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ORIGINAL ARTICLE

Identification of risk groups for advanced liver fibrosis in the general population using the Fibrosis-3 index

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Author contribution: Takashi Kumada and Junko Tanaka were involved in the conceptualization of the study. Akemi Kurisu, Aya Sugiyama, Tomoyuki Akita, and Junko Tanaka were responsible for data curation. Takashi Kumada, Kazuhiro Nouso, Miwa Kawanaka, Akiko Wakuta, Shohei Shiota, and Junko Tanaka worked on the methodology. Kazuya Kariyama wrote the original draft. Kazuhiro Nouso handled the writing review and editing.

Abstract

Background and Aim: We conducted a study using the Fibrosis-3 (FIB-3) index, which is the established age-independent index of fibrosis in nonviral liver disease and addresses the limitations of the FIB-4 index in older age group, to assess the liver fibrosis risk among diverse demographic groups in the general population.
Methods: We analyzed 31 327 individuals who underwent health examinations between 2013 and 2020 and investigated the distribution of the FIB-3 index by age group. In addition, we examined the age distribution of the FIB-3 index stratified by background factors, such as sex, body mass index (BMI), alcohol consumption habits, and the presence or absence of fatty liver.
Results: In terms of age-specific distribution, the FIB-3 index remained below 1.5 in >90% of cases until the age of 50 years but exceeded 1.5 beyond the age of 50 years, in approximately 30% among those aged 70 years. Notably, the FIB-3 index above 31 years old was significantly higher in men than in women. Among the different BMI categories, individuals with BMI < 18.5 exhibited the highest prevalence of fibrosis. Habitual drinkers had a higher proportion with FIB-3. index ≥1.5, and some had FIB-3 index ≥2.5, raising the suspicion of advanced hepatic fibrosis. No distinct association was identified between the FIB-3 index and the presence of fatty liver.
Conclusions: The FIB-3 index was useful for identifying cases of advancing hepatic fibrosis in a health checkup population. Liver fibrosis progresses with age in the general population, especially among men, those with low BMI, and habitual drinkers.

Introduction

In recent years, successful elimination of hepatitis C virus (HCV) by direct-acting antiviral drugs (DAA) and good control of hepatitis B (HB) virus by nucleic acid analogs (NA) has reduced the incidence of problematic viral liver diseases but has led to an increase in nonviral liver diseases, especially metabolic liver diseases, such as metabolic dysfunction-associated steatotic liver disease, metabolic dysfunction-associated alcohol-related liver disease, and alcohol-related liver disease.[1–5] Unlike viral liver diseases, metabolic liver diseases are not regularly followed up, and at the time of diagnosis, liver fibrosis has often already progressed, with some cases even presenting with liver cirrhosis or advanced hepatocellular carcinoma (HCC).[6,7] Angulo *et al.* reported that among the histological findings in patients with non-alcoholic fatty liver disease (NAFLD), only liver fibrosis was associated with long-term mortality, liver transplantation, and liver-related events.[8]

However, identifying cases with progressive liver fibrosis on routine health check in the general population is a major challenge. Various imaging diagnostics, such as ultrasound, computed tomography, magnetic resonance imaging, FibroScan (Integral Corporation, Tokyo, Japan), and magnetic resonance elastography, have been reported as useful for identifying liver fibrosis progression.[9–13] However, implementing these tests as part of routine screening is impractical. Therefore, the ideal approach involves the use of noninvasive liver fibrosis prediction scores based on simple blood tests.

Although hyaluronic acid, type IV collagen 7S, Mac-2 Binding Protein Glycosylation isomer (M2BPGi), and autotaxin

are commonly used as noninvasive tests for liver fibrosis,[14–17] measuring these is not usually performed during health checkup of the general population and would be unrealistic in all subjects. The Fibrosis-4 (FIB-4) index has attracted attention for its higher diagnostic accuracy, compared with the other reported liver fibrosis indices that can be calculated from routine health checkup measurements, such as the aspartate aminotransferase/alanine aminotransferase (ALT) ratio and aspartate aminotransferase (AST) to platelet ratio index.[18–21] However, the FIB-4 index factors in age, which changes the optimal cutoff value and poses a significant problem.[22] In addition, in the general population of individuals who are considered to not have liver disease, the FIB-4 index is above the commonly used cutoff value of 1.3 in most elderly people, making it inaccurate for liver fibrosis screening.[23] To diagnose HCC early, a method that can noninvasively identify highly fibrotic cases in the general population is important to establish, but various problems have been identified in the existing scoring systems.

