

Histological severity and hepatic outcomes in patients with MASLD and discrepant FIB-4 and liver stiffness measurement

Short title: Clinical significance of discrepant NILDA

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List of abbreviations

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, Fibrosis-4 index; HCC, hepatocellular carcinoma; LREs, liver-related events; LSM, liver stiffness measurement; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; NILDA, noninvasive liver disease assessments; VCTE, vibration-controlled transient elastography

Author contributions

VW-SW designed the study. TC-FY, HL, HWL, ET, SP, EB, MY, M-HZ, HH, JB, JLC, GB-BG, W-KC, RG-D, AJS, VdL, PNN, J-GF, GL-HW, GP, AA, AN, W-YL, YS, MdS-L, EL, KKJT, CL-R, AA, SM, CMC,

MR-G, SUK and VW-SW collected data in this study. ET, SP, EB, M-HZ, HH, JB, JLC, GB-BG, W-KC, AJS, VdL, PNN, MR-G, SUK and VW-SW supervised the project. TC-FY, and VW-SW were responsible for data analysis and data interpretation, and drafted the manuscript. TC-FY prepared the figures. All authors provided review and editing of the manuscript, and approved the final version of the manuscript.

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Data sharing statement

Data are available upon reasonable request to corresponding authors.

ABSTRACT

Background/Aims: Current guidelines recommend a 2-step approach for identifying advanced fibrosis in metabolic dysfunction-associated steatotic liver disease (MASLD), using FIB-4 followed by liver stiffness measurement (LSM) via vibration-controlled transient elastography. However, some patients may exhibit discordant results. This study evaluates the histological severity and outcomes in patients with discordant FIB-4 and LSM results.

Methods: This secondary analysis of the VCTE-Prognosis study included 12,950 patients evaluated for MASLD at 16 tertiary centers, of whom 2,915 underwent liver biopsy. Patients were categorized into four groups based on established FIB-4 (1.3) and LSM (8 kPa) cutoffs.

Results: F3-F4 fibrosis was observed in 6.4%, 13.7%, 30.6%, and 62.4% in low-FIB-4-low-LSM (n=6,403), high-FIB-4-low-LSM (n=3,017), low-FIB-4-high-LSM (n=1,363), and high-FIB-4-high-LSM (n=2,167) groups, respectively. During a median follow-up of 47.4 months, 248 patients experienced hepatic decompensation, hepatocellular carcinoma, liver transplantation, or liver-related death. The incidence rates of liver-related events (LREs) were 0.67, 1.19, 2.58, and 21.30 per 1,000 person-years, respectively. Compared to low-FIB-4-low-LSM patients, those with low-FIB-4-high-LSM (adjusted subdistribution hazard ratio [aSHR] 4.2) and high-FIB-4-high-LSM (aSHR 21.3) had a significantly higher risk of LREs, while high-FIB-4-low-LSM patients did not. Similar findings were observed when hepatic decompensation and hepatocellular carcinoma were analyzed separately.

Conclusions: Approximately 30% of patients in tertiary centers exhibit discordant FIB-4 and LSM results, with LSM more likely reflecting true severity. While some patients with discordant results may have advanced fibrosis, the overall incidence of LREs remains low.

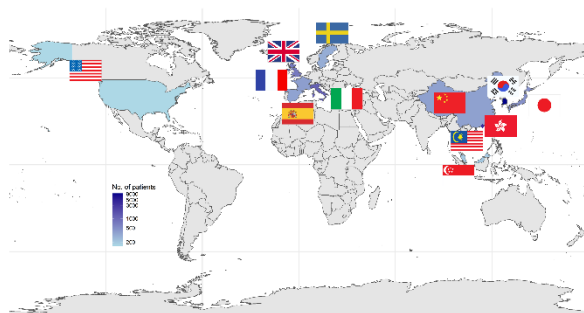
Keywords: steatotic liver disease; fatty liver; Fibrosis-4 index; vibration-controlled transient elastography; liver fibrosis

HIGHLIGHTS

Around 30% of patients in tertiary centers exhibit discrepant FIB-4 and VCTE-LSM results, with LSM more likely reflecting true severity. A small but significant proportion of these patients may still have at-risk MASH and advanced fibrosis, although the absolute incidence of LREs in 5 years remains low. Compared to patients with low-FIB-4-low-LSM, those with low-FIB-4-high-LSM and high-FIB-4-high-LSM had a significantly higher risk of LREs, while patients with high-FIB-4-low-LSM did not.

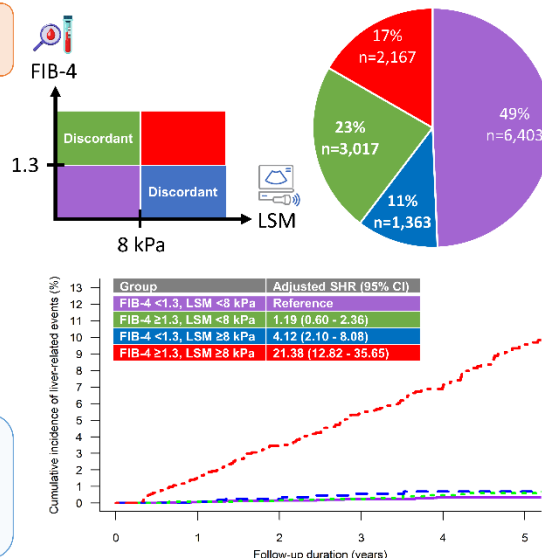
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12,950 patients with MASLD who underwent VCTE from 16 centers in 12 countries/regions (prospective at 14 centers)



Conclusions:

- Around 30% of patients in tertiary centers exhibit discordant FIB-4 and LSM results, with LSM more likely reflecting true severity
- While some patients with discordant results may have advanced fibrosis, the overall incidence of liver-related events remains low



INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) affects over 30% of the global population and is emerging as one of the leading causes of cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC) ¹. Among the histological features of MASLD, the fibrosis stage has the strongest association with liver-related events (LREs) ². Similarly, various noninvasive liver disease assessments (NILDA), including simple fibrosis scores such as the Fibrosis-4 index (FIB-4) ^{3, 4}, specific fibrosis biomarkers like the enhanced liver fibrosis score ⁵, and liver stiffness measurement (LSM) through vibration-controlled transient elastography (VCTE) or magnetic resonance elastography ⁶⁻⁹, have demonstrated a strong correlation with LREs. In particular, VCTE has shown similar prognostic performance to histological fibrosis staging in the LITMUS individual participant data meta-analysis and the multicenter VCTE-Prognosis study ^{6, 10}. A high FIB-4 of ≥ 3.25 or LSM of ≥ 20 kPa, or LSM ≥ 15 kPa in patients with FIB-4 ≥ 1.3 , also suggested a high risk of HCC of exceeding 1% per year, in which HCC surveillance may be warranted.¹¹

Given that MASLD is a highly prevalent disease and the majority of patients are seen in primary care and non-hepatology settings, the cost and availability of NILDA should be considered when designing clinical care pathways ¹². Consequently, professional societies have provided largely concordant recommendations in recent years, advocating for the use of FIB-4 as an initial assessment, followed by a more specific second-line test in cases of elevated FIB-4 ¹³⁻¹⁷. Compared to the use of second-line tests for all patients with MASLD, the 2-step approach has shown similar prognostic performance and is thus more cost-effective ¹⁸.

When a patient undergoes two or more NILDA, discrepancies among tests may occur. Potential management strategies for discrepant results include repeating the original tests, performing another NILDA, or proceeding with a liver biopsy. Before recommending the best approach, it is important to understand the frequency and clinical significance of discrepant NILDA. In this study, we investigated the histological severity and incidence of LREs in patients with concordant and discordant FIB-4 and VCTE-LSM in the well-characterized multicenter VCTE-Prognosis study.

MATERIALS AND METHODS

Study design and participants

This was a multicenter cohort study of patients with MASLD at 16 tertiary centers in the US, Europe, and Asia, among which the data were collected prospectively at 14 centers. Details of the study design were reported previously^{6, 11}. We included adult patients aged 18 years or older with MASLD diagnosed by imaging or histology plus at least one cardiometabolic risk factor¹⁹. For this study, we only included patients with both FIB-4 and VCTE examinations. We excluded patients with concomitant chronic viral hepatitis, HIV infection, excessive alcohol consumption (≥ 20 g per day in women or ≥ 30 g per day in men), secondary causes of hepatic steatosis, or a history of HCC, hepatic decompensation, liver resection, liver transplant, or other malignancies. The study protocol was approved by the institutional review board of the participating centers and conforms to the principles of the Declaration of Helsinki. The patients provided informed written consent for participating in the prospective cohorts, but consent for this secondary analysis was waived.

Assessments

The medical history was recorded at each clinic visit. Body mass index (BMI) was calculated as body weight (kg) divided by height (m) squared. Blood tests including liver biochemistry, renal function test, and platelet count were taken after overnight fasting of at least 8 hours. FIB-4 was calculated as $(\text{age} \times \text{aspartate aminotransferase [AST (U/L)]}) / (\text{platelet count} (\times 10^9/\text{L}) \times \text{the square root of alanine aminotransferase [ALT (U/L)]})$ ²⁰. Consistent with guideline-recommended two-step approaches, FIB-4 was considered elevated at a cutoff of ≥ 1.3 . LSM was performed using VCTE (FibroScan, Echosens, Paris, France) by operators following standard protocol and training by the manufacturer. The patients needed to have at least 10 valid acquisitions. As this analysis focused on discrepancies between FIB-4 and VCTE-LSM, the ≥ 8 kPa cutoff was used to define elevated VCTE-LSM, consistent with the low FIB-4 cutoff described above. In the subgroup of patients with concomitant liver biopsy, fibrosis was staged using the Nonalcoholic Steatohepatitis Clinical Research Network system²¹.

Outcomes

In the liver biopsy subgroup, the primary outcome was F2-F4 fibrosis (significant fibrosis), and secondary outcomes included metabolic dysfunction-associated steatohepatitis (MASH, defined as a nonalcoholic fatty liver disease activity score of ≥ 4 with at least one point in each of its components), “at-risk” MASH (MASH plus F2-F4 fibrosis), F3-F4 fibrosis (advanced fibrosis), and F4 fibrosis (cirrhosis). In the overall cohort, the primary outcome was LRE, a composite endpoint comprising hepatic decompensation (ascites, variceal hemorrhage, hepatic encephalopathy, spontaneous bacterial peritonitis, or hepatorenal syndrome), HCC, liver transplant, and liver-related death. Secondary outcomes included hepatic decompensation and HCC, analyzed separately. The diagnosis of clinical outcomes was

ascertained by prospective follow-up, medical record review, or validated registries with positive predictive values of >90%.

