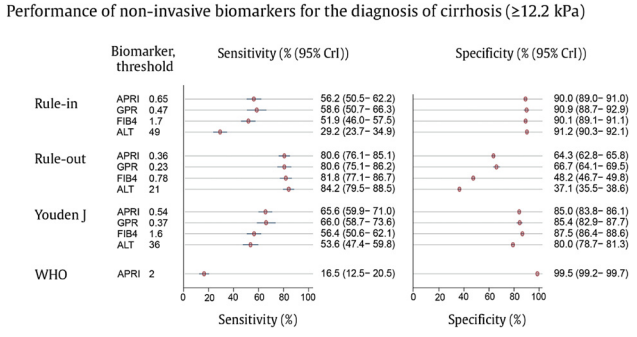
Low-cost non-invasive biomarkers of liver fibrosis are needed to identify patients at risk of HBV-related mortality who therefore require antiviral treatment. We evaluated the performance of the biomarkers APRI (AST to platelet ratio index), FIB-4 and GPR (GGT to platelet ratio) in an individual patient data (IPD) meta-analysis.

Method: We included data from HEPSANET, a network comprised of 12 cohorts of HBsAg-positive individuals in 8 sub-Saharan African countries. We used transient elastography as a reference test for cirrhosis (≥12.2 kPa) and significant fibrosis (≥7.9 kPa). We excluded patients who were pregnant, had hepatitis C, D, or HIV co-infection, were on hepatitis B therapy or had acute hepatitis. Upper limits of normal were 40 U/L for AST/AST and 61 U/L for GGT. We fitted a bivariate Bayesian IPD model with patient-level covariates and study-level random effects.

Results: We included 3549 patients. Median age was 33 years (IQR 28–41) and 60% were male. The prevalence of significant fibrosis and cirrhosis among included cohorts was 18% and 7% respectively. APRI and GPR had the best discriminant performance (area under curve 0.81 and 0.82) relative to FIB-4 (0.77) or ALT alone (0.70) for cirrhosis. The World Health Organization (WHO) threshold of APRI>2.0 was associated with sensitivity of 16.5% (95% credible interval 12.5–20.5) and specificity of 99.5% (99.2–99.7) for cirrhosis. At rule-in thresholds for cirrhosis APRI (cut-off 0.65) had sensitivity of 56.2% and specificity of 90.0%; GPR (cut-off 0.47) had sensitivity of 58.6% and specificity 90.9%. At rule out-thresholds for cirrhosis APRI (0.33) had sensitivity and specificity of 80.6% and 64.3%; GPR (0.23) had sensitivity 80.6% and specificity of 66.7% (Figure). The subset of asymptomatic patients who were diagnosed with HBV through routine screening had a mean cirrhosis prevalence of 2.5%, and APRI (cut-off 0.65) had a positive predictive value (PPV) of 13.2% and negative predictive value (NPV) of 98.8%. Among patients diagnosed with HBV due to suspected liver disease, cirrhosis prevalence was 27%; with APRI cut-off 0.65, PPV was 59.6% and NPV 84.5%.

Conclusion: APRI at the WHO-recommended threshold of 2.0 has a poor sensitivity for the diagnosis of cirrhosis in sub-Saharan Africa; WHO guidelines should be revised for the WHO African region to reflect these findings. APRI and GPR had equivalent diagnostic performance and performed best at ruling out cirrhosis but were less good at correctly identifying cases. Programs need to be aware of the significant trade-offs between under- and over-diagnosis of liver cirrhosis when implementing low-cost fibrosis markers in hepatitis B programs in sub-Saharan Africa.



OS016

Prediction of ten-year risk of severe liver disease in the general population using commonly available biomarkers

Hannes Hagström[1], Jacinth Yan[2], Mats Talbäck[2], Anna Andreasson[3], Göran Walldius[2], Matteo Bottai[2], Niklas Hammar[2]. [1]*Karolinska Institutet;* [2]*Karolinska Institutet, Sweden;* [3]*Stockholm University, Sweden*
Email: hannes.hagstrom@ki.se

Background and aims: Estimating risk for severe liver disease, including cirrhosis, in the general population is complicated in part due to the rarity of this outcome. Existing prediction tools are suboptimal and there is a need for improvement. Here, we aimed to identify subgroups of persons in the general population with high risks for development of severe liver disease using commonly available biomarkers.

Method: We used laboratory and clinical data on 126, 925 individuals aged 35–79, in Stockholm, Sweden, with clinical examinations between 1985 and 1996. No individuals had known chronic liver disease, a drug- or alcohol use disorder at baseline. Nationwide registries were used to ascertain ten-year cumulative incidence of severe liver disease, a composite of diagnoses corresponding to cirrhosis or its complications. Candidate biomarkers were selected based on if they meaningfully improved prediction of severe liver disease in addition to the established FIB-4 score. They were then categorized and combined, creating subgroups with different risk profiles.

