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FIB-4 and incident severe liver outcomes in patients with undiagnosed chronic liver disease: A Fine-Gray competing risks analysis

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Abstract

Background & Aims: The Fibrosis-4 Index (FIB-4) can reliably assess fibrosis risk in patients with chronic liver disease and advanced fibrosis is associated with severe liver disease (SLD) outcomes. However, CLD is under-diagnosed in primary care. We examined the association of FIB-4 risk strata and the incidence of SLD preceding a CLD diagnosis while considering incident CLD diagnoses as competing risks.

Methods: Using primary care clinic data between 2007 and 2018, we identified patients with two FIB-4 scores and no liver disease diagnoses preceding the index FIB-4. Patients were followed from index FIB-4 until an incident SLD (a composite of cirrhosis, hepatocellular carcinoma, or liver transplantation), CLD, or were censored. Hazard ratios were computed using a Fine-Gray competing risk model.

Results: Of 20,556 patients, there were 54.8% in the low, 34.8% in the indeterminate, 6.6% in the high, and 3.8% in the persistently high-risk FIB-4 strata. During a mean 8.2 years of follow-up, 837 (4.1%) patients experienced an SLD outcome and 11.5% of the sample received a CLD diagnosis. Of patients with an SLD event, 49% received no preceding CLD diagnosis. In the adjusted Fine-Gray model, the indeterminate (HR 1.41; 95% CI 1.17 – 1.71), high (HR 4.65; 95% CI 3.76 – 5.76), and persistently high-risk (HR 7.60; 95% CI 6.04 – 9.57) FIB-4 risk strata were associated with a higher incidence of SLD compared to the low-risk stratum.

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Conflicts of Interest

All authors report no conflicts of interest with this study.

Ethics

The Institutional Review Board at the Medical University of South Carolina approved this study.

Conclusions: FIB-4 scores with indeterminate and high-risk values are associated with an increased incidence of SLD in primary care patients without known CLD.

Lay Summary

The Fibrosis-4 Index (FIB-4) provides non-invasive, accessible, and inexpensive fibrosis risk assessment in patients with known chronic liver disease. However, missed and delayed diagnosis of chronic liver disease in primary care limits FIB-4's use in this setting. This study demonstrates that elevated FIB-4 scores are associated with severe liver disease outcomes even in patients where chronic liver disease has gone undiagnosed.

Keywords

Fibrosis-4 Index; non-invasive testing; advanced fibrosis; chronic liver disease

Introduction

Advanced liver fibrosis is associated with increased risk of cirrhosis, hepatocellular carcinoma, and liver-related mortality in patients with chronic liver diseases.^{1–7} Efforts to improve the non-invasive detection of advanced fibrosis have included the use of the Fibrosis-4 Index (FIB-4), a serologic advanced fibrosis risk assessment tool that relies upon readily available blood tests (aminotransferases and platelet count) stored within the electronic health record (EHR).^{8–11} FIB-4 has provided accurate fibrosis risk assessment in biopsy-proven NAFLD cohorts, patients with viral hepatitis, other chronic liver diseases, and demonstrated promise in identifying patients with elevated fibrosis risk in primary care.^{8,9,11–18}

Beyond fibrosis assessment in patients with known chronic liver disease (CLD), high-risk FIB-4 scores have also been associated with severe liver outcomes in population-based studies.^{19–22} Hagstrom and colleagues first demonstrated this relationship between single and recurrent FIB-4 scores in a population-based Swedish dataset from 1985–1996.²⁰ We reinforced this relationship using contemporary data and stratified Cox models.²² Results from these studies demonstrate an association between high-risk FIB-4 scores and severe liver disease (SLD) outcomes even in patients without known CLD diagnoses. To this point, FIB-4 calculation and interpretation has been recommended only after a CLD diagnosis is made. Unfortunately, under-diagnosis of CLD in primary care prevents the application of FIB-4 in this setting.

Despite strong and potentially practice-changing associations between high-risk FIB-4 scores and SLD outcomes in these previous analyses, limitations in the analytic approaches warrant consideration before liberalizing the use of FIB-4 for clinical decision-making in primary care. When evaluating the risk of SLD in a general population using Cox proportional hazards models, it is important to recognize that patients' baseline risk is inherently not proportional.²³ A patient has a significantly greater risk for SLD if they have a known CLD. We attempted to address this issue by developing a Cox regression model stratifying patients by known CLD and our findings confirmed the strong association of high-risk FIB-4 scores with SLD outcomes (HR 6.54; 95% CI 5.49–7.77); demonstrated

significant hazard ratios for patients with known NAFLD (HR 7.71; 95% CI 3.62–16.45) and other CLD (HR 11.12; 95% CI 8.33–14.82); and still showed increased hazard of SLD outcomes in patients with high-risk FIB-4 and no previously known CLD (HR 4.04; 95% CI 3.10–5.28).²² But stratified Cox regression models also have limitations, as variable stratification can reduce estimation efficiency, complicate the ability to stratify for other predictor variables, and challenge our ability to make inferences for the stratification variable.^{23,24} These Cox regression methods could not fully account for the contribution of known CLD to an SLD outcome, potentially overestimating the relationship with FIB-4 in patients without a prior CLD diagnosis.^{22,25}

To improve our understanding of FIB-4's association with SLD for patients with undiagnosed CLD in primary care, we considered the knowledge of CLDs as competing risks for SLD outcomes. The cumulative incidence function (CIF) can illustrate the incidence of SLD while accounting for known competing CLD etiologies.²³ Fine and Gray introduced the sub-distribution hazard model as a method for modeling the CIF, which considers the rate of an event (i.e. SLD) in patients who have not previously experienced the outcome or those who endured a competing event (CLD diagnosis).^{26,27} The Fine-Gray sub-distribution hazard model allows for the estimation of covariates' effect on the CIF for an outcome event of interest, and allows for variables that do not satisfy the proportional hazards assumption.^{26,27} For clinical applications, covariates associated with increases in the sub-distribution hazard function will be associated with an increased incidence of the primary outcome.^{22,26,28}

We conducted a retrospective cohort study of primary care patients to better characterize the relationship between combinations of repeated FIB-4 scores and the incidence of SLD in patients with undiagnosed CLD using a Fine-Gray sub-distribution hazard model. We hypothesized that even when accounting for the knowledge of CLD diagnoses, combinations of FIB-4 scores including high-risk assessments would be associated with an increased incidence of SLD outcomes in primary care patients with undiagnosed CLD.

