

# INVITED SPEAKERS ABSTRACTS

# Burden and epidemiology of alcohol-related liver diseases in Europe and North America

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Motivating and sustaining policies to tackle effectively the challenge of alcohol-related ill-health needs reliable information about the burden of diseases in populations. At a national level, showing that a country has a higher rate of alcohol-related disease than others can be a powerful argument for a government to take action. In this presentation we will explore the extent to which available comparative data on the burden of alcoholic-liver disease across countries is coherent. Understanding the strengths and limitations of these data is important if we are to mount the best arguments aimed at reducing this quintessentially modifiable burden.

Information on the incidence of alcoholic liver disease that is directly compared between countries is very sparse. For this reason international comparisons of the burden of alcoholic liver disease rely heavily on mortality data. However, as is well known, the interpretation of mortality rates between countries is problematic. For example, when certifying deaths from alcoholic liver disease doctors may deliberately put cirrhosis of the liver without mention of alcohol as the underlying cause, thus concealing the true mortality rate. The situation is further complicated by the fact that deaths occurring due to alcohol may be classified as being from other types of alcohol-related mortality, such as mental and behavioural disorders due to alcohol.

We will examine the coherence of differences in mortality rates from alcoholic liver cirrhosis with that from other causes in which alcohol is explicitly mentioned across a range of countries in Europe, North America and elsewhere. Using a specific example we will demonstrate that better use could be made of the full multi-cause information on a death certificate to quantify alcoholic liver disease and other alcohol-related deaths. We will revisit the evidence that there is a substantial burden of alcoholic liver disease hidden within liver cirrhosis that is not specified as alcohol-related. Finally, armed with this critical perspective, we will look at how mortality from alcohol-related causes relate to the best estimates of alcohol consumption by country. This will demonstrate the huge variation in the burden of alcoholic liver disease and other alcohol-related conditions across Europe and North America: a problem that in many requires urgent attention in many countries we have considered.

**Disclosure of Interest:** None Declared

# Put us out of business: Role of health policy in controlling alcohol consumption

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There is no doubt that effective health policy could put hepatologists out of the business of alcoholic liver disease. The drivers of alcohol consumption and the consequent harm are well established and evidence-based: price, availability and marketing. The strongest single driver of harm is price and the cost has fallen in real terms in the UK as it has in most parts of the world. This is particularly the case in 'off-sales' – liquor stores and supermarkets – where alcohol is seen as a strong hook for bringing in customers and so often heavily discounted. Low prices can be tackled by increasing duty or other sales taxes, but the most attractive is to set a floor price based on alcohol content (in the UK termed a minimum unit price), as this targets the cheapest alcohol bought by the most vulnerable and under-age drinkers. Increasing availability is an issue in most countries, again particularly in the off-trade sector, where alcohol can be sourced 24/7. Some countries like Sweden have managed to keep state-control over outlets.

Finally, marketing has become increasingly sophisticated, including newer markets in developing countries, targeting women and young people, sports sponsorship and finally the use of internet / social media. France has gone some way to tackling this by a complete ban on sports sponsorship and broadcast advertising for alcohol products.

Unfortunately, the power of all three tools is also well understood not just by public health experts but also by the alcohol producers and retailers. The lobbying power of industry far outweighs that of public health and there are numerous examples of industry-funded 'assistance' in the promotion of responsible drinking. These tend to target less effective tools such as education, and go just far enough to keep regulation at bay. Governments under financial pressure seek partnerships with producers despite the history of previous failures in areas like tobacco and alcohol. There are, however, some encouraging signs of some governments such as Scotland waking up to the huge financial burden of alcohol-related harm and at last following the evidence in bringing in effective public health interventions.

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# Genetics of ALD: What do we learn from the risk loci about the disease?

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The elucidation of the genetic basis of alcoholic liver disease has made significant progress in the last years. While the genetic component of acute alcoholic hepatitis is still a controversial topic, we have good and well replicated genetic risk variants for alcoholic liver cirrhosis (ALC) in the context of chronic at risk consumption. These well replicated loci (in decreasing order of phenotypic impact) include *PNPLA2*, *TM6SF2* and *MBOAT7*. While further genome-wide association studies will be needed to address the unexplained genetic risk in ALC, these loci already provide intriguing insights into the pathophysiology of ALD and offer potential use for individual lifestyle counseling:

1. The genetic risk profile of alcohol misuse and ALD appear to be clearly distinct
2. The allelic risks conferred by variants in *PNPLA2*, *TM6SF2* and *MBOAT7* ranges from ~2.5 to 1.3 and is thus surprisingly high for a genetically complex disorder. The combination risk genotypes thus allows the definition of subgroups that differ in ALC risk by a factor of 10. Thus, these variants point to an individual alcohol tolerance level, that may vary be the same factor and needs to be evaluated in prospective studies.
3. All three genes are at the same time risk variants for NALFD. In fact, based on the most solidly replicated risk variants, the genetic risk profile of ALD and NAFLD seem to be indistinguishable, which is an intriguing finding.
4. All three risk genes are "lipid genes" - an equally intriguing observation for ALD. *PNPLA3* is a triglyceride lipase, *TM6SF2* plays a role in VLDL lipidation and *MBOAT7* is a lysoposphoinositol acyltransferase.
5. Combining ALD and NAFLD a simplified model of risk genes on the disease process may be suggested: *PNPLA3*: is relevant for steatosis and HCC, *TM6SF2* is relevant for inflammation/fibrosis and HCC and *MBOAT7* is important for fibrosis and has no or minor impact on HCC risk.
6. The mechanistic basis of the risk variants is incompletely understood, but *PNPLA3* and *MBOAT7* seem to have a "drugable" mode of action, while *TM6SF2* inhibition does not appear as a likely drug target, because the risk variants protects against cardiovascular disease due to lower systemic VLDL lipids.

In summary, further functional and epidemiological studies are needed utilize the genetic findings to transform patient care in ALD.

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# Inflammation as a driver of ALD

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Innate immunity plays a critical role in the development of alcohol-induced liver inflammation. Activation of liver resident macrophages, Kupffer cells, and recruitment of inflammatory macrophages and neutrophil leukocytes contributes to the pro-inflammatory cell and cytokine milieu in alcoholic liver disease that becomes amplified in alcoholic hepatitis. Activated inflammatory cells via their cytokine and mediator production contribute to hepatocyte injury, stellate cell activation and liver fibrosis. Understanding of the interrelationship of signals from within and outside of the liver that trigger liver inflammation is pivotal for development of novel therapeutic targets of alcoholic liver disease (ALD). Complex interactions between the intestinal microbiome, metabolome and the gut-liver axis in ALD are some of the driving factors of innate immune activation and resulting inflammation in ALD. Pathogen-derived molecular patterns (PAMPs) from the gut are sensed by various pattern recognition receptors expressed on immune cells as well as liver parenchymal cells to initiate inflammation. In addition to PAMPs, cellular alcohol-induced sterile inflammatory signals are induced by alcohol and its metabolites that trigger inflammation through pattern recognition receptors such as Toll-like receptors, Nod-like receptors, helicase receptors and the inflammasome complex. Activation of the NLRP3 inflammasome and the role of IL-1 $\beta$  in amplification of alcoholic hepatitis highlight the crucial role of inflammasomes in integration of inflammatory signals in ALD. Quantitative and qualitative accumulation of inflammatory signals and engagement of these receptor systems provides the basis for increasing complexity of inflammatory signals that propel progressive liver damage, inflammation and fibrosis. A growing body of evidence also indicates the diversity of pro-inflammatory signals, disruption of homeostatic anti-inflammatory mechanisms and involvement of recruited liver macrophages and neutrophils on their differential contribution to alcohol-induced liver inflammation. Studies to date have identified a multitude of new therapeutic targets in the spectrum of inflammation, some of which are currently being tested in patients with severe alcoholic hepatitis. These treatments aim to strengthen the intestinal barrier, ameliorate liver inflammation, and augment hepatocyte regeneration.

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# Role of miRNAs in the sensitization of TLR4 signaling by ethano

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Increased inflammatory signaling by Kupffer cells contributes to alcoholic liver disease (ALD). Kupffer cells are activated both in response to increased exposure to PAMPs and DAMPs, as well as due to a sensitization of TLR signaling. Understanding the mechanisms for this sensitization, as well as the identification of anti-inflammatory agents is critical to the development of therapeutic strategies to treat ALD. Hyaluronan (HA), an abundant extracellular matrix component, is a polysaccharide strictly composed of repeating disaccharides of D-glucuronic acid and N-acetylglucosamine. HA communicates with cells in a size-specific manner, using at least five signaling receptors including CD44, RHAMM (receptor for HA mediated motility), Layilin, as well as TLR2 and TLR4. Specific-sized HA fragments can be either pro-inflammatory or anti-inflammatory, depending on the HA receptor and cell type involved in the response. Here we investigated the impact of small-specific sized hyaluronic acid of ~35kD (HA35) on ethanol-induced sensitization of Kupffer cells, as well as ethanol-induced liver injury in mice.

**Methods:** Un-biased analysis of microRNA (miRNA) expression in Kupffer cells identified miRNAs regulated by both ethanol and HA35. TLR4-mediated signaling was assessed in primary cultures of Kupffer cells from ethanol- and pair-fed rats after treatment with HA35. Female C57BL6/J mice were fed ethanol or pair-fed control diets and treated or not with HA35.

**Results:** TLR4 signaling was increased in Kupffer cells by ethanol; this sensitization was normalized by *ex vivo* treatment with HA35. Next Generation Sequencing of Kupffer cell miRNA identified miRNAs that were reciprocally regulated by ethanol and HA35. Expression of miRNA181b-3p was decreased by ethanol and restored by HA35, while miRNA291b was increased by ethanol and normalized by HA35. *In silico* analysis identified potential targets for these miRNAs. Importin  $\alpha$ 5, a protein involved in p65 translocation to the nucleus, was identified as a target of miR181b-3p; importin  $\alpha$ 5 protein was increased in Kupffer cells from ethanol-fed rats, but decreased by HA35 treatment. Overexpression of miR181b-3p decreased importin  $\alpha$ 5 expression and normalized LPS-stimulated TNF $\alpha$  expression in Kupffer cells from ethanol-fed rats. Further, Tollip, a negative regulator of TLR4, was identified as a target of miR291b. Tollip expression was decreased in hepatic macrophages from ethanol-fed rats, but treatment with HA35 or transfection with a miR291b hairpin inhibitor restored Tollip expression and normalized TLR4-stimulated TNF $\alpha$  expression. Since HA35 normalized multiple pathways involved in the up-regulation of TLR4 signaling, we next investigated whether HA35 could protect mice from ethanol-induced liver injury. Oral provision of HA35 protected mice from ethanol-induced liver injury. Ethanol feeding decreased miR181b-3p in liver and increased expression of importin  $\alpha$ 5 in non-parenchymal cells. Treatment with HA35 normalized these changes.

**Conclusions:** Multiple miRNAs are dynamically regulated in Kupffer cells and mouse liver in response to ethanol, cumulatively contributing to enhanced inflammatory responses. Importantly, treatment with HA35 can normalize specific miRNA expression and also protect mice from ethanol-induced liver injury.

**Disclosure of Interest:** None Declared

# From microbiome to intestinal inflammation in ALD

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The intestinal microbiota and the human body have a symbiotic relationship. A dysbalance of this delicate homeostasis between host and microbes can lead to disease. Alcoholic liver disease is associated with changes in the gut microbiota. Alcohol-associated intestinal dysbiosis is characterized by an increase in bacterial numbers and changes in the bacterial composition. We have recently demonstrated that chronic alcohol consumption is also associated with altered intestinal fungi (mycobiota). It has been recognized for a long time that alcoholics have a disrupted gut barrier. The integrity of the intestinal barrier is of specific importance to limit bacteria and bacterial products from translocating and reaching extraintestinal sites. A disrupted intestinal barrier allows bacteria and fungi, and their products to translocate to the portal circulation and reach the liver. Translocated microbial products induce a systemic and hepatic inflammatory response, and aggravate liver disease, while translocated viable bacteria can cause infections.

Recent studies emphasized the importance of intestinal inflammation for the onset of gut barrier disruption and microbial translocation. Antibiotics prevent intestinal inflammation and a disruption of the gut barrier in preclinical models suggesting that dysbiosis initiates and mediates a disruption of the intestinal barrier. The contribution of dysbiosis to alcoholic liver disease goes beyond a dysfunction of the intestinal barrier. Microbial metabolites are equally important for the progression of liver disease. Manipulation of the intestinal microbiota might be an effective strategy for attenuation of alcohol-related liver disease.

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# Impaired pathways of liver regeneration in chronic liver disease: Future therapeutic target for severe ALD?

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Alcohol-induced steatohepatitis is a dynamic process. Although it can regress to steatosis or smolder at sub-clinical levels for decades, it also increases the risk for both clinically severe acute alcoholic hepatitis and cirrhosis. The mechanisms that control the outcomes of steatohepatitis are poorly understood but emerging evidence suggests that some of the heterogeneity might reflect differences in processes that control liver cell plasticity. Morphogenic signaling pathways that control cell fate decisions during fetal development, such as the Hedgehog pathway, become reactivated to resume similar functions in injured adult livers. Overly-exuberant activation of these pathways correlates with dysregulated liver repair and increases short- and long-term mortality by promoting acute alcoholic hepatitis or cirrhosis. Manipulating signaling via these pathways may be a novel therapeutic approach to optimize liver cell reprogramming and thus, prevent defective regenerative responses that cause acute and chronic liver failure.

