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Age-dependent differences in FIB-4 predictions of fibrosis in patients with MASLD referred from primary care

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Abstract

Background: Fibrosis 4 (FIB-4) is widely used to triage patients with metabolic dysfunction–associated steatotic liver disease. Given that age is part of FIB-4, higher scores may be expected in the elderly population. This led to the proposal of using a higher threshold of FIB-4 to triage patients aged ≥65. Our main objective is to evaluate how age modifies the association between the FIB-4 index and disease severity based on the vibration-controlled transient elastography (VCTE) "rule of 5s."

Methods: In this cross-sectional study, we prospectively analyzed data from a primary care referral pathway. We used liver stiffness measurement by VCTE as a reference standard for liver risk. We modeled with ordinal regression the exceedance probabilities of finding different liver stiffness measurement thresholds according to FIB-4, and how age modifies FIB-4 predictions.

Results: Nine hundred eighty-five participants with complete data were used for modeling. Participants aged ≥65 had a higher prevalence of advanced liver disease estimated by VCTE and higher FIB-4 values than those <65 (85.9% vs. 20.2% for FIB-4 ≥1.3, and 46.5% vs. 6.5% for FIB-4 ≥2.0). In participants age ≥65, the negative predictive value for VCTE ≥10 kPa of FIB-4 <1.3 was 100% versus FIB-4 <2.0 was 83%. Age significantly modified FIB-4–based prediction of fibrosis, but predictions at a threshold of 1.3 or 2 were only minimally altered. For higher FIB-4 threshold (ie, 2.7), age strongly modified FIB-4 predictions of liver stiffness measurement.

Conclusions: Age does not relevantly modify FIB-4 predictions when using the common threshold of 1.3. Our data suggest no rationale for increasing

Abbreviations: cACLD, compensated advanced chronic liver disease; FIB-4, Fibrosis 4; IQR/M, interquartile range/median ratio; LSM, liver stiffness measurement; MASLD, metabolic dysfunction–associated steatotic liver disease; NITs, noninvasive tests; NPV, negative predictive value; RN, registered nurse; VCTE, vibration-controlled transient elastography.

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the FIB-4 threshold to 2 for undergoing further testing in patients aged ≥65. However, the meaning of a FIB-4 of 2.7 strongly changes with age. This cutoff for ages over 65 is not enough to define high-risk and would not warrant direct referral.

Keywords: ALT, cACLD, cirrhosis, NITs, VCTE

INTRODUCTION

Metabolic dysfunction–associated steatotic liver disease (MASLD), previously known as NAFLD, is estimated to affect ~30% of the world population.[1] In Canada, the prevalence of MASLD is estimated to increase by 20% between 2019 and 2030.[2] This includes a 65% increase in cases with fibrosis stage F3, and a 95% increase in cases of fibrosis stage F4.[2] In comparison to the general population, there is a higher prevalence of MASLD in older adults.[3–5] It is estimated that the prevalence of MASLD in patients between the ages of 60 and 74 is 40.3% in the United States.[5] In addition, higher prevalence of advanced fibrosis is also reported in older patients with MASLD compared to younger populations,[6,7] although results are difficult to interpret since they use either noninvasive tests (NITs) such as NAFLD fibrosis score (NFS) in which age is part of the score[5] or are based on biopsies where the higher prevalence may be related to selection bias.[6] Since patients with MASLD and advanced liver fibrosis (METAVIR scoring stages F3 and F4) are at higher risk of liver complications,[8,9] older patients with MASLD could be, overall, at higher risk of liver-specific complications than their younger counterparts. In fact, studies have shown that older age is associated with a higher risk of HCC and other liver-related complications in patients with MASLD.[10–12] All-cause mortality is also shown to be higher in the elderly population between ages 60 and 74 with MASLD compared to patients without MASLD of the same age, but it is unclear if this is related to the presence of liver-related events.[5] Interestingly, this difference in mortality appears to disappear after age 75 between patients with or without MASLD.[5]

Due to the sheer number of referrals to hepatology service, several NITs and biomarkers with high negative predictive value (NPV) have been developed to predict which patients would have low probability of advanced fibrosis and therefore, could be managed in the primary care setting without further testing.[13] These are commonly incorporated into a 2-step approach in which the first step uses simple tests based on commonly available variables, and the second step involves more specialized tests, such as vibration-controlled transient elastography (VCTE). Indeed, VCTE is becoming the reference standard for risk prediction and to make therapeutic decisions in patients with compensated advanced chronic liver disease (cACLD).[14–17]