Methods

Using retrospective data from an academic primary care clinic's electronic health record (EHR), we identified patients with the laboratory results necessary to calculate FIB-4 scores and investigated the association of FIB-4 risk strata and SLD in undiagnosed patients while accounting for CLD diagnoses as competing risks.

Patients

We evaluated all patients receiving care from the internal medicine clinic at the Medical University of South Carolina (MUSC) between 2007 and 2018. The practice conducts 32,000 patient visits yearly and delivers care to a diverse (39% non-white), adult (mean age 59 years) population. Patients with alanine (ALT) and aspartate (AST) aminotransferase results (must have included at least one pair with both values < 500 U/L) during the period were identified, and index FIB-4 scores were calculated ($FIB-4 = [(Age \times AST) / (Platelets \times ALT)]$) for the earliest available set of aminotransferase values where a platelet count was available at the time of, or in the 2 months preceding the ALT and AST results.^{11,22} The

patient's age at the time of the aminotransferase results was used for calculating the FIB-4. After the index FIB-4 values were determined, we searched for the next set of qualifying ALT, AST, and platelet count values and calculated a "second" FIB-4. We required the next set of values to be at least 2 months after the index FIB-4 to ensure that unique aminotransferase and platelet results were used in the calculations. All patients with two FIB-4 scores were considered for the patient sample. We excluded all patients with an International Classification of Diseases (ICD)-9/10 code for a CLD (NAFLD, viral hepatitis, hemochromatosis, Wilson's disease, etc.) or outcome (cirrhosis, hepatocellular carcinoma, or liver transplantation) prior to the index FIB-4 score (Table S1). Patients undergoing liver transplant for acute liver failure were also excluded.²²

All patient FIB-4 scores were categorized by advanced fibrosis risk: low-risk (FIB-4 < 1.3); indeterminate-risk (FIB-4 = 1.3 – 2.67); and high-risk (FIB-4 > 2.67) using the risk thresholds established for NAFLD.^{9,12,22,29} After categorization of each patient's index and second FIB-4 scores, patients were categorized by combinations of FIB-4 risk scores: persistently high, high, indeterminate, and low (Figure 1). The persistently high category included patients with two high-risk assessments; the high category included patients with only one high-risk assessment; the indeterminate category included patients with at least one indeterminate score and no high scores; and the low category comprised patients with only low-risk FIB-4 assessments.

Outcomes and Follow-Up

The first occurrence of an SLD outcome served as the primary event of interest. This outcome was defined by a composite of ICD-9/10 diagnostic codes for cirrhosis, hepatocellular carcinoma, and liver transplantation (Table S1).^{30,31} Hepatology clinic notes and pathology results in the EHR were reviewed to accurately assign liver transplantation dates. Diagnoses of CLDs were the secondary events, or competing risks, in this analysis. These were defined as the occurrence of ICD-9/10 codes for either NAFLD or other CLD (e.g. viral hepatitis B and C, alcohol-related liver disease, autoimmune hepatitis, etc.) prior to the incidence of an SLD outcome or the end of the study period. NAFLD was emphasized due to its emergence as the leading cause of CLD in primary care and the growing body of literature supporting FIB-4's application for fibrosis risk stratification in patients with NAFLD.^{10,32,33} Beginning with the index FIB-4, patients were followed until the primary event or the end of the study period (December 31, 2018). In this analysis, subjects who did not suffer an SLD outcome by the end of the study period were considered censored. The outcome variable for the survival analysis was defined as a composite of the categorical variable event status (0=censored, 1=CLD, 2=SLD) and the time in days from index FIB-4 to the event of interest or end of the study.

Independent Variables

The primary predictor variable of interest was the FIB-4 risk stratum, categorized as low, indeterminate, high, and persistently high (Figure 1). In patients experiencing the primary liver outcome prior to their 2nd FIB-4 score, their FIB-4 risk strata were determined by the risk category of their index FIB-4 score (low, indeterminate or high) and precluded them from being categorized as persistently high-risk.

A sensitivity analysis also evaluated the association between elevated ALT and SLD outcomes. ALT values used for the first and second FIB-4 calculations were categorized as normal (ALT < 30 IU/L in M; ALT < 19 IU/L in F) and elevated (ALT > 30 in M; ALT > 19 in F). A three-level categorical predictor variable of combinations of ALT normality was created: low ALT, high ALT, and persistently high ALT (Figure S1).

Covariates

Other independent variables of interest included demographic, vital sign, and comorbidity data. Gender was coded dichotomously as Male / Female. Race was a three-level, categorical variable coded as Black, White, and Other. Body mass index (BMI, kg/m²) was coded as a continuous variable of the patient's BMI recorded at the time of, or just prior to, the index FIB-4 score. Using the Elixhauser comorbidity index, the comorbidities of hypertension, diabetes mellitus, hyperlipidemia, cardiovascular disease, hypothyroidism, and kidney disease were identified by ICD-9/10 code placed at any time during the patient's inclusion in the study.^{22,34}

Data Sources

All data came from Medical University Hospital Authority Enterprise and EPIC© (EPIC Systems Corporation, WI) Clarity databases. Clinical, laboratory, and demographic data were obtained in the ambulatory, emergency room, and inpatient settings at MUSC during the study period.