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# Animal models of ALD and alcoholic hepatitis: Intragastric alcohol feeding model for identifying key therapeutic pathways

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For an animal model to be useful for research on alcoholic liver disease (ALD), it has to meet fundamental requirements that faithfully reflect behavior, etiological background and natural history of ALD patients.

Firstly and of utmost importance, symptomatic ALD is the disease of heavy drinkers who are addicted to alcohol. Alcoholics with physical dependence on ethanol, titrate their ethanol intake throughout the day to sustain high blood ethanol concentrations (BACs) and to avoid unpleasant withdrawal symptoms. These threshold BACs are often raised in alcoholics due to metabolic and physical tolerance, driving a vicious cycle of enforcing increased and sustained ethanol intake – a definition of alcoholism. Indeed, alcoholic hepatitis (AH) and cirrhosis are associated with continuous or steady drinking rather than frequent or episodic drinking pattern (Alcohol Alcohol 34:330; J Hepatol 62:106).

Secondly, ALD is the disease which develops after 15-20 years of heavy drinking. This chronicity is an important consideration and translates to 2-6 months of heavy and sustained drinking in rodents.

Thirdly, binge drinking pattern superimposed to steady heavy drinking is associated with AH (J Clin Gastroenterol 40:833; Clin Liver Dis 16:371).

Finally, ALD is a multifactorial disease with genetic and environmental risk factors, and the animal model must allow precise loss and gain approaches for these factors. An intragastric ethanol infusion model was developed to meet these requirements. By incorporating risk factors common in ALD patients, it reproduces chronic alcoholic steatohepatitis (micro- and macro-vesicular steatosis, balloon cell degeneration, mononuclear cell infiltration, and pericellular and perisinusoidal liver fibrosis). Superimposing weekly binge shifts this pathology to alcoholic neutrophilic hepatitis, even recapitulating a prognostic histology marker of AH patients: ductular reactions - oval cell proliferation (Hepatology 61:129). By performing proteomic and transcriptomic analyses of these two pathologic entities, several signature pathways are identified which appear to mediate the pathologic shift to AH.

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# Alcohol use disorder: diagnosis and management

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Alcohol Use Disorder (AUD) represents a chronic and relapsing disease affecting nearly 10 % of the general population both in the USA and in Europe, with a widespread burden of morbidity and mortality. AUD represents the most common cause of liver damage in the Western world. Continued alcohol consumption after the onset of liver disease, increases the risk of morbidity and mortality. Consequently, the ideal treatment of AUD patients affected by liver disease should aim at achieving long-term total alcohol abstinence and preventing relapse.

The present talk will be focused on the management of AUD in patients with liver disease, underlying limits and options in this subset of patients. Increasing evidence suggests that the most effective strategy to reduce alcohol intake, promote abstinence and prevent relapse in AUD is the combination between psychosocial and pharmacological interventions. Among medication useful for the treatment of AUD, Disulfiram, naltrexone and acamprosate have been approved for this indication; sodium oxybate (SO also namely GHB) is approved in Italy and Austria. However, these drugs have not been tested in patients with advanced liver disease. Amongst other emerging pharmacotherapies for AUD, topiramate, ondansetron, and baclofen seem the most promising ones. Both topiramate and ondansetron have a safe profile in alcoholic patients; however, none of them has been tested in AUD patients with advanced liver disease. To date, baclofen represents the only anti-craving medication formally tested in a RCT in AUD affected by liver cirrhosis, although additional confirmatory studies are warranted. Future studies are needed to investigate the role of other anticraving medications in patients with liver disease.

**Disclosure of Interest:** None Declared

# Assessment of cofactors for alcoholic liver disease

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Alcohol consumption is widespread in many communities across the world. Specifically a large segment of the population engage in risky drinking behavior which increase the probability of development of end-organ disease. At the same time, over the last three decades, there has been a progressive rise in the prevalence of obesity and type 2 diabetes in the general population with an associated increase in cardio-metabolic and renal disease. Furthermore, viral hepatitis affects several million individuals in the general population, It is therefore not surprising that multiple risk factors for liver disease can often co-exist in the same patient. Despite the obvious importance of such co-factors, there is a relative paucity of high quality data on the subject. There are several key questions related to such co-factors. The first issue has to do with non-hepatic co-factors that impact outcomes. A recent analysis of electronic medical records demonstrated that the Charlson Comorbidity Index has increased substantially over the last decade and that patients in the USA presenting with alcoholic hepatitis are older and more likely to have multiple systemic comorbidities such as COPD etc [1]. Thus, alcoholic hepatitis is often superimposed on the setting of severe underlying non-hepatic disease in many cases. Another key comorbidity is obesity and diabetes. A population-based assessment of fatty liver disease found that obese individuals who consumed alcohol had the greatest likelihood of having hepatic steatosis and alcohol consumption increased the risk of fatty liver [2]. Other studies have shown that the presence of obesity may impact clinical outcomes adversely in those with alcohol associated liver disease.

The combination of alcohol consumption and type 2 diabetes as well as obesity are already well known risk factors for hepatocellular cancer the prevalence of which is increasing in the general population. On the other hand, coffee drinking has been recently found to have a protective effect and an interaction with coffee consumption and the I148M PNPLA3 mutation identified. From a pathophysiological perspective, distinct changes in the fecal and circulating microbiome have been identified with obesity and non-alcoholic fatty liver disease versus alcoholic hepatitis. Specifically, heavy alcohol consumption has been linked to increase in Fusobacteria whereas Proteobacteria are increased in NAFLD. How these interact in the obese individual who consumes alcohol remains to be fully defined. Together, all of the potential interactions between alcohol consumption and co-factors both from a pathogenic and clinical perspective represent complex biological systems. It is anticipated that deep learning tools applied on large data sets will provide novel insights on such interactions which can be better leveraged to improve the outcomes of individuals with alcohol associated liver disease.

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# Liver histology and AH/ALD - what is its role?

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Liver histology is usually not required for patient management and treatment decisions in alcoholic liver disease (ALD). However, it is necessary for confirming the diagnosis of alcoholic hepatitis/ steatohepatitis (AH/ASH) for entrance in therapeutic protocols and for evaluating concurrent liver disease. In addition, liver histology provides prognostic information regarding ALD severity and fibrosis stage [1].

Current guidelines differ in their recommendation for liver biopsy in the management of patients with AH. Supporters of liver biopsy highlight the importance of diagnosing concurrent or unsuspected liver disease. Indeed, only 70-80% of patients with a heavy alcohol intake may have alcohol-associated histological liver injury, while the remaining have other liver disease, including viral or granulomatous hepatitis, cholangitis, passive venous congestion or nonspecific changes. In ALD patients presenting with acute deterioration of cirrhosis, early liver biopsy has been shown to be safe and to provide important diagnostic and prognostic information contributing to treatment decisions [2].

ALD injury initially involves acinar zone 3 (centrilobular area). The earliest pathologic finding is steatosis, which is typically macrovesicular, but not consistently present in all forms of ALD. The minimal criteria for diagnosing steatohepatitis are steatosis, lobular inflammation and hepatocyte ballooning. Early fibrosis in AH/ASH is pericellular/sinusoidal and usually starts in zone 3. Sinusoidal fibrosis may be dense and can involve large parenchymal areas manifesting clinically with portal hypertension, even in the absence of cirrhosis. Steatosis and steatohepatitis may or may not persist in ALD-cirrhosis but phlebosclerosis and veno-occlusive disease are often present. Other histological features in ALD include Mallory-Denk bodies (MDB), megamitochondria, 'ground-glass'-like and oncocytic hepatocytes, intrahepatic cholestasis and non-zonal iron deposition [1].

In AH, timing of liver biopsy from admission and start of treatment is usually variable and is unreported in most clinical trials. However, timing may affect the accuracy of AH diagnosis. It has been shown that early biopsy (1-7 days, median 3 days from admission) is more sensitive in confirming the diagnosis of AH, while delay (biopsy 7-28 days from admission) may result in loss of diagnostic features, such as ballooning, inflammation or steatosis [2].

Two semi-quantitative histological scores with prognostic value specific for AH have been published to date. The first is based on lobular inflammation and hepatocyte ballooning detected using keratin 8/18 immunostaining and predicts survival of patients with acute deterioration of alcoholic cirrhosis [2]. The second, known as Alcoholic Hepatitis Histological Score (AHHS), can stratify acute AH patients in high, intermediate and low risk of death and includes histological features that are independently associated with 90-day survival, such as lobular inflammation by polymorphs, bilirubinostasis, presence megamitochondria, and fibrosis stage [3]. The latter is the main predictor of long-term survival in early/compensated ALD, while a combination of clinical (gender), biochemical (bilirubin, international normalized ratio [INR]) and histological parameters (extent of pericellular fibrosis) has been shown to predict survival in decompensated ALD [4].

In simple alcoholic fatty liver, the severity of steatosis and the extent of hepatic fibrosis indicate increasing risk of progression to cirrhosis. In ASH, predictors of progression to cirrhosis include the severity of hepatocyte necrosis or apoptosis, extent of pericellular and perivenular fibrosis, fibrous septa with elastic fibres, architectural distortion, diffuse parenchymal disease, widespread obliteration of hepatic venules, large number of MDB, severe intraparenchymal cholestasis, and presence of megamitochondria [1, 5].

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# Liquid Biopsy and Biomarkers is a Diagnostic Measure in Surrogate End Point in Alcoholic Hepatitis

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One of the major unmet needs in diagnosis, prognosis, and management of patients with alcoholic hepatitis is a lack of effective biomarkers. At the present time, standard of care in terms of biomarkers largely focuses on clinical nomograms derived from serum tests, such as MELD score and other such diagnostic and prognostic models. However, with advances in our molecular understanding of the disease, it is hoped that more sophisticated biomarkers could be developed. One of the major areas of progress relates to extracellular vesicles. There is increasing evidence now that liver injury, especially from alcohol leads to the increase in release of extracellular vesicles from injured and stressed hepatocytes. These vesicles, in turn, likely facilitate paracrine signaling with adjacent molecules thereby playing a role in pathophysiology.

From a biomarker perspective, it is also possible that these vesicles contain molecules that could predict the level of injury and/or response to therapy. A number of different microRNAs and protein targets have been identified in extracellular vesicles, and some of this data will be reviewed, especially new data relating to detection of PDGFR-alpha in extracellular vesicles as well as ceramide family members contained within extracellular vesicles in patients with alcoholic hepatitis. Separate from extracellular vesicles, a number of potential biomarkers are also present in the serum itself. There is mixed data relating to CK18 and its ability to predict liver-related death in patients with alcoholic liver disease, LPS, CRP, and procalcitonin have also been proposed as serum-based biomarkers. One of the challenges has been that, through much of the western hemisphere, liver biopsy is not routinely performed in patients with alcoholic hepatitis. Therefore, a detailed molecular annotation of patients is not easily attainable. However, some studies have been done, especially utilizing samples obtained from other parts of the world where biopsies are more commonplace. A detailed ChIP-seq and RNA-Seq analysis was performed from such samples, and some of this data will be reviewed during this talk. Finally, two additional areas where biomarker progress is being made relate to breath biosensors, which are useful not just to detect and prognose alcoholic hepatitis based on one recent study but also may have even greater promise for detecting alcohol consumption.

Finally, *in vitro* assays using peripheral blood cells obtained from patients as an *in vitro* platform to assess treatment response has also been evaluated in preliminary fashion. To the present time, the ability of such assays to perform better than the previously-mentioned clinical nomogram, such as Lille score, have not been established. In summary, this talk will review the current state of biomarkers in alcoholic hepatitis and provide new data in a number of emerging relevant areas.

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# Chronic liver inflammation promotes cancer through inactivation of immunosurveillance

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Chronic hepatitis caused by hypernutrition (NASH) or alcohol consumption (ASH) increases the risk of hepatocellular carcinoma (HCC), the major form of primary liver cancer and the second leading cause of cancer related death. By investigating clinical specimens a highly appropriate mouse model of NASH in which HCC development depends on ongoing oxidative stress we found that chronic liver inflammation and fibrosis results in accumulation of IgA+ immunosuppressive plasmacytes (ISP) that express the immunoregulatory molecules PD-L1 and IL-10. By engaging PD-1, ISP induce the exhaustion of liver infiltrating CD8+ T cells, some of which recognize tumor specific antigens that are expressed by HCC progenitor cells (HcPC). This allows the growth of HcPC into established HCC, a malignant progression that is even further accelerated by total CD8+ T cell ablation. Conversely, genetic and pharmacological interventions that reactivate exhausted CD8+ T cells and unleash their cytotoxic activity result in the regression of established HCC. These findings establish the importance of immunosurveillance in preventing liver cancer and the contribution of a specific immunosuppressive mechanism in alcohol and obesity induced HCC.