Results: During a follow-up of average 9.3 years, we ascertained 630 incident cases of severe liver disease (0.5%). On top of the FIB-4 score we identified age, impaired glucose, and gamma-glutamyl transferase (gGT) to meaningfully improve a classification of risk. 24 risk groups were created, with a cumulative incidence of severe liver disease at ten years ranging from 0.2% (age 35–65, low FIB-4, no impaired glucose and normal gGT) to 32.1% (age 35–65, high FIB-4, impaired glucose and high gGT). A heatmap of these risk groups was created (Figure 1).

Cumulative incidence of severe liver disease at ten years			FIB-4 Low	FIB-4 Intermediate	FIB-4 High
gGT high	Impaired glucose	age ≥66	13.0	13.7	29.1
		age 35-65	2.6	10.7	32.1
	No Impaired glucose	age ≥66	3.6	0.0	22.7
		age 35-65	2.2	7.4	25.4
gGT normal	Impaired glucose	age ≥66	1.3	2.8	12.5
		age 35-65	0.6	1.0	6.0
	No Impaired glucose	age ≥66	0.6	0.7	2.5
		age 35-65	0.2	0.4	5.5

Figure 1: Heatmap of subgroups with differing risk for severe liver disease at ten years, in percent.

Conclusion: Estimates of risk of severe liver disease in the general population using the FIB-4 score can be substantially improved by adding age and biomarkers commonly available in the primary care setting.

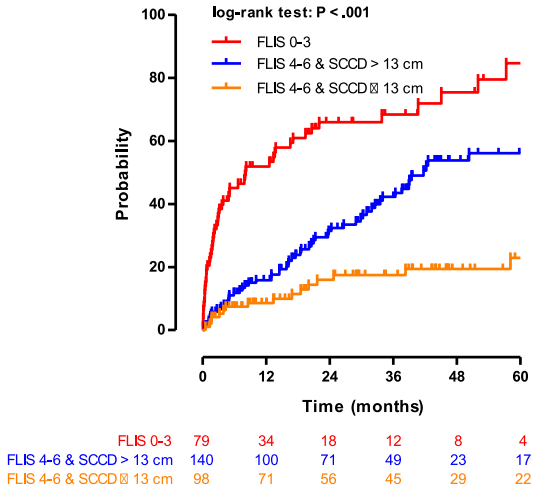
OS017

Gadoxetic acid-enhanced MRI-derived Functional Liver Imaging Score (FLIS) and spleen diameter provide complementary information for risk stratification in ACLD

Nina Bastati[1], Lucian Beer[1], Ahmed Ba-Ssalamah[1], Sarah Poetter-Lang[1], Raphael Ambros[1], Antonia Kristic[1], David Lauber[1], Lorenz Balcar[1], Katharina Pomej[2], Teresa Binter[2,3], Benedikt Simbrunner[2,3], Georg Semmler[2,3], Yesim Bican[1], Jacqueline C. Hodge[1], Thomas Wrba[4], Michael Trauner[2], Thomas Reiberger[2,3], Mattias Mandorfer[2,3]. [1]*Department of Biomedical Imaging and Image-Guided Therapy, Medical University of Vienna, Vienna, Austria;* [2]*Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria;* [3]*Vienna Hepatic Hemodynamic Lab, Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria;* [4]*IT-Systems and Communications, Medical University of Vienna, Vienna, Austria*
Email: mattias.mandorfer@meduniwien.ac.at

Background and aims: The Functional Liver Imaging Score (FLIS) derived from gadoxetic acid-enhanced MRI (GA-MRI) correlates with hepatic function in chronic liver disease (CLD) patients. Splenic metrics, i.e., volume and craniocaudal diameter (SCCD) are markers of portal hypertension, a key driver of disease progression.

We aimed to investigate the prognostic utility of FLIS and SCCD for hepatic decompensation and transplant-free mortality in CLD.
Method: Three hundred ninety-seven CLD patients undergoing GA-MRI were included. The FLIS was calculated by summing the points (0–2 each) assigned to three hepatobiliary phase features: hepatic enhancement, biliary excretion, and portal vein signal intensity. Patients were stratified into 3 clinical groups according to FIB-4 and presence/history of decompensation: non-advanced CLD (non-ACLD), compensated ACLD (cACLD), and decompensated ACLD (dACLD). The associations between SCCD/FLIS and decompensation/transplant-free mortality were investigated using Cox regression analysis and log-rank test.
Results: We observed a strong correlation between spleen volume and SCCD (Spearman's rho: 0.887; $p < 0.001$), and thus, the simple measure SCCD was used for further analyses. The inter-reader (intraclass coefficient, ICC: 0.982; $n = 241$) and intra-reader (ICC: 0.997; $n = 41$) agreement for the SCCD were excellent. Median SCCD showed stepwise increases from non-ACLD (11.8 cm), cACLD (13.3 cm), to dACLD (15.2 cm; $p < 0.001$).
Since non-ACLD patients are at negligible risk of decompensation/liver-related death, we abstained from analysing direct end points in this subgroup. In patients with cACLD, SCCD predicted decompensation (adjusted-hazard-ratio, [aHR]: 1.1, 95% confidence interval [95% CI]: 1.02–1.18; $p = 0.014$) in an analysis adjusted for MELD and albumin; dichotomizing SSCD resulted in an aHR of 2.51 (95%CI: 1.22–5.21, $p = 0.01$) for those with a SCCD >13 cm. In patients with ACLD (i.e., cACLD/dACLD combined), FLIS (0–3 vs. 4–6 points) was a risk factor for transplant-free mortality (aHR: 2.64, 95%CI: 1.61–4.01, $p < 0.001$), even after adjusting for age, MELD, and albumin. Of note, FLIS (0–3 vs. 4–6 points; aHR: 1.74, 95%CI: 1.18–2.58, $p = 0.005$) and SCCD (>13 vs. ≤13 cm; aHR: 2.16, 95%CI: 1.44–3.24, $p < 0.001$) were independently predictive of the composite end point of decompensation/transplant-free mortality, even after adjusting for the previously mentioned prognostic indicators. Grouping patients according to FLIS/SCCD accurately stratified the risk of decompensation/transplant-free mortality (Figure).



