Validating non-invasive tests for diagnostic prediction of fibrosis in patients with biopsy-proven MASLD: CORE, LiverRisk, and FIB-4

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Introduction & Objectives

- Several non-invasive blood-based tests have been proposed for finding advanced fibrosis in patients with known or suspected MASLD.
- Many of these scores are based on other outcomes such as clinical events or VCTE, and have been shown to perform well for those types of outcomes.
- Their diagnostic performance when determining the fibrosis stage according to liver biopsy–which is still the gold standard for diagnosis—is less certain.
- Here, we validated the novel risk scores CORE and LiverRisk, compared with the current first-line test FIB-4 for predicting the stage of liver fibrosis according to biopsy in patients with biopsy-proven MASLD.
- Due to recently approved treatments, patients with earlier stages of fibrosis (F2) may also be of interest for referral to hepatology. Therefore, we evaluate the performance for predicting both ≥F3 and ≥F2.

The Scores we validated

and what they were originally developed to predict

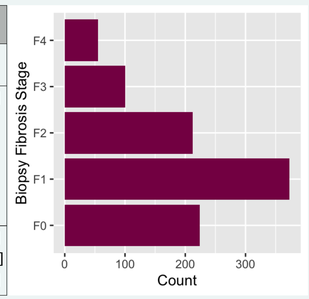
- **FIB-4:** Advanced fibrosis (≥F3) in patients with Hepatitis C & HIV.
- **LiverRisk*:** Liver stiffness (kPa) in a general population setting.
- **CORE**:** The 10-year risk of compensated/decompensated cirrhosis or HCC in a general primary care population setting.

Predictors in each risk score

Score	Age	Sex	ALT	AST	GGT	Platelets	Cholesterol	Glucose
CORE	X	X	X	X	X			
FIB-4	X		X	X	X	X		
LiverRisk	X	X	X	X	X	X	X	X

Patient characteristics and frequencies of biopsy fibrosis stage. Table values are 'median [quartiles]' or %.

	F0-F1 (N=597)	F2 (N=212)	F3-F4 (N=155)
Age	48 [37, 57]	54 [38, 62]	58 [51, 66]
Sex (=male)	64.8%	61.3%	51.0%
AST (U/L)	38.1 [29.4, 51.6]	48.3 [34.4, 64.8]	60.6 [46.2, 91.5]
ALT (U/L)	66.0 [45.0, 101]	85.2 [54.0, 117]	84.0 [52.8, 120]
GGT (U/L)	65.4 [38.4, 118]	67.2 [39.9, 96.0]	100 [57.9, 198]
Platelets (10^9/L)	246 [210, 292]	235 [188, 283]	208 [158, 251]
Cholesterol (mmol/L)	5.8 [5.0, 6.6]	5.7 [4.6, 6.4]	5.6 [4.4, 6.4]
Glucose (mmol/L)	5.4 [4.9, 6.2]	5.60 [5.0, 6.7]	6.7 [5.6, 10.0]
CORE (%)	0.65 [0.29, 1.58]	0.97 [0.39, 2.54]	3.45 [1.60, 6.93]
LiverRisk	6.21 [5.29, 7.73]	6.49 [5.53, 8.14]	9.02 [7.44, 11.50]
FIB-4	0.91 [0.63, 1.25]	1.06 [0.73, 1.78]	2.07 [1.29, 3.08]



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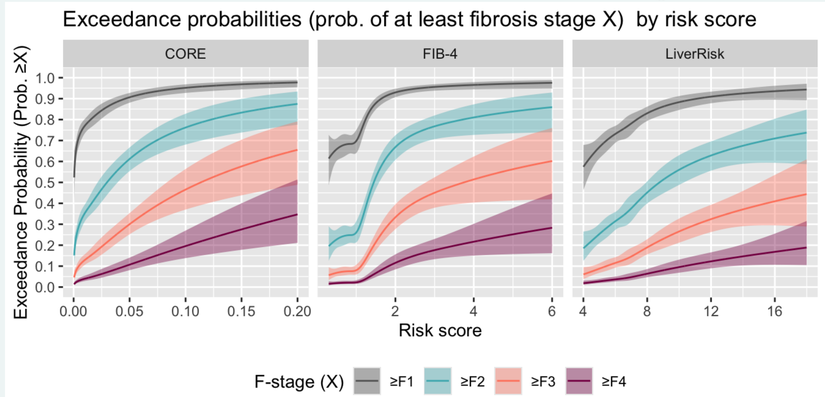
Methods & Data

We used a cohort of 964 patients biopsied and diagnosed with MASLD in Sweden between 1974-2019. The included patients had no history of liver decompensation, HCC, or liver transplantation at the time of biopsy. For a detailed description of the cohort, see [1].

