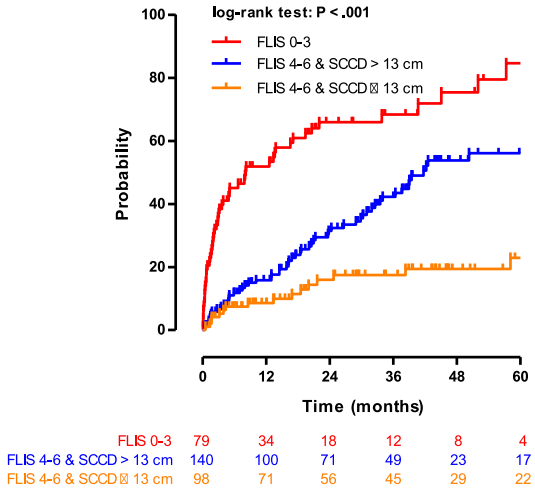
We aimed to investigate the prognostic utility of FLIS and SCCD for hepatic decompensation and transplant-free mortality in CLD.
Method: Three hundred ninety-seven CLD patients undergoing GA-MRI were included. The FLIS was calculated by summing the points (0–2 each) assigned to three hepatobiliary phase 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

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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%).

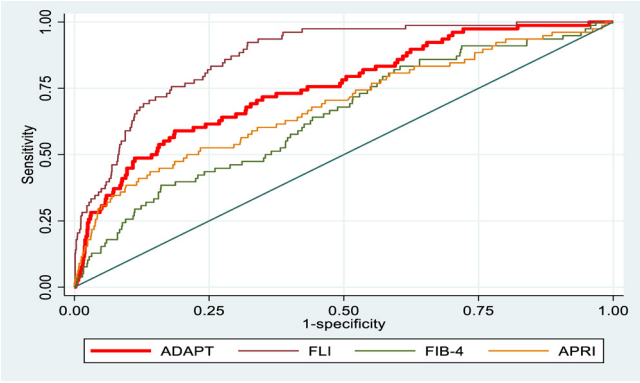

Figure: ROC curves of non-invasive fibrosis scores for prediction of significant fibrosis.

Conclusion: In this population-based study, the ADAPT composite score that includes PRO-C3 offers superior predictive accuracy for the diagnosis of significant liver fibrosis as compared to other recommended screening tools such as FIB-4 and APRI. The individual components of ADAPT are easily accessible clinical parameters and as such could be used as a tool for the early detection of liver fibrosis in the general population, particularly in a sequential-type approach.

Immune-mediated and cholestatic: Experimental and pathophysiology

OS019

Novel anti-cholestatic treatment strategies by combining inhibition of the Apical sodium-dependent bile acid transporter with stimulation of urinary bile salt excretion or lowering bile salt synthesis