**Disclosure of Interest:** None Declared

# Early liver transplantation in AH – Pro and Con debate: I do not favour broader use of early liver transplantation for AH

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I accept that rescue liver transplantation (LT) for severe alcoholic hepatitis (AH) has shown encouraging effectiveness in proof of concept pilot studies. By taking the 'con' side of this argument, I do not state that I would never favor the adoption of rescue LT as the standard of care for severe life-threatening AH. Rather, I believe that there are considerable barriers that will need to be overcome before rescue LT becomes the norm in treating patients with severe AH unresponsive to medical management. Let me list four hurdles to more widespread use of rescue LT that I see:

1. Predicting prognosis: we need more accurate methods to determine which AH patients will survive without LT, in order to identify those who might benefit from rescue LT.
2. Patient selection. The process for selection requires clarification into a simple, transparent, reproducible set of criteria, assessments and practices in relation to alcohol use disorder (AUD) and AH. For example, currently unresolved issues include whether rescue LT be restricted to patients with a first episode of AH; are previous failed treatments for AH or AUD a contraindication to selection for rescue LT; should patients be required to undergo addiction treatment in every case; and what are the roles of addiction specialists, psychiatrists and medical social workers in the selection process?
3. Outcome determination: we need to establish a new consensus on the acceptable outcomes for rescue LT in severe AH. Should the goal be extended patient and graft survival, or is abstinence from alcohol the key parameter of success?
4. Finally, while we will have to convince primary care providers, gastroenterologists and the general public that rescue LT for medically unresponsive AH is the best use of resources. Without a broader consensus, referral to a transplant center will remain a capricious process for the patient with severe AH.

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# Post-transplant complications/what is specific for ALD

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Alcoholic liver disease (ALD) represents the second most common indication for liver transplantation (LT) worldwide. Outcomes of LT for ALD are comparable with those of liver transplantation for other aetiologies of liver disease; however, it's still considered a controversial indication to LT.

Survival rates of LT patients for ALD are comparable with those of patients transplanted for non-alcohol related liver disease [1]. In a recent study based on ELTR (European Liver Transplant Registry) database [1], it has been shown that patient survival at 1, 3, 5 and 10 years from LT was 84%, 78%, 73% and 58%, respectively, significantly higher in patients with ALD compared to HCV and HBV-related liver disease recipients (82%, 74%, 70%, 60%;  $p=0.04$ ) and patients with cryptogenic cirrhosis (78%, 73%, 69%, 61%;  $p=0.05$ ). When survival rates after LT for ALD were analyzed according to HCV or HBV co-infection, patient survival at 1, 3, 5 and 10 years from LT was significantly lower in patients with ALD/HCV compared with patients with ALD/HBV infection (84%, 75%, 65%, 52% vs. 89%, 85%, 81%, 64%, respectively;  $p=0.0002$ ). Causes of death or graft loss after LT for ALD significantly differ compared to non-ALD LT patients, being cardiovascular causes and de novo malignancies more frequent in the first group [2, 3]. Considering cardiovascular events, these are more frequent in ALD recipients, as they are at higher risk for post-transplant metabolic complications and for the development of metabolic syndrome [4, 5].

Transplanted patients present per se a higher risk of the de novo malignancies in comparison to general population [6, 7], accounting for 30%-40% of all deaths in LT recipients who survive the first year after transplantation [8, 9]. The development of malignancy has a significant impact on patient survival, with about 38% and 53% risk of death at 1 and 5 years after diagnosis [10]. The risk of developing de novo malignancies is 1.5-2 folds higher in patients transplanted for ALD compared to those transplanted for non-alcohol-related etiologies [11-13]. This risk can increase up to 10 fold when upper aero-digestive cancers are considered [10-12, 14]. The mechanisms involved in predisposing patients transplanted for ALD to malignancy are poorly understood. Oncogenic properties of acetaldehyde, a metabolite of alcohol, and the inhibition of DNA methylation have been blamed [15]. Other environmental factors, such as pre and post-transplant cigarette smoking, increase the risk for upper aerodigestive cancers [16, 17], as well as obesity [18]. Furthermore, a clear association between de novo malignancies and alcohol relapse after LT has not been identified yet.

Lastly, it has been shown that incidence of deaths due to social causes is significantly higher in patients with an ALD, compared to other etiologies (1.3% vs. 0.7% in HCV or HBV vs 0.4% in cryptogenic cirrhosis, respectively;  $p=0.03$ ) [1]. Psychosocial efforts during the pre and post LT periods should be focused not only on alcohol relapse, but also on preventing and treating modifiable risk factors for cardiovascular events and de novo malignancies, such as obesity and cigarette smoking. Implementation of intensive surveillance protocols in the post-transplant period has been shown to improve survival by detection of upper aerodigestive and urothelial cancers at an early stage [19, 20]. However, clear guidelines for cancer surveillance of LT recipients have not been developed yet.

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# Alcohol relapse after transplantation: does it matter?

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After LT for alcoholic liver disease (ALD), only a minority of patients return to heavy drinking associated with histological evidence of alcohol damage. Most patients remain abstinent or occasional drinkers. The variability between the reports is in part explained by the definition of relapse taken into consideration. Indeed, it is important to differentiate patients having minor, irregular and punctual consumptions (called "slips"), those having regular but moderate alcohol intakes and finally those returning to a major and harmful drinking. In other terms, relapse to drinking differs from relapse to alcoholism. Numerous clinical studies have identified the predictors of alcoholic relapse, in particular shorter pre-LT sobriety (< 6 months), young age, psychiatric co-morbidities, poor social support and integration, alcohol-dependence, multiple treatment failures, and a family history of alcoholism.

It is acknowledged that a proportion of ALD patients will resort to some alcohol intake after transplantation, and alcohol abuse is diagnosed in 11- 26% of cases in recent experience. However, with a careful selection, graft loss from recurrence of ALD or poor treatment adherence is low, and 5-year survival rates are similar to those found for other indications. Interestingly, some studies have suggested that beyond 5 years, a decreased survival could be observed in patients transplanted for ALD, particularly related to alcohol relapse. We would like to emphasize 3 points : a history of excessive alcohol consumption is present in patients listed for non-alcoholic liver disease, excessive alcohol consumption occurs after LT in patients transplanted for alcoholic and non-alcoholic liver disease, excessive alcohol consumption is responsible for an increased mortality beyond 5 years post-transplantation, related to recurrence of initial disease and non-cutaneous malignancies. Recently, we have shown that recurrent alcoholic cirrhosis affected one third of patients with severe alcoholic relapse 10 years after LT and was associated with a poor prognosis. In this experience, death was mainly due to graft failure, but also to other complications of alcoholism such as *de novo* malignancies and suicide.

Finally, a recent study conducted with addiction specialists confirm that post-LT alcohol relapse is common and difficult to detect during standard posttransplant consultations. A questionnaire such as the AUDIT-C could improve screening but only moderately for excessive drinking. Screening is really improved by systematic addiction consultation, regardless of the primary indication for LT and any abnormal laboratory findings.

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# Cost and mortality attributed to Alcoholic Liver Disease

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Alcoholic Liver Disease (ALD) has been identified as one of the top 30 causes of death in recent Global Burden of Disease studies.

Aims:

- To estimate mortality and years of life lost due to ALD.
- To estimate costs of ALD and cost-effective interventions to reduce mortality burden due to ALD.

## Comparative risk assessment

Mortality figures were taken from Global Burden of Disease, and from WHO Global Health Estimates.

Risk relations were based on own systematic reviews and meta-analyses.

1. Global burden of mortality due to ALD continues to be high, both in terms of numbers of deaths and in terms of years of life lost.
2. Prior estimates underestimate the burden of ALD, in part because the role of alcohol in fatal liver disease is underestimated for people whose disease was originally caused by other factors.
3. Cost for ALD are high, and cost be reduced markedly with better alcohol policy measures.
4. While alcohol policy measures such as the three best buys are the most cost-effective measures to reduce mortality burden of ALD, interventions and treatment for alcohol problems and alcohol use disorders should also be increased.

## Conclusions

ALD continues to be a major cause for premature death, but there are interventions to reduce its burden.

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# EMA process to validate end-points for drug approval: specific requirements for AH

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The European Medicines Agency offers scientific advice to support the qualification of innovative development methods for a specific intended use in the context of research and development into pharmaceuticals.

The advice is given by the Committee for Medicinal Products for Human Use (CHMP) on the basis of recommendations by the Scientific Advice Working Party (SAWP). This qualification process leads to a CHMP qualification opinion or CHMP qualification advice.

## CHMP qualification opinions

The CHMP can issue an opinion on the acceptability of a specific use of a method, such as the use of a novel methodology or an imaging method in the context of research and development. The method can apply to non-clinical or to clinical studies, such as the use of a novel biomarker.

The opinion is based on the assessment of data submitted to the Agency.

Before final adoption of qualification opinion, the CHMP makes its evaluation open for public consultation by the scientific community. This ensures that the CHMP shares information, as agreed with the applicant, and is open to scientific scrutiny and discussion.

## CHMP qualification advice

The CHMP can issue advice on protocols and methods that are intended to develop a novel method with the aim of moving towards qualification.

The advice is based on the evaluation of the scientific rationale and on the preliminary data submitted to the Agency.

Based on qualification advice, the Agency may propose a letter of support as an option, when the novel methodology under evaluation cannot yet be qualified but is shown to be promising based on preliminary data.

Letters of support aim to encourage data-sharing and to facilitate studies aimed at eventual qualification for the novel methodology under evaluation.

These letters include a high-level summary of the novel methodology, context of use, available data, and on-going and future investigations.

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# Patient characteristics and end-points in clinical trials for early ALD

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According to WHO 2014 report, an estimated 3.3 million deaths, or 5.9 % of all deaths worldwide, were attributable to alcohol consumption in 2012, with about half a million due to liver cirrhosis. Alcohol is the main cause of cirrhosis worldwide, accounting for 50% of the cases [1].

However, a recent study found that the mean research attention for alcoholic liver disease (ALD) in Europe and in the United States is only 5%, concerning the years 2010-2015. When the burden of disease was balanced with the degree of research attention, that is the attention-to-Burden Index (ABI), ALD received marked inadequate attention, comparing with other liver diseases such as viral hepatitis B and C, and non-alcoholic fatty liver disease (NAFLD) [2]. Also, the efficacy rate of current pharmacological agents is much lower for ALD than for diseases with an elevated ABI, such as chronic viral hepatitis B and C.

Consequently, efforts need to be done to increase the research in ALD in order to identify and test new pharmacological agents to treat ALD either in the pre-cirrhotic phase or when cirrhosis is already present to prevent the progression to advanced stages of the disease.

In the field of ALD, most of research has been done either in alcoholic hepatitis or, less frequently, in the decompensated phase of advanced liver cirrhosis. Looking at the registries of ClinicalTrials.gov, the large majority of studies include patients with alcoholic hepatitis, with a notable lack of interventional studies on early ALD.

The major reason for the absence of studies in early ALD, is probably that patients with ALD tend to present to medical care, either in a phase of decompensated disease manifested by ascites, encephalopathy or variceal bleeding, or with the full-blown picture of alcoholic hepatitis, mostly with jaundice. On the opposite, other chronic liver diseases, such as viral hepatitis or NAFLD tend to present due to elevated aminotransferases, or abnormal findings in abdominal ultrasound (US), mostly in ambulatory clinics. This makes the design of studies to evaluate early stages of ALD disease particularly defiant.

Early ALD is usually defined as the presence of liver disease associated with excessive alcohol intake, in the absence of decompensation. Ideally we would want to recruit patients in a pre-cirrhotic phase aiming to prevent progression to cirrhosis. Realistically, the majority of patients that might be recruited will already have advanced degrees of fibrosis / cirrhosis and the aim will be preventing decompensation and reducing mortality.

The characteristics of these patients should be: alcohol intake potentially hepatotoxic; elevated aminotransferases, besides isolated GGT; evidence of liver disease in ultrasound, besides steatosis; evidence of significant fibrosis; exclusion of concomitant risk factors, such as metabolic risk factors or viral hepatitis. Additionally, clinical trials in cohorts of patients with associated metabolic risk factors should also be done.

Interventional studies in early ALD should include the following end-points: overall mortality, liver-related mortality, development of liver cancer, progression to advanced stages (first decompensation: ascites, encephalopathy, jaundice or variceal bleeding) and reduction in fibrosis degree evaluated by liver biopsy or non-invasive methods.

One important issue is where to recruit patients for these clinical trials. One possible source is alcohol addiction clinics, where screening should be done for the presence of early liver disease in all patients. Patients with evidence of early ALD should be referred and enrolled in clinical trials. Another potential source is general practitioners, who should perform proper screening for harmful alcohol intake and early ALD, so those patients could be referred to specialists and enrolled in clinical trials. To assist in detection of early ALD, there is the need to develop and validate non-invasive methods to assess organ injury, such as for instance the Southampton Traffic Light test [3]. Lastly, early ALD could also be detected through screening

in patients admitted to hospital with alcohol related conditions, since 40% of patients diagnosed with ALD had a previous admission to hospital for any reason with an average of 2.8 admissions.

Designing and accomplishing clinical trials in early ALD is challenging, but since that is the major cause of liver disease, action has to be taken.

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# Current treatments in alcoholic hepatitis (lessons learned) and ongoing clinical trials

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Patients categorized as having severe alcoholic hepatitis, based on a Maddrey's discriminant function  $\geq 32$  have a high mortality rate over 28 and 90 days. Early trials reported mortality rates of 30 – 45% at 28 days. However, in the three most recent large clinical trials mortality rates at 28 days ranged between 12.4 – 24% at 28 days and 26-34% at 90 days. It is not currently possible to explain the differences in survival but it is reasonable to speculate two causes:

1. The patient population that we currently see with alcoholic hepatitis are less likely to suffer with malnutrition and sarcopaenia than those seen in previous generations.
2. The general management of patients with decompensated liver disease has improved in the 40 years since the first alcoholic hepatitis trials were published.