Conclusion: The FLIS and SCCD are simple GA-MRI-based imaging markers providing complementary information for risk stratification in patients with advanced chronic liver disease.
N.B. and L.B. contributed equally.

OS018

ADAPT, a score incorporating PRO-C3, for the early detection of liver fibrosis in a large population-based study

Ann T. Ma[1,2,3], Guillem Pera[3,4], Martina Perez[1,2,3,5], Mette Juul Nielsen[6], Morten Karsdal[6], Diana Leeming[6], Carmen Expósito[4], Alba Martínez-Escudé[4,7], Isabel Graupera[1,2,3], Maja Thiele[8,9], Aleksander Krag[8,9], Núria Fabrellas[2,3,5], Llorenç Caballeria[3,4], Pere Ginès[1,2,3,5]. *[1]Liver Unit, Hospital Clínic de Barcelona, Barcelona, Spain; [2]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; [3]Centro de Investigavción Biomédica en Red de Enfermedades Hepática y Digestivas (CIBEREHD), Madrid, Spain; [4]Unitat de Suport a la Recerca (USR) Metropolitana Nord, Fundació Institut Universitari d'Investigació en Atenció Primària Jordi Gol i Gurina (IDIAP Jordi Gol), Mataró, Spain; [5]Facultat de Medicina-Universitat de Barcelona, Barcelona, Spain; [6]Nordic Bioscience, Herlev, Denmark; [7]Centre d'Atenció Primària La Llagosta, La Llagosta, Spain; [8]Department of Gastroenterology and Hepatology, Odense University Hospital, Denmark; [9]Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark*
Email: pgines@clinic.cat

Background and aims: Non-invasive screening of liver fibrosis in the general population has become an important target in order to identify liver disease early and avoid its progression. Novel biomarkers of extracellular matrix formation, including PRO-C3, a marker of type III collagen formation, have emerged as accurate predictors of advanced fibrosis in NAFLD and alcohol-related liver disease. A composite score known as ADAPT, that includes PRO-C3, age, platelet count, and diabetes, has recently been validated in both these patient populations, but its effectiveness to screen for liver fibrosis in asymptomatic subjects in the general population is unknown.
Method: This study was performed in a large population-based cohort of randomly selected subjects aged 18–75 in the Barcelona metropolitan area without known liver disease (mean age 54, 43% male, 10% with type 2 diabetes, 28% with metabolic syndrome, 9% with at-risk alcohol consumption). Serum PRO-C3 levels were measured by enzyme-linked immunosorbent assay in 2670 subjects. Liver fibrosis was estimated by measuring liver stiffness with transient elastography (TE). Significant fibrosis was defined as a TE ≥9.2 kPa based on previous data supporting that this cut-off had the best diagnostic accuracy for fibrosis ≥F2 on liver biopsy (Clin. Gastroenterol. Hepatol. 2018 PMID 29452268).
Results: The prevalence of significant fibrosis was 3.1% (83/2670). The median level of PRO-C3 was higher in subjects with significant fibrosis compared to those without (14 vs. 12 ng/ml, $p < 0.001$). The ADAPT score predicted significant fibrosis with moderate accuracy (AUROC 0.76; 95% CI 0.71–0.82), higher than scores frequently used to identify fibrosis in the general population, such as FIB-4 or APRI, and similar to NAFLD Fibrosis Score (NFS). Fatty liver index (FLI) exhibited the highest discriminative ability (AUROC 0.87; 95% CI 0.84–0.91; Figure 1). Amongst subjects with metabolic/alcohol risk factors and a high FLI≥60, the sequential use of ADAPT using the best cut-off of 6.1 had an excellent negative predictive value for significant fibrosis (Se 51%, Sp 82%, PPV 20%, NPV 95%).