To address this issue, we developed the Fibrosis-3 (FIB-3) index, which excludes age as a factor and has been confirmed to predict the degree of liver fibrosis, regardless of age.[24]

The FIB-3 index as an indicator of fibrosis in nonviral liver disease was validated in two different cohorts in an original paper for its ability to predict liver fibrosis, with both cohorts showing comparable ability to predict liver fibrosis compared with the FIB-4 index, with fewer false positives and increased diagnostic accuracy in older people.[24] The age-independent validity of the FIB-3 index has also been validated in another large cohort study with similar results (in submission).

We have also introduced the mADRES score,[25] which replaces the FIB-4 index, a factor in the original ADRES score,[26] with the FIB-3 index. Original ADRES score has been reported to be useful in predicting carcinogenesis in post-HCV elimination cases. Our findings indicate that the mADRES score, which incorporates the FIB-3 index, further improves the predictive ability of the ADRES score, suggesting that the FIB-3 index is also valuable in predicting carcinogenesis in these cases.

In this study, we aimed to identify risk groups for advanced liver fibrosis in different demographic groups using the FIB-3 index, which predicts liver fibrosis with less age-related bias than the Fibrosis-4 index.

Methods

Data sources and clinical assessment. This study used a database of 208 279 individuals who underwent health checkup between 2013 and 2020 at the Foundation for Community Health and Medicine Promotion in Hiroshima Prefecture. Cases without data on AST/ ALT ($n = 11\,667$) and platelet ($n = 165\,122$) and those who were positive for HBsAg ($n = 118$) and HCV antibody ($n = 45$) were excluded, leaving 31 327 cases for analysis. Based on the medical interview, there were 7605 habitual drinkers (26.1%) and 404 cases with a history of liver disease (1.3%) (Fig. 1). Among the 15 511 cases who underwent abdominal ultrasound, fatty liver was detected in 4281 cases (27.6%). The other data extracted were body mass index (BMI), daily alcohol intake, and the presence of fatty liver on ultrasound. Biochemical tests were performed on venous

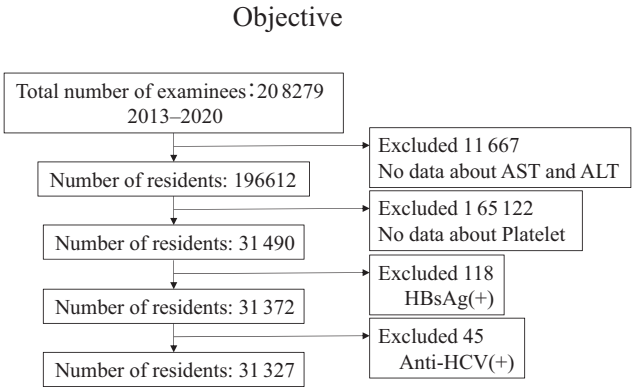

Figure 1 Procedure for selecting the study subjects. Flowchart of selecting the study subjects from the health checkup database in Hiroshima prefecture. After excluding a total of 208 279 individuals without aspartate aminotransferase, alanine aminotransferase, and platelet and those with negative HBsAg and hepatitis C virus antibody, 31 327 residents are included in this study.

blood samples obtained after fasting for ≥8 h. The FIB-3 and FIB-4 indices were computed using available parameters.[20,24]

The study protocol conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki and was approved by the institutional review board of Hiroshima University (approval number E-1989-1).

Distribution of the FIB-3 index by age. We investigated the distribution of the FIB-3 indices by age. In the original study, the FIB-3 index was established to be 1, 2, 3, and 4 for liver fibrosis stage 1, 2, 3, and 4, respectively. Therefore, the cutoff values used in this study were set at 1.5 for mild fibrosis and 2.5 for advanced fibrosis.[21] Using these cutoff values, we divided the subjects into three groups (Groups 1 [FIB-3 index <1.5], 2 [FIB-3 index ≥1.5 and <2.5], and 3 [FIB-3 index ≥ 2.5]) and examined the distribution of FIB-3 index by age (every 5 years).