Mortality rates at specific timepoints are key outcome measures in clinical trials and therefore the expected mortality has an impact on sample size calculations for clinical trials. It is likely that treatment would influence mortality up to 90 days after admission but we now know that the mortality after 6 months is mainly determined by abstinence behavior. It has therefore been suggested that 90 day mortality should now be considered as the primary endpoint in clinical trials in severe alcoholic hepatitis.

The STOPAH trial and network meta-analysis of published trials demonstrated that prednisolone marginally improves survival at 28 days with no impact on survival beyond this time. The initial benefit of prednisolone may be lost due to the increased risk of infection associated with corticosteroid use. Patients with high levels of circulating bacterial DNA appear to be at risk of early infection and increased mortality. It is not clear whether this bacterial DNA represents translocation of bacterial products across the gut mucosa or early development of systemic infection. However, measurement of circulating bacterial DNA could be used to stratify infection risk and guide the use of antimicrobial therapy in the future. Evaluation of the effects of novel therapeutic agents on susceptibility to infection will need to be carefully incorporated into future clinical development plans with standardization of the detection and monitoring strategies for infection.

There are a number of clinical trials for alcoholic hepatitis in progress registered on ClinicalTrials.gov and elsewhere. The therapeutic agents and rationale are detailed in the table below.

Intervention	Rationale
Rifaximin	Decreases intestinal bacteria growth and lowers endotoxin level in the blood
Amoxicillin/Clavulanic acid	Decreases intestinal bacteria growth
Ciprofloxacin	Decreases intestinal bacteria growth
Probiotics	Alters gut microbiome to decrease intestinal permeability or endotoxin levels
Bovine colostrum	Binds and removes endotoxin
Obeticholic acid	FXR agonist that decreases fat synthesis
Anakinra or Cannakinumab	Bind/block interleukin-1 (anti-inflammatory)
Mycophenolate	Inhibits inflammation
Caspase inhibitors	Inhibits caspase-mediated cell death
Interleukin-22	Stimulate hepatic regeneration
ASK-1 inhibitor	Anti-inflammatory/ anti-fibrogenic

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# Clinical trial design: What is the optimal plan of development from phase I to Phase III?

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As in other fields of medical research, an urgent need exists to create the optimal scientific conditions for the development of new drugs in alcoholic hepatitis. These conditions include a clear definition of disease, a rational evaluation of severity to calculate sample size, the choice and validation of end points, the development and correct assessment of surrogate markers of outcome, as well as study designs for phase I to phase III trials. This scientific approach is necessary to correctly assess the effect of tested strategies on chosen end points. Alcoholic hepatitis is an acute process that occurs on a chronic liver disease. Data on this topic have been misinterpreted because drugs with a short-term effect have been evaluated for their long-term effect while no long-term strategy has been proposed.

Most initial studies testing molecules in the field of alcoholic hepatitis underestimated the importance of this scientific approach. As an example, there was no precise definition of the severity of liver disease in previous trials, as shown by mortality in the control groups ranging from 0 to 100%. Some experts do not recommend liver biopsy to diagnose alcoholic hepatitis and define disease severity. They suggest using combined clinical and biological criteria that have not yet been validated as diagnostic tools. Thus studies that are not based on a histological diagnosis of disease have a 10–50% risk of including patients without disease. These false positive inclusions substantially bias the statistical hypothesis by increasing the risk of type I and type II errors, because, by definition, the outcome of patients without alcoholic hepatitis should not be affected by molecules targeting the specific pathways driving disease progression.

Experts need to agree on the different primary end points for phase I, II and III studies, so that pharmaceutical companies and scientific societies can plan on the development of future molecules. For example, phase I–II studies evaluating safety and the influence of molecules on liver injury must include patients with a minimal competitive risk of mortality to ensure sufficient exposure time. On the other hand, phase III studies should focus on proof-of-efficacy on the basis of validated primary end points. Mortality alone should not be used as an end point, but to develop and propose surrogate markers strongly associated with outcome, such as early improvement of liver function.

During the short-term period, alcohol relapse will have a minor influence on the analysis of because this parameter does not significantly affect short-term mortality. Conversely, the major impact of alcohol intake on the long-term outcome is demonstrated. The optimal goal of long-term management after an episode of severe alcoholic hepatitis should be to obtain complete abstinence.

Any recurrent alcohol consumption influences outcome whatever the type of response to medical therapy and an additive effect is observed between these two factors. Thus, one should be very cautious when interpreting long-term data in studies evaluating short-term exposure to therapy in relation to the risk of recurrent alcohol consumption over the time.

Therapeutic strategy for severe alcoholic hepatitis must target liver injury for the short term and alcohol consumption for the long term. Health agencies can identify endpoints in future trials that are adapted to the time-frame of the factors influencing mortality. With this in mind, drugs targeting mechanisms involved in liver injury should be tested for the short-term period that switch the patient from decompensated to compensated status alone. However, after recovery from liver injury, new strategies must be evaluated to decrease long-term relapse to heavy drinking or alcohol intake.

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# How can large epidemiologic studies, registries and bio-banks may help in the setting of AH and ALD

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Alcohol is the leading cause of cirrhosis in the world and ALD represent a huge burden on patients, healthcare systems and societies. Still the field is lagging behind and the burden of disease is not reflected in overall funding, number of publications and drug development programmes. Within the last decades the natural history of many disease has changes due to several new treatments that has reduced mortality and morbidity. Hepatitis C is being eliminated –few would have imagined that some years back. Currently drug development in NASH is on the agenda in industry and academia. ALD is the next frontier. However, it seems that the battle must be fought with knowledge and driven by academia due to limited industry interest. But as the NASH field matures ALD will likely be fuelled due to overlap and similarities. In that setting epidemiologic studies, registries and bio-banks can be helpful to advance knowledge and open the path to new treatments in AH and ALD.

Epidemiologic studies is the go to approach for assessing incidence rates, which is very important to monitor and forecast burden of disease and expected impact and demands in the healthcare systems. Further such studies can assess risk factors to developing ALD and AH (i.e. drinking patter, age, co-morbidity, ethnicity etc.), natural history and risk of developing complications such as HCC.

Collecting new research data is often time consuming and expensive and it may be difficult to recruit volunteers. In registries the data are already available, bias due to non-responders is not a problem, register-based research can be done without risk of unwanted disclosure of personal data and it involves no invasive procedures. However, such studies only identify associations – not causality or document efficacy of new interventions. But they can suggest effects of known drugs before clinical trials. Registries studies in ALD and AH are currently hampered due to lack of commonly accepted and implemented diagnostic criteria.

Bio-banks are essential and all larger research initiatives should include a bio-bank for future research. This can speed up the processes of studying biomarkers; diagnostic, prognostic and mechanistic markers. Biomarkers as surrogates for efficacy of intervention are pivotal to advance drug development, because it can speed up drug-screening trials. A modern bio-bank should include various biological material stored and handled to enable various analyses including the multiple omics technologies. Equally important, the bio-banks must be combined with extensive clinical phenotyping and at best include follow up and sequential sampling. Follow up will allow analyses of impact of various factors such as drugs.

These types of studies are relatively cheap, fast to perform compared to clinical studies and can provide important knowledge on burden of disease, risk factors and prognostic factors. The data generated can provide background for clinical trials and input for prioritisation and strategy in healthcare systems. Further such data can promote important discussions on societal barriers as alcohol availability, price and advertising policies. Collaborative efforts to increase visibility, power and generalizability or differences across countries and regions are essential as we move forward. The data are complimentary to clinical studies but can never substitute.

**Disclosure of Interest:** None Declared

# Liver transplantation and severe Alcoholic Hepatitis

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Although ALD becomes the first or second indication for liver transplantation (LT) in Europe and the USA, it continues to be the most controversial in terms of public reaction [1].

Most programmes require a 6-month period of abstinence prior to evaluation of alcoholic patients. The 6-month period of abstinence is presumed: a) to permit some patients to recover from their liver disease and obviate the need for LT; and b) to identify subsets of patients likely to maintain abstinence after LT [2]. There is limited evidence to document the validity of this criterion alone in predicting alcoholic relapse.

Despite the frequent use of the 6-month rule, the United Network for Organ Sharing (UNOS) [3], the EASL clinical practical guidelines on ALD [1] and the French Conference Consensus on Liver Transplantation did not endorse this measure as a formal recommendation.

The 6-month rule in the context of severe alcoholic hepatitis (AH) not-responding to medical therapy

At present, LT for patients with AH remains under investigation and a panel of experts noted that the potential role of LT in managing patients with severe AH remains an undecided issue. Members of UK LT units listed AH as a contraindication for LT [4] although other experts consider that a period of sobriety as a policy for transplant eligibility is unfair to patients with severe AH non-responding to medical therapy, as most of them will have died prior to the end of the 6-month sober period [5].

Early Liver Transplantation (eLT) in patients with alcoholic Hepatitis not responding to medical therapy

A case controlled study showed an unequivocal improvement of survival in patients with severe alcoholic hepatitis failing to respond to medical therapy who received eLT [6]. These patients were selected using strict criteria and failure of medical therapy was identified using Lille score  $\geq 0.45$  [7] or worsening of liver function by day 7. This study on eLT [8] challenges previous expert opinion. These favorable results have been recently confirmed by two American studies [9, 10]. Alcohol relapse between the 3 studies was low, around 10-25%, similar compared to transplanted patients with more than 6 months of abstinence. The 2 American studies showed that eLT in severe AH can be adapted to a US medical environment [11]. The results from these three studies support future evaluation of LT in a carefully-selected subgroup of patients with severe AH failing to respond to medical therapy, despite the fact that eLT in such patients contravenes the 6-month abstinence rule [1]. eLT could affect organ donation from the public and their confidence in the fairness of transplant programs. However, a recent survey of 503 Americans, trained in answering surveys via a well-known crowdsourcing marketplace, showed that 82% of them were neutral about the eLT program for AH [12]. Doctors should inform the public that ethical principles recommend active treatment of patients, without discrimination, according to the best scientific knowledge. As raised by a recent review there are no major ethical barriers for further evaluation of eLT in severe AH not responding to medical therapy [13]. Investigators and scientific societies should communicate in a transparent manner with the public.

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# Which Therapeutic Targets Will Be the Most Attractive in the Future?

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Clinical trials over this time have yielded some overall benefits in survival, most of which are likely related to improved general medical care. Unfortunately, the most widely used drug treatments do not appear to yield robust therapeutic effects. Indeed, the STOPAH trial showed no statistically significant beneficial effects of steroids or pentoxifylline on short-term or one-year survival rates. Moreover, the reasons for drug dosing and duration of therapy for many current agents, such as steroids and pentoxifylline, are not well defined. It is well documented that almost all patients are malnourished and require nutritional support. Protein intake is usually <60gm/day for patients with moderate/severe AH, with most studies showing that >85gm are needed for positive nitrogen balance. Late evening snacks also improve muscle mass. AH patients are at risk for sarcopenia for multiple reasons including inactivity, aging, inadequate protein intake, and inadequate anabolic hormone activity, to name only a few. Supplements with nutrients such as zinc and/or anti-inflammatory lipids may also be of benefit. Factors that modulate the gut-liver axis, such as anti-endotoxins, pre- and probiotics, and others, are already in clinical trials. The importance of the gut-liver axis in the development/progression of AH is increasingly appreciated.

The current NIAAA U01 network is evaluating two anti-endotoxins and one probiotic. These agents are generally safe, but the question of who to treat, and with what agents remains unclear. A recent small study of fecal transplant in AH reported clinical benefit. However, at least in the US, there are important concerns about use of fecal transplant outside of its role in *C. difficile* colitis. Inflammation plays a critical role in alcoholic hepatitis, and anti-inflammatory agents such as anakinra (IL-1 receptor antagonist) and ceniciviroc (CCR2, CCR5 antagonists) are examples of potential anti-inflammatory therapies. Anakinra has been the lead anti-inflammatory agent in the NIAAA-funded DASH U01 AH Consortium study, and this study is ongoing. Dosing and optimal duration of therapy for such agents has not been extensively investigated in AH. Nuclear hormone receptor modulators represent an area of intense investigation, with both extensive preclinical and some early clinical trials underway. Inhibition of cell death is another likely target, and caspase inhibitors, as well as agents that diminish ER- or mitochondrial- stress are being evaluated. A small study using a caspase inhibitor in AH has been discontinued. Agents that specifically target the mitochondria are a potential option, with some showing efficacy in animal models. Drugs that enhance liver repair/liver regeneration have been somewhat overlooked until recently. Granulocyte colony-stimulating factor (G-CSF) mobilizes bone marrow cells and improves liver regeneration by stimulating oval cell proliferation and bone marrow cell engraftment in a rat model of liver injury. G-CSF has been used in small studies of acute-on-chronic liver failure (ACLF) and AH with improvement in survival and several other outcome measures.

These studies form part of a basis for the use of G-CSF in the proposed NIAAA clinical trial. However, stem cell therapy has generally been unrewarding to this point. A recent 3-month prospective randomized trial in clinically-decompensated ALD, compared standard medical therapy (SMT) alone versus SMT combined with bone marrow mononuclear cell mobilization and infusion into the hepatic artery. A similar improvement in MELD and survival was noted in both groups, and there was no major evidence of enhanced regeneration in the bone marrow cell-treated group. Finally, greater attention should be paid to reducing continued alcohol abuse. It has been well documented for over a half century that discontinuing drinking improves mortality in patients with both decompensated and as well as compensated alcoholic liver disease. Unfortunately, in most AH trials, the majority of patients returned to drinking within one year. There are limited studies evaluating pharmacologic (or drug) therapy aimed at limiting alcohol intake in patients with AH. Anti-inflammatory agents that may decrease alcohol craving by modulating the gut-liver-brain axis are particularly attractive. They could attenuate both liver and brain Inflammation.