Statistical Analysis

Patient characteristics were reported as frequency counts and proportions for categorical variables, and mean and standard deviation for continuous variables. Patient characteristics were presented for the overall sample and by the occurrence of an SLD outcome. Continuous variables were compared by the occurrence of an SLD outcome using two sample t-tests and categorical variables were compared using chi-square tests.

Cumulative incidence function (CIF) curves for SLD events were plotted by FIB-4 risk strata. The curves used time in days (but displayed as years) as the time scale from index FIB-4 to the outcome of interest or the end of the study period. We modeled the sub-distribution hazard function for SLD outcomes using Fine-Gray regression technique.²⁷ We performed an unadjusted model with the primary predictor variable of FIB-4 risk strata, using the low-risk stratum as the reference. We then developed a Fine-Gray regression model adjusting for gender, race, marital status, smoking history, BMI, and comorbidities. The comorbidities included hypertension, diabetes, hyperlipidemia, cardiovascular disease, hypothyroidism, and kidney disease. Covariates were selected *a priori* from primary care variables associated with chronic liver disease.⁵ Model residual assessments were performed to ensure we used the most appropriate data fit and to identify any potential outliers or influential observations. Additional model assumptions were checked via residual analysis.

As a sensitivity analysis, CIF curves were also plotted for SLD by ALT abnormality groups. The sub-distribution hazard was modeled using Fine-Gray regression methods. Unadjusted and adjusted models were developed with combinations of ALT abnormality as the primary

predictor variable (low ALT was the reference). Statistical analyses were performed using SAS version 9.4 (Cary, NC).

Results

Overall, 20,556 patients were included (Figure 2) and the sample had a mean age of 51 years, was 65% female, and 45% Black (Table 1). The mean BMI for the cohort was 29 kg/m², and 67%, 30%, and 54% of the sample had diagnoses of hypertension, diabetes, and hyperlipidemia, respectively. The median time between qualifying FIB-4 scores was 384 days (IQR: 168–825). After categorizing patients by their combinations of FIB-4 risk strata, 54.8% were in the low, 34.8% were in the indeterminate, 6.6% were in the high, and 3.8% were in the persistently high FIB-4 risk strata. Of included patients, 8,885 (43.2%) had normal ALT values used for both FIB-4 calculations.

During a mean 8.2 years of follow-up, 837 (4.1%) patients experienced an SLD outcome. Of the cohort, 2,365 (11.5%) of the sample received a diagnosis for a CLD, including the assignment of 577 (2.8%) NAFLD diagnoses, 603 (2.9%) HCV diagnoses, and 997 (4.9%) diagnoses of alcohol-related liver disease (ARLD). Of patients diagnosed with SLD, 411 (49%) received no preceding CLD diagnosis. In those with SLD and no preceding CLD, 190 (46%) had diabetes, 163 (40%) had a BMI > 30 kg/m², and 254 (62%) had either diabetes or were obese (BMI > 30 kg/m²). In patients with two FIB-4's preceding an SLD outcome, there was a mean time of 1,087 days (median 1,162 days) from the second FIB-4 until the SLD diagnosis.

In the univariate analysis, higher proportions of patients experiencing an SLD event were in the high and persistently high FIB-4 risk strata compared to those without an SLD event. Also, a higher proportion of patients suffering an SLD outcome were male (49% vs. 35%, $p < 0.001$), unmarried (65% vs. 54%, $p < 0.001$), and current smokers (24% vs. 12%), $p < 0.001$. Patients with SLD diagnoses had lower mean BMIs (28.8 vs. 29.9, $p = 0.001$) and higher burdens of hypertension (81% vs. 67%, $p < 0.001$), diabetes (46% vs. 29%, $p < 0.001$), cardiovascular disease (39% vs. 26%, $p < 0.001$), chronic kidney disease (42% vs. 17%, $p < 0.001$), and CLD (51% vs. 9%, $p < 0.001$).

Figure 3 demonstrates the adjusted cumulative incidence function curves by FIB-4 risk strata. In the unadjusted Fine-Gray model, the indeterminate (HR 1.54; 95%CI 1.28 – 1.84), high (HR 6.25; 95%CI 5.16 – 7.57), and persistently high (10.83; 95%CI 8.86 – 13.23) FIB-4 risk strata were all associated with a higher incidence of SLD outcomes, compared to the low-risk stratum (Table 2). After adjusting for demographic and clinical covariates in the Fine-Gray model, the indeterminate (HR 1.41; 95%CI 1.17 – 1.71), high (HR 4.65; 95%CI 3.76 – 5.76), and persistently high (HR 7.60; 95%CI 6.04 – 9.57) FIB-4 risk strata continued to associate with a higher incidence of SLD events, compared to the low risk stratum. When FIB-4 risk strata were compared pairwise in the unadjusted and adjusted models, each successive risk category was associated with an increased incidence of SLD compared to the preceding risk stratum (Figure 4).

The unadjusted Fine-Gray model using the combinations of abnormal ALT variable demonstrates an association between high ALT (HR 1.79; 95%CI 1.50–2.13) and persistently high ALT (HR 2.19; 95%CI 1.85–2.59) with the incidence of SLD compared to the low ALT group (Table 3, CIF curves Figure S2). The adjusted models also show the association of high (HR 2.01; 95%CI 1.69–2.40) and persistently high (HR 2.89; 95%CI 2.43–3.44) ALT with SLD outcomes.