Among the initial tests, the Fibrosis 4 (FIB-4) index, due to its simplicity, is the most widely recommended by guidelines[17–19] and has been implemented in several jurisdictions as the first step for MASLD evaluation in primary care.[20] FIB-4 uses patient age, AST, ALT, and platelet count. A FIB-4 of ≥1.3 is recommended as the threshold to consider additional assessments. Furthermore, a FIB-4 >2.67 is suggested in the guidelines as warranting a direct referral to hepatology without additional testing.[21] Higher FIB-4 scores have been demonstrated to correlate with an increase in all-cause mortality and major adverse liver outcomes in patients with MASLD.[22] Since age is a component of the FIB-4, the resultant score will increase as patients become older, even if other components of the score remain unchanged. In addition, there is evidence of a decrease in ALT associated with aging.[12,23]

Despite the extensive literature on the diagnostic accuracy of the sequential approach in the general population, there remains inconsistency on how to use the FIB-4 index according to age, with some groups and guidelines using a corrected threshold of 2.0 above 65 years of age,[17,21,24] and other programs using a single threshold of 1.3 for all patients.[13,20,25]

Even if other NITs for assessment of patients with MASLD might be less impacted by age,[26] and FIB4 is far from a perfect test in terms of sensitivity,[27] its use is now widespread, and likely to continue to expand. The investment in implementation and education has been immense. It is, therefore, important to have a deep understanding of the factors that might modify its interpretation, so its use can be refined.

In the present study, we aimed to assess how age modifies the performance characteristics of FIB-4 as a first step in risk stratification before VCTE in patients referred from primary care with suspected MASLD and whether different thresholds of FIB-4 should be used in patients with young and advanced age. Furthermore, we assessed the performance of FIB-4 in excluding the values of VCTE defining the “rule of 5s,” which is widely used as a simplified prediction tool in patients with MASLD.

METHODS

Referral pathway and patient population

This is a cross-sectional study evaluating data from patients referred by primary care practitioners using a standardized MASLD primary care pathway to the outpatient hepatology clinic at the University of Alberta in Edmonton, Alberta, Canada.[13] This study was approved by the University of Alberta Research Ethics Board as a quality improvement project, and written consent was waived. Using the pathway, patients were referred by primary care providers based on elevated transaminases and/or abdominal imaging suggesting liver steatosis. Patients with jaundice or decompensated liver disease followed a different referral route and were excluded from the pathway. All patients assessed up to 2021 were reviewed by a registered nurse (RN) and had a VCTE examination regardless of FIB-4 value. After that date, a "FIB-4 first" strategy was implemented so patients with a FIB-4 of <1.3 were triaged back to primary care without performing a VCTE. Therefore, this manuscript reports data from 2016 to 2021 only. We included patients aged ≥ 18 with diagnoses of NAFLD. Patients with viral hepatitis, primary biliary cholangitis, autoimmune hepatitis, Wilson disease, and significant alcohol intake (defined as >14 standard drinks per week in women and >21 standard drinks per week in men)[28] were excluded.

Definitions of comorbidities

We consider the diagnosis of diabetes mellitus in participants when their HbA1c is $\geq 6.5\%$, fasting plasma glucose was ≥ 7.0 mmol/L, or were on diabetes medications.[29] Obesity was defined as body mass index over 30 kg/m^2.[30] Indications for statins in dyslipidemia are defined as per Canadian Cardiology Society guidelines.[31]

VCTE

VCTE assessments were completed by an RN using Fibroscan 502 touch (M Probe or XL Probe; Echosens). VCTE reliability criteria have been previously described; unreliable results were defined as liver stiffness evaluation median ≥ 7.1 with interquartile range/median ratio (IQR/M) >0.30.[32,33]

Statistical analysis

Negative and positive predictive values were calculated for different VCTE thresholds (10, 15, 20, and 25 kPa), at the proposed FIB-4 index thresholds of 1.3 and 2. VCTE <10 kPa defines the absence of "compensated advanced chronic liver disease" (cACLD), a concept that reflects the increased risk of liver-related events in the follow-up.[14] The other cutoffs represent the "rule of 5's" heuristic, indicating increased risks, which has been extensively used since its first proposal by Pons et al[34] and later endorsement in Baveno VII guidelines.[14]