Early human trials using phosphodiesterase (PDE) inhibitors and extensive preclinical data suggest this may be a promising target. Lastly, future therapy will likely consist of combinations of multiple agents given over varying periods of time. Different agents will also likely be used for different levels of severity of disease. In conclusion, multiple promising new therapies that impact several mechanistic pathways are in various stages of evaluation to treat this disease which has such high morbidity/mortality.

# The NASH CRN and DILI Network in the United States

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The Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN) and the Drug Induced Liver Injury Network (DILIN) are two ongoing and successful initiatives funded by the National Institute for Diabetes, Diabetes, and Kidney Diseases (NIDDK). These are funded as cooperative U01 agreements between the awardee institutions and the NIH where the NIH project scientists have significant input and oversight into the proceeds of these networks.

Established in 2002, the NASH CRN (<https://jhuccs1.us/nash/>) consists of several clinical centers with expertise in non-alcoholic fatty liver disease research and a data coordinating center. This network is funded by the NIDDK every 5-7 years and 8 clinical centers and one DCC were selected initially based on an open competition. This network has been refunded two more cycles but through limited competition (i.e., no new PIs can apply). However, a number of pediatric investigators have been added to the NASH CRN as subsites to those 8 initially chosen clinical centers. The NASH CRN has conducted several observational studies as well as clinical trials (PIVENS, TONIC, FLINT, and CyNCh). To date, it has initiated 117 ancillary studies related to NAFLD and NASH in adults and children and has published more than 85 full length peer-reviewed manuscripts. Over the years, the NASH CRN has engaged pharma partners for collaborations, but due to federal funding its collaborations with industry partners is bound by certain regulations specific to the United States. The NASH CRN has developed a rich resource of biosamples consisting serum, plasma, liver cDNA, and genomic DNA for future translational and mechanistic studies. In due course these samples will be placed in public domain.

Established in 2004, the DILIN consists of several clinical centers with expertise in DILI and a data coordinating center which is located at the Duke University (<http://www.dilin.org/>). This network is funded by the NIDDK as 5 year funding cycles and the selection has been on an open competition basis. The focus has largely been on adult centers and is limited to idiosyncratic drug induced liver injury. Its primary study is the DILIN Prospective Study which has enrolled more than 2000 individuals with suspected DILI from across the United States. To date, 55 full length original papers have been published and more than 30 ancillary studies have been initiated and/or completed. The DILIN has also developed a rich biosample repository of plasma/serum and genomic DNA for mechanistic and translational research.

Key factors which defined the success of these networks are the leadership of the steering committees, camaraderie and scientific zeal of the investigators, and stable and sustained funding from the NIDDK. Both consortia are well supported by highly capable data coordinating centers – Johns Hopkins led by Dr James Tonascia for the NASH CRN and Duke University led by Dr Huiman Barnhart. Some of the challenges include budgetary constraints, tensions related to pharmaceutical company interactions, investigators moving to different institutions, and more recently costs related to obtaining samples from biorepositories.

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**Disclosure of Interest:** None Declared

**ePOSTER  
ABSTRACT  
PRESENTATIONS**

## POI-IYI

# Defining meaningful clinical trial endpoints in patients with alcohol induced chronic liver disease: results from a multicentre feasibility trial

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**Introduction:** Extra hepatic organ dysfunction is closely correlated with outcome in acutely decompensated liver cirrhosis and therefore is frequently recorded in clinical studies, often using complicated measures. We hypothesise that detecting early, rather than advanced, extra hepatic organ dysfunction in ward settings would be more clinically relevant for interventional studies in these patients as this is the tipping point for progression to multi organ failure and death.

**Aims:** Our aim was to develop pragmatic, reliable criteria to objectively detect earlier extra hepatic organ dysfunction, which is linked to poor clinical outcome, for use as a primary endpoint in a large RCT.

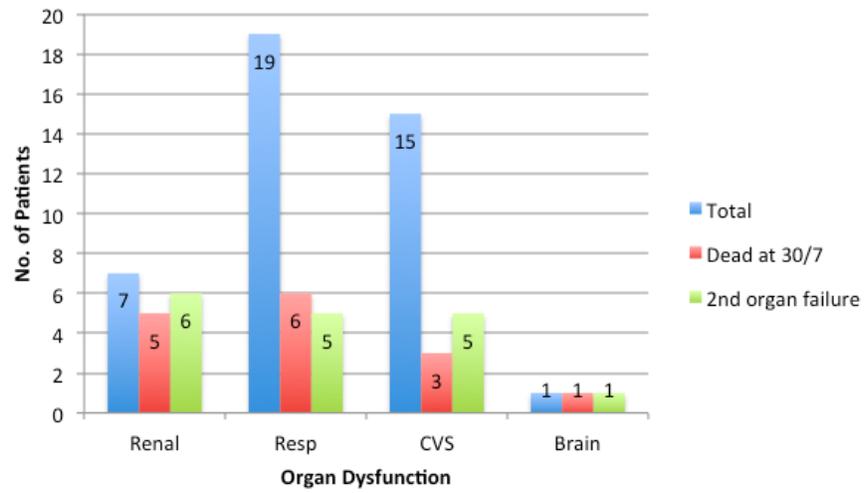
**Material and methods:** This prospective multicentre, single arm, feasibility trial recruited 79 patients admitted with cirrhosis complications from 10 centres in 6months. Modified extra hepatic components of the CLIF scoring system were used as organ dysfunction criteria:

1. Renal: Serum creatinine increase  $\geq 50\%$  compared to baseline
2. Respiratory: Single point increase in  $SpO_2/FiO_2: 0=>357, 1=>214$  to  $\leq 357, 2=\leq 214$
3. Circulatory: MAP falls to  $<60$ mmHg
4. Hepatic encephalopathy: Grade III(drowsy)-Westhaven Criteria

**Results:** Mean age was 53.4 years (SD 11.63). Patients were recruited on average 1.8 days after admission to hospital. Mean MELD score was 20.9(SD 6.6.2). Alcohol was the primary cause of cirrhosis (96%). Figure 1 shows number of patients developing organ failures during the 14day trial period, those patients that died 30 days post recruitment and those that developed a 2<sup>nd</sup> organ failure.

**Conclusions:** Renal dysfunction uses an objective measurement, creatinine and patients developing this had poor prognosis, as expected. Therefore this measure can be reliably used. Only one patient developed hepatic encephalopathy ( $\geq$ grade 3) suggesting under reporting and objective assessment being challenging. The majority of patients that solely triggered respiratory and cardiovascular endpoints had a good outcome with several discharged within a few days. This is counterintuitive as organ dysfunction is a key predictor of poor prognosis. Assessment may be subject to technical difficulties such as a standard size blood pressure cuffs used in sarcopaenic patients and  $SaO_2/FiO_2$  recording of respiratory dysfunction greatly influenced by amount of oxygen delivered. We consider our data cast significant doubt over whether these dysfunctions can be recorded accurately in largely ward-based patients across multiple sites and therefore precludes use as part of a RCT primary endpoint.

Figure:



Disclosure of Interest: None Declared

# No consensus among nutritional assessment tools for identification of malnutrition in patients with alcoholic Liver disease

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**Introduction:** Background: Malnutrition is a major concern in alcoholic cirrhosis (AC) which needs urgent attention. Prevalence of malnutrition varies with the methods used for assessment. Gamut of methods ranging from traditional like anthropometry, functional status and composite scores, to reference methods like bioelectrical impedance analysis and radiological imaging are available for defining malnutrition.

**Aims:** To assess nutritional status of patients with AC using various methods

**Material and methods:** 147 consecutive pts with AC, from Jun2013 to Aug 2015 underwent complete nutritional workup using anthropometry [triceps skin fold (TSF) by Harpenden's calliper; mid arm muscle circumference (MAMC)] hand grip strength (HGS) by electronic dynamometer, Royal Free Hospital-Subjective Global Assessment (RFHSGA), Phase angle (PA) by multi frequency TANITA, & skeletal muscle index (SMI) by single slice L3 CT image by Slice-Omatic software. Dietary intake -using 24 hr dietary recall along with semi-quantitative food frequency method. Energy requirements(ER) were estimated using Harris Benedict equation. Protein requirements (PR) were assessed as 1.2gm/Kg IBW. Demographic, clinical, and biochemical data were also collected. The cut-offs for defining malnutrition by TSF(12.5 mm),MAMC(24.5 cm),HGS(37.5 Kg),Phase angle (5.4o ) were taken from literature while that of SMI(36.5 cm<sup>2</sup>/m<sup>2</sup> ) was from our own ethnic data of healthy controls (2SD below the mean; unpublished data)

**Results:** : In total 147 AC[M-100%;age- 44.08 ±9;BMI- 18.45±6.85;Child A:B:C-14%:38%:48%,disease duration8(1-40 mo),alcohol intake 112±30 gm] were studied. Mean intake of proximate principles was-calorie 1588.94 ± 566.68 Kcal (69.6% of EER), protein 57.6±25.2 (73% of PR) carbohydrates 263.3±20, fat32.7±4.2; erroneous dietary restrictions were practiced by 91.5% patients. Mean values of TSF, MAMC, HGS, PA, and SMI were11.73±5.52mm; 21.38±2.8cm; 25.37±6.98Kg; 4.97±1.3o; and46.2±10.4cm<sup>2</sup> /mviz. Prevalence of malnutrition as n (%) was: TSF-92(62.6%); MAMC-137(93.2%); HG-141(95.9%); RFH-SGA-123(83.6%), PA-102(69.4%) and SMI-23(15.6%).

**Conclusions:** Prevalence of malnutrition and dietary inadequacy is high in patients with ALD; however nutritional assessment tools do not uniformly identify patients as malnourished. Traditional as well as modern methods (TSF, MAMC, RFH-SGA, and PA) using western cut-offs may overestimate malnutrition while the reference method (SMI) using ethnic cut-offs challenge these values. Hence there is an urgent need for ethnic cut-offs for all methods to obtain uniformity.

**Disclosure of Interest:** None Declared

## POI-3

# Portal hemodynamics and systemic inflammation in patients with alcoholic hepatitis: a follow-up study

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**Introduction:** Deterioration of portal hemodynamics and increased HVPG participates to clinical manifestations of alcoholic hepatitis (AH), as a consequence of inflammation, recent exposition to alcohol and liver parenchymal alterations. How HVPG values change after weeks of follow-up in real life condition is not known.

**Aims:** To explore in details the evolution of portal and systemic hemodynamics in patients with alcoholic liver disease (ALD) presenting with or without AH, taking into consideration alcohol use, inflammation, and portal hypertension-related clinical events

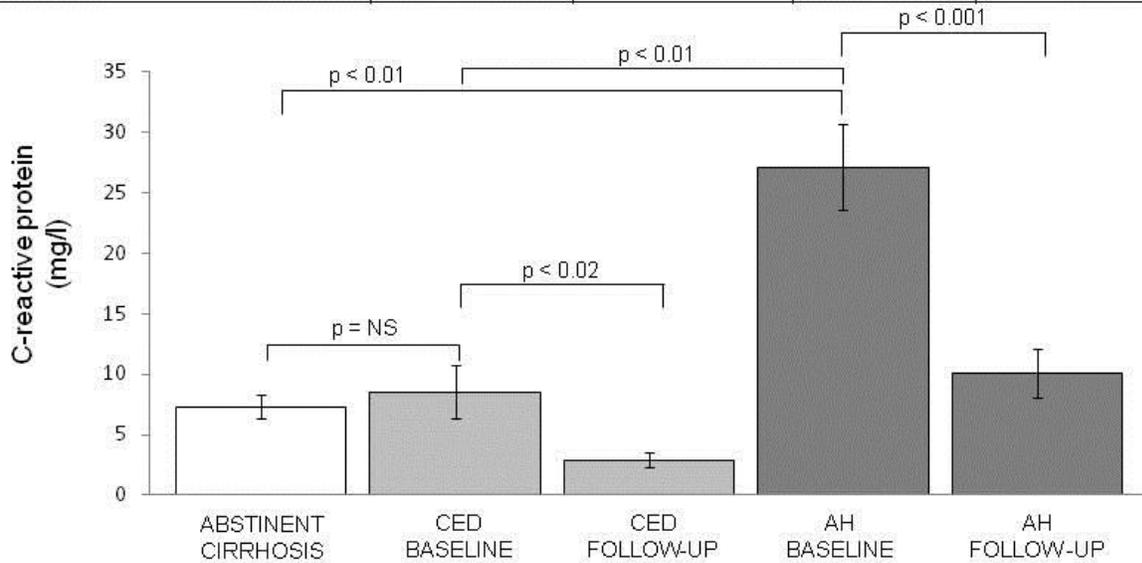
**Material and methods:** This prospective observational cohort included non septic patients with AH (n=33 ; mean age 52 yrs ; 97% with cirrhosis ; MELD 18.5 ; Maddrey score 43) and chronic alcohol drinkers (CED, n=15 ; mean age 54 yrs; 100% with cirrhosis ; MELD 10.5) with an indication for transjugular liver biopsy. A group of durably abstinent patients with alcoholic cirrhosis served as controls. After standard of care management (including steroids when indicated), patients were closely monitored with regards to alcohol use and liver related events, and measurement of HVPG was repeated after a median time of 100 days. Inflammation was assessed by determination of plasma C-reactive protein (CRP). **Results:** # p<0.01 vs baseline; \* p<0.001 vs baseline; § p<0.02 vs baseline

**Results:** Liver related complications were more frequent in patients with AH as compared to patients in the CED (27 vs 5, p< 0.01). Patients with AH who achieved abstinence were more likely to reach a > 20% decrease in HVPG as compared to baseline (45% versus 0%, p < 0.01). CRP plasma level correlated with Maddrey's score (r=0.46), but not with changes in HVPG. No correlation were observed between changes in CRP and HVPG values in either groups. No significant modifications were observed regarding systemic hemodynamics.

