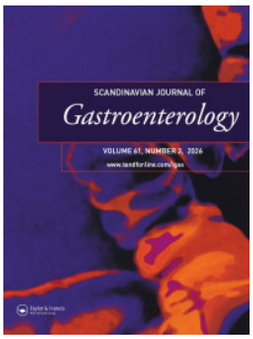

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BRIEF REPORT

Metabolic biomarkers add little to diagnostic performance of FIB-4 in MASLD

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ABSTRACT

Background: Advanced fibrosis is the main risk factor for liver-related complications in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). The first line-test for evaluating presence of advanced fibrosis, Fibrosis-4 index (FIB-4), has limitations. Here, we investigated whether the diagnostic performance of FIB-4 could be improved by incorporating commonly analyzed metabolic biomarkers, including C-reactive protein (CRP), Hemoglobin A1c (HbA1c), the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), or uric acid.

Methods: This cross-sectional study included 276 adult (≥18 years) patients with MASLD from seven Swedish university hospitals. All patients underwent liver stiffness measurement (LSM) for assessment of advanced fibrosis, defined as LSM ≥12 kPa. The performance of FIB-4, CRP, HbA1c, HOMA-IR, and uric acid, alone and in combination, was assessed using logistic regression models. The area under the curve (AUC) was calculated.

Results: An LSM value of ≥12 kPa was found in 45 patients (16%). Combining FIB-4 with CRP, HbA1c, HOMA-IR, and uric acid yielded the highest AUC (0.810; 95% confidence interval [CI] = 0.732–0.889), which was not significantly better than the AUC for FIB-4 alone (0.774, 95%CI = 0.701–0.847).

Conclusions: Adding CRP, HbA1c, HOMA-IR, or uric acid to FIB-4 did not result in any statistically significant improvement in diagnostic performance, suggesting limited additional value of these biomarkers in identifying advanced fibrosis.

Abbreviations: AUC: area under the curve; CRP: C-reactive protein; FIB-4: fibrosis-4 index; FLiS-2: fatty liver in Sweden part 2; HbA1c: hemoglobin A1c; HCC: hepatocellular carcinoma; HOMA-IR: homeostatic model assessment for insulin resistance; LSM: liver stiffness measurement; MASLD: metabolic dysfunction-associated steatotic liver disease; VCTE: vibration-controlled transient elastography

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MASLD; non-alcoholic fatty liver disease; liver fibrosis; non-invasive tests; fibrosis-4 index

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) has become a significant health concern, with a global prevalence of approximately 38% and is currently the most common chronic liver disease worldwide [1]. Over a period of 15–20 years, approximately 3% of patients with MASLD are expected to develop major adverse liver outcomes, including cirrhosis and hepatocellular carcinoma (HCC) [2]. The stage of fibrosis is the strongest predictor of liver-related complications and mortality in patients with MASLD, where biopsy-verified advanced fibrosis (fibrosis stages 3–4 [F3–F4]) poses the highest risk [3]. While biopsy is unsuitable for screening of advanced fibrosis in a highly prevalent disease such as MASLD, the recommended first-line non-invasive test is Fibrosis-4 index (FIB-4), due to its simplicity, high availability, low cost, and extensive validation – including in populations with obesity and type 2 diabetes [4]. However, although high negative predictive value for exclusion of advanced fibrosis,

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FIB-4 has limited diagnostic performance in detecting presence of advanced fibrosis, and there is currently a lack of other simple, cost-effective non-invasive tests with better accuracy. Furthermore, as primary care plays a key role in early detection of MASLD in patients with other common metabolic comorbidities, such as overweight and type 2 diabetes, improved tools for early risk assessment are particularly important in this setting. Therefore, we aimed to determine whether a model with superior diagnostic performance compared to FIB-4 alone could be developed by incorporating inexpensive biomarkers for metabolic health and insulin resistance commonly used in primary care. These biomarkers included C-reactive protein (CRP), hemoglobin A1c (HbA1c), the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), and uric acid, all of which, when elevated, have been associated with fibrosis progression in patients with MASLD [5–8].

