.03-44.02	46,311	46	0.99	3.56 (1.92-6.59)	0.56 (0.25-1.27)

Abbreviations: CI, confidence interval; FIB-4 score, fibrosis-4 score; OR, odds ratio.

[†]Estimated from Cox proportional hazard models.

References

[1]   Shah AG, Lydecker A, Murray K, et al. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. Clinical gastroenterology and hepatology 2009;7:1104-12.

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[3]   Sumida Y, Yoneda M, Hyogo H, et al. Validation of the FIB4 index in a Japanese nonalcoholic fatty liver disease population. BMC gastroenterology 2012;12:1-9.

[4]   Kariyama K, Nouso K, Toyoda H, et al. Utility of FIB4-T as a prognostic factor for hepatocellular carcinoma. Cancers 2019;11:203.

[5]   Rinella ME, Lazarus JV, Ratziu V, et al. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. Annals of Hepatology 2023:101133.