Sex, BMI, alcohol consumption history, and the presence of fatty liver on ultrasound are involved in liver fibrosis; therefore, to elucidate the factors associated with liver fibrosis, we examined the age-specific distribution of the FIB-3 index (every 10 years) categorized by sex, BMI, and alcohol consumption habits, which are believed to impact liver fibrosis. In addition, for the 15 511 cases that had data on abdominal ultrasound findings, we investigated the age-specific distribution of the FIB-3 index based on the presence or absence of fatty liver (additionally, the age-specific FIB-3 index distribution according to HbA1c levels for diabetes is shown in Figure S2, supporting information). Habitual drinkers were defined as those who consume alcohol daily or those who consume 60 g or more of ethanol several times per week.

Statistical analysis. Continuous variables were presented as median and range or as mean and standard deviation. The Mann–Whitney *U*-test was used to compare the median values. Differences with p values of 0.05 were considered statistically significant. The Bonferroni correction was employed to address

the issue on multiplicity. Furthermore, chi-square tests were performed to assess the differences in FIB-3 index distribution across age groups. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan)[27] and a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).[28]

Results

Patient characteristics. Among the 31 327 individuals included in the study, the median age was 48 years; 23 314 (71.2%) were men, and the mean BMI was 23.2 kg/m^2. The prevalence of daily alcohol consumption was 32.0% (9348 cases), and 27.6% (4281 cases) had fatty liver on ultrasound (Table 1).

Distribution of the FIB-3 index by age. In the age-specific distribution of the FIB-3 index, Group 1 (<1.5), which had a FIB-3 index that was below the mild fibrosis cutoff, accounted for over 90% of cases up to the age of 50 years. However, with increasing age, the proportion of patients in Groups 2 or 3 increased, reaching approximately 30% at the age of 71–75 years. In this general health checkup population, advanced liver fibrosis (FIB-3 index ≥2.5) was considered to be present in >10% of individuals aged ≥65 years (Fig. 2).

In the sex-specific analysis, the FIB-3 index was significantly higher in men than in women who were aged ≥31 years (Fig. 3a). In the BMI-stratified analysis, the FIB-3 index was significantly higher in the BMI < 18.5 group than in the BMI ≥ 18.5 group among individuals aged 41–70 years (Fig. 3b). Across the age groups of 31–70 years, the FIB-3 index was significantly higher in individuals who had alcohol consumption habits than in those who did not (Fig. 3c). In the ultrasound-based assessment, compared with the group without fatty liver, the group with fatty liver exhibited significantly higher FIB-3 index in the age group of 41–60 years but significantly lower FIB-3 index in the age group of 61–70 years (Fig. 3d). The proportions of the presence or absence of fatty liver on ultrasound examination for each BMI group are shown in Figure S3.

Further, the proportion of individuals with elevated FIB-3 index was significantly higher in the group with HbA1c ≥ 7.0% compared with the group with HbA1c < 7.0% within the age range of 31–70 years (Figure S2).

A similar analysis was also performed using the FIB-4 index, and the results are shown in Figure S3. Similar to the FIB-3 index, the FIB-4 index showed a trend of a higher proportion of advanced fibrosis cases among males, drinkers, and those with lower BMI. However, in the case of the FIB-4 index, it is evident that the proportion of advanced liver fibrosis is extremely high in the elderly population.

Table 1 Patients characteristics

Variables	
Number	31 327
Age	48 [17, 90]
Male sex (%)	22 314 (71.2%)
Body mass index	23.20 (3.74)
Alcohol frequency: every day/sometimes/none (%)	9348 (32.0)/9929 (34.0)/9920 (34.0)
Alcohol volume: ≤19 g/20–39 g/40–59 g/≥60 g (%)	15 759 (54.8)/8593 (29.9)/3417 (11.9)/964 (3.4)
Habitual drinker (%)	7605 (26.1)
Ultrasound performed	15 511
Ultrasound findings of fatty liver (%)	4281 (27.6)
Platelet (/μL)	24.40 [1.60, 109.80]
Albumin (g/dL)	4.50 [1.60, 5.70]
Alanine aminotransferase (U/L)	19 [1, 1336]
Aspartate aminotransferase (U/L)	20 [6, 2232]
γ-glutamyltransferase (U/L)	27 [4, 2840]
Total bilirubin (mg/dL)	0.80 [0.10, 3.50]

Data are expressed as median [range], and mean (standard deviation) unless otherwise noted.