Discussion

In a sample of primary care patients with two unique FIB-4 scores, combinations of FIB-4 risk categories including indeterminate- and high-risk FIB-4 values were associated with an increased incidence of SLD outcomes compared to consecutive low-risk FIB-4 assessments. Additionally, when comparing FIB-4 risk strata in ascending order of risk, each successive risk stratum was associated with a higher incidence of SLD events (Figure 4): indeterminate vs. low (HR 1.41; 95%CI 1.17–1.71), high vs. indeterminate (HR 3.30; 95%CI 2.71–4.01), and persistently high vs. high (HR 1.63; 95% CI 1.32–2.03).

By using a Fine-Gray sub-distribution hazard model, this work demonstrates a strong relationship between high-risk FIB-4 scores and SLD outcomes in patients with undiagnosed liver disease while accounting for known CLD diagnoses as competing risks. These findings are important because though FIB-4 can accurately predict advanced fibrosis in patients with biopsy-proven CLD, we do not know how well FIB-4 performs in a primary care population where the prevalence of advanced fibrosis is expected to be lower and only a subset of patients have received CLD diagnoses.^{11,35} Our results demonstrate that the occurrence of indeterminate, high, and repeatedly high-risk FIB-4 scores are associated with an increased incidence of SLD events even in situations where CLD is undiagnosed. Our use of a competing risk model in this work focuses on diagnostic information. Classically, competing risk models consider survival data where included subjects can only experience one of several different types of events (e.g. cardiovascular death vs. death from other causes).²³ From a pathophysiology perspective, we would expect most patients to have a CLD prior to an SLD event. However, only some of those patients experiencing the ultimate outcome carried a prior CLD diagnosis (426 [50.9%]). We wanted to know if FIB-4 as a “signal” was associated with SLD in patients with undiagnosed CLD. In our model, knowledge of a CLD diagnosis was the competing risk, since receiving a CLD diagnosis is mutually exclusive of having undiagnosed liver disease and suffering an SLD outcome. Ultimately, improving the diagnosis of CLD in primary care would have the biggest impact on optimizing care delivery to patients and predicting the risk for future SLD events. As work continues to address under-diagnosis, developing methods to identify patients at risk for SLD with incomplete diagnostic information remains important. The baseline hazard of SLD is not proportional for all primary care patients and our currently limited administrative diagnostic information incompletely addresses this variability. Competing risk analyses, like Fine-Gray, can refine our understanding of the relationship between FIB-4 and SLD outcomes in patients with undiagnosed liver disease using known CLD diagnoses as competing risks to provide more conservative hazard ratio estimates than stratified Cox regression and Cox proportional hazards models.

Our findings may highlight the importance of high-risk FIB-4 scores, or demonstrate the value of repeated low-risk FIB-4 assessments in ruling out advanced fibrosis. FIB-4 assessments < 1.3 (low-risk) have been found to have high negative predictive values (90% and up) for advanced fibrosis in previous studies, and we would expect patients with repeated low-risk fibrosis assessments to also have a low risk for future SLD outcomes.^{8,9} Low-risk FIB-4s help identify patients with CLD, specifically NAFLD, who can remain in the primary care domain.^{10,12,18,36} But, the pairwise comparisons of risk strata emphasize the potential value in indeterminate and high-risk FIB-4 scores for signaling a hazard of future SLD (Table 2). The hazard ratio was significantly higher in patients with two high-risk FIB-4s compared to patients with one high-risk score, patients with one high-risk score were at greater hazard than those with only indeterminate scores, and patients with indeterminate scores had a higher incidence of SLD outcomes compared to those with only low-risk FIB-4 values. High-risk FIB-4 scores, and to some extent indeterminate-risk values, signal future risk for SLD events, and may do so better than ALT elevations alone. Since FIB-4 can be easily calculated, often without incurring additional cost, we should consider routinely performing this test and interpreting the results in primary care. All high-risk scores (FIB-4 > 2.67), and arguably indeterminate-risk scores, could prompt primary care physicians to look for CLD, since nearly half of patients progressing to SLD in our study had no prior CLD diagnosis. Based on the low prevalence of NAFLD diagnoses (2.8%) compared to the expected NAFLD prevalence in the U.S. population ($\approx 25\%$), we believe a significant proportion of patients with an SLD outcome and no preceding CLD diagnosis likely had undiagnosed NAFLD.^{33,37} This hypothesis was supported by the high proportion (62%) of these previously undiagnosed CLD patients with either diabetes or obesity (BMI $> 30\text{kg/m}^2$). In situations where CLD is identified, or is already known, FIB-4 scores would signal to PCPs those patients needing specialty care, intensified therapies, or heightened surveillance.

One of FIB-4's advantages in primary care is the availability of the necessary inputs for calculation. Aminotransferases (as part of complete metabolic and liver function test panels) and platelet counts (as part of complete blood counts) are among some of the most frequently ordered tests in medicine and, along with patient age, exist in a structured format in most EHRs.³⁸ The frequency with which new values are available for calculation would likely result in many FIB-4 values being available for interpretation. This study only focuses on the first two qualifying FIB-4 scores during the study period, simplifies each score by risk category, and combines the risk categories into strata. While this approach costs us information, we hoped to study a signal that might be manageable to perform in an already busy primary care practice. Further, we used a FIB-4 risk threshold established for NAFLD (high-risk > 2.67), as this is likely to be the CLD most often encountered by PCPs in the future, and this threshold is the one currently endorsed for escalating advanced fibrosis risk assessment.^{9,39} Our results suggest that a provider recognizing a high-risk (and to some extent, an indeterminate-risk) score in a patient's last two FIB-4 calculations should consider diagnostic action, or escalation of surveillance and management in situations where liver disease is known. Investigation of the relationship of repeated FIB-4 scores over time with future SLD outcomes is warranted.