Statistical analysis

The baseline date was defined as the date of VCTE or blood tests, whichever was later, to avoid immortal time bias. All analysis was performed using R (4.4.3, R Core Team 2025). Continuous variables were expressed in mean (SD) or median (25th to 75th percentile) and compared using the Kruskal-Wallis test as appropriate, and categorical variables were expressed as number (percentage) and compared using the chi-square test. The patients were classified into four groups based on normal or elevated FIB-4 and VCTE-LSM at the cutoffs of 1.3 and 8.0 kPa, respectively. Sensitivity analyses on discrepancy of FIB-4 and LSM were performed among patients with FIB-4 <1.3 (or 2.0 in those aged ≥65 years) and LSM <8 or ≥8 kPa, patients with FIB-4 <1.3 and LSM <10 or ≥10 kPa, patients with FIB-4 <1.3 and LSM <12 or ≥12 kPa, patients with FIB-4 between 1.3 and 2.67 and LSM <15 or ≥15 kPa, and patients with FIB-4 >2.67 and LSM <15 or ≥15 kPa. Cumulative incidence function of primary and secondary outcomes was estimated and compared by Gray's method and Gray's test, respectively. Non-liver-related death was treated as a competing event for LREs and HCC, whereas non-liver-related death and HCC were treated as competing events for hepatic decompensation. Independent factors associated with LREs were determined using the Fine-Gray proportional subdistribution hazards model. The proportional subdistribution hazards assumption was assessed by modified weighted Schoenfeld residuals, which did not detect any significant violation. Model 1 adjusted for baseline age and sex, and Model 2 also adjusted for baseline BMI, diabetes, and hypertension. Factors associated with FIB-4 <1.3 and LSM ≥8 kPa, and FIB-4 ≥1.3 and LSM <8 kPa were examined using two separate logistic regression

models. Variance inflation factors were calculated and found no evidence of significant multicollinearity, with all values <5 . Missing data were assumed missing at random and were replaced using multiple imputation by chained equations to create five complete data sets after the initial ten iterations. The imputed baseline covariates (missing percentage) were controlled attenuation parameter (12.4%), diabetes (0.02%), hypertension (0.02%), BMI (4.7%), gamma-glutamyl transpeptidase (7.4%), albumin (2.2%), total bilirubin (0.9%), and creatinine (2.2%). The covariates included in the imputation model were the imputed baseline covariates, LSM, FIB-4, age, sex, center, ALT, AST, platelets, and the outcome indicator. Statistical significance was taken as a two-sided P of <0.05 .

RESULTS

From February 2004 to January 2023, 17,949 patients underwent VCTE examination, among whom 12,950 fulfilled the inclusion and exclusion criteria and were included in the final analysis (**Figure 1**). The mean age of the cohort was 51.7 (SD 13.9) years, and 41.1% were female (**Table 1**). VCTE and FIB-4 measurements were predominantly performed on the same day (median [25th to 75th percentile]: 0 [0 to 1] day). Overall, 8,570 (66.2%) patients had concordant FIB-4 and VCTE-LSM, with 6,403 (49.4%) having FIB-4 <1.3 and LSM <8 kPa, and 2,167 (16.7%) having FIB-4 ≥ 1.3 and LSM ≥ 8 kPa. Conversely, 4,380 (33.8%) patients had discordant FIB-4 and VCTE-LSM, with 1,363 (10.5%) having FIB-4 <1.3 but LSM ≥ 8 kPa, and 3,017 (23.3%) having FIB-4 ≥ 1.3 but LSM <8 kPa. Patients with FIB-4 ≥ 1.3 were older, and those with concordant FIB-4 ≥ 1.3 and LSM ≥ 8 kPa were female predominant, more likely to have diabetes and hypertension, had higher liver enzyme levels, and had the lowest platelet count (**Table 1**).

Histological severity

Among 2,915 patients who had undergone liver biopsy, 925 (31.7%) had FIB-4 <1.3 and LSM <8 kPa, 633 (21.7%) had FIB-4 <1.3 and LSM ≥8 kPa, 430 (14.8%) had FIB-4 ≥1.3 and LSM <8 kPa, and 927 (31.8%) had FIB-4 ≥1.3 and LSM ≥8 kPa (**Table 2**). The median interval between VCTE and liver biopsy was 1.0 (25th to 75th percentile: 0 to 7.8) months. Compared to patients with LSM <8 kPa, the median fibrosis stage was increased in those with FIB-4 <1.3 but LSM ≥8 kPa, and the highest in those with concordant FIB-4 ≥1.3 and LSM ≥8 kPa. The proportion of patients with MASH was similarly high at around 65% in both subgroups with LSM ≥8 kPa. In contrast, the proportion of at-risk MASH (13.4%), F2-F4 fibrosis (21.4%), F3-F4 fibrosis (6.4%), and cirrhosis (0.8%) was the lowest among patients with concordantly low FIB-4 <1.3 and LSM <8 kPa, and the highest among patients with concordantly high FIB-4 ≥1.3 and LSM ≥8 kPa (corresponding proportions 54.0%, 77.2%, 62.4%, and 20.9%, respectively). Among patients with discrepant FIB-4 and LSM, the proportions of at-risk MASH, F2-F4 fibrosis, F3-F4 fibrosis, and cirrhosis were between those in the two concordant groups, though the discrepant group with FIB-4 <1.3 and LSM ≥8 kPa were consistently more likely to harbor these histological features than the discrepant group with FIB-4 ≥1.3 and LSM <8 kPa (at-risk MASH: 36.5% vs 21.4%, F2-F4 fibrosis: 53.2% vs 32.8%, F3-F4 fibrosis: 30.6% vs 13.7%, cirrhosis: 5.1% vs 1.4%). This suggested that LSM was often the more accurate test in case of discrepancy. Patients with a BMI ≥30 kg/m² exhibited a higher prevalence of MASH and more advanced fibrosis compared to those with a BMI <30 kg/m². Consistent with the main findings, LSM provided a more accurate assessment in cases of diagnostic discrepancy across both BMI subgroups (**Supplementary Tables 1 and 2**).

Liver-related events

At a median follow-up of 47.4 (25th-75th percentile 23.3-72.3) months in the overall study population, 248 (1.9%) patients developed LREs at an incidence rate of 4.32 per 1,000 person-years (**Table 3**). These included 109 cases of HCC and 174 cases of hepatic decompensation, among which ascites was the most common decompensating event. Forty-one (0.3%) patients died of liver disease, and 15 (0.1%) underwent liver transplantation. Similar to the results of liver histology, the incidence rate was the lowest among patients with concordantly low FIB-4 <1.3 and LSM <8 kPa at 0.67 per 1,000 person-years and the highest among those with concordantly high FIB-4 ≥1.3 and LSM ≥8 kPa at 21.30 per 1,000 person-years (**Table 3** and **Figure 2A**, $P<0.001$ by Gray's test). However, both discrepant groups had low incidence rates of LREs at 2.58 per 1,000 person-years for FIB-4 <1.3 and LSM ≥8 kPa, and 1.19 per 1,000 person-years for FIB-4 ≥1.3 and LSM <8 kPa. Similar findings were observed when HCC and hepatic decompensation as well as its individual components were analyzed separately (**Figures 2B-C**), and after excluding 160 patients with unreliable LSM (**Supplementary Figures 1A-C**). In sensitivity analyses, a low incidence of LREs was observed in patients with low FIB-4 (*i.e.*, <1.3 [or 2.0 in those aged ≥65 years]) and LSM ≥8 kPa, as compared to those with low FIB-4 and LSM <8 kPa; and patients with FIB-4 <1.3 and LSM ≥10 kPa compared to those with FIB-4 <1.3 and LSM <10 kPa. Among 7,766 patients with FIB-4 <1.3, 434 (5.6%) had LSM ≥12 kPa and these patients had a higher risk of LREs than those with LSM <12 kPa. Among 3,912 patients with FIB-4 between 1.3 and 2.67, 385 (9.8%) had LSM ≥15 kPa and these patients also had a higher risk of LREs than those with LSM <15 kPa. Among 1,272 patients with FIB-4 >2.67, 661 (66.1%) patients had LSM <15 kPa. While these 661 patients had a lower risk of LREs than those with FIB-4 >2.67 and LSM ≥15 kPa, their risk of LREs was still considerably high, with a 5-year cumulative incidence of 3.53% (95% CI 2.15%-5.45%) (**Table 4**).

By univariable Fine-Gray proportional subdistribution hazards model, compared with patients with concordantly low FIB-4 <1.3 and LSM <8 kPa, the two subgroups with LSM ≥8 kPa had significantly increased risk of LREs, whereas the subgroup with FIB-4 ≥1.3 but LSM <8 kPa did not (**Table 5**). In the fully adjusted model, compared with patients with FIB-4 <1.3 and LSM <8 kPa, the adjusted subdistribution hazard ratios were 4.12 (95% CI 2.10-8.08) for patients with FIB-4 <1.3 but LSM ≥8 kPa, and 21.38 (95% CI 12.82-35.65) for patients with concordantly high FIB-4 ≥1.3 and LSM ≥8 kPa. The corresponding adjusted subdistribution hazard ratios were 6.89 (95% CI 2.42-19.63) and 45.90 (95% CI 19.10-110.32) for hepatic decompensation, and 2.42 (95% CI 0.92-6.37) and 12.50 (95% CI 6.75-23.13) for HCC, respectively. Similar results were observed in the complete case sensitivity analysis (**Supplementary Table 3**) and in the subgroups of patients with BMI <30 kg/m² (**Supplementary Table 4**). Among patients with BMI ≥30 kg/m², compared with patients with FIB-4 <1.3 and LSM <8 kPa, those with FIB-4 <1.3 and LSM ≥8 kPa were not associated with a higher risk of LREs, with an adjusted subdistribution hazard ratio of 3.09 (95% CI 0.92-10.43) (**Supplementary Table 5**).