Discussion

In this study, on a general health checkup population, the FIB-3 index was found to increase with age; it was relatively high in men, individuals with BMI < 18.5, and habitual alcohol drinkers; and showed no clear trend when analyzed according to the presence or absence of fatty liver on ultrasound.

The FIB-3 index, which does not consider age as a factor, was developed to compensate for the FIB-4 index weakness of an increasing proportion of cases with high FIB-4 index with age, reaching approximately 80% among those aged 70 years (Figure S4). In addition, more than 97% of individuals <40 years old had an FIB-4 index of <1.3 (Figure S4), potentially leading to an increased risk of false negatives in detecting progressive liver fibrosis in younger individuals.

In a study on the prevalence of progressive hepatic fibrosis in a health checkup cohort, Yamamura *et al.*[29] performed a two-step diagnosis of first selecting subjects with a FIB-4 index of ≥1.3, followed by performing shear wave elastography (SWE) on these subjects to diagnose progressive hepatic fibrosis in cases with liver stiffness of ≥8.07 kPa. They reported that the prevalence of progressive hepatic fibrosis increased with age, reaching approximately 30% in those aged 65–74 years and >40% in those aged ≥75 years. Consistently, in our present study, although SWE was not used, the proportion of cases with FIB-3 index ≥1.5, which corresponds to stages 1–2 fibrosis, accounted for only <30% in those aged 66–75 years and approximately 40% in those aged 76–90 years. This suggested that the FIB-3 index successfully addressed the tendency of the FIB-4 index to yield false-positive results in the elderly and was able to identify cases of progressing hepatic fibrosis in a health checkup population, even without the use of SWE. In these cohorts, as reported by Tokushige *et al.*,[30] the HCC incidence rate is relatively high in nonviral liver diseases, with 11.3%/5 years in metabolic dysfunction-associated steatohepatitis (MASLD) cirrhosis and 12.5%/5 years in alcoholic cirrhosis. The proportion of patients with advanced liver fibrosis is considered to increase dramatically in subjects with a FIB-3 index ≥2.5, and it is believed that many cases of liver cirrhosis exist among these individuals. Therefore, it is recommended to perform screening using ultrasound examination for these subjects.

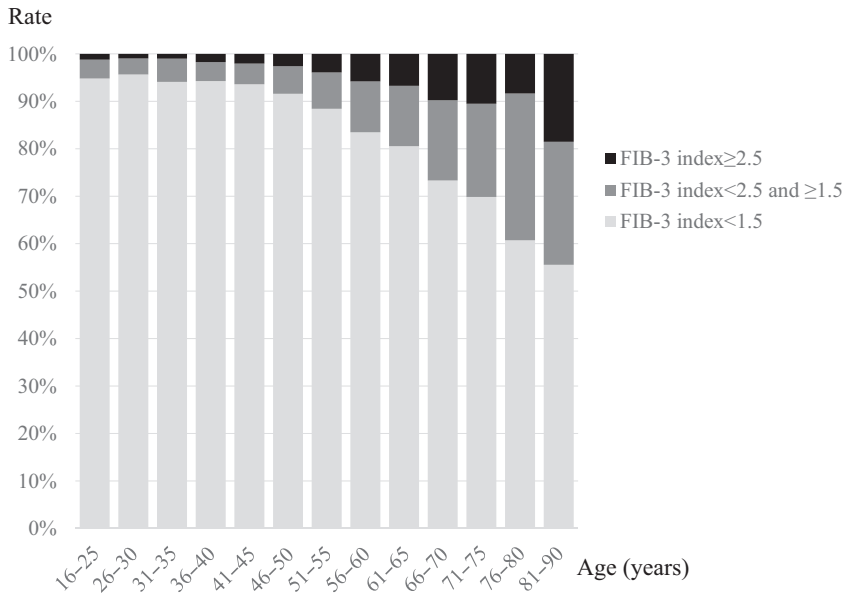

Figure 2 Distribution of the Fibrosis-3 (FIB-3) index by age. The individuals are stratified into three groups according to cutoff FIB-3 indices of 1.5 for mild fibrosis and 2.5 for advanced fibrosis. The group with FIB-3 index <1.5 accounts for >90% up to the age of 50 years, but the proportion of groups with FIB-3 index <2.5 and ≥1.5 and with FIB-3 index ≥2.5 increases with age, reaching 30% at 71–75 years. Advanced fibrosis is seen in >10% of individuals aged ≥65 years.