We then modeled the association between FIB-4 and VCTE, and the potential impact of age. Any cut point of VCTE to define "high risk" MASLD is arbitrary, and there is an ongoing discussion around the threshold of VCTE to refer to hepatology. To construct a model without assuming beforehand a definite target threshold of VCTE, we used an ordinal regression model for a continuous outcome (in this case, VCTE), where there is no distributional assumption for the response variable (VCTE) given a setting of predictors (in this case age, FIB-4, and their interaction). We used for this ordinal model the log-log link since it provided a better fit than a logit link (see details of the modeling process in Supplemental Data, http://links.lww.com/HC9/B848).[35] This model allows calculating the exceedance probabilities for every threshold of VCTE, according to any value of age and FIB-4. FIB-4 was modeled with restricted cubic splines with 4 knots, and age was modeled linearly after excluding nonlinearity.

RESULTS

Participants characteristics

We included 1035 people with MASLD after excluding participants with alternative liver diagnoses or significant alcohol use. An additional 50 participants were excluded due to unavailable FIB-4 index results or nonreliable or nontechnically feasible VCTE scans. Finally, 985 participants were included in the modeling stage of the study (Figure 1). We show participant characteristics and the number of participants with available data in Table 1. The majority of the patients were under age 50, accounting for about 67% of the sample (68 participants with age ≥ 65, and 28 participants with age ≥ 70). Supplemental Figure S1, http://links.lww.com/HC9/B848, shows the age distribution of the sample. Mean body mass index was similar among the different age groups, whereas the prevalence of diabetes, a major risk factor for advanced fibrosis, progressively increased with advanced age. Mean ALT was lower in older patients. Finally, the proportion of high liver stiffness measurement (LSM) (ie, LSM >10, 15, 20, or 25) increased with age (Table 1). Supplemental Figures S2–S4, http://links.lww.com/HC9/B848, show descriptive plots with the distribution of continuous variables according to age brackets.

Proportion of patients classified as low risk with FIB-4 at different age groups

When FIB-4 <1.3 was used to define "low-risk" patients, the proportion of low-risk patients progressively

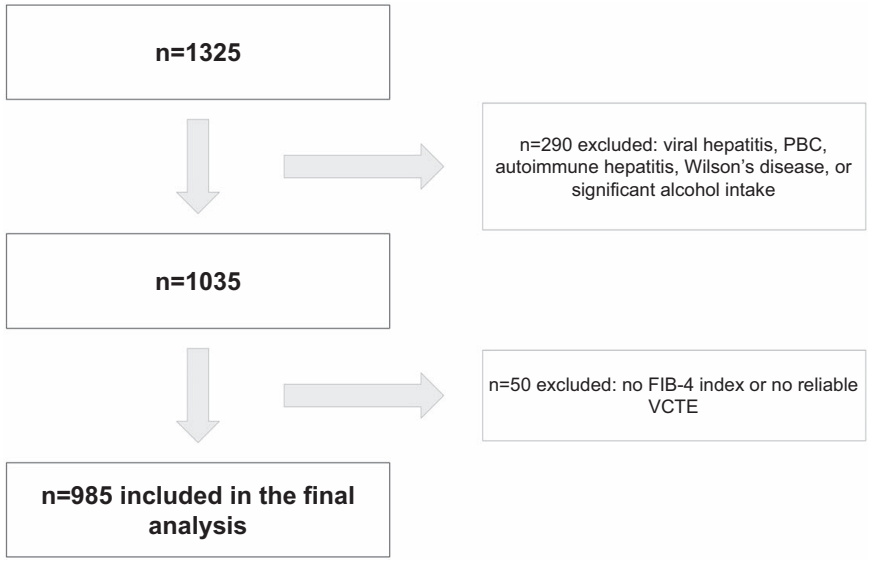

FIGURE 1 Flow chart for patient inclusion and exclusion criteria. Abbreviations: FIB-4, Fibrosis 4; PBC, primary biliary cholangitis; VCTE, vibration-controlled transient elastography.

decreased with older age (from 98% in patients below age 35 to 13% in participants ≥65 years old) (Table 1). When a higher threshold was used (FIB-4 <2.0), the proportion of "low-risk" patients was markedly increased in the older population (Table 1). Indeed, 48% of patients aged ≥65 had a FIB-4 below 2.0.