Factors associated with discrepancy of FIB-4 and LSM

Patients from Europe or US centers compared to Asian centers, as well as those with a higher controlled attenuation parameter, higher BMI, presence of diabetes and hypertension, lower gamma-glutamyl transpeptidase, and lower total bilirubin were associated with higher odds to having a FIB-4 <1.3 but LSM ≥8 kPa, than patients with FIB-4 <1.3 and LSM <8 kPa and patients with FIB-4 ≥1.3 and LSM ≥8 kPa. Patients with a higher controlled attenuation parameter, higher albumin, and lower total bilirubin were associated with higher odds of having a FIB-4 ≥1.3 but LSM <8 kPa, compared to patients with FIB-4 <1.3 and LSM <8 kPa and

patients with FIB-4 ≥ 1.3 and LSM ≥ 8 kPa (**Table 6**). Similar results were observed in complete case analysis (**Supplementary Table 6**).

DISCUSSION

In 2021, the American Gastroenterological Association published the clinical care pathway for MASLD, recommending the use of FIB-4 as the first-line assessment, followed by VCTE or other second-line tests in cases of indeterminate FIB-4 results ²². This recommendation has garnered significant support from other professional societies ¹³⁻¹⁵. Since then, several studies have examined the performance of this clinical care pathway using registry data ^{23, 24}. A common criticism is that FIB-4 fails to identify a proportion of patients with VCTE-LSM ≥ 8 kPa. However, this critique assumes that VCTE-LSM is the definitive measure, while false-positive VCTE-LSM results can occur, particularly in obese patients ²⁵. When FIB-4 is < 1.3 and LSM is ≥ 8 kPa, it is possible that FIB-4 is indeed the correct result. Given this context, our large multicenter cohort study provides insights into the clinical implications of discrepant results between FIB-4 and LSM.

First, we found that approximately 30% of patients with MASLD seen at tertiary centers exhibited discrepancies between FIB-4 and VCTE-LSM results. In a secondary analysis of the 2017 to 2020 National Health and Nutrition Examination Surveys dataset, 10% of participants with FIB-4 < 1.3 had LSM ≥ 8 kPa, while 62.8% of those with FIB-4 > 2.67 had LSM < 8 kPa ²⁴. Our study further evaluated the histological severity and clinical outcomes in patients with concordant and discordant NILDA (**Table 2**). All clinically relevant histological features, including at-risk MASH and the degree of fibrosis, were least severe in patients with FIB-4 < 1.3 and LSM < 8 kPa, and most severe in those with FIB-4 ≥ 1.3 and LSM ≥ 8 kPa, though false-

negative and false-positive results remained possible despite concordant NILDA. Among the two discrepant groups, patients with FIB-4 <1.3 but LSM \geq 8 kPa exhibited more severe histology than those with FIB-4 \geq 1.3 but LSM <8 kPa. Specifically, F3-F4 fibrosis was found in 33.2% of patients with FIB-4 <1.3 and LSM \geq 8 kPa, compared to 13.4% in those with FIB-4 \geq 1.3 and LSM <8 kPa. This suggests that when the two NILDA do not agree, VCTE-LSM is more often the correct measure. Based on our findings, patients with low FIB-4 but elevated LSM may require further evaluation to confirm or exclude advanced fibrosis. This can be done through repeating another LSM or performing a third NILDA. Although such patients are not identified by the two-step approach, their 5-year risk of liver-related events remained relatively low. Nonetheless, repeating FIB-4 measurements every 1-3 years remains important. Also, among patients with FIB-4 <1.3, those with metabolic comorbidities, such as high BMI, diabetes, or hypertension, are more likely to have an LSM \geq 8 kPa. They may be considered for VCTE examination if there is clinical suspicion. Consequently, relying solely on FIB-4 as the first-line test may miss some patients with advanced fibrosis. In another study involving patients with type 2 diabetes from primary care and endocrinology clinics in the USA, Ajmera and colleagues demonstrated that the two-step approach would result in 18% of patients being referred to hepatology, while missing 3.3% of those who had LSM \geq 3.63 kPa as determined by magnetic resonance elastography²⁶. It is important to note, however, that VCTE and magnetic resonance elastography share similar mechanisms, which may lead to an overestimation of the clinical care pathway's performance.

As expected, the incidence of LREs was lowest in patients with concordantly low FIB-4 <1.3 and VCTE-LSM <8 kPa, and highest in those with concordantly high FIB-4 \geq 1.3 and LSM \geq 8 kPa (**Table 3**). Interestingly, although the two discrepant groups had incidence rates of LREs that

fell between the two concordant groups, the absolute incidence was low: 3.28 per 1,000 person-years for FIB-4 <1.3 and LSM \geq 8 kPa, and 1.10 per 1,000 person-years for FIB-4 \geq 1.3 and LSM <8 kPa, compared to 22.50 per 1,000 person-years when both measures were elevated. This aligns with previous studies indicating that persistently low FIB-4 is associated with a very low incidence of LREs^{3, 4, 27}. Our group previously showed that the 2-step approach was non-inferior to performing VCTE for all patients with MASLD in predicting LREs¹⁸. Taken together, while FIB-4 is not perfect and may overlook some patients with advanced fibrosis, those with low FIB-4 levels are unlikely to develop LREs in the short to intermediate term, and the current clinical care pathway remains robust.

Ongoing efforts continue to refine serum prediction models for fibrosis and LREs, including the steatosis-associated fibrosis estimator (SAFE) and LiverPRO scores, which aim to detect F2-F4 fibrosis in primary care²⁸⁻³⁰, as well as the metabolic dysfunction-associated fatty liver disease fibrosis score for F3-F4 fibrosis³¹. Additionally, LiverRisk and metabolic dysfunction-associated fibrosis (MAF-5) scores have been modeled against LSM and validated against LREs^{32, 33}. Generally, these new scores are more accurate than FIB-4 but require more clinical parameters. Their performance warrants further validation, and it is crucial to assess whether the increased complexity of these models might hinder their implementation³⁴.

Our study benefits from a large sample size, a multicenter design, and the inclusion of both histological and clinical outcome correlations. However, it does have limitations. First, the results reflect the performance of NILDA in tertiary centers; future studies are needed to independently elucidate the clinical significance of discordant NILDA in primary care. It is reasonable to anticipate that the incidence of LREs would be even lower in patients with

discrepant FIB-4 and VCTE-LSM in primary care settings and community-based studies. Second, the study evaluated only FIB-4 and VCTE-LSM, as these are most often recommended by international guidelines. Evaluating different first- and second-line tests, such as LiverRisk score, LiverPRO, enhanced liver fibrosis, and magnetic resonance elastography, will yield numerous possible combinations for future assessment. Third, liver histology was available only in a subset of patients, as it is not routinely performed in individuals with MASLD. Interobserver variability in histologic assessment may affect the evaluation of histological severity of patients with concordant or discordant FIB-4 and LSM.³⁵ Central reading of liver biopsies is not part of routine clinical practice and was therefore not performed in this study. Fourth, while widely accepted cutoffs of FIB-4 and LSM were used, categorization of LSM and FIB-4 may mask within-group variability. Thus, Table 1 reports the distribution of FIB-4 and LSM among patients with concordant and discordant FIB-4 and LSM. As age is a component of FIB-4, its sensitivity decreases in older individuals. Table 4 shows sensitivity analyses of the discrepancy of FIB-4 and LSM using different cutoffs, including an age-specific cutoff for FIB-4. Fifth, the median follow-up was only 47.4 months. However, as current guidelines recommend NILDA testing at intervals of 1 to 3 years, the prognostic performance observed in this study is clinically relevant for the intermediate term. Sixth, although clinical outcomes were predefined in the study protocol, interpretation of clinical outcome definitions may vary across centers. To reflect real-world practice, we used standard criteria routinely applied at each site. Key outcomes were identified through prospective follow-up, medical record review, or validated registries with positive predictive values $\geq 90\%$. Consistent findings across multiple outcomes, which included unequivocal measures like mortality, support the credibility of our results.

In conclusion, approximately 30% of patients in tertiary centers exhibit discrepant FIB-4 and VCTE-LSM results. A small but significant proportion of these patients may still harbor at-risk MASH and advanced fibrosis, although the absolute incidence of LREs remains low. Our findings support current recommendations for the use of FIB-4 followed by a specific second-line test in evaluating MASLD, while also highlighting the importance of follow-up testing to avoid missing patients with advanced liver disease and disease progression.

Potential conflict-of-interest statements

ET served as a consultant for Pfizer, Madrigal, MSD, NovoNordisk, Boehringer, and Siemens Healthineers; and a speaker for Boehringer, Abbvie, Astra Zeneca, NovoNordisk, Echosens, and Dr Falk. SP served as a speaker or advisor for AbbVie, Echosens, MSD, Novo Nordisk, Pfizer, and Resalis. EB served as a consultant for Boehringer, MSD, Novo Nordisk, and Pfizer; and a speaker for MSD, Novo Nordisk, and Madrigal. She received research grants from Gilead Sciences. MY received research grant from Gilead Sciences and speaker for KOWA. AN received research grants from Mochida Pharmaceutical, Astellas Pharma, ASKA pharmaceutical, Biofermin Pharmaceutical and EA pharma; a speaker for Mochida Pharmaceutical, Kowa, Biofermin Pharmaceutical, MSD, Boehringer, Novo Nordisk, GlaxoSmithkline, EA pharma. HH's institutions have received research funding from Astra Zeneca, EchoSens, Gilead, Intercept, MSD, Novo Nordisk, Takeda and Pfizer. He has served as consultant, speaker or on advisory boards for Astra Zeneca, Boehringer Ingelheim, Bristol Myers-Squibb, GSK, Echosens, Ipsen, MSD and Novo Nordisk and has been part of hepatic events adjudication committees for Arrowhead, Boehringer Ingelheim, KOWA and GW Pharma. JB served as a consultant for AstraZeneca, Echosens, Intercept, and Siemens; a speaker for AbbVie, Gilead Sciences, Intercept, and Siemens; and an advisory board member