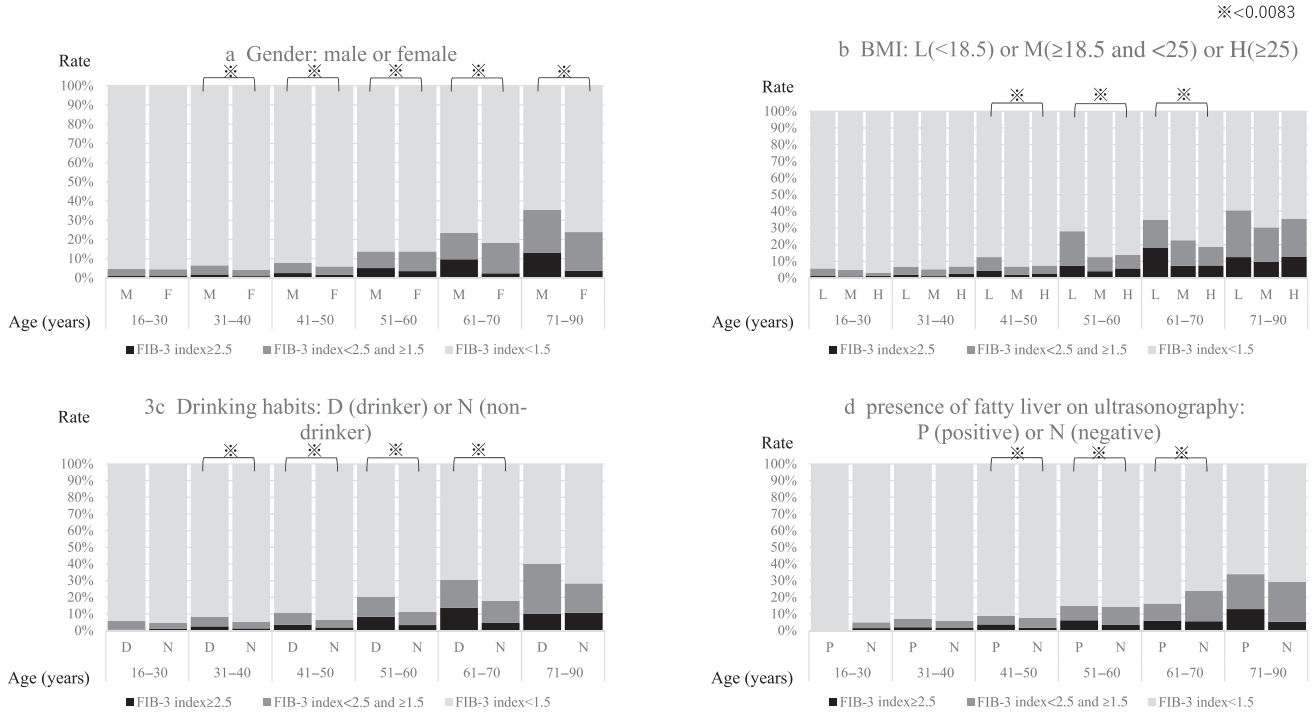

Figure 3 Distribution of the Fibrosis-3 (FIB-3) index by age in the subgroups. The FIB-3 index is significantly higher (a) in men than in women in individuals aged ≥31 years, (b) in the body mass index (BMI) <18.5 group than in the BMI ≥ 18.5 group among individuals aged 41–70 years, and (c) in habitual alcohol drinkers than in nondrinkers across a wide range of age groups from 31 to 70 years, (d) but the FIB-3 index distribution has no distinct trend according to the presence of fatty liver on ultrasound. L, BMI < 18.5; M, BMI ≥ 18.5 and <25; H, BMI ≥ 25; D, drinker; N, nondrinker; P, positive; N, negative. **P* value <0.0083.

