

underwent causality assessment through an expert opinion process. Patients with confirmed IRH were classified into the IRH group, whereas those with non-IRH constituted the control group. The severity of liver injury was assessed using both the Common Terminology Criteria for Adverse Events (CTCAE) and the international expert working group (EWG) criteria for drug-induced liver injury (DILI).

Results: Of 15,835 patients screened, 4,641 (29.3%) were adjudicated as having IRH, while 10,043 served as non-IRH controls. Based on CTCAE criteria, 3,736 patients (80.5%) experienced grade 1 liver injury and 444 (9.6%) developed high-grade IRH ($\geq$ grade 3). In contrast, by EWG criteria, 4,148 patients (89.4%) did not meet the diagnostic threshold for DILI, and only 9 (0.2%) were classified as having $\geq$ grade 3 liver injury. Although biochemical normalization was observed in most patients, 50 (1.1%) died or required liver transplantation within 21 days of the first IRH episode. Multivariable analysis demonstrated that younger age and anti-cancer regimen were independently associated with all-grade IRH. Hepatocellular carcinoma and higher baseline aminotransferase levels were additionally associated with an increased risk of high-grade IRH. Among patients with high-grade IRH, 184 (41.4%) were rechallenged with ICI, of whom 86 (46.7%) developed recurrent IRH, including 29 (33.7%) with high-grade IRH.

Conclusion: Marked discrepancies were observed between CTCAE and EWG grading of IRH severity. Younger age and anti-cancer regimen were consistently associated with increased risk of IRH, and rechallenge appeared feasible even in patients with prior high-grade IRH.

Acute liver failure and drug induced liver injury – Experimental and pathophysiology

TOP-193-VI

Serum glycomics at admission predict liver transplantation-free survival in patients with acetaminophen-induced acute liver failure

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Background and aims: Acute liver failure (ALF) is a rare but potentially life-threatening clinical syndrome characterized by hepatocellular damage and impaired liver function. In the Western world, the majority of cases are caused by acetaminophen (APAP) overdose. In subjects not responding to medical therapy, emergency liver transplantation (ELT) is required to avoid fatal outcome. The decision to list a subject for ELT is based on imperfect prediction rules with strong specificity, but limited sensitivity, thereby providing good

ruling-in capacity but unacceptably poor ruling-out performance. We investigated the potential to derive a serum glycomics biomarker able to predict transplant-free survival.

Method: We performed a prospective, multicenter study in five referral centers for ELT in Belgium, between 2014 and 2024. In 91 patients with APAP-related ALF, serum samples were collected within 24 hours of admission for analysis of the total serum N-glycome. Relative glycan abundancies underwent central log-ratio transformation before comparison between outcome groups to enable robust comparison of compositional data. Elastic net regression was used to derive a glycan score predictive of ELT. The optimal cut-off for classification was defined by the Youden index.

Results: Seven out of 91 (7.7%) subjects underwent ELT, with two deaths occurring after liver transplantation. Another five (5.5%) subjects died without undergoing prior ELT. In subjects in need of ELT, we observed an increase of the agalacto, core-fucosylated glycan NGA2F, and of the agalacto, core-fucosylated, bisecting glycan NGA2FB (independent t-test, p-values 0.0356 and 0.0239, respectively). After elastic net regression, a glycan score predictive of liver transplantation was derived, mainly characterized by a relative increase of undergalactosylation and fucosylation, and decreased branching of glycans. At the optimal cut-off of 0.0815, this biomarker predicted ELT with a sensitivity of 85.7%, specificity of 73.8%, and a negative predictive value of 98.4%. The area under the receiver operating curve was 0.833 (95% confidence interval: 0.711–0.955).

Conclusion: A distinct glycomics signature can be determined on serum admission samples of APAP-ALF patients, reliably ruling-out subjects not requiring ELT. Application of this serum biomarker could avoid unnecessary harm in subjects who would otherwise undergo ELT, and thus avoid significant morbidity and healthcare costs.

TOP-194

A novel mechanism by which the FABP4/CD36 axis exacerbates cholestasis via antagonizing FXR signaling

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Background and aims: Cholestatic liver injury involves multi-cell crosstalk, with liver macrophage activation key to amplifying injury. However, specific mediators directly disrupting bile acid (BA) homeostasis remain unclear. Farnesoid X receptor (FXR), a master regulator of BA metabolism (synthesis, transport, detoxification), is a common cholestasis driver due to impaired function. Our prior clinical data showed fatty acid-binding protein 4 (FABP4)—a macrophage-enriched lipid chaperone—is significantly elevated in cholestatic liver disease serum. Given its role in metabolic inflammation, we proposed that FABP4 drives liver injury not only through classical pro-inflammatory effects but, more importantly, by directly interfering with the hepatoprotective FXR signaling axis, thereby dominating the dysregulation of BA homeostasis.

Method: We used a multidisciplinary approach (genetic: *Fxr*-deficient mice; pharmacological: FABP4 inhibitor BMS309403) to induce cholestasis with alpha-naphthylisothiocyanate (ANIT). Liver injury was assessed via histology, serum biochemistry (ALT/AST, ALP, etc), and inflammatory markers. Molecular mechanisms were explored using immunohistochemistry, Western blotting, qRT-PCR, and in vitro experiments.

Results: In vivo results showed that inhibition of FABP4 by BMS309403 significantly protected WT mice against ANIT-induced liver injury, inflammation, and cholestasis. However, this protection was lost in *Fxr*^{-/-} mice. Regardless of whether they received BMS309403 treatment, *Fxr*^{-/-} mice exhibited comparable levels of necrosis, inflammation, elevated serum ALT/AST levels, and cholestasis, suggesting that the regulatory effect of the BMS inhibitor on key downstream targets (i.e., the BA synthetic enzymes CYP7A1 and