**Conclusions:** We confirm in this real life situation that a marked deterioration of portal hemodynamics occurs in AH, which improves after several weeks of follow-up particularly in patients who achieve alcohol abstinence as compared to those who returned to harmful drinking. These observations could help motivating patients to stop alcohol after an episode of AH

Figure:

Variable	AH (n=33)		CED (n=15)	
	Baseline	Follow-up	Baseline	Follow-up
Time interval (days)	100 [80-220]		98 [69-145]	
OH relapse (n, %)	10 (30)		10 (66) <sup>s</sup>	
MELD score	18.5 ± 0.8	12.7 ± 0.7*	9.2 ± 0.5	8.5 ± 0.6 <sup>s</sup>
Steroid responder (n, %)	16 (80)		-	
CRP (mg/l)	27.2 ± 3.6	10.1 ± 2 <sup>#</sup>	8.5 ± 2.1	2.9 ± 0.6
Beta-blockers (%)	21	18	13	13
Heart rate (bpm)	85 ± 2	79 ± 2.4	76 ± 2.8	76 ± 2.3
MAP (mmHg)	77 ± 1.9	80 ± 1.4	83 ± 1.6	87 ± 1.7
HVPG (mmHg)	18.1 ± 0.6	15.8 ± 0.6*	13.8 ± 1.4	11.5 ± 1.2



Disclosure of Interest: None Declared

## POI-4

# The utility of alcohol screening tests in clinical practices in patients with end stage liver disease awaiting liver transplantation - experience of a tertiary hepatology center

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**Introduction:** Monitoring alcohol consumption and related harm in cirrhotic patients included on the waiting list for liver transplantation is important to identify high-risk groups and trends in alcohol use in order to elaborate strategies to avoid alcohol relapse after LT.

**Aims:** The aim of our study was to detect the pattern of alcohol consumption in cirrhotic patients by using three Alcohol Screening Tests.

**Material and methods:** 59 patients with liver cirrhosis admitted to our hepatology unit between February-April 2017 were prospectively evaluated by CAGE, AUDIT-C and FAST (based on AUDIT 10 questions) questionnaires. Sensitivity, specificity and areas under the receiver operating characteristic (AUROC) curves were measured in order to predict active drinking.

**Results:** There were 11 females and 48 males with a mean age was  $53.8 \pm 9$  years, 27.11% being active drinkers and 55.7% had stopped alcohol consumption or had non-alcohol related chronic liver disease. There was a significant negative weak correlation between ALT values and AUDIT-C score ( $r = -0.25$ ,  $p = 0.04$ ) and a positive correlation between GGT values and AUDIT-C score ( $r = 0.28$ ,  $p = 0.02$ ). CAGE ( $p = 0.02$ ) and FAST ( $p = 0.006$ ) scores differed statistical significant according to the type of alcohol consumption (binge/chronic/social), while AUDIT-C reached only marginal statistical significance ( $p = 0.06$ ). The calculated area under the ROC curve was 0.96 for FAST, 0.89 for CAGE and 0.82 for AUDIT-C questionnaires (significantly statistical difference between AUROC of FAST and AUDIT-C  $p = 0.01$ ). The cut-off scores for each questionnaire to detect active drinking were:  $>9$  for FAST (sensitivity 100%, specificity 86.4%),  $>2$  for CAGE (Se 86.7% and Sp 84.1%) and  $>3$  for AUDIT-C (Se 80% and Sp 81.9%).

**Conclusions:** FAST, CAGE and AUDIT-C questionnaires have a very good clinical utility in detecting active drinking in patients with various end stage liver diseases included on the waiting list for liver transplantation.

**Disclosure of Interest:** None Declared

# Opportunities to reach high-risk populations for alcoholic liver cirrhosis: Systematic review and meta-analysis

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**Introduction:** Alcoholic liver cirrhosis is a preventable disease caused by years of heavy drinking. Few in the general population have an alcohol intake at this level and targeted interventions may be a more feasible opportunity for prevention than interventions aimed at the whole population.

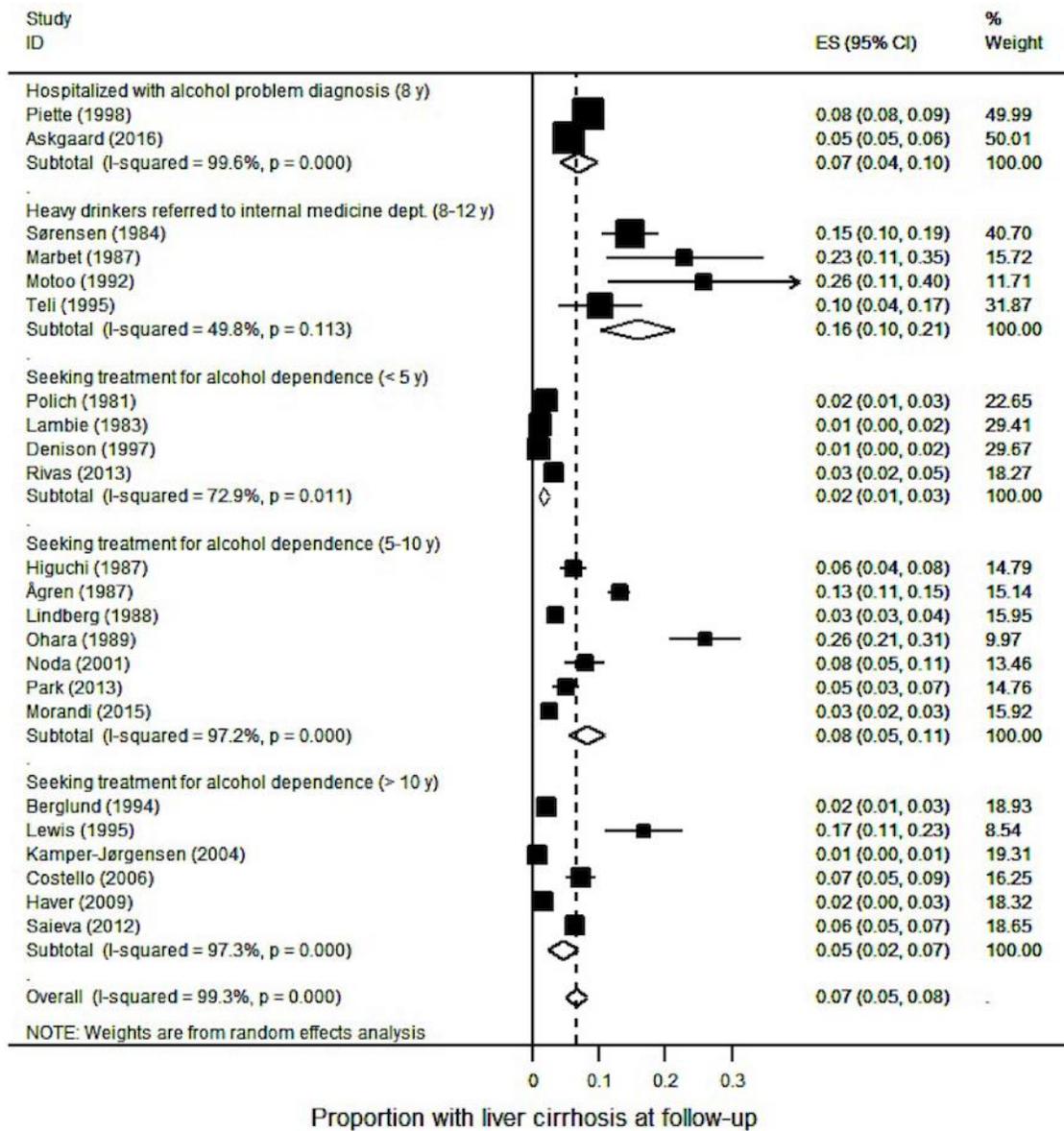
**Aims:** To undertake a systematic review with meta-analysis to identify opportunities to reach high-risk populations for alcoholic liver cirrhosis.

**Material and methods:** Following MOOSE guidelines, we included observational studies published 1980-2016. Prospective studies were included to investigate to which extent alcohol-problem cohorts have a high risk of alcoholic liver cirrhosis. Studies on the alcohol amount consumed by alcoholic liver cirrhosis patients were included to compare with the alcohol amount consumed by the general population. Finally, studies on alcohol-related healthcare contacts prior to alcoholic liver cirrhosis diagnosis were included to identify opportunities to offer preventive interventions. Meta-analyses with random effects on proportions were performed to allow for between-study heterogeneity.

**Results:** Of 6083 screened references, 36 studies (N = 120,706) were eligible for inclusion. Alcohol-problem cohorts were high-risk populations for alcoholic liver cirrhosis with 7 to 16% diagnosed with alcoholic liver cirrhosis after 5-12 years (Figure 1). The alcohol amount consumed in alcoholic liver cirrhosis patients applied to only a small proportion of the general population. For example, 45% (95%CI 30, 61) of alcoholic liver cirrhosis patients were drinking more than 110 g alcohol per day compared to less than 6% in the general population drinking more than 50 g alcohol per day. Finally, 40-61% of alcoholic liver cirrhosis patients had alcohol-related healthcare contacts prior to diagnosis.

**Conclusions:** Alcohol-problem cohorts are high-risk populations for alcoholic liver cirrhosis and there seems to be opportunities to reach around half of alcoholic liver cirrhosis cases with preventive interventions in health-care settings.

Figure:



Disclosure of Interest: None Declared

P02-2YI

## Effect of candesartan cilexetil on striatin/nitric oxide pathway in regulating endothelial dysfunction in alcoholic liver disease

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**Introduction:** Our recent clinical study in decompensated cirrhotic patients show decreased systemic striatin concentration, which was negatively correlated with systemic cGMP concentration; indeed the underlined molecular mechanism remains obscure.

**Aims:** Our aims were to identify the striatin/NO pathway in a mouse model of alcoholic liver disease (ALD) and further to determine the effect of candesartan cilexetil (CC) in regulating endothelial dysfunction through modulation of striatin/NO pathway in ALD.

**Material and methods:** Male Swiss mice (n=10/group) were studied for 60 days. Four groups were studied. 1) naïve, 2) naïve + CC (8mg/kg for two weeks from day 45), 3) alcohol (6.32 g/kg daily by gastric lavage, for 60 days) and 4) alcohol+CC (as prior dosing).

**Results:** Compared to naïve mice, alcohol supplementation significantly ( $p<0.05$ ) increased plasma levels of ALT, TNF  $\alpha$ , Ang II, and von Willebrand factor. CC treatment to alcohol-fed mice corrected these indices significantly. Moreover, alcohol administration had markedly increased eNOS and caveolin-1 protein expression ( $p<0.01$ , for both); but iNOS expression was insignificantly increased ( $p=0.1$ ). CC treatment to alcohol-fed mice showed significantly ( $p<0.05$ ) decreased eNOS and caveolin-1 expression, but iNOS expression was unchanged. Hepatic striatin expression was significantly ( $p<0.01$ ) lowered in the alcohol-fed group when compared to naïve. CC treatment to alcohol-fed mice showed significantly ( $p<0.05$ ) increased striatin protein expression. Furthermore, compared with alcohol alone; hepatic cGMP was increased to naïve levels following CC treatment whilst remaining significantly lower in the alcohol group. Liver histology showed that mice given alcohol had ballooning and macrovesicular type of fatty changes in the hepatocytes. CC treatment to alcohol-fed mice showed reduced these pathological changes.

**Conclusions:** These data provide the first in vivo evidence in rodents that lowered hepatic striatin correlated with decreased hepatic cGMP levels and increased caveolin-1 and thus endothelial dysfunction in ALD. CC treatment to alcohol-fed mice resulted in the increase of hepatic striatin and NO synthesis and improved endothelial dysfunction in ALD. Our further study will pinpoint the effect of CC on nitric oxide pathway and portal pressure reduction in alcoholic hepatitis patients.

**Disclosure of Interest:** None Declared

## P02-3

# Ethanol-Induced Oxidative Stress in Primary Human Hepatocytes is suppressed by VTL C3A Cell-Secreted Factors

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**Introduction:** Hepatocellular mitochondrial dysfunction is a key mechanism in alcoholic hepatitis (AH) and leading cause of liver-related deaths. Both chronic and binge drinking can activate signaling pathways through induction of reactive oxygen species (ROS) and cause mitochondrial dysfunction.

**Aims:** To evaluate if VTL C3A cell-secreted factors from the ELAD System, an investigational human hepatic cell-based liver treatment comprised of four metabolically active cartridges with ancillary delivery device components and cell support circuitry to treat severe AH, can dampen ethanol-induced oxidative stress and improve mitochondrial function in a primary human hepatocyte (PHH) model.