Patients and method

This was a cross-sectional study based on the baseline visit of the Fatty Liver in Sweden part 2 (FLiS-2) study. FLiS-2 is an ongoing multicenter cohort including adult (≥18 years) patients with MASLD from seven Swedish university hospitals (Karolinska, Örebro, Uppsala, Linköping, Umeå, Göteborg and Skåne). Participants were recruited between 2016 and 2022 through primary care referrals for suspected MASLD (e.g. imaging-detected liver steatosis or elevated transaminases in patients with cardiometabolic risk factors) or by invitation of patients with a prior diagnosis of MASLD. The MASLD diagnosis required either imaging-confirmed hepatic steatosis (ultrasound, or CT) or persistent aminotransferase elevation in the presence of at least one cardiometabolic risk factor, in accordance with current MASLD diagnostic criteria [9]. All MASLD diagnoses were confirmed by hepatologists at each participating study site. Liver biopsy was performed only when clinically indicated, such as in cases with suspected advanced fibrosis or potential alternative diagnoses. Patients with pre-existing chronic liver disease diagnoses, identified through ICD-10 codes listed in Supplementary Table S1, or alcohol overconsumption (>30 g/day for men or >20 g/day for women), were excluded. All remaining patients subsequently underwent standardised hepatitis serology screening (HBsAg, anti-HBc, anti-HCV with confirmatory testing as required) as well.

At baseline, participants underwent liver stiffness measurement (LSM) by Vibration-Controlled Transient Elastography (VCTE, FibroScan® [Echosens, Paris, France]), after fasting for at least 3 h, to assess fibrosis. Additional data were collected within 30 days of the LSM and included demographics (age, sex), comorbidities and treatments (self-reported and from hospital records), anthropometrics (height, weight, waist and hip circumference), blood pressure, smoking status, alcohol consumption (standard units/week, Alcohol Use Disorders Identification Test - Consumption [AUDIT-C] score, and phosphatidylethanol [PEth, µmol/L]), and laboratory data, including aspartate aminotransferase (AST) and alanine aminotransferase (ALT, both U/L), platelet count (x10^9/L), uric acid (µmol/L), fasting glucose (mmol/L), fasting insulin (mIU/L), and HbA1c. Standard CRP (mg/L) value was used for analysis when available, otherwise high-sensitivity CRP (hs-CRP) was used. hs-CRP was measured by immunoturbidimetry at all participating sites except in Skåne, where nephelometry was used. Analyses were based on the CRP value available per patient. FIB-4 was calculated using the established formula [10] and categorized as low (<1.3), intermediate (1.3–2.67), or high risk (>2.67), independent of age. HOMA-IR [11] was calculated for participants without insulin treatment.

Exclusion criteria for this study were (i) patients with completely missing data, (ii) patients not meeting the nomenclature criteria of MASLD from 2023 [9] on retrospective re-evaluation, and (iii) patients with an incomplete (absence of LSM, IQR [interquartile range], or both) or unreliable LSM by VCTE. The LSM was considered reliable if at least 10 valid individual readings were obtained, and the IQR was ≤30% of the median LSM when LSM was >7.1 kPa, as described by Boursier et al. [12]. Advanced fibrosis was defined as LSM ≥12 kPa, in accordance with European guidelines [13]. After exclusions, the final study population consisted of 276 patients. Supplementary Figure S1 shows a flowchart of participant inclusion and exclusion.

Statistical analyses were conducted using R (version 4.5.0; R Foundation for Statistical Computing, Vienna, Austria). Patient characteristics were presented as counts (n) with percentages (%), or as medians with IQR, due to non-parametric data. Missing data, assumed missing at random, were handled by multiple imputation (mice-package in R). Five complete datasets were generated with five iterations each. Diagnostic performance for detecting advanced fibrosis was assessed using the Area Under the Curve (AUC, pROC package in R) derived from predicted probabilities fitted by logistic regression models. AUCs were calculated for both univariable models, where each biomarker (FIB-4, CRP, HbA1c, HOMA-IR, and uric acid) was analyzed separately, and for multivariable models, where combinations of biomarkers were included in the same model. Estimates for AUC values and 95% confidence intervals

(CI) were pooled across the imputed datasets using Rubin's rules [14]. The models were plotted using average predicted probabilities across the five imputed datasets to illustrate the diagnostic performance of FIB-4 and the best-performing models. The difference in AUC between FIB-4 alone (reference) and the biomarker-based models was calculated using DeLongs test within each imputed dataset. The z-test statistics were then pooled across imputations using the mean value, and two-sided p-values were calculated from the pooled z-statistic. A p-value <0.05 was considered statistically significant. Ethical approval for the FLiS-2 study was granted from the Swedish Ethical Review Authority: dnr 2016/2137-31. Patients provided written and oral consent.