for Bristol-Myers-Squibb, Intercept, Pfizer, MSD, and Novo Nordisk. His institution has received research funding from Diafir, Echosens, Intercept, Inventiva, and Siemens. JLC served as a consultant and speaker for Echosens, Gilead Sciences, and AbbVie. GB-BG served as a consultant for Roche and Ionis Pharmaceuticals; and a speaker for Echosens, Viatrix, Abbott and Novo Nordisk. WKC served as a consultant for Abbott, Roche, AbbVie, Novo Nordisk, IPSEN, Zuellig Pharma and Boehringer Ingelheim; and a speaker for Abbott, Novo Nordisk, Echosens, Hisky Medical, and Viatrix; and received research grants from Abbott and Roche. AJS served as a consultant for 89Bio, Akero, Allergan, Alnylam Pharmaceuticals, Amgen Inc, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Genentech, Gilead Sciences, Histoindex, Intercept Pharmaceuticals, Inventiva, Madrigal, Merck, Novartis, Novo Nordisk, Pfizer, Poxel, Salix Pharmaceuticals, Siemens, Sun Pharmaceutical Industries Inc, Terns, and Valeant Pharmaceuticals; and a data safety monitoring board or advisory board member for Bard Peripheral Vascular Inc, NGM Biopharmaceuticals, and Sequana. He has received research funding from Albireo, Allergan, Echosens, Eli Lilly, Gilead Sciences, Intercept Pharmaceuticals, Mallinckrodt LLC, Merck, Novo Nordisk, Perspectum, Pfizer, Salix Pharmaceuticals, and Zydus; and holds the stocks of Durect, Exhalenz, Gen t, and Tiziana. MR-G served as a consultant for Siemens; and a speaker for Siemens and Echosens. He has received research funding from Siemens, Echosens, and Novo Nordisk. PN served as a consultant for Novo Nordisk, Boehringer Ingelheim, Gilead Sciences, Intercept, Poxel Pharmaceuticals, Pfizer, BMS, Eli Lilly, Madrigal, and GSK; and a speaker for Novo Nordisk and AiCME. He has received research funding from Novo Nordisk. LC served as a consultant for Boston pharmaceutical, Echosens, Gilead, GSK, Madrigal, MSD, Novo Nordisk, Pfizer, Sagimet and Siemens Healthineers and as speaker for Echosens, Gilead, Inventiva, Madrigal and Novo Nordisk. CF-P is an employee of Echosens. GL-HW served as a consultant for AstraZeneca,

Gilead Sciences, GlaxoSmithKline and Janssen; and a speaker for Abbott, Abbvie, Bristol-Myers Squibb, Echosens, Furui, Gilead Sciences, GlaxoSmithKline and Roche. She has received research funding from Gilead Sciences. MS-WC is an employee of Echosens. VW-SW served as a consultant or advisory board member for AbbVie, Boehringer Ingelheim, Echosens, Gilead Sciences, Intercept, Inventiva, Novo Nordisk, Pfizer, Sagimet Biosciences, TARGET PharmaSolutions, and Visirna; and a speaker for Abbott, AbbVie, Gilead Sciences, Novo Nordisk, and Unilab. He has received a research grant from Gilead Sciences, and is a co-founder of Illuminatio Medical Technology.

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Table 1. Clinical characteristics of patients with concordant or discordant fibrosis-4 index (FIB-4) and liver stiffness measurement (LSM).

	All	FIB-4 <1.3 LSM <8 kPa	FIB-4 <1.3 LSM ≥8 kPa	FIB-4 ≥1.3 LSM <8 kPa	FIB-4 ≥1.3 LSM ≥8 kPa
N	12950	6403	1363	3017	2167
Age (years)	51.7 (13.9)	46.0 (12.3)	43.2 (13.8)	60.9 (10.0)	60.7 (10.5)
Female sex, n (%)	5316 (41.1)	2373 (37.1)	514 (37.7)	1311 (43.5)	1118 (51.6)
Body mass index (kg/m ²)	27.2 (24.7 to 30.4)	26.7 (24.4 to 29.5)	30.5 (27.3 to 34.4)	26.1 (24.1 to 28.7)	29.0 (25.9 to 32.6)
Diabetes, n (%)	4429 (34.2)	1595 (24.9)	558 (40.9)	1089 (36.1)	1187 (54.8)
Hypertension, n (%)	4835 (37.3)	1686 (26.3)	572 (42.0)	1324 (43.9)	1253 (57.8)
Alanine aminotransferase (U/L)	38 (24 to 64)	35 (23 to 58)	57 (34 to 95)	32 (20 to 51)	49 (31 to 77)
Aspartate aminotransferase (U/L)	31 (23 to 47)	26 (20 to 35)	36 (26 to 53)	34 (25 to 51)	51 (36 to 75)
Gamma-glutamyl transpeptidase (U/L)	44 (27 to 78)	38 (24 to 65)	57 (36 to 91)	37 (23 to 66)	71 (45 to 128)
Albumin (g/L)	44.8 (3.8)	45.5 (3.3)	45.0 (5.1)	44.3 (3.4)	43.2 (4.3)
Total bilirubin (μmol/L)	12.0 (8.6 to 16.0)	12.0 (8.6 to 15.4)	10.3 (8.0 to 15.4)	12.0 (10.2 to 17.1)	12.0 (9.0 to 17.0)
Platelet count (×10 ⁹ /L)	239 (200 to 282)	263 (231 to 301)	266 (228 to 307)	205 (178 to 236)	189 (149 to 230)
Creatinine (μmol/L)	72 (60 to 83)	73 (61 to 82)	71 (60 to 82)	72 (61 to 85)	68 (58 to 80)
FIB-4	1.1 (0.7 to 1.7)	0.8 (0.6 to 1.0)	0.8 (0.6 to 1.1)	1.7 (1.5 to 2.2)	2.3 (1.7 to 3.3)
Vibration-controlled transient elastography					
- LSM (kPa)	5.9 (4.6 to 8.3)	5.1 (4.3 to 6.1)	10.2 (8.8 to 12.9)	5.3 (4.4 to 6.4)	12.6 (9.8 to 19.5)
- IQR-to-median ratio of LSM	0.13 (0.09 to 0.17)	0.12 (0.08 to 0.16)	0.14 (0.10 to 0.18)	0.12 (0.09 to 0.16)	0.14 (0.10 to 0.19)
- Controlled attenuation parameter (dB/m)	303 (274 to 335)	302 (274 to 333)	331 (302 to 358)	289 (266 to 319)	311 (280 to 343)

Continuous variables are expressed in mean (standard deviation) or median (25th to 75th percentile). Categorical variables are expressed as number (percentage).

FIB-4, Fibrosis-4 index; IQR, interquartile range; LSM, liver stiffness measurement

Table 2. Histological severity of patients with concordant or discordant fibrosis-4 index (FIB-4) and liver stiffness measurement (LSM).

	All	FIB-4 <1.3 LSM <8 kPa	FIB-4 <1.3 LSM ≥8 kPa	FIB-4 ≥1.3 LSM <8 kPa	FIB-4 ≥1.3 LSM ≥8 kPa	P
N	2915	925	633	430	927	
FIB-4	1.2 (0.8 to 2.0)	0.8 (0.6 to 1.0)	0.9 (0.6 to 1.1)	1.9 (1.5 to 2.5)	2.1 (1.7 to 2.9)	-
LSM	8.4 (6.0 to 12.2)	5.8 (4.8 to 6.7)	10.6 (9.1 to 13.4)	6.0 (4.9 to 6.9)	13.3 (10.4 to 20.0)	-
Steatosis grade	2 (1 to 2)	2 (1 to 2)	2 (1 to 2)	2 (1 to 2)	2 (1 to 2)	<0.001
Lobular inflammation	1 (1 to 2)	1 (1 to 1)	1 (1 to 2)	1 (1 to 2)	1 (1 to 2)	<0.001
Hepatocyte ballooning	1 (0 to 1)	1 (0 to 1)	1 (1 to 1)	1 (0 to 1)	1 (1 to 2)	<0.001
NAFLD activity score	4 (3 to 5)	4 (3 to 5)	4 (3 to 5)	4 (3 to 5)	4 (3 to 5)	<0.001
Fibrosis stage	1 (1 to 3)	1 (0 to 1)	2 (1 to 3)	1 (1 to 2)	3 (2 to 3)	<0.001
MASH*, n (%)	1667 (57.2)	449 (48.5)	398 (62.9)	203 (47.2)	617 (66.6)	<0.001
At-risk MASH*, n (%)	948 (32.5)	124 (13.4)	231 (36.5)	92 (21.4)	501 (54.0)	<0.001
F2-F4 fibrosis, n (%)	1392 (47.8)	198 (21.4)	337 (53.2)	141 (32.8)	716 (77.2)	<0.001
F3-F4 fibrosis, n (%)	890 (30.5)	59 (6.4)	194 (30.6)	59 (13.7)	578 (62.4)	<0.001
Cirrhosis, n (%)	239 (8.2)	7 (0.8)	32 (5.1)	6 (1.4)	194 (20.9)	<0.001

Histological scores are expressed as median (25th to 75th percentile). Categorical variables are expressed as number (percentage).

Continuous variables were compared by Kruskal-Wallis test. Categorical variables were compared by chi-square test.

*MASH was defined as a NAFLD activity score ≥4 with at least 1 point in all steatosis, lobular inflammation and hepatocyte ballooning. At-risk MASH was defined as MASH plus F2-F4 fibrosis.

FIB-4, Fibrosis-4 index; LSM, liver stiffness measurement; MASH, metabolic dysfunction-associated steatohepatitis; NAFLD, nonalcoholic fatty liver disease

Table 3. Liver-related events in patients with concordant or discordant fibrosis-4 index (FIB-4) and liver stiffness measurement (LSM).