In a study from Italy on Metabolic dysfunction-associated fatty liver disease (MAFLD) hepatic fibrosis using elastography, Ciardullo *et al*. concluded that the degree of hepatic fibrosis progressed as the BMI increased.[31] However, different results were obtained in this present study that used the FIB-3 index. The reasons for these discrepancies remain unclear based on the current study alone, and further investigations are warranted in the future.

In this study, habitual drinkers had a higher proportion of elevated FIB-3 index, compared with that in nondrinkers. In a study by Chang *et al*., the multivariate-adjusted hazard ratios (95% CIs) for incident fatty liver disease + moderate/high FIB-4 index was 1.15 (1.04–1.27) for mild drinkers and 1.49 (1.33–1.66) for moderate drinkers, compared with nondrinkers, indicating that even mild habitual drinking can increase the FIB-4 index.[31] Furthermore, an abundance of evidence has indicated alcohol consumption as an important risk factor for hepatic fibrosis.[32–36] Therefore, similar results in this study using the FIB-3 index were reasonable. However, actual liver fibrosis stage confirmation using liver biopsy was not carried out in this study, and the prediction of fibrosis using the FIB-3 index in drinkers requires further investigation.

In this study, FIB-3 index was higher in patients with fatty liver than in those without fatty liver among the age group of 41–60 years, but opposite result was observed among the age group of 61–70 years (Fig. 3d). The presence of fatty liver in all cases was 27.5/33.5/28.8% for the age groups 41–50/51–60/61–70 years, respectively. In contrast, among cases considered to have advanced fibrosis with FIB-3 index ≥1.5, the proportion of fatty liver decreased rapidly in those over 61 years old, with 30.6/34.4/21.5% for the age groups 41–50/51–60/61–70 years, respectively. This explains the reversal in the proportion of cases with FIB-3 index ≥1.5 between the age groups 41–60 and 61–70 years, when stratified by the presence or absence of fatty liver. It is generally known that as liver fibrosis progresses, the fat content in hepatocytes decreases, leading to a so-called "burned-out NASH" state. In this study, one possible explanation for the observed results is that among the elderly population over 61 years old, there was an increased proportion of cases with advanced liver fibrosis presenting with burned-out NASH.

There were some limitations in this population-based study. First, the accuracy of the FIB-3 index could not be validated by histological findings from liver biopsies. Second, the diagnosis of fatty liver was based on ultrasound, which is operator-dependent. Third, the study population comprised only Japanese individuals; therefore, care should be taken when extrapolating these results to other ethnic groups, and comparative studies are needed to confirm our findings.

Nevertheless, the FIB-3 index can effectively diagnose the extent of liver fibrosis in patients of all ages. The age-independent FIB-3 index was useful in identifying cases of progressive liver fibrosis in the health screening population. Further studies on other cohorts are required to confirm the risk factors.

Acknowledgments

We gratefully acknowledge all the doctors who collaborated on this project by collecting data from the patients registered in their respective hospitals.

Ethics approval

The study protocol conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki and was approved by the institutional review board of Hiroshima University (approval number E-1989-1).

Data availability statement. The data, analytical methods, and research materials used in this study are not available to other researchers.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Figure S1. Distribution of the FIB-4 index. More than 50% of the patients aged >60 years in the general population are categorized to have liver fibrosis.

Figure S2. Distribution of the FIB-3 index by age according to value of HbA1c. The subjects were divided into two groups based on HbA1c values (group 0 < 7.0%, group 1 ≥ 7.0%), and the distribution of FIB-3 index by age was plotted. Regardless of HbA1c values, both groups showed a gradual increase in FIB-3 index values as age increased.

Figure S3. Presence of fatty liver on ultrasonography by body mass index (BMI). The positive rate of fatty liver on ultrasound examination for each BMI category is shown. While fatty liver was very rare in subjects with BMI < 18.5, more than 60% of those with BMI ≥ 25 presented with fatty liver.

Figure S4. Distribution of FIB-4 index by age according to each factor. When examining the FIB-4 index by age for each factor, the results were unclear regarding the presence or absence of true advanced liver fibrosis because, with the FIB-4 index, a high proportion of individuals aged 61 years and older had a FIB-4 index ≥1.3 in all groups, regardless of the factor considered.