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Background and aims: The apical sodium-dependent bile acid transporter (ASBT) is primarily expressed in the small intestine and kidney, where it prevents bile salts from being excreted in respectively feces and urine. Intestine-restricted drugs that inhibit ASBT are currently clinically explored to reduce toxic accumulation of bile acids during cholestasis. Intestine-restricted ASBT inhibitors (ASBTi) may be less effective in severe cholestasis and also yield gastrointestinal side-effects in case of high bile salt load in the colon. Here, we test two ASBT-targeting treatment strategies in pre-clinical models with cholestasis-induced liver injury. First, systemic ASBT inhibition, to increase renal bile acid excretion and second a combination treatment with obeticholic acid (OCA) to limit bile salt synthesis and reduce colonic bile acid load.
Method: Systemic ASBT inhibition was tested by performing a bile duct ligation (BDL) in adult ASBT knock-out (KO) mice (129P2/OlaHsd background, Jackson) and wild-type littermates to induce severe cholestasis. In our second strategy, BDL was performed in adult wild-type C57Bl/6 mice after 2 days oral gavage pre-treatment with OCA and ASBTi. In a different model, wild-type C57Bl/6 mice were fed a 0.1% 3, 5-diethoxycarbonyl-1, 4-dihydrocollidine (DDC) diet while receiving daily treatment with either placebo, OCA, ASBTi or both (OCA + ASBTi). After sacrifice, liver injury was determined by plasma liver enzymes, RT-qPCR and liver histology, while HPLC analysis was used to quantify bile salt concentrations in plasma, liver, small intestine and feces.
Results: ASBT KO mice had reduced liver necrosis, reduced bilirubin and alkaline phosphatase (ALP) levels compared to wild-type mice after BDL. ASBT KO mice also showed a trend to reduced bile salt pool size, and increased urinary bile salt excretion. OCA + ASBTi treatment reduced the total bile salt pool size before cholestasis-onset and resulted in reduced bilirubin, ALP and a ~60% reduction in liver necrosis compared to placebo control in a BDL model. Besides, OCA + ASBTi treatment decreased fecal bile salt excretion compared to monotherapy with ASBTi.
Conclusion: Systemic ASBT inhibition effectively reduces BDL-induced liver damage. Combined OCA + ASBTi treatment lowers the bile salt pool size and improves liver health after BDL-induced cholestasis, while it also shows therapeutic potential by reducing fecal bile salt excretion.

OS020

Low-dose IL-2 alleviates drug-induced primary biliary cholangitis in mice by improving Treg and Th17 balance

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Background and aims: The imbalance of regulatory T (Treg) and T helper 17 (Th17) cells correlates with increased risk of autoimmune diseases. Their imbalance was also reported in primary biliary cholangitis (PBC) patients. Previous studies have suggested that low-dose IL-2 can alleviate disease severity through modulating $CD4^+$T cell subsets in patients with autoimmune diseases. However, the efficacy of low-dose IL-2 in PBC remains unexplored. Hence, the present study aimed to examine effects of low-dose IL-2 in PBC mouse models.
Method: PBC was induced in female C57BL/6 mice by two immunizations with 2-nonynoic acid (2OA-BSA) at two-week intervals. Besides, polyinosinic polycytidylic acid (poly I:C) was injected i.p. every three days. The control group was injected with PBS instead of 2OA-BSA and poly I:C. PBC mice were divided into the treated and untreated groups, and low-dose IL-2 was injected s.c. every three days after four weeks from modeling in the treated group (Fig. A)and the untreated group was replaced with saline. The serum was isolated from blood sampled by eyeball extirpating for biochemical detection. Th17 and Tregs were analyzed by flow cytometry, and the related cytokines were analyzed by ELISA. Liver histopathology was examined by HandE and immunohistochemical staining. The experimental data were analyzed by SPSS 24.0 software. $P < 0.05$ indicated statistical significance.
Results: Eight weeks after modeling, the serum AMA was positive and the ALP was significantly increased in PBC mice compared with control group. The pathology showed lymphocyte infiltration in the portal area, and damage and reactive proliferation of small bile duct, and $CD4^+$ and $CD8^+$ T cells were infiltrated around the bile duct. Flow cytometric examination of spleen cells revealed recovery of reduced Tregs and increased Th17 after low-dose IL-2 treatment (Treg/CD4%:9.26 ± 0.50 vs 6.10 ± 0.14 vs 8.24 ± 0.04; Th17/CD4%: 0.29 ± 0.20 vs 1.00 ± 0.17 vs 0.33 ± 0.09) ($p < 0.05$) (Fig. B). Low-dose IL-2 treatment inhibited IL-17A levels (0 vs 4549 ± 597.5 vs 1928 ± 387) ($p < 0.05$) and improved serum biochemical index (ALP: 119.1 ± 6.20 vs 82.36 ± 12.6 U/L) (Fig. C). Histopathological examination of liver revealed the improvement of portal area inflammation and reactive bile duct hyperplasia and damage after low-dose IL-2 treatment (Fig. D).