	All	FIB-4 <1.3 LSM <8 kPa	FIB-4 <1.3 LSM ≥8 kPa	FIB-4 ≥1.3 LSM <8 kPa	FIB-4 ≥1.3 LSM ≥8 kPa
N	12950	6403	1363	3017	2167
All liver-related events, n (%)	248 (1.9)	19 (0.3)	16 (1.2)	16 (0.5)	197 (9.1)
Incidence rate of liver-related events, per 1,000 person-years	4.32	0.67	2.58	1.19	21.30
Hepatocellular carcinoma, n (%)	109 (0.8)	13 (0.2)	6 (0.4)	10 (0.3)	80 (3.7)
Hepatic decompensation, n (%)	174 (1.3)	6 (0.1)	9 (0.7)	8 (0.3)	151 (7.0)
Ascites, n (%)	112 (0.9)	3 (0.0)	5 (0.4)	4 (0.1)	100 (4.6)
Spontaneous bacterial peritonitis, n (%)	10 (0.1)	2 (0.0)	1 (0.1)	1 (0.0)	6 (0.3)
Variceal hemorrhage, n (%)	58 (0.4)	0 (0.0)	4 (0.3)	2 (0.1)	52 (2.4)
Hepatic encephalopathy, n (%)	45 (0.3)	1 (0.0)	4 (0.3)	1 (0.0)	39 (1.8)
Hepatorenal syndrome, n (%)	8 (0.1)	1 (0.0)	0 (0.0)	0 (0.0)	7 (0.3)
Liver transplantation, n (%)	15 (0.1)	1 (0.0)	2 (0.1)	1 (0.0)	11 (0.5)
Liver-related death, n (%)	41 (0.3)	0 (0.0)	0 (0.0)	2 (0.1)	39 (1.8)

FIB-4, Fibrosis-4 index; LSM, liver stiffness measurement

Table 4. Sensitivity analysis on risk of liver-related events for patients with concordant or discordant fibrosis-4 index (FIB-4) and liver stiffness measurement (LSM).

	5-year cumulative incidence (95% CI) of liver-related events	5-year cumulative incidence (95% CI) of hepatic decompensation	5-year cumulative incidence (95% CI) of hepatocellular carcinoma
FIB-4 <1.3 (age ≤65 years)/2.0 (age >65 years) and			
• LSM <8 kPa (N=6,942)	0.38% (0.23% - 0.59%)	0.13% (0.05% - 0.28%)	0.27% (0.15% - 0.45%)
• LSM ≥8 kPa (N=1,531)	1.13% (0.61% - 1.93%)	0.58% (0.24% - 1.25%)	0.55% (0.23% - 1.15%)
FIB-4 <1.3 and			
• LSM <10 kPa (N=7,029)	0.33% (0.20% - 0.53%)	0.11% (0.04% - 0.25%)	0.22% (0.12% - 0.39%)
• LSM ≥10 kPa (N=737)	1.08% (0.45% - 2.26%)	0.35% (0.07% - 1.21%)	0.73% (0.25% - 1.79%)
FIB-4 <1.3 and			
• LSM <12 kPa (N=7,332)	0.32% (0.19%-0.51%)	0.10% (0.04%-0.24%)	0.21% (0.11%-0.38%)
• LSM ≥12 kPa (N=434)	1.81% (0.75%-3.75%)	0.59% (0.12%-1.99%)	1.23% (0.41%-2.96%)
1.3 ≤ FIB-4 ≤2.67 and			
• LSM <15 kPa (N=3,527)	1.05% (0.69%-1.54%)	0.66% (0.39%-1.06%)	0.53% (0.28%-0.91%)
• LSM ≥15 kPa (N=385)	8.67% (5.68%-12.44%)	5.71% (3.39%-8.86%)	4.21% (2.16%-7.30%)
FIB-4 >2.67 and			
• LSM <15 kPa (N=841)	3.53% (2.15%-5.45%)	1.92% (0.99%-3.39%)	2.39% (1.28%-4.08%)
• LSM ≥15 kPa (N=431)	27.96% (22.79%-33.35%)	22.43% (17.82%-27.38%)	10.42% (7.11%-14.46%)

FIB-4, Fibrosis-4 index; LSM, liver stiffness measurement

Table 5. Fine-Gray proportional subdistribution hazards model on liver-related events.

Group	Univariable SHR	95% CI	<i>P</i>	Model 1 aSHR	95% CI	<i>P</i>	Model 2 aSHR	95% CI	<i>P</i>
Liver-related events									
FIB-4 <1.3 LSM <8 kPa	Ref			Ref			Ref		
FIB-4 <1.3 LSM ≥8 kPa	3.92	2.01 - 7.63	<0.001	4.33	2.23 - 8.43	<0.001	4.12	2.10 - 8.08	<0.001
FIB-4 ≥1.3 LSM <8 kPa	1.83	0.94 - 3.57	0.078	1.22	0.62 - 2.40	0.575	1.19	0.60 - 2.36	0.610
FIB-4 ≥1.3 LSM ≥8 kPa	32.91	20.37 - 53.15	<0.001	22.69	13.77 - 37.37	<0.001	21.38	12.82 - 35.65	<0.001
Hepatic decompensation									
FIB-4 <1.3 LSM <8 kPa	Ref			Ref			Ref		
FIB-4 <1.3 LSM ≥8 kPa	7.01	2.49 - 19.68	<0.001	7.71	2.75 - 21.60	<0.001	6.89	2.42 - 19.63	<0.001
FIB-4 ≥1.3 LSM <8 kPa	2.91	1.00 - 8.41	0.049	1.92	0.65 - 5.68	0.239	1.83	0.62 - 5.43	0.273
FIB-4 ≥1.3 LSM ≥8 kPa	78.73	34.66 - 178.82	<0.001	52.74	22.29 - 124.77	<0.001	45.90	19.10 - 110.32	<0.001
Hepatocellular carcinoma									
FIB-4 <1.3 LSM <8 kPa	Ref			Ref			Ref		
FIB-4 <1.3 LSM ≥8 kPa	2.13	0.81 - 5.60	0.128	2.39	0.91 - 6.31	0.078	2.42	0.92 - 6.37	0.072
FIB-4 ≥1.3 LSM <8 kPa	1.65	0.72 - 3.77	0.237	1.03	0.45 - 2.36	0.947	1.02	0.44 - 2.34	0.965
FIB-4 ≥1.3 LSM ≥8 kPa	18.37	10.09 - 33.45	<0.001	12.43	6.84 - 22.59	<0.001	12.50	6.75 - 23.13	<0.001

aSHR, adjusted subdistribution hazard ratio; CI, confidence interval; FIB-4, Fibrosis-4 index; LSM, liver stiffness measurement; SHR, subdistribution hazard ratio

Model 1: Adjusted for baseline age and sex

Model 2: Model 1 + adjustment for baseline body mass index, diabetes, and hypertension

Table 6. Logistic regression model on factors associated with discrepancy of fibrosis-4 index (FIB-4) and liver stiffness measurement (LSM).

Patients with FIB-4 <1.3 but LSM ≥8 kPa vs Patients with FIB-4 <1.3 and LSM <8 kPa; and patients with FIB-4 ≥1.3 and LSM ≥8 kPa				
	Univariable analysis		Multivariable analysis	
Parameters	OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Male sex (Ref: female)	1.14 (1.01-1.28)	0.035	1.03 (0.88-1.21)	0.686
Europe/US center (Ref: Asia)	1.84 (1.63-2.08)	<0.001	1.47 (1.26-1.71)	<0.001
CAP (dB/m)	1.013 (1.011-1.014)	<0.001	1.005 (1.003-1.007)	<0.001
BMI (kg/m ²)	1.09 (1.08-1.11)	<0.001	1.03 (1.02-1.04)	<0.001
Diabetes	1.44 (1.28-1.62)	<0.001	1.38 (1.19-1.59)	<0.001
Hypertension	1.39 (1.23-1.56)	<0.001	1.39 (1.19-1.61)	<0.001
GGT (U/L)	1.000 (1.000-1.001)	0.155	0.999 (0.998-1.000)	0.004
Albumin (g/L)	1.01 (0.99-1.02)	0.465	1.00 (0.98-1.01)	0.667
Total bilirubin (μmol/L)	0.98 (0.97-0.98)	<0.001	0.99 (0.98-0.99)	0.003
Creatinine (μmol/L)	0.998 (0.995-1.001)	0.253	0.998 (0.995-1.002)	0.366
Patients with FIB-4 ≥1.3 but LSM <8 kPa vs Patients with FIB-4 <1.3 and LSM <8 kPa; and patients with FIB-4 ≥1.3 and LSM ≥8 kPa				
	Univariable analysis		Multivariable analysis	
Parameters	OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Male sex (Ref: female)	0.89 (0.82-0.97)	0.009	0.95 (0.84-1.08)	0.436
Europe/US center (Ref: Asia)	0.70 (0.62-0.78)	<0.001	0.96 (0.81-1.14)	0.644
CAP (dB/m)	0.993 (0.992-0.994)	<0.001	1.004 (1.002-1.006)	<0.001
BMI (kg/m ²)	0.94 (0.93-0.95)	<0.001	1.01 (1.00-1.02)	0.281
Diabetes	1.18 (1.08-1.28)	<0.001	1.03 (0.90-1.17)	0.696
Hypertension	1.50 (1.38-1.63)	<0.001	1.11 (0.97-1.27)	0.132
GGT (U/L)	0.999 (0.999-1.000)	0.002	1.000 (1.000-1.001)	0.446
Albumin (g/L)	0.95 (0.94-0.97)	<0.001	1.02 (1.00-1.04)	0.028
Total bilirubin (μmol/L)	1.00 (1.00-1.01)	0.171	0.99 (0.98-1.00)	0.021
Creatinine (μmol/L)	1.000 (1.000-1.000)	0.737	1.000 (1.000-1.000)	0.473

Age, AST, ALT, platelets, and LSM were also adjusted in the models.

BMI, body mass index; CAP, controlled attenuation parameter; CI, confidence interval; FIB-4, Fibrosis-4 index; GGT, gamma-glutamyl transpeptidase; LSM, liver stiffness measurement; OR, odds ratio.

Figure legends

Figure 1. Study participant flow.