NPVs for LSM of FIB-4 1.3 and 2.0 cutoffs according to age

Table 2 shows the NPVs of the FIB-4 1.3 and 2.0 cutoffs for excluding values of VCTE according to the rule of 5's, in different age groups. Using FIB-4 of 1.3 thresholds generated higher NPVs than FIB-4 of 2.0 for all LSM thresholds in all age categories. When combining all age groups, both FIB-4 thresholds of 1.3 and 2.0 would generate an NPV over 90%. When focusing on specific age categories, using FIB-4 of 2.0 thresholds performed significantly more inferior compared to FIB-4 of 1.3 in older age groups. In participants over the age of 65, FIB-4 of <1.3 had an NPV of 100%, whereas FIB-4 of <2.0 had an NPV of 83% for ruling out LSM ≥10 kPa.

Modeled exceedance probabilities of different VCTE thresholds according to FIB-4: Impact of age

To further understand the impact of age on FIB-4 predictions, we modeled the association between FIB-4, age, and values of VCTE with ordinal regression. This provides the exceedance probabilities of every VCTE value for any combination of FIB-4 and age. Details of the modeling process, and of the final equations to calculate the predictions are provided in Supplemental Data, http://links.lww.com/HC9/B848. Age ($p = 0.0001$) and its interaction with FIB-4 ($p = 0.03$) had a significant additional contribution to the prediction of VCTE values on top of FIB-4 (Supplemental Table S1, http://links.lww.com/HC9/B848). Calibration of the model is shown in Supplemental Figure S5, http://links.lww.com/HC9/B848, showing excellent agreement between the predicted and observed probabilities.

First, this indicates that age significantly modifies FIB-4 prediction of VCTE. Indeed, in the presence of FIB-4, age had an overall negative association with VCTE values (Supplemental Figure S6, http://links.lww.com/HC9/B848). This suggests that the weight of age in FIB-4 is overestimated when using it for MASLD risk stratification (Supplemental Figure S6, http://links.lww.com/HC9/B848).

Second, due to the presence of a significant interaction between age and FIB-4, the modifying effect of age is different for different levels of FIB-4. Older age attenuated the positive association between FIB-4 and VCTE. However, while this affected the interpretation of higher levels of FIB-4 (ie, 2.0 and 2.7), it had a minimal impact on the interpretation of lower levels of FIB-4 (ie, 1.3).

Figure 2 provides an illustration of this concept. With increased age, predicted VCTE for a FIB-4 of 1.3 or 2.0 does not substantially change. However, the predicted VCTE for FIB-4 of 2.7 is substantially higher at younger ages than at older ages. For example, as shown in the summary provided in Table 3, with a FIB-4 value of 1.3, the probability of having a VCTE of ≥10 kPa is very similar for an age of 40 (13%) and an age of 70 (11%). In contrast, with a FIB-4 of 2.7, the probability of having a VCTE of ≥10 kPa is very different at age 40 (46%)

TABLE 1 Characteristics of the patients in the study sample according to age group