Results

The median age of the study population was 56 years (IQR 45–64), and 51% were male. Advanced fibrosis was detected in 45 patients (16%). The distribution of LSM values was: <8 kPa, 165 participants (60%); 8–12 kPa, 66 participants (24%); and ≥12 kPa, 45 participants (16%). Among the study population, 82 (36.1%) participants without advanced fibrosis and 27 (61.4%) participants with advanced fibrosis underwent biopsy.

The AUC for FIB-4 alone was 0.774 (95%CI = 0.701–0.847). Combinations of FIB-4 with the individual biomarkers yielded AUCs ranging from 0.77 to 0.81, with no statistically significant differences in AUC compared to FIB-4 alone (Supplementary Table S2). The highest performance was observed for the model combining FIB-4 with all examined biomarkers (AUC = 0.810, 95%CI = 0.732–0.889), closely comparable with the model combining FIB-4 with CRP, HbA1c, and uric acid, with overlapping confidence intervals. The best performing biomarker alone was HbA1C (AUC = 0.698, 95%CI = 0.600–0.796). AUCs for FIB-4 and the two best-performing models are presented in Figure 1.

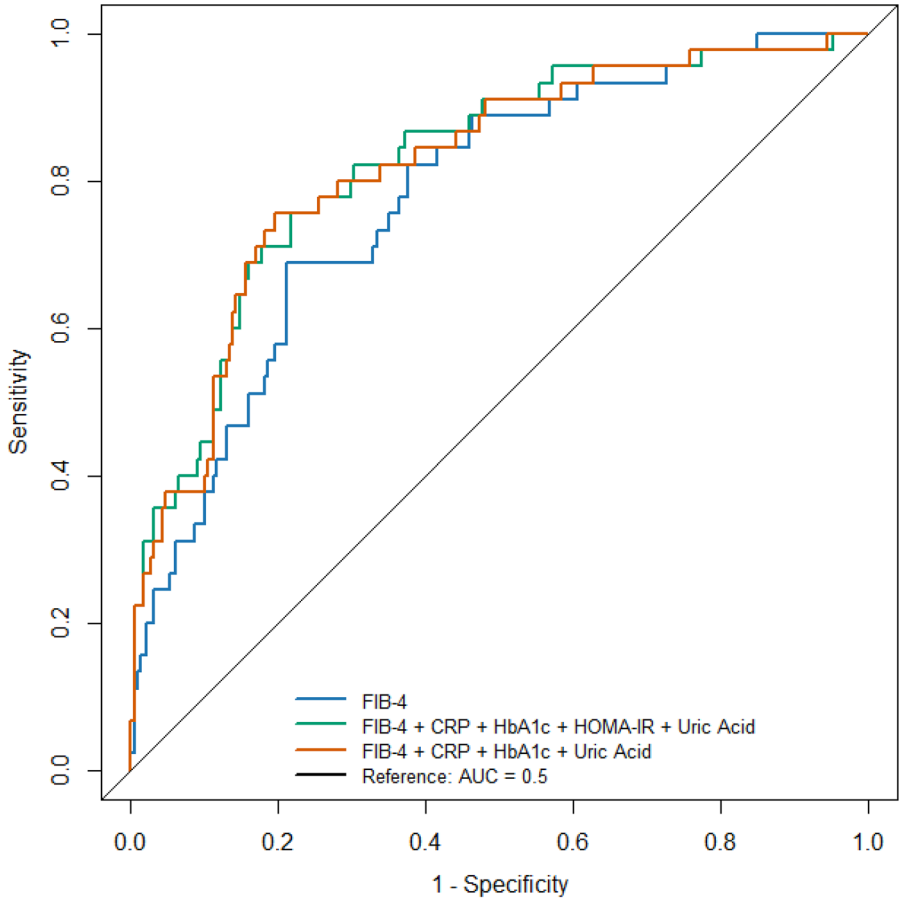

Figure 1. Area under the curve (AUC) for the FIB-4 model and the two best-performing models for detecting advanced fibrosis. The curves are based on average predicted probabilities from five imputed datasets. The pooled AUC was 0.774 (95%CI = 0.701–0.847) for FIB-4, 0.810 (95%CI = 0.732–0.889) for the model combining FIB-4 with all examined biomarkers, and 0.808 (95%CI = 0.726–0.890) for the model combining FIB-4 with CRP, HbA1c and uric acid.

Abbreviations: AUC, Area Under the Curve; CI, Confidence Interval; CRP, C-reactive Protein; FIB-4, Fibrosis-4 index; HbA1c, Hemoglobin A1c; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance.

Discussion

This cross-sectional study investigated whether the diagnostic performance of FIB-4 in detecting advanced fibrosis, defined as a liver stiffness value of at least 12 kPa, in Swedish patients with MASLD could be improved by incorporating CRP, HbA1c, HOMA-IR, or uric acid. The models demonstrated consistently moderate diagnostic performance of advanced fibrosis, with the highest AUC reaching 0.81 in the model combining all examined biomarkers. None of the models showed a statistically significant improvement compared to FIB-4 alone.

Evidence on the diagnostic performance of CRP, HbA1c, HOMA-IR, or uric acid for detecting advanced fibrosis in patients with MASLD is limited. The few existing studies have suggested that HOMA-IR [15] and HbA1c combined with age [16] have only moderate diagnostic performance, comparable to FIB-4. However, comparisons with our study are limited due to differences in fibrosis definitions and FIB-4 cut-offs.