We recognize limitations in this work. First, these results require cautious interpretation since FIB-4 was originally designed and studied for predicting risk for advanced fibrosis in patients with viral hepatitis C. FIB-4 performance has been studied extensively in patients with known CLD, but its performance in a general population is not known. Also, sub-distribution hazard ratios can provide overlapping information, but we think the total hazard is clinically meaningful here, particularly in the setting of under-diagnosis. Thus, we chose Fine-Gray over a cause specific hazard model for analyzing SLD outcomes with competing risks. Other limitations include the reliance on a composite of diagnostic codes (ICD-9/10) for CLD and our outcome of interest.^{37,40} To address this concern, we utilized previously validated techniques to capture CLD and cirrhosis diagnostic codes and performed a chart review on patients with a liver transplantation outcome.^{30,31,41} Also, data on patient deaths in our EHR are suboptimal. Patients dying in the hospital are accurately recorded, but those dying out of the hospital are incompletely ascertained and documented. On account of this, we were unable to use death as a right censoring event, resulting in the attribution of prolonged survival periods. Thus, our results overestimate our sample's survival time, and this leads to a conservative underestimation of hazard ratios. Alcohol use is also inadequately recorded and available within the EHR, and is a critical variable in understanding the risk of future severe liver events.⁴² Additionally, FIB-4 calculations come from lab results during the study period, but we did not determine why labs were obtained. We restricted qualifying FIB-4 calculations by degree of AST and ALT elevation (<500 IU/L) and the timing of the platelet counts (within 2 months) to limit the number and frequency with which these data derived from acute liver diseases. Lastly, these data come from a single center and only include patients with laboratory inputs for 2 FIB-4 values which could threaten generalizability. However, the primary care focus, the distribution of comorbid conditions, and the number of included patients with normal ALT values on both sets of included liver chemistries (n=8,885, 43%) reflect patients in the general population.

Conclusion

Combinations of consecutive FIB-4 scores with indeterminate and high-risk values are associated with an increased incidence of SLD outcomes in primary care patients without known CLD. FIB-4 calculation and application in primary care may serve as a signal to pursue a liver diagnosis and provide prognostic information in the management of patients with known chronic liver diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Sharing Statement:

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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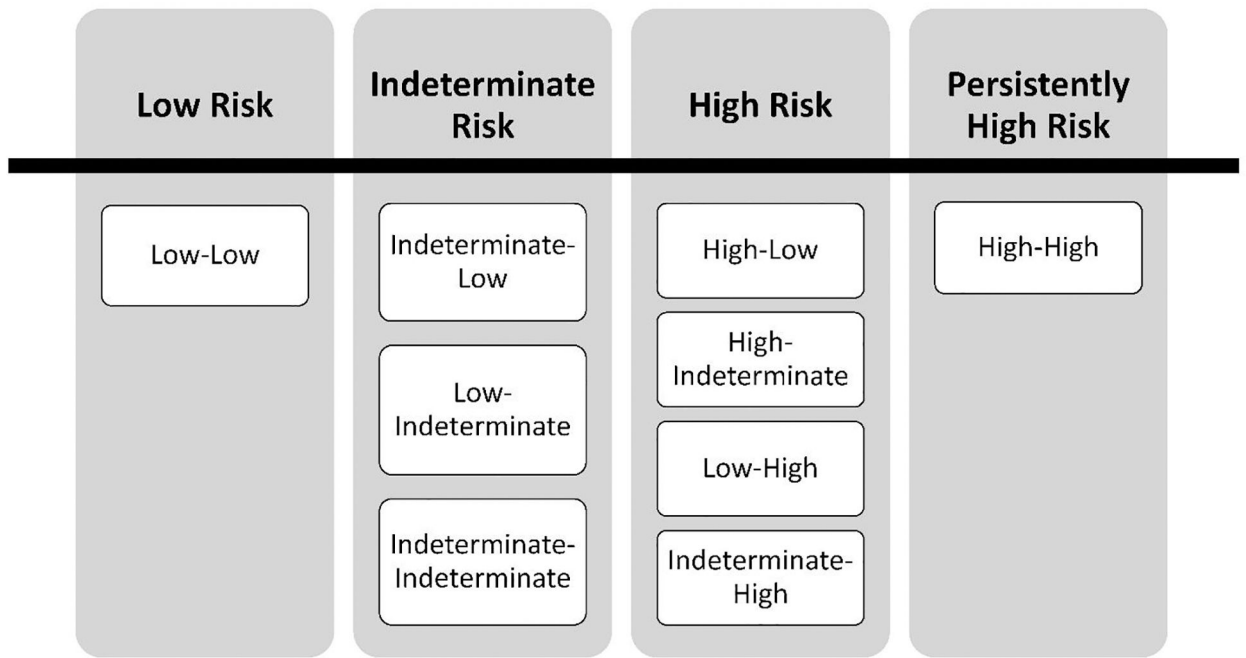


Figure 1:
FIB-4 combination risk strata.