**Material and methods:** Cryopreserved PHH were plated overnight in William's E media (WEM) and treated with WEM or VTL C3A cell-conditioned medium (CM) diluted 1:1 in WEM 1 h prior to exposure to 100 mM ethanol (EtOH) for 4 h. Mitochondrial ROS and ATP were measured in PHH using MitoSOX Red and CellTiter-Glo, respectively. Further, total ROS, H<sub>2</sub>O<sub>2</sub>, and superoxide dismutase (SOD) were measured in mitochondria isolated from PHH after exposure to EtOH for 30 min, using 2',7'-dichlorofluorescein diacetate, Amplex Red, and Nitroblue Tetrazolium, respectively.

**Results:** CM reduced oxidative stress and mitochondrial dysfunction in PHH in each part of the SOD pathway investigated. EtOH treatment increased mitochondrial-specific ROS by 49% in PHH in WEM only; in contrast, there was a 21% increase in ROS observed in PHH with CM. EtOH lowered ATP by 44% in WEM, whereas ATP was unaffected in CM-treated PHH. Total ROS was 16% lower in the CM-treated mitochondria than WEM alone prior to EtOH exposure. ROS increased significantly in response to EtOH in mitochondria in WEM, but was blunted by CM-treatment (34% vs. 14%, respectively). Total SOD and manganese SOD (MnSOD) activities increased in PHH-isolated mitochondria by 24% and 6%, respectively, in response to EtOH in WEM, whereas EtOH did not affect either total SOD or MnSOD activity of mitochondria in the CM-treated cells. EtOH treatment induced H<sub>2</sub>O<sub>2</sub> in PHH mitochondria by 58% in WEM. EtOH failed to induce H<sub>2</sub>O<sub>2</sub> in mitochondria isolated from CM-treated PHH, consistent with no change in SOD activity in mitochondria exposed to CM.

**Conclusions:** VTL C3A cell-secreted factors protected PHH against EtOH-mediated oxidative stress and mitochondrial dysfunction. The identification of the specific factors responsible for these findings is the focus of further investigation.

**Disclosure of Interest:** J. Dammanahalli: Employee: Vital Therapies, Inc., J. Lapetoda: Employee: Vital Therapies, Inc., L. Landeen: Employee: Vital Therapies, Inc., P. Bedard: Employee: Vital Therapies, Inc.,

## Infections in Severe Alcoholic Hepatitis: Mayo Clinic Experience

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**Introduction:** Severe alcoholic hepatitis is the most severe form of alcohol-induced liver disease and is associated with a high mortality rate, notably from infectious complications.

**Aims:** To understand common infectious etiologies in severe alcoholic hepatitis and risk factors associated with increased mortality.

**Material and methods:** A retrospective chart review was conducted of all of the patients diagnosed with alcoholic hepatitis at the Mayo Clinic. The NIAAA definition of Alcoholic hepatitis was used to identify patient with alcoholic hepatitis. Qualitative analysis was performed on patient demographics, clinical history, and laboratory evaluations. Patients age <18 were excluded.

**Results:** 212 patients (143 male, median age 48 years) were identified with alcoholic hepatitis. The median follow up in this cohort was 4.8 years. Only 6% were on steroids and 21% were on Pentoxifylline. The cohort had an average MELD score of 25 and Maddrey score of 39. The rates of infection in this population of 38% of which 44 (21%) were community acquired infections (before admission and up to 48 hours), 14 (8%) were hospital acquired (>48 hours after admission), and 23 (11%) were post hospitalization (after discharge from the hospital and up to 6 months). The most common types of infection during the hospitalizations are as list in the table 1 below. In total, the mortality rate was 47%, of which 8% occurred during the hospitalizations.

Table 1.

Infection Type	N(%)
Urinary	30 (14)
Bacteremia	26 (12)
SBP	18 (8)
Respiratory	17 (8)
Abdominal	6 (3)
Line Infection	4 (2)

**Conclusions:** Conclusion: Severe alcoholic hepatitis is associated with high mortality rate. The majority of deaths occur usually within 6 months post hospitalization. Prophylactic strategies to reduce this high mortality should be assessed in future trials.

**Disclosure of Interest:** None Declared

## P03-IYI

# Liver.pt: a picture of alcoholic liver disease ambulatory patients through a national multicentric registry

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**Introduction:** Liver.pt is a Portuguese multicentric national registry initiated in 2015, where patients followed in hepatology ambulatory clinics are registered, in order to gather data on patient's characteristics and evolution, according to the diagnosis.

**Aims:** To characterize the demographics and clinical data of patients with the diagnosis of alcoholic liver disease (ALD), registered in Liver.pt database.

**Material and methods:** Analysis of data collected from 8 centres of different areas of the country.

**Results:** A total of 391 patients had ALD as their principal diagnosis, and 26 as a secondary diagnosis. Among the 391 with ALD as principal diagnosis, mean age was 63±11 (range: 34-93) years, mostly males: 326 (83.0%). The majority had clinical evidence of cirrhosis: 289 (76%), while it was suspected in 21 (5.5%) and absent in 66 (17.5%). In 30 (7.6%) patients there was evidence of hepatocellular carcinoma (HCC). Mean follow-up time since diagnosis was 5.4±6.0 years. Considering the last registered consultation, among the 197 that have Child registry: Child A: 119 (60,4%); Child B: 55 (27,9%), and Child C 23 (11,7%). Mean MELD was 11, MELD<15: 56 (80%) MELD ≥15 and <30: 36 (18%); MELD>30:4 (2%). The more frequent previous decompensation was ascites. Other decompensations are reported in Table. In 190 patients where there is reference to esophageal varices: absent-33%; small-43%; large-24%. Elastography is registered in 60 patients, with a mean value of 19.8±20.3 kPa. Among 354 patients with data on alcohol consumption, 222 (62%) reported to be abstinent, while 25 (7%) decreased consumption. During this period there were 29 registered deaths, 16 patients were referred to liver transplantation and 3 were transplanted.

**Conclusions:** Ambulatory ALD are seriously ill patients, mostly already cirrhotics with previous decompensations, frequently belonging to Child B and C class. Only a minority underwent liver transplantation. Efforts need to be done for an earlier referral of ALD patients.

Figure:

Descompensation	Patients	%
Ascitis	139	67.2%
Esophageal variceal bleeding	71	34.3%
Encefalopathy	57	27.5%
Jaundice	34	16.4%
Spontaneous bacterial peritonitis	15	7.3%
Alcoholic hepatitis	8	3.9%
Hepatorenal Syndrome	8	3.4%
Hypertensive portal gastropathy	2	1%
Gastric variceal bleeding	1	0.5%

**Disclosure of Interest:** E. Gravito-Soares: : None Declared, M. Gravito-Soares: : None Declared, M. Machado: : None Declared, C. Martins: : None Declared, I. Cotrim: : None Declared, J. Branco: : None Declared, A. Martins: : None Declared, J. Pinto : : None Declared, H. Ribeiro: : None Declared, I. Mocanu : : None Declared, A. Laranjo: : None Declared, C. Teixeira: : None Declared, A. Alves: : None Declared, S. Santos: : None Declared, C. Bernardes: : None Declared, H. Cortez-Pinto: Consultant: Intercept; Genfit

## P03-2YI

# TCell cytokine profile predicts 90-day outcome in patients with severe alcoholic hepatitis

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**Introduction:** Severe alcoholic hepatitis (SAH) is an acute inflammatory condition leading to liver failure and death in 30% of patients within 90 days. Corticosteroids have a proven short-term survival benefit but non-responders have the highest mortality. We have previously demonstrated that in vitro lymphocyte steroid sensitivity predicts 90-day outcome [1]. Furthermore, it is CD4<sup>+</sup> T cells, in particular Th17 cells, that are most steroid refractory [2]. We therefore hypothesised that CD4<sup>+</sup> T cells from patients with SAH have altered cytokine expression favouring Th17 cytokines with altered response to steroids.

**Aims:** We aimed to determine CD4<sup>+</sup> T cell cytokine expression in patients with SAH.

**Material and methods:** Consecutive patients with SAH, defined as recent onset jaundice with bilirubin > 80 µmol/L in heavy alcohol drinkers (> 60 g or 80 g ethanol / day in females and males respectively) with DF > 32, were recruited. All patients were treated with prednisolone for 28 days after exclusion or adequate treatment of infection. 90-day outcome was recorded. Blood was taken at baseline and CD4<sup>+</sup> T cells isolated by negative selection. T cells were cultured for 4 days with anti-CD3/CD28 T cell receptor stimulation with or without 10µM Dexamethasone before intracellular cytokine expression was quantified by flow cytometry.

**Results:** 30 patients were recruited (13 male; mean age 52, baseline DF 69). 90-day mortality was 20%. Baseline IL-17 expression was similar between survivors and non-survivors (percent of T cells expressing IL-17: 3.8% v 3.2%; p=0.41) as was interferon gamma (13.5% v 11.2%; p=0.08) but IL-10 was higher in non-survivors at day 90 (1.5% v 2.4%; p=0.02) with reversal of IL-10/IL-17 ratio (0.56 v 1.2; p=0.04). IL-10 expression was not induced by steroids in either survivors or non-survivors (1.0 v 1.4 fold change; p=0.52).

**Conclusions:** These data suggest that CD4<sup>+</sup> T cells from patients who die from SAH have an altered phenotype favouring suppression of inflammation. These dysfunctional T cell cytokine responses may contribute to disease pathogenesis and have the potential to be used as markers of immune function and outcome in SAH.

### References

- [1] AD Dhanda et al. Hepatology 2015; Mar;61(3):1099
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P03-3YI

## Outcomes and recidivism in patients undergoing living donor liver transplantation for severe alcoholic hepatitis

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**Introduction:** Patients with severe alcoholic hepatitis (SAH), especially steroid ineligible/non-responders, have high mortality. Early deceased donor liver transplantation (DDLT) for steroid non-responsive SAH is shown to be associated with improved survival. There is paucity of data with regards to living donor liver transplantation (LDLT) for SAH

**Aims:** We did this study to assess outcomes of early LDLT for SAH and risk of recidivism of alcohol abuse

**Material and methods:** We evaluated patients with SAH from July 2013 to June 2017 who underwent LDLT, after extensive psychiatric, social and clinical evaluation. Primary end-point was survival at 12 months and secondary end point was recidivism of alcohol consumption

**Results:** Forty-three patients with alcoholic liver disease underwent LDLT. Of these, 12 had alcohol abstinence for less than 6 months. Eight (18.6%) had severe alcoholic hepatitis and were steroid ineligible; median discriminant factor 93.5[62-190], median MELD 26 [16-40], aged 40± 8. Thirty-five (81.4%) patients were transplanted for decompensated cirrhosis; median MELD 16 [14-34], aged 52±9.5. The 12 month survival rate was 87.5% (7/8) in SAH and 91.4% (32/35) in decompensated cirrhosis. Recidivism was not seen in any patient with SAH, but in two patients with decompensated cirrhosis (Abstinence period of 8 months in both prior to transplant). Recidivism occurred at 4 and 10 months after transplant)

**Conclusions:** This study shows that LDLT for SAH in steroid ineligible patients has excellent outcomes with low risk of early recidivism in carefully selected patients

**Disclosure of Interest:** None Declared

# Abstinence period before liver transplantation: a meta-analysis of the 6 months rule

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**Introduction:** Liver transplantation (LT) is an established therapy for end stage alcoholic liver disease (ALD). Relapse to alcohol abuse is a threat to organ and patient health. To minimize this risk, patients are required to abstain from alcohol for 6 months to qualify for LTx in many centres (6 months rule, 6MR). This policy excludes some patients from a possibly lifesaving procedure. Earlier studies reported a bad test performance and little supporting evidence.

**Aims:** We aimed to summarize published evidence on the impact of pre-transplant abstinence on post-LT relapse risks and to estimate the prognostic performance of the 6MR by a meta-analysis of studies on LT for ALD.