	N	< 35 (N = 272)	35–49 (N = 395)	50–64 (N = 250)	≥ 65 (N = 68)	Test statistic
Female (%)	985	19%	27%	51%	56%	$p < 0.001$[a]
Albumin (g/L)	984	46.00 (44.00–48.00) 46.11 ± 2.68	45.00 (44.00–47.00) 44.89 ± 3.39	44.00 (42.00–46.00) 44.82 ± 14.57	41.00 (38.00–44.00) 41.19 ± 3.52	$p < 0.001$[b]
Bilirubin (μmol/L)	984	12.00 (9.00–17.00) 13.52 ± 7.01	11.00 (9.00–15.00) 12.51 ± 6.03	12.00 (9.00–16.00) 13.40 ± 7.08	10.00 (8.00–12.00) 10.93 ± 4.56	$p = 0.027$[b]
BMI	985	31.32 (27.54–35.59) 31.93 ± 6.13	30.67 (27.80–34.69) 31.49 ± 5.53	31.04 (27.32–35.18) 31.40 ± 5.66	30.88 (28.12–35.03) 31.66 ± 4.97	$p = 0.803$[b]
Total cholesterol (mmol/L)	976	4.96 (4.35 –5.54) 5.02 ± 1.05	4.94 (4.28–5.6) 4.98 ± 1.00	4.71 (4.02–5.35) 4.75 ± 1.15	4.14 (3.63–5.61) 4.47 ± 1.21	$p < 0.001$[b]
Triglycerides (mmol/L)	976	1.65 (1.17–2.44) 1.902 ± 1.015	1.72 (1.25–2.42) 2.025 ± 1.341	1.61 (1.23–2.03) 1.728 ± 0.758	1.53 (1.06–2.24) 1.807 ± 1.105	$p = 0.053$[b]
Diabetes status	985					$p < 0.001$[a]
Prediabetes		35%	44%	40%	37%	
Diabetes		11%	18%	36%	44%	
MCV (fL)	985	87.00 (85.00–89.00) 87.23 ± 10.61	88.00 (86.00–91.00) 88.59 ± 17.29	90.00 (87.00–92.00) 90.21 ± 13.68	91.00 (88.25–94.00) 91.5 ± 5.61	$p < 0.001$[b]
AST (U/L)	985	39 (30–53) 48 ± 33	35 (27–44) 40 ± 23	33 (27–49) 43 ± 29	42 (28–56) 46 ± 27	$p < 0.001$[b]
ALT (U/L)	985	79 (55–105) 92 ± 61	60 (43–79) 68 ± 45	53 (35–78) 64 ± 45	47 (33–66) 55 ± 34	$p < 0.001$[b]
AST/ALT	985	0.52 (0.44–0.62) 0.565 ± 0.230	0.59 (0.49–0.75) 0.650 ± 0.251	0.69 (0.56–0.84) 0.728 ± 0.241	0.82 (0.71–1.03) 0.905 ± 0.293	$p < 0.001$[b]
AST/sqrALT	985	4.58 (4.00–5.34) 4.99 ± 2.04	4.43 (3.92–5.24) 4.91 ± 1.70	5.03 (4.12–6.00) 5.33 ± 1.93	5.61 (4.81–7.14) 6.19 ± 2.16	$p < 0.001$[b]
Platelet count ($\times 10^9$/dL)	985	251 (211–291) 254 ± 59	237 (206–278) 243 ± 59	223 (186–260) 226 ± 65	201 (157–251) 207 ± 65	$p < 0.001$[b]
FIB-4	985	0.54 (0.42–0.67) 0.60 ± 0.27	0.82 (0.67–1.07) 0.93 ± 0.45	1.34 (0.99–1.76) 1.53 ± 1.18	2.07(1.62–2.77) 2.34 ± 1.23	$p < 0.001$[b]
FIB-4 > 1.3	985	2%	12%	53%	87%	$p < 0.001$[a]
FIB-4 > 2	985	0%	3%	14%	52%	$p < 0.001$[a]
FIB-4 > 2.7	985	0%	1%	5%	28%	$p < 0.001$[a]
LSM (kPa)	985	5.15 (4.30–6.10) 5.71 ± 2.59	5.20 (4.40–6.40) 6.10 ± 4.89	5.50 (4.40–6.90) 7.20 ± 6.37	6.35 (4.40–14.30) 10.32 ± 8.35	$p = 0.001$[b]
LSM > 10 kPa	985	6%	6%	13%	37%	$p < 0.001$[a]
LSM > 15 kPa	985	1%	2%	6%	20%	$p < 0.001$[a]
LSM > 20 kPa	985	1%	1%	3%	15%	$p < 0.001$[a]
LSM > 25 kPa	985	0%	1%	3%	7%	$p < 0.001$[a]

Note: *a* (*b*–*c*) represents median (25th–75th percentiles). *x* ± *s* represents X ± 1 SD. N is the number of non-missing values.
[a]Test used: Pearson test.
[b]Test used: Kruskal-Wallis test.
Abbreviations: BMI, body mass index; FIB-4, Fibrosis 4; LSM, liver stiffness measurement; MCV, mean corpuscular volume.

and at the age of 70 (28%). Table 3 provides additional probabilities of exceedance of different VCTE values relevant for decision-making, for different combinations of FIB-4 and age.

DISCUSSION

In this study, we provide a thorough assessment of the impact of age on the performance of FIB-4 as an initial triage tool for predicting patients having high-risk VCTE values. We show that (1) the prevalence of high-risk VCTE values was higher among referred patients with advanced age, (2) advanced age alters the association between FIB-4 and VCTE values, and (3) this impact is minor at the low threshold commonly used in the referral pathway for MASLD (1.3) but has a major impact on the predictions of the cutoff suggested to define high-risk (2.7), which guidelines identify as lack of need for a second test. These findings challenge the concept that a different threshold to define low risk should be used in patients ≥65. It also suggests that the 2.7 (or 2.67)

TABLE 2 NPVs of FIB-4 values of 1.3 or 2.0 at different ages, for different LSM-based classifications