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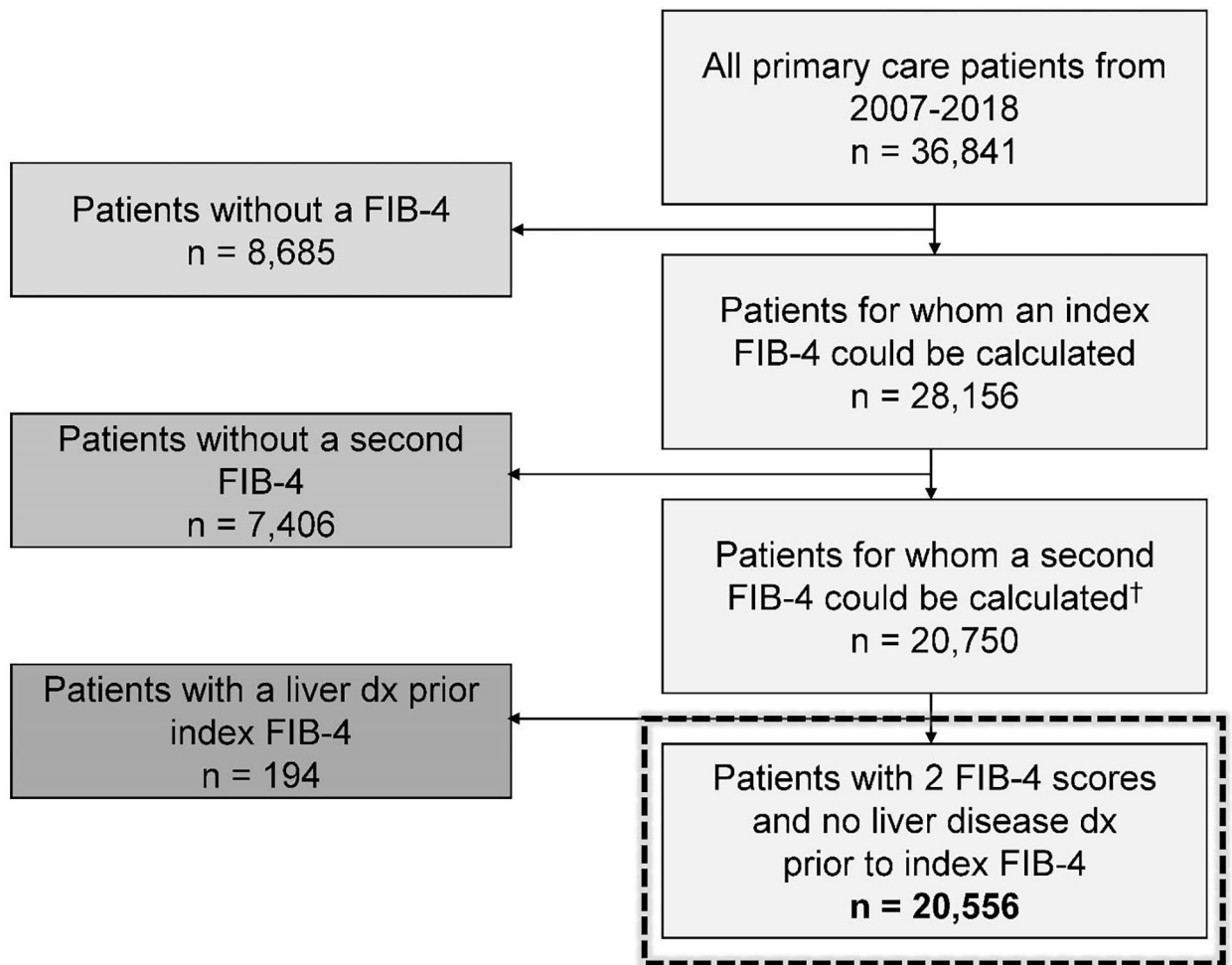


Figure 2:
Consort diagram.