Footnotes: FIB-4, Fibrosis-4 index; LREs, liver-related events; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease; VCTE, vibration-controlled transient elastography

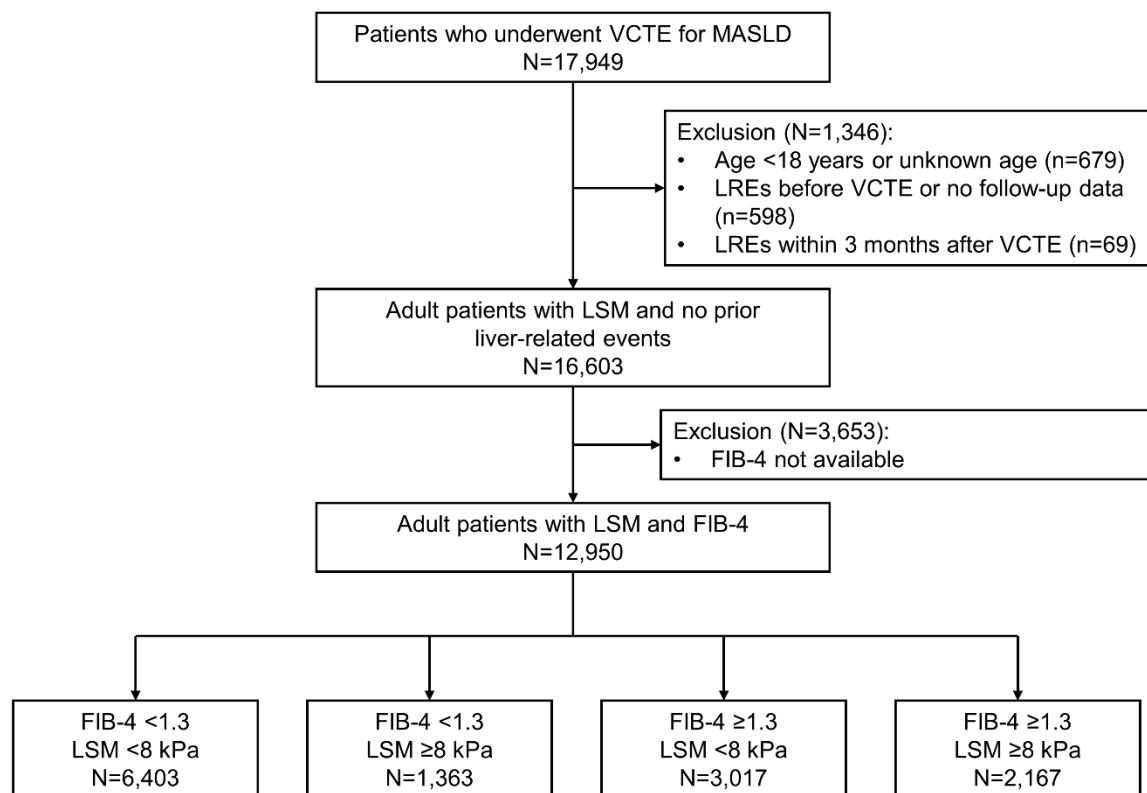
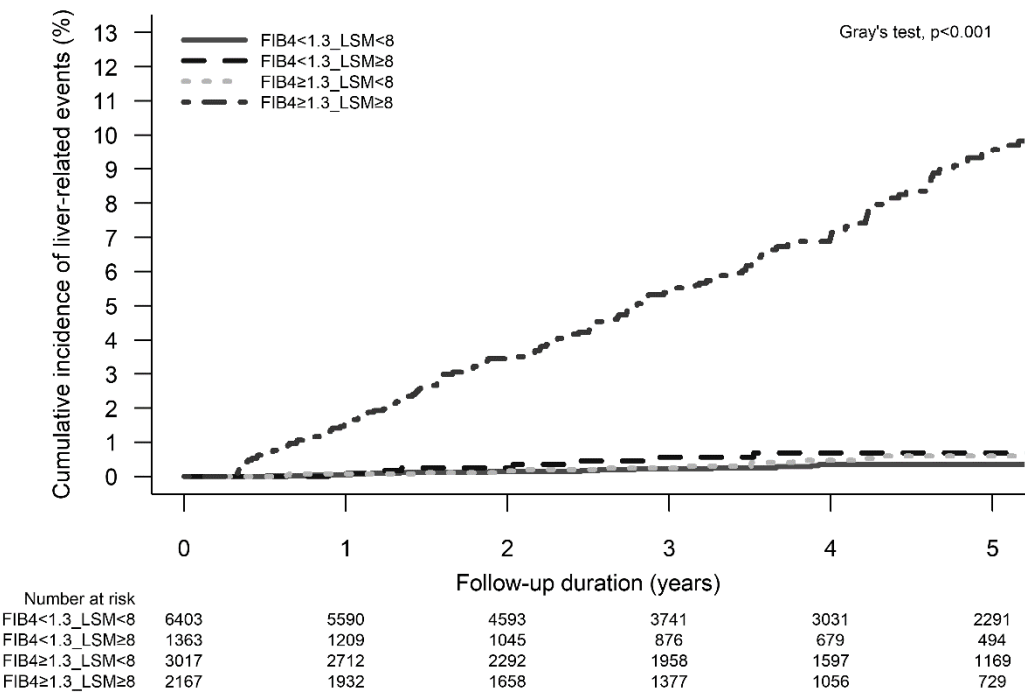
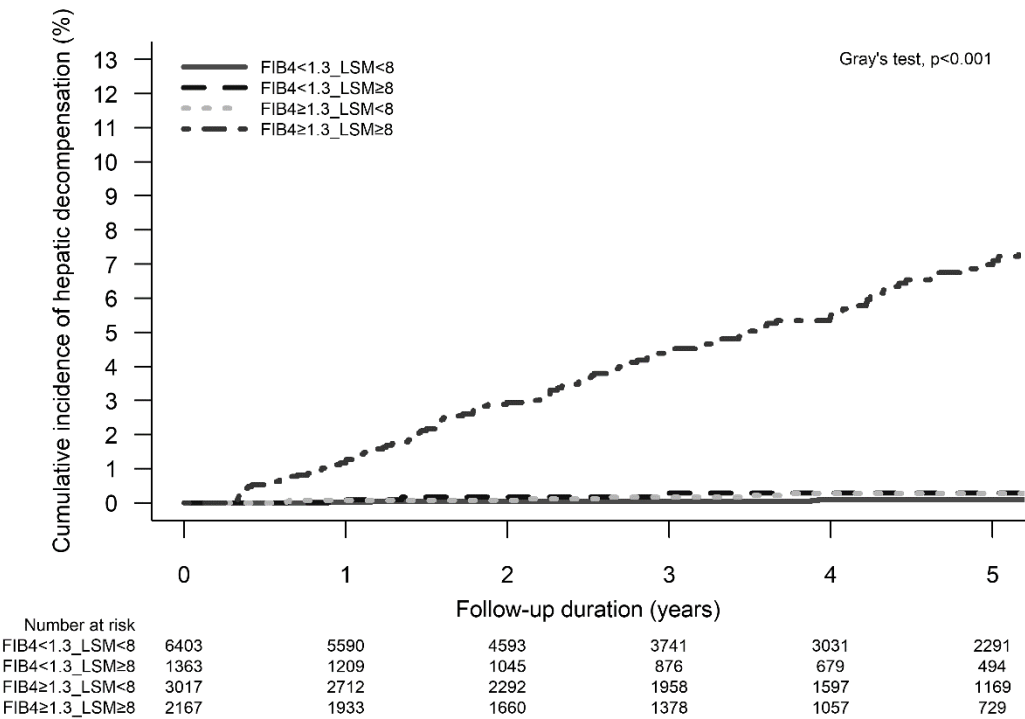


Figure 2. Cumulated incidence of (A) liver-related events, (B) hepatic decompensation, and (C) hepatocellular carcinoma in patients with concordant and discordant Fibrosis-4 index (FIB-4) and liver stiffness measurement (LSM) by vibration-controlled transient elastography.

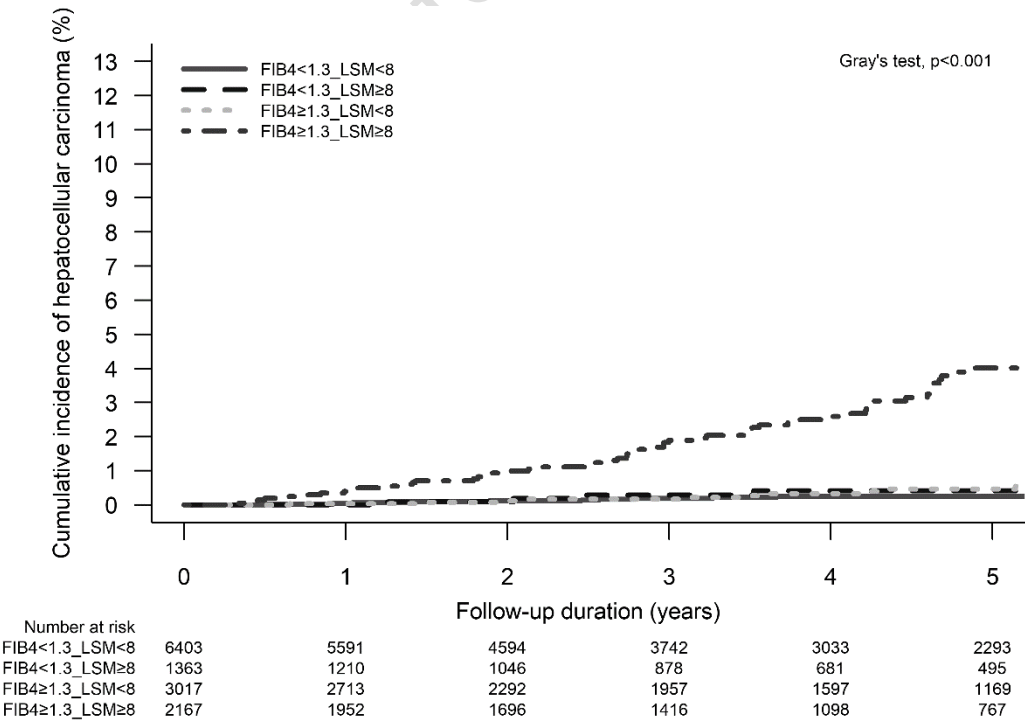
(A)



(B)



(C)



Supplementary materials

Supplementary Table 1. Histological severity of patients with a body mass index of <30 kg/m², and concordant or discordant fibrosis-4 index (FIB-4) and liver stiffness measurement (LSM).