The strengths of this study include the use of a cohort with a heterogeneous study population in terms of age- and sex distribution, as well as nationwide representation across all levels of LSM by VCTE. These factors increase the generalizability of the findings to populations in other Western counties. Furthermore, this study applied the recommended rule-in cut-off for advanced fibrosis at a LSM of 12 kPa, consistent with the European guidelines [13], which thereby increases both the clinical relevance and comparability.

Several limitations should be considered. First, LSM measurements were performed by multiple operators across sites, which introduces a risk of measurement bias due to inter-operator variability. Second, patients were primarily referred from primary care to specialist centers, which could introduce selection bias compared with population screening. Third, we used the same lower FIB-4 cut-off (1.3) across all age groups, whereas European guidelines recommend a higher lower cut-off (2.0) for individuals >65 years [13]. However, a recent study found no added clinical benefit of age-adjusted cut-offs [17]. Fourth, including patients <35 years, for whom FIB-4 has low diagnostic accuracy [4], may have influenced the AUC, as the age component of FIB-4 can misclassify younger patients with fibrosis as low-risk. Finally, the performance of biomarker-based models has only been evaluated in this single study. However, as the models are not significantly better, and not suggested to replace FIB-4, this is of minor concern.

In conclusion, in this multicenter cross-sectional study of Swedish patients with MASLD, no statistically significant improvement in diagnostic performance was observed for any model combining the traditional FIB-4 score with CRP, HbA1c, HOMA-IR, or uric acid, compared to FIB-4 alone for detecting advanced fibrosis.

Authors' contributions

CRediT: **Sofia Ullman**: Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing; **Hannes Hegmar**: Conceptualization, Data curation, Investigation, Methodology, Writing – review & editing; **Johan Vessby**: Data curation, Investigation, Writing – review & editing; **Patrik Nasr**: Data curation, Investigation, Writing – review & editing; **Stergios Kechagias**: Data curation, Investigation, Writing – review & editing; **Nils Nyhlin**: Data curation, Investigation, Writing – review & editing; **Åsa Danielsson Borssén**: Data curation, Investigation, Writing – review & editing; **Mattias Ekstedt**: Data curation, Investigation, Writing – review & editing; **Hannes Hagström**: Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Writing – review & editing.

Disclosure statement

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Data availability statement

Individual patient data are not available due to Swedish regulations. The authors may, upon reasonable request, perform additional analyses.

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