<15%. An understanding of the genetic factors underlying severe AH may be essential to improving risk-stratification and identifying novel therapeutic targets for this understudied syndrome.

**Methods** Cases with severe AH were recruited from the UK Steroids or Pentoxifylline for Alcoholic Hepatitis (STOPAH) trial (n = 812). Controls with a history of alcohol dependence but without evidence of significant liver injury were recruited from the Centre of Hepatology, Royal Free Hospital, London (n = 936). All participants were of white British/Irish descent. DNA was genotyped using two platforms Illumina HumanCoreExome Beadchip (Illumina, San Diego, USA) and Illumina PsychArray Beadchip (Illumina, San Diego, USA). Separate GWAS analyses were undertaken on each array using Plink v1.9 followed by meta-analysis in METAL. MAGMA gene and gene-set analyses were carried out using FUMA.

**Results** The variant rs738409 in PNPLA3 was associated with severe AH at genome-wide significance (PTHRESHOLD<5 × 10^-8; P = 6.66 × 10^-12; Z score = 6.865). Three additional independent risk loci were identified at the suggestive significance threshold, in ATP2C2 (ATPase Secretory Pathway Ca2+ Transporting 2), (PTHRESHOLD<1 × 10^-5; PMETA = 4.33 × 10^-7; Z score = 5.054), PHYH (Phytanoyl-CoA 2-Hydroxylase) (PMETA = 3.16 × 10^-6; Z score = 4.66) and ANGPT1 (Angiopoietin 1) (PMETA = 5.12 × 10^-6; Z score = -4.56). In addition, nine gene-sets were identified at statistical significance (PBON < 0.05) involving pathways associated with sterol regulatory element-binding protein signalling (PBON = 1.21 × 10^-5), interleukin 17 secretion (PBON = 1.01 × 10^-4) and regulation of natural killer T cell proliferation (PBON = 1.88 × 10^-4).

**Conclusions** The pivotal role of PNPLA3:rs738409 in determining the risk for developing severe AH was confirmed in this study. In addition, potential risk loci were identified in ATP2C2, which encodes a Mn+/Ca2+ transporter and is highly expressed in the gastrointestinal tract; PHYH which is implicated in phytanic acid metabolism; phytanic acid binds to and/or activates the transcription factors PPAR-alpha and retinoid X receptor; and ANGPT1 which encodes the angiogenic promoter angiopoietin 1. Additionally, a number of potential pathways were identified, through gene set analysis, which appear to be involved in severe AH, influencing lipid metabolism and inflammation. These novel findings open new avenues for investigation and therapeutic endeavour.

**09 REDEFINING POOR PROGNOSTIC CRITERIA FOR ACETAMINOPHEN-INDUCED ACUTE LIVER FAILURE USING REGENERATION AND CELL-DEATH LINKED miRNA SIGNATURES**

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**Background** Acute liver failure (ALF) remains a rare but life-threatening condition which requires early prognostication for transplantation (LTx). Existing models such as the King’s College Criteria (KCC) lack sensitivity. We have previously demonstrated the potential for regeneration linked miRNA to perform as biomarkers in acute and chronic liver disease. The aim of this study was to develop a miRNA-based prognostic model for acetaminophen (APAP) ALF.

**Methods** Samples were provided by the US ALF Study Group. We assessed serum miRNA expression from 193 patients (94 survivors, 89 non-survivors) with APAP-ALF at two time points (early; day 1, late; day 3–5). Transplanted patients were excluded. A panel of 24 miRNA identified from our previous studies were analysed. Multiple logistic regression was used to create early and late miRNA outcome prediction models. Clinical data were incorporated to improve prognostication.