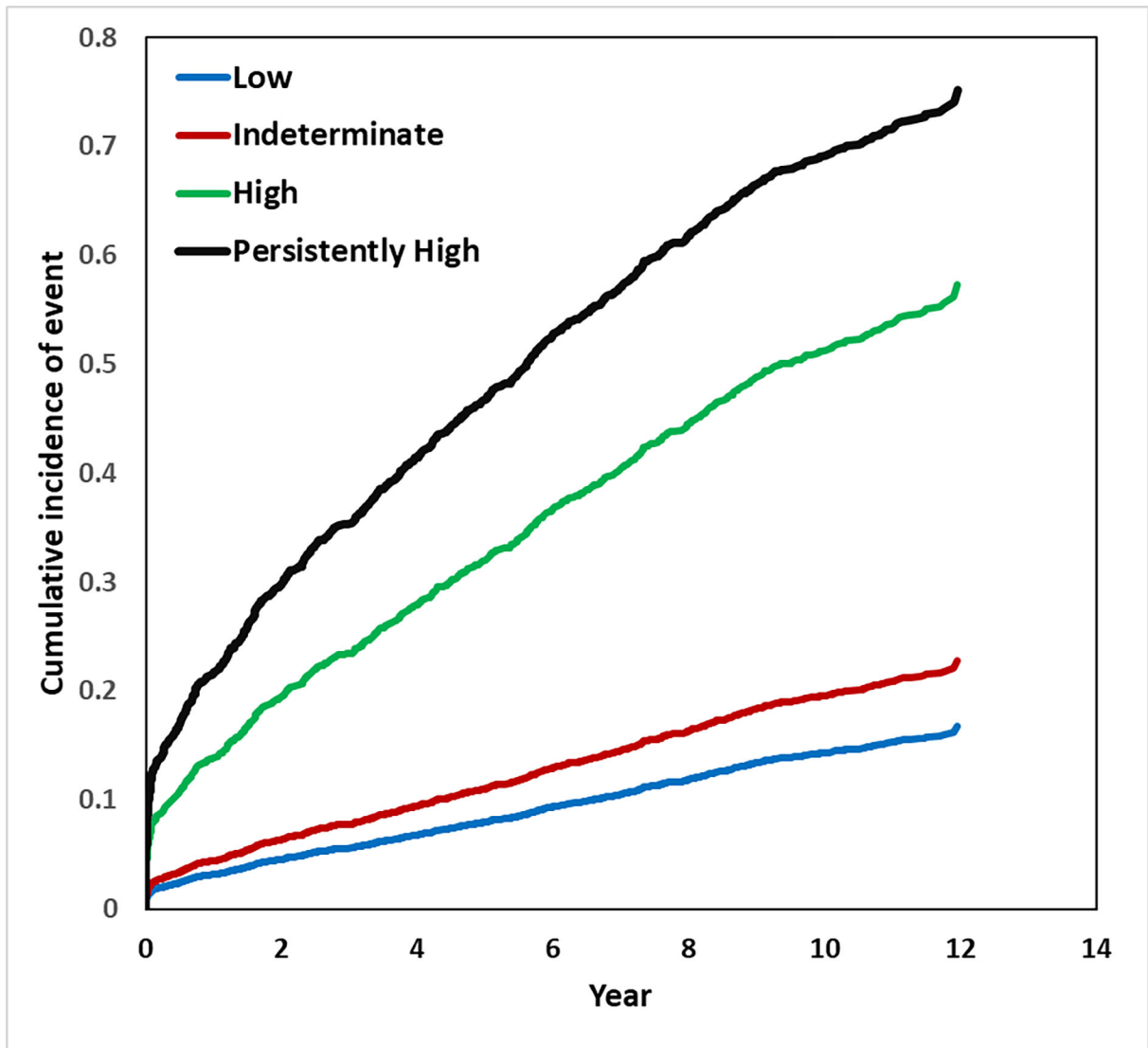


Figure 3.

Adjusted cumulative incidence function curves for the outcome of severe liver disease by combined FIB-4 risk strata.*

*Full adjusted model controls for gender, race, marital status, smoking history, body mass index, and the presence of hypertension, diabetes, hyperlipidemia, cardiovascular disease, hypothyroidism, and kidney disease.

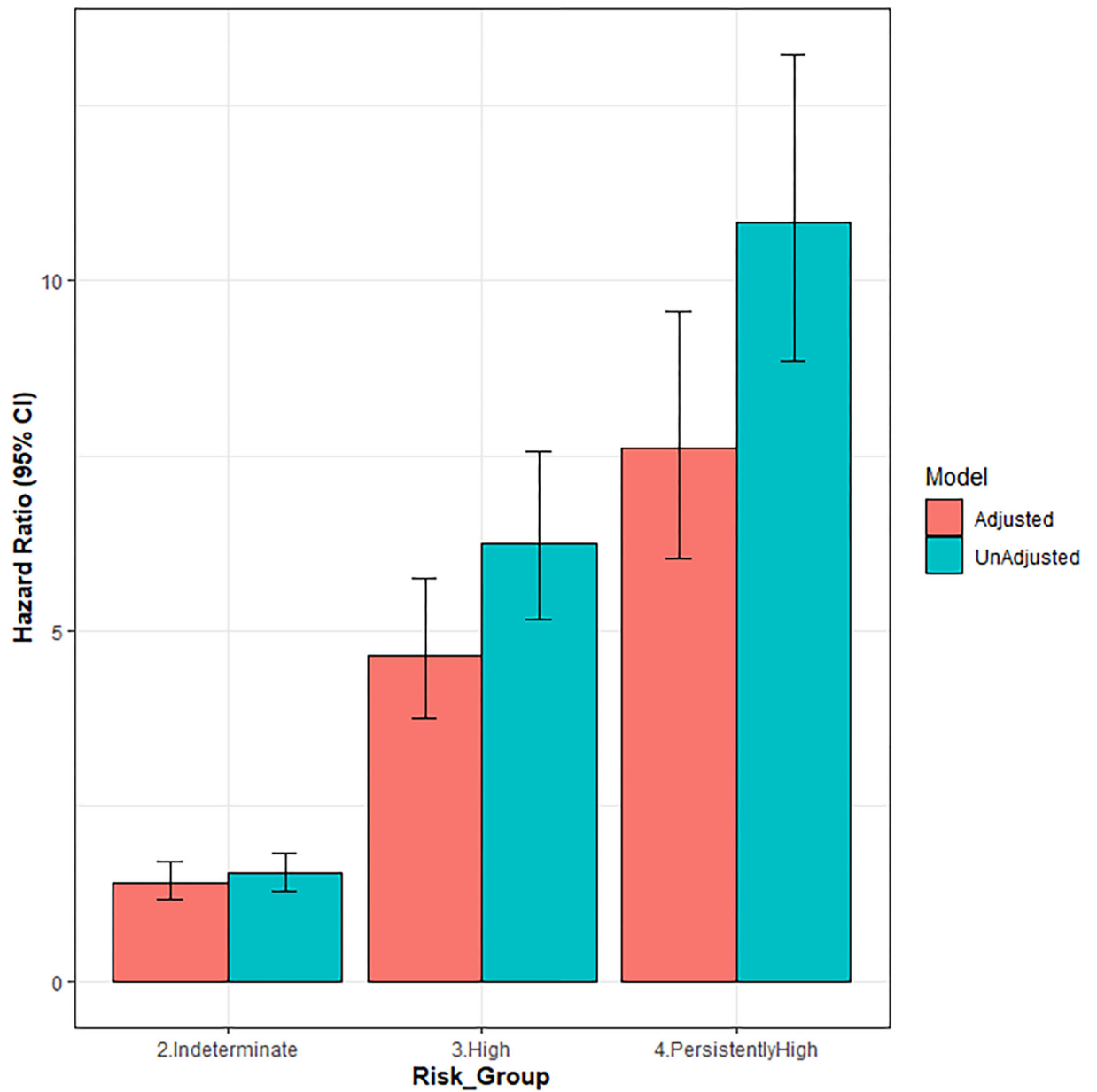


Figure 4. Unadjusted and adjusted Fine-Gray estimated hazard ratios by FIB-4 combination risk strata for the outcome of severe liver disease.

Table 1.

Patient characteristics by severe liver outcomes.