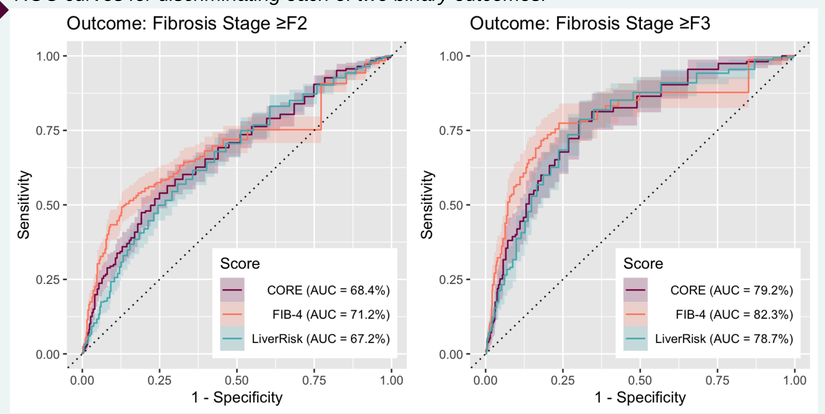
Receiver Operator Characteristic (ROC) curves were estimated using each score. We fitted ordinal proportional odds models with fibrosis stage as the outcome and each score as the predictor with restricted cubic splines. We then estimated the exceedance probabilities for each stage, and the net benefit using these probabilities as risk thresholds.

Results

As each score increases, the probabilities of fibrosis at or above each stage increases:



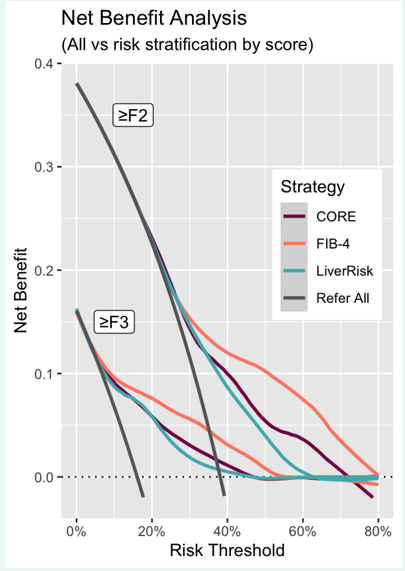
ROC curves for discriminating each of two binary outcomes:



Net benefit and Decision Curves

Decision curves comparing the net benefit of treating or referring patients suspected of having either fibrosis stage ≥F2 of ≥F3. Risk stratification by each score is compared to referring everyone.

Guide: *Depending on the reader's perception of the relative benefit of correctly referring one patient with the outcome relative to the harms/costs of incorrectly referring one patient without the outcome, a corresponding risk threshold should be chosen.*
For example, if we think the benefit is twice as high as the harm, the threshold should be 1/3=33% (a 2:1 balance); if the harm is three times the benefit, the threshold should be 3/4=75% (1:3), etc.
The referral strategy with the highest net benefit at that threshold is then the preferred strategy.



Conclusions

For predicting the current stage of fibrosis in this selected cohort of patients with MASLD

FIB-4 > CORE ≥ LiverRisk

This suggests that risk scores derived from a general population (CORE and LiverRisk) perform less well in patients with more severe disease and with a higher prevalence of fibrosis. The use of any diagnostic or prognostic model should be considered within the context of use.

Outstanding Questions:

- What is the appropriate and clinically actionable outcome we should focus on? (biopsy results, severe liver events, liver stiffness, ...)
- What benefit would we provide to patients if we could predict their outcome?
- Which risk threshold is appropriate for further action? (balancing the benefits to true positives against the harms/costs of false positives)

*While the formula for LiverRisk has not been published, it can nonetheless be reverse engineered from its online calculator by feeding it example values. In this study we used the following formula, which is accurate up to rounding errors in the online calculator: LiverRisk = 3.75 + 0.265[sex=male] + 0.0147[age] + 0.47[glucose] - 0.357[cholesterol] + 0.021[AST] + 0.00178[ALT] + 0.0164[GGT] - 0.00495[platelets]

**Paper still under review. Formula and code available at github.com/ricstra/CORE

References:

[1] Akbari C, et al. Long-term major adverse liver outcomes in 1,260 patients with non-cirrhotic NAFLD. JHEP Rep. 2023 Sep 25;6(2):100915.

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