	All	FIB-4 <1.3 LSM <8 kPa	FIB-4 <1.3 LSM ≥8 kPa	FIB-4 ≥1.3 LSM <8 kPa	FIB-4 ≥1.3 LSM ≥8 kPa	P
N	1469	560	217	273	419	
FIB-4	1.2 (0.8 to 2.0)	0.8 (0.6 to 1.0)	0.9 (0.7 to 1.1)	2.0 (1.6 to 2.7)	2.2 (1.7 to 3.0)	-
LSM	7.3 (5.5 to 10.8)	5.7 (4.8 to 6.6)	10.1 (8.9 to 12.0)	5.8 (4.8 to 6.8)	12.4 (10.2 to 16.9)	-
Steatosis grade	2 (1 to 2)	2 (1 to 2)	2 (1 to 2)	1 (1 to 2)	2 (1 to 2)	<0.001
Lobular inflammation	1 (1 to 2)	1 (1 to 1)	1 (1 to 2)	1 (1 to 2)	1 (1 to 2)	<0.001
Hepatocyte ballooning	1 (0 to 1)	1 (0 to 1)	1 (1 to 1)	1 (0 to 1)	1 (1 to 2)	<0.001
NAFLD activity score	4 (3 to 5)	4 (3 to 5)	4 (3 to 5)	3 (2 to 4)	4 (3 to 5)	<0.001
Fibrosis stage	1 (1 to 2)	1 (0 to 1)	1 (1 to 3)	1 (1 to 2)	3 (1 to 3)	<0.001
MASH*, n (%)	778 (53.0)	260 (46.4)	128 (59.0)	117 (42.9)	273 (65.2)	<0.001
At-risk MASH*, n (%)	392 (26.7)	66 (11.8)	66 (30.4)	46 (16.8)	214 (51.1)	<0.001
F2-F4 fibrosis, n (%)	602 (41.0)	109 (19.5)	105 (48.4)	79 (28.9)	309 (73.7)	<0.001
F3-F4 fibrosis, n (%)	367 (25.0)	32 (5.7)	59 (27.2)	32 (11.7)	244 (58.2)	<0.001
Cirrhosis, n (%)	104 (7.1)	4 (0.7)	10 (4.6)	4 (1.5)	86 (20.5)	<0.001

Histological scores are expressed as median (25th to 75th percentile).

Continuous variables were compared by Kruskal-Wallis test. Categorical variables were compared by chi-square test.

*MASH was defined as a NAFLD activity score ≥4 with at least 1 point in all steatosis, lobular inflammation and hepatocyte ballooning. At-risk MASH was defined as MASH plus F2-F4 fibrosis.

FIB-4, Fibrosis-4 index; LSM, liver stiffness measurement; MASH, metabolic dysfunction-associated steatohepatitis; NAFLD, nonalcoholic fatty liver disease

Supplementary Table 2. Histological severity of patients with a body mass index of ≥ 30 kg/m², and concordant or discordant fibrosis-4 index (FIB-4) and liver stiffness measurement (LSM).

	All	FIB-4 <1.3 LSM <8 kPa	FIB-4 <1.3 LSM ≥ 8 kPa	FIB-4 ≥ 1.3 LSM <8 kPa	FIB-4 ≥ 1.3 LSM ≥ 8 kPa	P
N	1313	313	384	142	474	
FIB-4	1.2 (0.8 to 1.9)	0.8 (0.5 to 1.0)	0.9 (0.6 to 1.1)	1.7 (1.5 to 2.3)	2.1 (1.6 to 2.8)	-
LSM	9.7 (6.9 to 14.4)	6.0 (5.1 to 6.9)	11.4 (9.2 to 14.3)	6.3 (5.4 to 7.2)	14.3 (10.6 to 21.6)	-
Steatosis grade	2 (1 to 2)	2 (1 to 2)	2 (1 to 2)	2 (1 to 2)	2 (1 to 2)	0.053
Lobular inflammation	1 (1 to 2)	1 (1 to 1)	1 (1 to 2)	1 (1 to 2)	1 (1 to 2)	<0.001
Hepatocyte ballooning	1 (1 to 1)	1 (0 to 1)	1 (1 to 1)	1 (0 to 1)	1 (1 to 2)	<0.001
NAFLD activity score	4 (3 to 5)	4 (3 to 5)	4 (3 to 5)	4 (3 to 5)	4 (3 to 5)	<0.001
Fibrosis stage	2 (1 to 3)	1 (0 to 2)	2 (1 to 3)	1 (1 to 2)	3 (2 to 3)	<0.001
MASH*, n (%)	823 (62.7)	170 (54.3)	253 (65.9)	77 (54.2)	323 (68.1)	<0.001
At-risk MASH*, n (%)	520 (39.6)	53 (16.9)	156 (40.6)	41 (28.9)	270 (57.0)	<0.001
F2-F4 fibrosis, n (%)	736 (56.1)	81 (25.9)	216 (56.2)	56 (39.4)	383 (80.8)	<0.001
F3-F4 fibrosis, n (%)	488 (37.2)	25 (8.0)	127 (33.1)	22 (15.5)	314 (66.2)	<0.001
Cirrhosis, n (%)	122 (9.3)	3 (1.0)	21 (5.5)	1 (0.7)	97 (20.5)	<0.001

Histological scores are expressed as median (25th to 75th percentile).

Continuous variables were compared by Kruskal-Wallis test. Categorical variables were compared by chi-square test.

*MASH was defined as a NAFLD activity score ≥ 4 with at least 1 point in all steatosis, lobular inflammation and hepatocyte ballooning. At-risk MASH was defined as MASH plus F2-F4 fibrosis.

FIB-4, Fibrosis-4 index; LSM, liver stiffness measurement; MASH, metabolic dysfunction-associated steatohepatitis; NAFLD, nonalcoholic fatty liver disease

Supplementary Table 3. Fine-Gray proportional subdistribution hazards model on liver-related events in the complete case analysis.

Group	Univariate SHR	95% CI	P	Model 1 aSHR	95% CI	P	Model 2 aSHR	95% CI	P
Liver-related events									
FIB-4 <1.3 LSM <8 kPa	Ref			Ref			Ref		
FIB-4 <1.3 LSM ≥8 kPa	3.92	2.01 - 7.63	<0.001	4.33	2.23 - 8.43	<0.001	4.24	2.12 - 8.51	<0.001
FIB-4 ≥1.3 LSM <8 kPa	1.83	0.94 - 3.57	0.078	1.22	0.62 - 2.40	0.575	1.27	0.64 - 2.53	0.502
FIB-4 ≥1.3 LSM ≥8 kPa	32.91	20.37 - 53.15	<0.001	22.69	13.77 - 37.36	<0.001	21.24	12.53 - 36.01	<0.001
Hepatic decompensation									
FIB-4 <1.3 LSM <8 kPa	Ref			Ref			Ref		
FIB-4 <1.3 LSM ≥8 kPa	7.01	2.49 - 19.68	<0.001	7.71	2.75 - 21.60	<0.001	7.14	2.50 - 20.39	<0.001
FIB-4 ≥1.3 LSM <8 kPa	2.91	1.00 - 8.41	0.049	1.92	0.65 - 5.68	0.239	1.80	0.61 - 5.36	0.289
FIB-4 ≥1.3 LSM ≥8 kPa	78.73	34.66 - 178.82	<0.001	52.74	22.29 - 124.77	<0.001	41.93	17.32 - 101.49	<0.001
Hepatocellular carcinoma									
FIB-4 <1.3 LSM <8 kPa	Ref			Ref			Ref		
FIB-4 <1.3 LSM ≥8 kPa	2.13	0.81 - 5.60	0.128	2.39	0.91 - 6.31	0.078	2.27	0.80 - 6.42	0.122
FIB-4 ≥1.3 LSM <8 kPa	1.65	0.72 - 3.77	0.237	1.03	0.45 - 2.36	0.947	1.09	0.47 - 2.54	0.835
FIB-4 ≥1.3 LSM ≥8 kPa	18.37	10.09 - 33.45	<0.001	12.43	6.84 - 22.59	<0.001	12.35	6.54 - 23.32	<0.001

aSHR, adjusted subdistribution hazard ratio; CI, confidence interval; FIB-4, Fibrosis-4 index; LSM, liver stiffness measurement; SHR, subdistribution hazard ratio

Model 1 (N=12,950): Adjusted for baseline age and sex

Model 2 (N=12,338): Model 1 + adjustment for baseline body mass index, diabetes, and hypertension

Supplementary Table 4. Fine-Gray proportional subdistribution hazards model on liver-related events in patients with a body mass index of <30 kg/m².

Group	Univariate SHR	95% CI	P	Model 1 aSHR	95% CI	P	Model 2 aSHR	95% CI	P
Liver-related events									
FIB-4 <1.3 LSM <8 kPa	Ref			Ref			Ref		
FIB-4 <1.3 LSM ≥8 kPa	3.84	1.57 - 9.38	0.003	4.14	1.70 - 10.06	0.002	4.17	1.70 - 10.22	0.002
FIB-4 ≥1.3 LSM <8 kPa	1.95	0.93 - 4.08	0.079	1.41	0.66 - 3.03	0.378	1.41	0.66 - 3.02	0.379
FIB-4 ≥1.3 LSM ≥8 kPa	34.60	19.88 - 60.20	<0.001	25.59	14.07 - 46.52	<0.001	25.46	13.97 - 46.41	<0.001
Hepatic decompensation									
FIB-4 <1.3 LSM <8 kPa	Ref			Ref			Ref		
FIB-4 <1.3 LSM ≥8 kPa	9.45	2.54 - 35.20	<0.001	10.13	2.74 - 37.43	<0.001	9.55	2.57 - 35.48	<0.001
FIB-4 ≥1.3 LSM <8 kPa	3.58	1.04 - 12.29	0.043	2.64	0.73 - 9.53	0.139	2.57	0.71 - 9.26	0.150
FIB-4 ≥1.3 LSM ≥8 kPa	95.40	35.08 - 259.44	<0.001	70.38	23.61 - 209.76	<0.001	64.27	21.64 - 190.92	<0.001
Hepatocellular carcinoma									
FIB-4 <1.3 LSM <8 kPa	Ref			Ref			Ref		
FIB-4 <1.3 LSM ≥8 kPa	0.95	0.13 - 6.72	0.957	1.05	0.15 - 7.42	0.961	1.09	0.15 - 7.79	0.932
FIB-4 ≥1.3 LSM <8 kPa	1.47	0.59 - 3.69	0.409	0.93	0.37 - 2.39	0.887	0.94	0.37 - 2.39	0.891
FIB-4 ≥1.3 LSM ≥8 kPa	18.48	9.38 - 36.42	<0.001	12.84	6.48 - 25.46	<0.001	13.16	6.61 - 26.19	<0.001

aSHR, adjusted subdistribution hazard ratio; CI, confidence interval; FIB-4, Fibrosis-4 index; LSM, liver stiffness measurement; SHR, subdistribution hazard ratio

Model 1: Adjusted for baseline age and sex

Model 2: Model 1 + adjustment for baseline body mass index, diabetes, and hypertension

Supplementary Table 5. Fine-Gray proportional subdistribution hazards model on liver-related events in patients with a body mass index of ≥ 30 kg/m².