Characteristics	Severe Liver Outcomes			p-value
	Total n=20,556	Yes n=837	No n=19,719	
FIB-4 Combination Risk Strata (%)				< 0.001 *
Low	11,255 (54.8)	231 (27.6)	11,024 (55.9)	
Indeterminate	7,159 (34.8)	239 (28.6)	6,920 (35.1)	
High	1,356 (6.6)	125 (14.9)	1,231 (6.2)	
Persistently High	786 (3.8)	242 (28.9)	544 (2.8)	
ALT Combination Risk Strata (%)				<.0001 *
Low	8,885 (43.2)	225 (26.9)	8,660 (43.9)	
High	5,715 (27.8)	209 (25.0)	5,506 (27.9)	
Persistently High	5,956 (29.0)	403 (48.1)	5,553 (28.2)	
Age (mean ± SD)	51.0 ± 16.6	51.7 ± 13.6	51.0 ± 16.8	0.179 †
Gender (%)				< 0.001 *
Female	64.8	51.3	65.4	
Male	35.2	48.7	34.6	
Race (%)				0.430 *
Black	45.3	47.1	45.2	
Other	2.6	2.9	2.6	
White	52.2	50.1	52.3	
Marital status (%)				< 0.001 *
Married	45.5	34.6	45.9	
Unmarried	54.5	65.4	54.1	
Current smoker (%)				< 0.001 *
Yes	12.5	23.7	12.0	
BMI (mean ± SD)	29.8 ± 8.2	28.8 ± 7.7	29.9 ± 8.2	< 0.001 †
Hypertension (%)	67.1	81.0	66.5	< 0.001 *
Diabetes (%)	29.5	46.1	28.8	<.0001 *
Hyperlipidemia (%)	54.4	50.9	54.6	0.037 *
CVD (%)	26.5	39.1	26.0	< 0.001 *
Hypothyroid (%)	16.0	17.4	16.0	0.255 *
Kidney disease (%)	18.4	42.3	17.4	< 0.001 *
Chronic liver disease (%)				
None	18,290	411 (49.1)	17,879 (90.7)	< 0.001 *
NAFLD	577	74 (8.8)	503 (2.6)	< 0.001 *

Severe Liver Outcomes				
Characteristics	Total n=20,556	Yes n=837	No n=19,719	p-value
Other Liver Dx [†]	1,788	373 (44.6)	1,415 (7.2)	< 0.001 [*]
HBV	152	31 (3.7)	121 (0.6)	< 0.001 [*]
HCV	603	207 (24.7)	396 (2.0)	< 0.001 [*]
ARLD	997	166 (19.8)	831 (4.2)	< 0.001 [*]
Autoimmune ^{**}	50	24 (2.9)	26 (0.1)	< 0.001 [*]
Metabolic	197	22 (2.6)	175 (0.9)	< 0.001 [*]

* Chi-square tests comparing proportions by severe liver outcome occurrence

[†] Two-sample t tests used to compare means by severe liver outcome occurrence.

[‡] 1,788 unique patients had another CLD, but some patients received more than 1 CLD code.

^{**} Includes autoimmune hepatitis and PBC. FIB-4=Fibrosis-4 index. SD=standard deviation. BMI=body mass index (kg/m²). CVD=cardiovascular disease. NAFLD=nonalcoholic fatty liver disease. Dx=diagnosis. HBV=hepatitis B virus. HCV=hepatitis C virus. ARLD=alcohol-related liver disease.

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Table 2.

Estimated Hazard Ratio and 95% Confidence Intervals using Fine-Gray proportional hazard regression models for the association between combined FIB-4 risk strata and severe liver disease.[†]

Combined FIB-4 Risk Strata	Fine and Gray Regression Models			
	Unadjusted Model		Adjusted Model [†]	
	HR	95% CI	HR	95% CI
Low (ref.)				
Indeterminate	1.54	1.28 – 1.84	1.41	1.17 – 1.71
High	6.25	5.16 – 7.57	4.65	3.76 – 5.76
Persistently High	10.83	8.86 – 13.23	7.60	6.04 – 9.57
Pairwise FIB-4 Risk Strata Comparison				
Indeterminate vs. Low	1.54	1.28 – 1.84	1.41	1.17 – 1.71
High vs. Indeterminate	4.07	3.37 – 4.93	3.30	2.71 – 4.01
Persistently High vs. Indeterminate	7.06	5.79 – 8.61	5.39	4.38 – 6.63
Persistently High vs. High	1.73	1.40 – 2.14	1.63	1.32 – 2.03

[†]Full adjusted model is in the Appendix. All models use days from the index FIB-4 score as the time scale. The adjusted model controls for gender, race, marital status, smoking history, body mass index, and the presence of hypertension, diabetes, hyperlipidemia, cardiovascular disease, hypothyroidism, and kidney disease (Full model in the appendix). FIB-4=Fibrosis-4 index. HR=hazard ratio. CI=confidence interval.

Table 3.

Estimated Hazard Ratio and 95% Confidence Intervals using Fine-Gray proportional hazard regression models for the association between combined ALT abnormality strata and severe liver disease.[†]

Fine and Gray Regression Models				
Combined ALT Strata	Unadjusted Model		Adjusted Model[†]	
	HR	95% CI	HR	95% CI
Low ALT (ref.)				
High ALT	1.79	1.50 – 2.13	2.01	1.69 – 2.40
Persistently High ALT	2.19	1.85 – 2.59	2.89	2.43 – 3.44
Pairwise ALT Strata Comparison				
Persistently High vs. High	1.22	1.04 – 1.44	1.44	1.22 – 1.69

[†]The adjusted model controls for gender, race, marital status, smoking history, body mass index, and the presence of hypertension, diabetes, hyperlipidemia, cardiovascular disease, hypothyroidism, and kidney disease.