**Results** Early up-regulation of miR-150 and down-regulation of -16,-2 were associated with mortality. The early detection of miR-20a and absence of miR-149 were associated with mortality. Late up-regulation of miR-30a and down-regulation of -122, 16-2 and -21 were significantly associated with mortality. Late detection of miR-149, -17 and -191 were associated with mortality. Prognostic models were made for early and late miRNA expression. The early model contained miRNA associated with regeneration (miR-20a, -27a, -140, -150, -191) and achieved an area under the receiver operator curve (AUC) of 0.78 (95% CI 0.71–0.84, p<0.0001). This model was enhanced when combined with the Model for End-Stage Liver Disease score (MELD) and vasopressor requirement (AUC 0.83, 95% CI 0.78-0.89, p<0.0001). The late model contained miRNA associated with cell death (miR-16-2, -30a, -122, -149, -191) and achieved an AUC of 0.83. (95% CI 0.76–0.89, p<0.0001). This model was enhanced when combined with MELD and vasopressor requirements (AUC 0.91, 95% CI 0.86–0.96, p<0.0001). Conventional outcome prediction models performed as follows; KCC (early AUC 0.60, 95% CI 0.48–0.73, p=0.07, late AUC 0.69, 95% CI 0.56–0.82, p=0.01), MELD (early AUC 0.72, 95% CI 0.64–0.79, p<0.0001, late AUC 0.86, 95% CI 0.80–0.91, p<0.0001) and ALF Study Group Prognostic Index (early AUC 0.76, 95%CI 0.69–0.83, p<0.0001, late AUC 0.88, 95% CI 0.82–0.94, p<0.001).

**Conclusion** We demonstrate that specific serum miRNA have prognostic value as biomarkers in ALF. Our early model utilised regeneration linked miRNA whereas our late model utilised cell-death linked miRNA; this may signify mechanistic differences at early and late time points which determine patient survival.

**O10 L-CARNITINE SUPPLEMENTATION IN NON-ALCOHOLIC FATTY LIVER DISEASE: EFFECTS ON INTRAHEPATIC TRIGLYCERIDE, MUSCLE LIPID FRACTIONS AND LIVER MITOCOCONDRIAL ENERGETICS – RESULTS FROM A PILOT RANDOMISED TRIAL**

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**Background** Leveraging in vivo imaging and physiological studies, we previously demonstrated robust associations between skeletal muscle fat accumulation, whole-body insulin resistance and perturbed hepatic energy kinetics in young, non-diabetic...
METHOTREXATE: AN INNOCENT BYSTANDER IN THE DEVELOPMENT OF LIVER FIBROSIS, FINDINGS OF THE STRATIFY STUDY

Introduction Methotrexate (MTX) is an effective treatment for immune-mediated diseases, used by several specialties. MTX-induced hepatotoxicity has been historically regarded with concern, more recent evidence has contradicted this. Non-alcoholic fatty liver disease (NAFLD) is highly prevalent, estimated to affect 1 in 5 in the UK.

Aim To compare the prevalence of liver fibrosis, by way of FibroScan®, between individuals taking MTX and those who have not, and cross-reference this against established risk factors for liver fibrosis.

Methods Following national Health Research Authority approval and local R&D registration, we recruited adults attending the rheumatology and dermatology outpatient clinics at York Hospital. Half of the cohort had never received MTX (control), whilst half (MTX) had taken MTX for at least six months. Pregnant women were excluded. Demographic details, past medical history, cumulative MTX dose, other drug history, physical activity levels and alcohol history were recorded.Transient elastography and body mass composite analysis were undertaken. Statistical analysis was conducted by means of independent 2-tailed t test and multiple regression analysis, using SPSS.

Results 600 participants were recruited. Baseline characteristics for the MTX and control cohorts were as follows; female (68 vs 70%, p = 0.44), mean body mass index (28.3 vs 28.4 kg/m², p = 0.77), hypertension (28 vs 23%, p = 0.19), hypercholesterolaemia (21 vs 20%, p = 0.76) and diabetes (8 vs 7%, p = 0.53) respectively. No difference in FibroScan® score was identified between the MTX group (5.9kPa 95% CI 5.3 – 6.5) and the control subjects (6.5kPa 95% CI 5.6 – 7.2) (p = 0.28).

Multiple regression analysis demonstrated MTX prescription (p = 0.58), cumulative dose of methotrexate (p = 0.47) and self-reported alcohol (by way of AUDIT-C) (p = 0.34) were not significant predictors of liver fibrosis. Positive predictors of liver fibrosis were waist circumference (p ≤ 0.01), BMI (p ≤ 0.01), and diabetes (p = 0.02).

Discussion This large cohort study has demonstrated no increased prevalence of liver fibrosis (by way of FibroScan®) in patients taking MTX. In keeping with other studies, risk factors for liver fibrosis.