Group	Univariate SHR	95% CI	P	Model 1 aSHR	95% CI	P	Model 2 aSHR	95% CI	P
Liver-related events									
FIB-4 <1.3 LSM <8 kPa	Ref			Ref			Ref		
FIB-4 <1.3 LSM ≥ 8 kPa	3.19	0.97 - 10.55	0.057	3.30	1.00 - 10.93	0.050	3.09	0.92 - 10.43	0.069
FIB-4 ≥ 1.3 LSM <8 kPa	1.26	0.23 - 6.88	0.788	0.69	0.13 - 3.72	0.663	0.65	0.12 - 3.58	0.624
FIB-4 ≥ 1.3 LSM ≥ 8 kPa	25.42	9.30 - 69.45	<0.001	14.17	5.17 - 38.84	<0.001	13.22	4.74 - 36.89	<0.001
Hepatic decompensation									
FIB-4 <1.3 LSM <8 kPa	Ref			Ref			Ref		
FIB-4 <1.3 LSM ≥ 8 kPa	3.21	0.59 - 17.48	0.177	3.30	0.61 - 17.99	0.168	2.98	0.53 - 16.90	0.217
FIB-4 ≥ 1.3 LSM <8 kPa	1.34	0.12 - 14.80	0.81	0.71	0.06 - 7.86	0.780	0.66	0.06 - 7.29	0.731
FIB-4 ≥ 1.3 LSM ≥ 8 kPa	41.32	10.06 - 169.64	<0.001	21.91	5.26 - 91.29	<0.001	19.16	4.49 - 81.70	<0.001
Hepatocellular carcinoma									
FIB-4 <1.3 LSM <8 kPa	Ref			Ref			Ref		
FIB-4 <1.3 LSM ≥ 8 kPa	3.38	0.63 - 18.28	0.157	3.50	0.65 - 18.92	0.146	3.48	0.63 - 19.12	0.152
FIB-4 ≥ 1.3 LSM <8 kPa	2.56	0.36 - 18.14	0.348	1.47	0.22 - 10.02	0.695	1.40	0.20 - 9.64	0.732
FIB-4 ≥ 1.3 LSM ≥ 8 kPa	18.15	4.30 - 76.62	<0.001	10.70	2.61 - 43.89	<0.001	10.57	2.51 - 44.55	0.001

aSHR, adjusted subdistribution hazard ratio; CI, confidence interval; FIB-4, Fibrosis-4 index; LSM, liver stiffness measurement; SHR, subdistribution hazard ratio

Model 1: Adjusted for baseline age and sex

Model 2: Model 1 + adjustment for baseline body mass index, diabetes, and hypertension

Supplementary Table 6. Logistic regression model on factors associated with discrepancy of fibrosis-4 index (FIB-4) and liver stiffness measurement (LSM) in the complete case analysis.

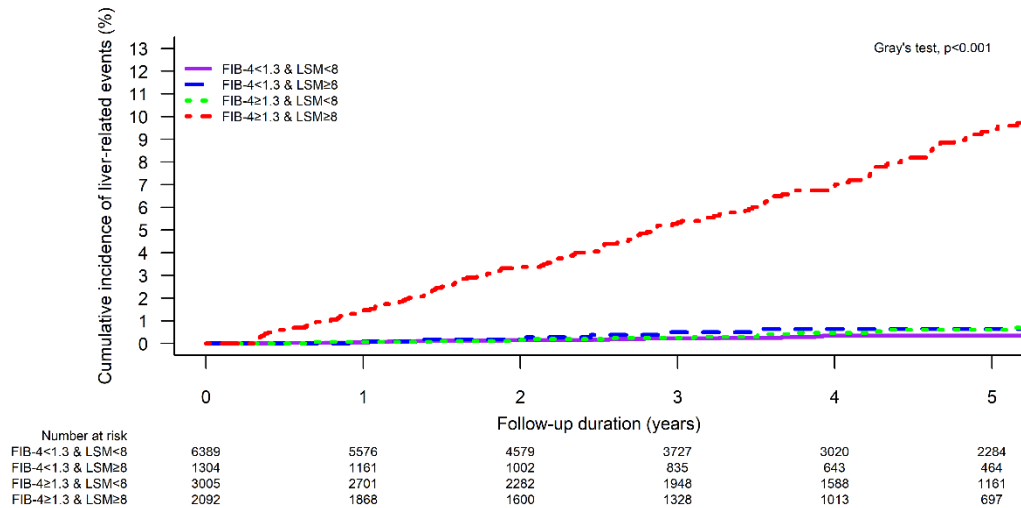
Patients with FIB-4 <1.3 but LSM ≥8 kPa vs Patients with FIB-4 <1.3 and LSM <8 kPa; and patients with FIB-4 ≥1.3 and LSM ≥8 kPa				
	Univariate analysis		Multivariable analysis	
Parameters	OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Male sex (Ref: female)	1.14 (1.01-1.28)	0.035	1.08 (0.90-1.31)	0.391
Europe/US center (Ref: Asia)	1.84 (1.63-2.08)	<0.001	1.42 (1.14-1.75)	0.001
CAP (dB/m)	1.013 (1.012-1.015)	<0.001	1.006 (1.004-1.008)	<0.001
BMI (kg/m ²)	1.10 (1.09-1.11)	<0.001	1.02 (1.01-1.04)	<0.001
Diabetes	1.44 (1.28-1.62)	<0.001	1.43 (1.21-1.69)	<0.001
Hypertension	1.39 (1.23-1.56)	<0.001	1.40 (1.18-1.66)	<0.001
GGT (U/L)	1.000 (1.000-1.001)	0.219	0.999 (0.998-1.000)	0.018
Albumin (g/L)	1.01 (0.99-1.02)	0.427	0.99 (0.98-1.01)	0.590
Total bilirubin (μmol/L)	0.98 (0.97-0.98)	<0.001	0.98 (0.97-0.99)	0.005
Creatinine (μmol/L)	0.998 (0.995-1.000)	0.248	0.998 (0.993-1.000)	0.275
Patients with FIB-4 ≥1.3 but LSM <8 kPa vs Patients with FIB-4 <1.3 and LSM <8 kPa; and patients with FIB-4 ≥1.3 and LSM ≥8 kPa				
	Univariate analysis		Multivariable analysis	
Parameters	OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Male sex (Ref: female)	0.89 (0.82-0.97)	0.009	0.91 (0.79-1.05)	0.186
Europe/US center (Ref: Asia)	0.70 (0.62-0.78)	<0.001	0.71 (0.56-0.90)	0.005
CAP (dB/m)	0.993 (0.992-0.994)	<0.001	1.005 (1.003-1.007)	<0.001
BMI (kg/m ²)	0.93 (0.92-0.94)	<0.001	1.00 (0.99-1.01)	0.609
Diabetes	1.18 (1.08-1.28)	<0.001	0.94 (0.81-1.09)	0.396
Hypertension	1.50 (1.38-1.63)	<0.001	1.10 (0.95-1.27)	0.206
GGT (U/L)	0.999 (0.999-1.000)	<0.001	1.000 (0.999-1.001)	0.510
Albumin (g/L)	0.95 (0.94-0.96)	<0.001	1.02 (1.00-1.04)	0.039
Total bilirubin (μmol/L)	1.00 (1.00-1.01)	0.142	0.99 (0.98-1.00)	0.069
Creatinine (μmol/L)	1.000 (1.000-1.000)	0.704	1.000 (1.000-1.000)	0.497

Age, AST, ALT, platelets, and LSM were also adjusted in the models.

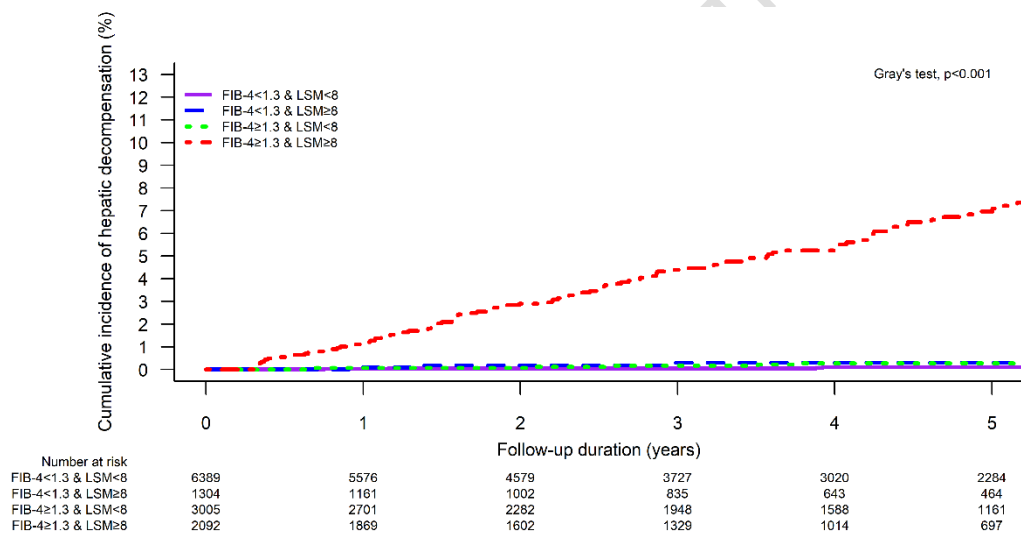
BMI, body mass index; CAP, controlled attenuation parameter; CI, confidence interval; FIB-4, Fibrosis-4 index; GGT, gamma-glutamyl transpeptidase; LSM, liver stiffness measurement; OR, odds ratio.

Supplementary Figure 1. Cumulated incidence of (A) liver-related events, (B) hepatic decompensation, and (C) hepatocellular carcinoma in patients with concordant and discordant Fibrosis-4 index (FIB-4) and liver stiffness measurement (LSM) by vibration-controlled transient elastography in 12,790 patients with reliable LSM.

A.



B.



C.