NPV (%)	All (n = 985)	Age ≤35 (n = 272)	Age 36–49 (n = 395)	Age 50–64 (n = 250)	Age ≥65 (n = 68)
LSM ≥10 kPa					
FIB-4 <1.3	95.09	93.99	96.59	92.97	100
FIB-4 <2.0	93.16	94.10	95.29	89.91	83.33
LSM ≥15 kPa					
FIB-4 <1.3	98.94	99.25	99.43	96.88	100
FIB-4 <2.0	98.02	99.26	98.69	96.33	91.67
LSM ≥20 kPa					
FIB-4 <1.3	99.60	99.25	99.72	100	100
FIB-4 <2.0	98.90	99.26	99.48	98.62	91.67
LSM ≥25 kPa					
FIB-4 <1.3	100	100	100	100	100
FIB-4 <2.0	99.45	100	99.74	99.08	94.44

Abbreviations: FIB-4, Fibrosis 4; LSM, liver stiffness measurements; NPV, negative predictive values.

cutoff is not enough to define high-risk patients for direct referral to hepatology clinics, except for young patients.

Previous studies using either liver biopsy[6,7] or liver stiffness[36] show a higher prevalence of advanced fibrosis in older people with MASLD. This is the case also for FIB-4 values, as we show in the present study (Supplemental Figure S3, http://links.lww.com/HC9/B848). This increase in the FIB-4 index may be

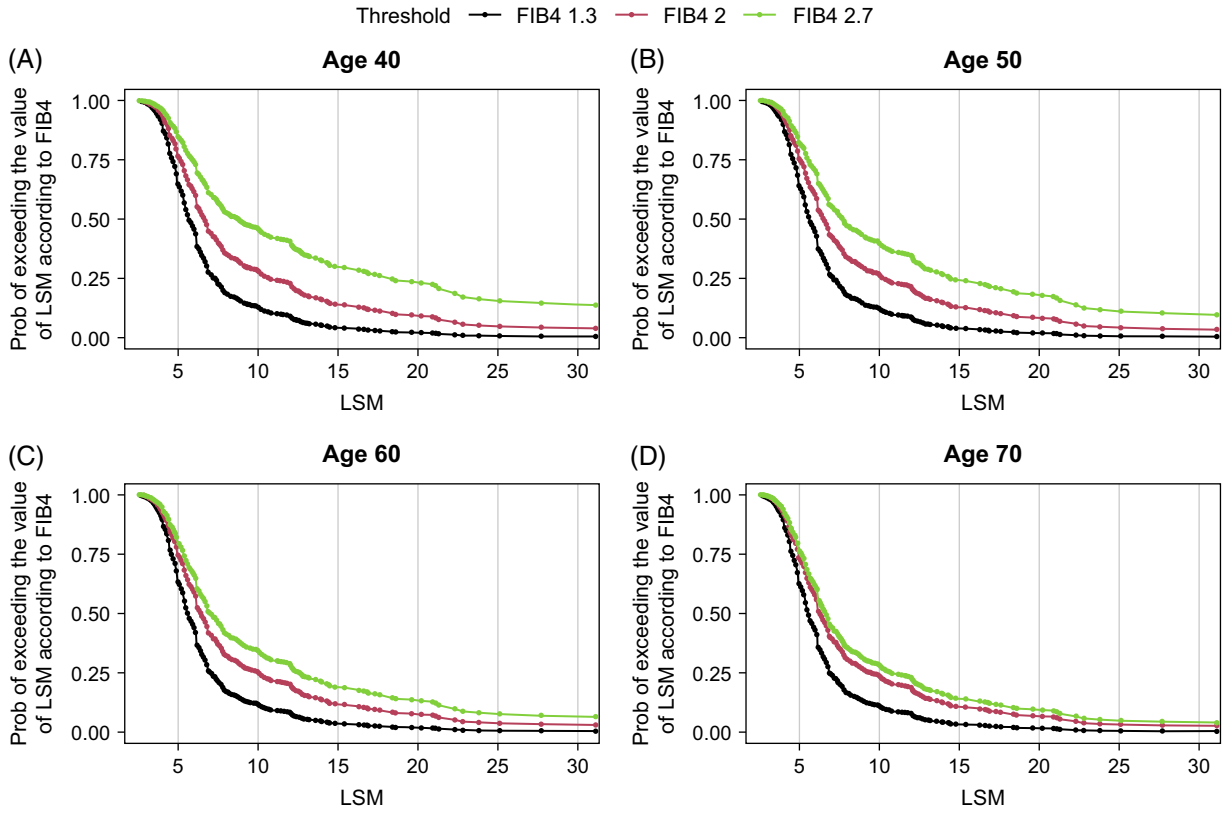

FIGURE 2 Exceedance probabilities of finding any VCTE values for FIB-4 pointwise values of 1.3, 2, and 2.7. The 4 panels represent predictions of LSM at different FIB-4 thresholds for patients at ages 40 (A), 50 (B), 60 (C), 70 (D). These are based on the ordinal model described in the Methods section, and a summary of specific values is provided in Table 3. As shown in the figure, a pointwise FIB-4 of 1.3 is associated with probabilities of 12%–14% of finding a VCTE ≥10 kPa. However, the chances of finding more advanced values of VCTE (≥20 or ≥25) are exceedingly low, close to zero. Age does not have a major influence on the interpretation of values of FIB-4 of 1.3 or 2. However, it majorly changes the interpretation of higher values (in the figure, exemplified by the 2.7 value). In younger people with MASLD, a 2.7 FIB-4 value is associated with a much higher probability of finding a high LSM value, than in older people with MASLD. Abbreviations: LSM, liver stiffness measurement; MASLD, metabolic dysfunction–associated steatotic liver disease; VCTE, vibration-controlled transient elastography.

TABLE 3 Probabilities of exceedance VCTE values of 10, 15, 20, and 25 kPa for FIB-4 values of 1.3, 2, and 2.7 at ages 40, 50, 60, and 70

	Age			
FIB-4 value	**40**	**50**	**60**	**70**
Probabilities of finding a VCTE ≥10 kPa				
1.3	0.13	0.12	0.12	0.11
2	0.28	0.27	0.25	0.24
2.7	0.46	0.40	0.34	0.28
Probabilities of finding a VCTE ≥15 kPa				
1.3	0.04	0.04	0.03	0.03
2	0.14	0.13	0.12	0.11
2.7	0.30	0.24	0.19	0.14
Probabilities of finding a VCTE ≥20 kPa				
1.3	0.02	0.02	0.02	0.02
2	0.09	0.08	0.07	0.07
2.7	0.23	0.18	0.13	0.09
Probabilities of finding a VCTE ≥25 kPa				
1.3	0.01	0.01	0.01	0.01
2	0.05	0.04	0.04	0.03
2.7	0.15	0.11	0.08	0.05

Abbreviations: FIB-4, Fibrosis 4; VCTE, vibration-controlled transient elastography.

partially explained by the increase in the prevalence of advanced fibrosis as shown by the larger proportions of LSM ≥10, ≥15, ≥20, and ≥25 kPa in participants with age ≥65, but it is unclear if the weight of age is overestimated when using FIB-4 in people with MASLD. We also found that ALT tends to decrease with aging (Table 1, Supplemental Figure S4, http://links.lww.com/HC9/B848), which is consistent with previous findings.[12,23,37,38] The exact mechanism for this reduction is still unclear and proposed explanation suggests decrease in liver mass or function with aging.[37,38] Ultimately, the combination of advanced age and decreased ALT may inadvertently lead to misclassification as a high risk for advanced fibrosis of a portion of elderly participants. This is demonstrated by an increase in false-positive rates with increased age in participants across all FIB-4 thresholds (Table 2). Furthermore, Table 3 demonstrates that the probabilities of suspected cACLD are lower in the older population compared to younger age groups at any given FIB-4. With this in mind, there is clearly a need to improve the use of FIB-4 to accurately identify advanced fibrosis without leading to a significant number of false-negative or false-positive cases in the older population where the risk of liver-related events and HCC is higher.

A modified FIB-4 threshold of 2.0 has been described and suggested for use in population aged ≥65.[17,21,24] In our study, a FIB-4 threshold of 2.0 consistently showed inferior NPV in age ≥65 across different VCTE thresholds compared to the FIB-4 threshold of 1.3 (Table 2). In a 2-step approach, a diagnostic test with high NPV is preferred in step 1 as this can help clinicians to safely rule out advanced fibrosis.[25,39,40] Using the FIB-4 threshold of 2.0 to rule out VCTE ≥10 kPa in participants ≥65 in our study population carries a negative predictive value of only 83%. This means that nearly 1 in 6 people with potential cACLD would have been missed if this threshold was applied. In comparison, using the FIB-4 threshold of 1.3 is associated with an NPV of 100% in the same age group. Considering the high prevalence of MASLD in the elderly population, the actual number of false negatives on a global scale would be substantially large if using a higher FIB-4 threshold of 2.0. FIB-4 cutoff below 1.3 has been shown to have good NPV to exclude patients with MASLD at risk of developing liver-related events.[41]

Based on our data, regardless of the patient's age, we suggest that an FIB-4 of <1.3 should continue to be the threshold to rule out cACLD, given its superiority compared to an FIB-4 of <2.0 in the initial step of the 2-step pathway (Table 2). On the other hand, the use of a FIB-4 threshold of 2.7 to identify higher-risk populations of advanced fibrosis may not be as straightforward as stated in the guidelines.[21] As shown in Figure 2 and Table 3, the exceedance probability of any value of LSM for FIB-4 value of 2.7 in participants age 70 is much lower than in younger populations. This implies that FIB-4 would not be an acceptable tool for ruling in advanced fibrosis in older adults, which confirms the need to maintain the second step of risk stratification in these patients.

Our study has important strengths. First, we use a robust modeling methodology (ordinal regression), incorporating the whole range of FIB-4, age, and VCTE values without any categorization. This model allows, in a second step, to calculate useful metrics, such as exceedance probabilities for given specific values of the predictors. This is a more stable strategy than dichotomizing upfront the tests (and outcomes) as positive or negative. Second, our referral pathway included a VCTE evaluation in all patients referred from primary care. With the implementation of 2-step triage mechanisms, there will be lower opportunities for concurrent VCTE and FIB-4 in unselected samples.

There are limitations in this study. First, the number of participants ≥65 years old was low, which leaves uncertainty in the predictions of the model at that range of age. Our initial activities to promote the pathway emphasized early detection of MASLD, which might have favored the referral of younger people. Still, the mean age of our sample (44) is not very different (48) from the one in the study originally validating FIB-4 for MASLD in the NASH-CRN cohort.[42] To mitigate this issue, age was modeled as a continuous variable, which makes the modeling process more robust.

Furthermore, the internal calibration of the model was excellent. Second, the number of participants with high VCTE values was also low, which reflects that this was a sample of patients referred from the primary care level. The predictions of very high values of VCTE, therefore, carry some uncertainty. Again, by modeling the whole range of VCTE, the model borrows information across the whole level of VCTE values, making the process more stable. Furthermore, the critical predictions are around VCTE levels ~10 kPa, which is what triggers the suspicion of cACLD and further specialized monitoring. Third, we did not have liver biopsy results in this study. We do not see this as a major limitation since, in recent years, NITs, especially VCTE, rather than biopsy, are becoming the reference to predict liver-related events.[15,16] Lastly, the data from this study represent the experience of a defined referral pathway in a single health care zone (Edmonton, Canada) and, therefore, might not generalize to different jurisdictions with different referral mechanisms from primary care.

In conclusion, we show in a sample of patients with MASLD referred from primary care that older age alters FIB-4 predictions of liver fibrosis (assessed with VCTE). Still, the performance of a FIB-4 threshold of 1.3 is only minimally altered by age, whereas higher values of FIB-4, such as 2.7, are associated with lower risk in older people with MASLD. Our results, with the inherent uncertainty related to the low number of older people in our sample, suggest that the FIB-4 1.3 threshold for referral to subsequent testing should not be altered in people ≥ 65, as suggested previously. In contrast, the finding of a FIB-4 value over 2.7 should not be used to classify elderly people with MASLD as high risk but should trigger further risk stratification with NITs.

AUTHOR CONTRIBUTIONS

Study concept and protocol development: Shuen Sung, Tracy Davyduke, Mang Ma, and Juan G. Abraldes. Statistical analysis: Shuen Sung, Mustafa Al-Karaghouli, Matthew Tam, and Juan G. Abraldes. Manuscript drafting: Shuen Sung, Yu Jun Wong, and Juan G. Abraldes. Manuscript revision for important intellectual content: Mustafa Al-Karaghouli, Matthew Tam, Saumya Jayakumar, Tracy Davyduke, and Mang Ma. Study supervision: Tracy Davyduke, Mang Ma, and Juan G. Abraldes.

CONFLICTS OF INTEREST

Juan G. Abraldes: consulting for 89bio, Agomab, Novo Nordisk, Boehringer Ingelheim, AstraZeneca, Terumo, and Boston Pharmaceuticals. Grant support: Salix, Gilead, and Cook. Mang Ma: Pharmaceutical grant support: Pfizer, BMS, GSK, Gilead, and Akero. The remaining authors have no conflicts to report.

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