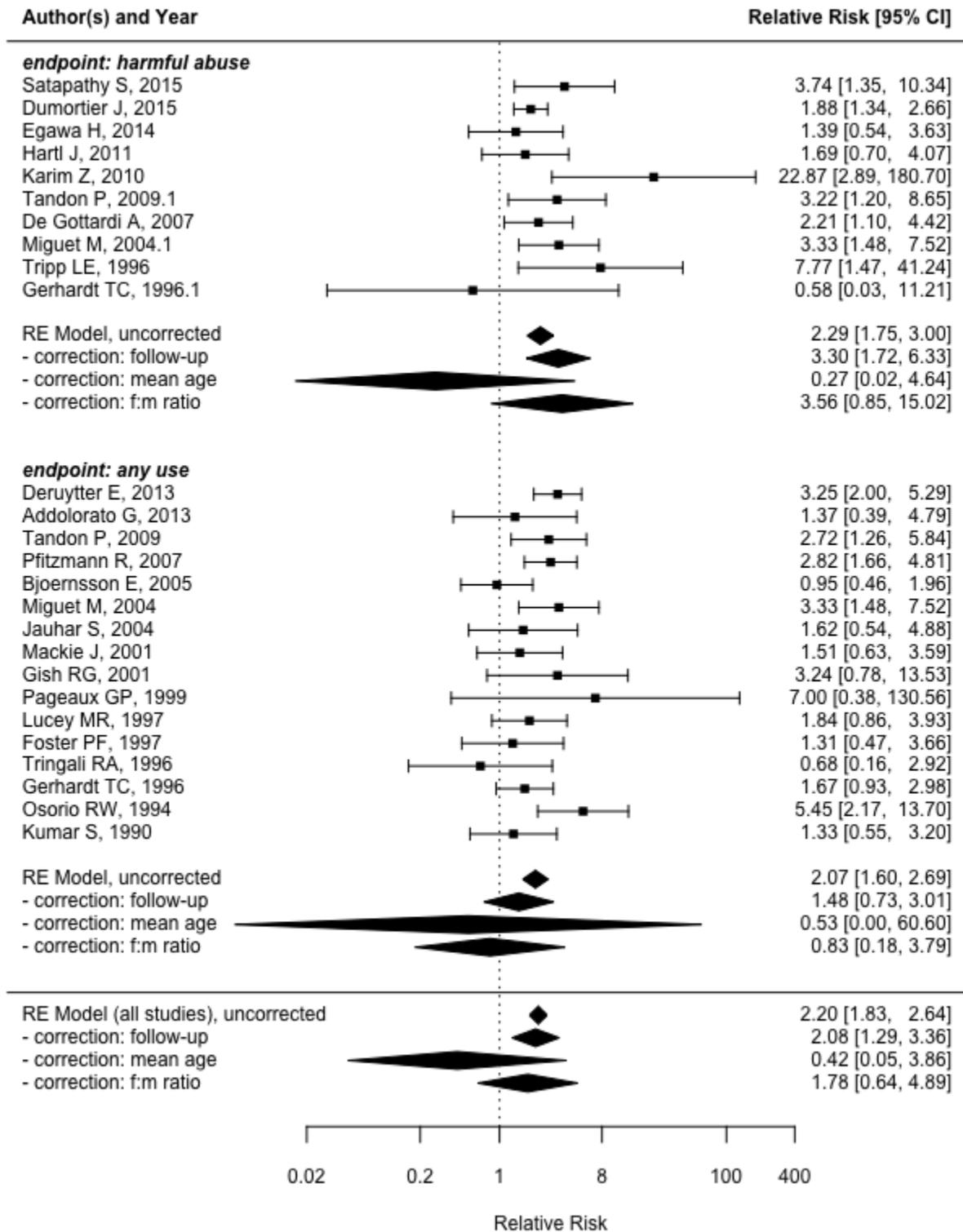
**Material and methods:** We conducted a systematic review and a meta-analysis on studies of relapse frequencies and outcomes in ALD by web based search combined with citation tracking. We excluded studies before the introduction of ciclosporin, as well as systematic reviews, meta-analyses, and registry studies. Meta-analytic calculations followed a mixed-effects model.

**Results:** 130 studies in 118 cohorts were reviewed, covering 5697 patients over an average median follow-up of 43 months. 27 studies reported on outcomes in relation to the 6MR. As in earlier meta-analyses, the overall relapse rate to any alcohol consumption is 24% (range, 3%>95%). Harmful relapse, as defined in the individual studies, occurred in 11% (0%>65%). Death directly attributable to alcohol abuse is rare in relation to the transplanted ALD population, but a serious threat for harmful relapsers. The RR for harmful relapse in patients with less than 6 months of abstinence is 2,29 (CI, 1.75-3). The RR for death in this group is 1.5 (CI, 0.97-2.3). The survival rate is comparable between NALD, ALD, and relapsing ALD patients over the course of approx. 5 years. Afterwards, mortality in relapsed ALD patients increases, mostly because of a high cancer incidence.

The 6MR test performance to predict recidivism is poor in the published cohorts, with a sensitivity of 32%, a specificity of 82%, translating to a number needed to deny of more than 6 patients to prevent one case of harmful post-LT recidivism. 27 studies reported on outcomes in relation to the 6-27 studies reported on outcomes in relation to the

**Conclusions:** A pre-LT abstinence time of less than 6 months is a risk factor for a relapse to alcohol drinking post LT in ALD patients. However, the test performance is disturbingly bad. We suggest to omit the six months rule as a single-tier exclusion criterion for liver transplantation.

Figure:



Disclosure of Interest: None Declared

## P03-5

# Peripheral blood CD4<sup>+</sup> T helper cells (Th1, Th2, Th17, Th22) are increased in severe alcoholic hepatitis

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**Introduction:** Alcoholic hepatitis (AH) is the most serious form of alcoholic liver disease with high mortality. The immune dysregulation has been critically implicated in the pathophysiology of inflammation in AH. There is evidence showing numerical/functional changes of circulating CD4<sup>+</sup> T cells in AH; however, detailed characterizations of CD4<sup>+</sup> T cell subsets in severe AH are still limited.

**Aims:** In this prospective study, the baseline phenotypes of CD4<sup>+</sup> T helper cells (Th1, Th2, Th17, Th22, TNF- and IL-10-producing cells) and regulatory T cells (Treg) were examined in a cohort of severe AH patients compared with stable alcoholic cirrhosis (AC) patients and healthy controls (HC).

**Material and methods:** Blood samples were collected from 25 biopsy-proven severe AH patients (DF>32), 22 stable AC patients and 25 HC. For profiling CD4<sup>+</sup> Th subsets, freshly isolated PBMC were rested overnight in culture, then followed by in vitro stimulation of PMA/Ionomycin in the presence of protein transport inhibitor for 4hrs before processing for cell surface markers and intracellular cytokine staining. The frequencies of individual CD4<sup>+</sup> Th subsets in PBMC (CD4<sup>+</sup>IFN $\gamma$ <sup>+</sup> for Th1, CD4<sup>+</sup>IL-4<sup>+</sup> for Th2, CD4<sup>+</sup>IL-17A<sup>+</sup> for Th17, CD4<sup>+</sup>IL-22<sup>+</sup> for Th22), TNF- and IL-10-producing CD4<sup>+</sup> cells were examined by flow cytometry analyses.

**Results:** Compared with HC and AC, there were significant increases in AH patients in the frequencies of Th1 (24.1  $\pm$  12.7%, 16.7 $\pm$ 8.8%, 14.8 $\pm$ 6.4% for AH, AC, HC, respectively; AH vs AC or HC p<0.05), Th17 (6.9 $\pm$ 4.7%, 2.7 $\pm$ 2.0%, 2.2 $\pm$ 1.4%, respectively; AH vs AC or HC p<0.05), Th2 (8.9 $\pm$ 6.3%; 3.3 $\pm$ 1.9%, 2.6 $\pm$ 1.5%, respectively; AH vs AC or HC p<0.05), Th22 (4.7 $\pm$ 3.2, 2.1 $\pm$ 1.6%, 1.7 $\pm$ 1.4%, respectively; AH vs AC or HC p<0.05) and CD4<sup>+</sup>TNF<sup>+</sup> T cells (60.5 $\pm$ 20.0%, 43.0 $\pm$ 18.9%, 44.9 $\pm$ 18.7%, respectively; AH vs AC or HC p<0.05). For each Th subset, AH was significantly different than AC and HC (p<0.05), but AC was not different from HC. Furthermore, the expression of activation marker CD69 on CD4<sup>+</sup> T cells was increased in AH patients. For the frequencies of anti-inflammatory/immunosuppressive Treg (CD4<sup>+</sup>FoxP3<sup>+</sup>) and CD4<sup>+</sup>IL-10<sup>+</sup> cells in PBMC and the expression of immune inhibitory molecule PD-1 on CD4<sup>+</sup> T cells, no differences were observed among the three groups.

**Conclusions:** Increased baseline frequencies of CD4<sup>+</sup> T helper cells (Th1, Th17, Th2, Th22) and pro-inflammatory CD4<sup>+</sup> TNF<sup>+</sup>T cells in PBMC of AH patients indicate that CD4<sup>+</sup> T helper cells are activated and may play a role in the pathophysiology of inflammation in severe AH.

**Disclosure of Interest:** None Declared

# Autonomic function is impaired across the spectrum of NAFLD and alcohol drinkers

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**Introduction:** Autonomic function is a critical component of cardiovascular function, with autonomic dysfunction (AD) associated with cardiac arrhythmias, coronary artery disease and increased mortality. Autonomic function across the NAFLD continuum and the impact of alcohol remain to be described.

**Aims:** The aims of this study were i) to assess autonomic function in NAFLD patients vs. controls, and ii) to assess whether NAFLD severity and alcohol intake impact upon autonomic function.

**Material and methods:** 96 patients were divided into 3 groups; 1. NAFLD GROUP: 46 patients with NAFLD defined as hepatic triglyceride content (HTGC) greater than 5% by magnetic resonance spectroscopy (MRS), in the absence of other causes of liver disease and who consumed no alcohol or <20g/day of alcohol (27 patients had histologically proven NASH); 2. HEPATIC STEATOSIS ALCOHOL (HeStA) drinkers GROUP: 16 patients with HTGC greater than 5% using MRS in the absence of other causes of liver disease consuming >20g/day of alcohol but less than criteria for alcoholism and CONTROL GROUP: 34 patients who had no overt evidence of cardiac, liver or metabolic disorders and who consumed no alcohol or <20g/day of alcohol.

**Results:** NAFLD and HeStA patients had significantly greater AD in nearly all variables including beat, cardiac, heart rate variability, diastolic blood pressure variability, systolic blood pressure variability (SBPV) and baro-reflex sensitivity (BRS) (all  $p < 0.05$ ) compared with controls. Mean blood pressure was 5% higher in the HeStA group ( $p \leq 0.02$ ), HFnu-DBP (parasympathetic activity) and LF/HF-DBP ratio were 29% lower and 26% higher respectively in the HeStA group than those with NAFLD ( $p = 0.03$  and  $0.04$ , respectively). HTGC was positively associated with up and down events for BRS ( $r = 0.27$ ,  $p = 0.04$  and  $r = 0.28$ ,  $p = 0.04$ , respectively), and negatively associated with cardiac output index ( $r = -0.28$ ,  $p = 0.03$ ), stroke volume index ( $r = -0.30$ ,  $p = 0.02$ ) and diastolic index ( $r = -0.28$ ,  $p = 0.03$ ). HbA1c was negatively associated with heart rate ( $r = -0.30$ ,  $p = 0.01$ ), and fasting glucose was negatively associated SBP ( $r = -0.26$ ,  $p = 0.04$ ), SV ( $r = -0.26$ ,  $p = 0.04$ ) and CO ( $r = -0.31$ ,  $p = 0.02$ ). NASH severity was significantly associated with DBP and autonomic function.

**Conclusions:** Here patients with hepatic steatosis greater than 5% had significantly impaired cardiac and autonomic impairments. These impairments appeared to be dependent on HTGC, metabolic dysfunction and fibrosis staging.

**Disclosure of Interest:** None Declared

## P04-2YI

# Functional polymorphisms of innate immunity pattern recognition receptors do not constitute the risk of bacterial infections other than spontaneous bacterial peritonitis and also not the progressive disease course in patients with cirrhosis

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**Introduction:** Innate immunity pattern recognition receptors (PRRs) recognize distinct pathogen-associated molecular patterns (PAMPs) on the cell surface or in the cytoplasm. Functional polymorphisms of various PRRs have been established to contribute to susceptibility to spontaneous bacterial peritonitis (SBP). However, their role in the development of cirrhosis-associated bacterial infections (BI) beyond SBP remains unknown.

**Aims:** We aimed to investigate the link between PRR gene variants, pathological bacterial translocation (BT) and thus the development of cirrhosis-associated complications.

**Material and methods:** 349 patients with cirrhosis (stable outpatients:243 and acute decompensation:106) were genotyped for the common *NOD2* (p.R702W, p.G908R and c.3020 insC), *TLR2* (g.6686T/A), *TLR4* (D299G) and *CD14* (c. 159C/T) gene variants. In the stable outpatients (male:116, age:56±11 yrs, alcohol:62.6%, ascites:36.2%, MELD score:11) incidence of BI, decompensating events (ascites, variceal bleeding and hepatic encephalopathy) and liver-related death were prospectively assessed in a 5-year follow-up observational study. BT was assessed based on the presence of anti-microbial antibodies (anti-OMP Plus IgA and/or endotoxin core IgA antibody [EndoCab]) or increased serum level of lipopolysaccharide-binding protein (LBP).

**Results:** Ninety-four (38.7%) patients encountered at least one episode of BI. Distribution of bacterial infections were as follows: urinary tract infection (39.4%), SBP(27.7%), pneumonia(13.8%) and miscellaneous(24.5%). 5.3% of the cases were multifocal. PRR genetic profile was not associated with prior BI episode and also not with the risk of overall BI or infection-related death during the follow-up. *NOD2* variants, however, were associated with an increased cumulative probability of SBP in patients with ascites(n=88) as compared to wild type (76.9% vs. 30.9%,  $p_{LogRank}=0.047$ ). Frequency of anti-microbial antibodies and LBP levels did not differ between various PRR genotypes. Correspondingly, PRR genetic profile was not able to predict the long-term disease course in cirrhosis.

**Conclusions:** In a Hungarian patient cohort with cirrhosis, common *NOD2* gene variants but not the other PRR polymorphisms enabled to improve identification of patients with high risk for SBP. None of the examined PRR gene variants influenced the risk of other types of BI or the long-term disease course. They were also not associated with serological markers of BT.

**Disclosure of Interest:** None Declared

## P04-3

# AlcoChange, A Pilot Study of a Smartphone Tool to Reduce Alcohol Consumption in Alcohol-Related Liver Disease - An Interim Analysis

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**Introduction:** Alcohol contributes to over 5% of deaths worldwide, and death rates from alcohol-related liver disease (ARLD) in the UK continue to rise sharply. On-going alcohol use in ARLD leads to markedly increased mortality (Thursz et al, 2015), and maintaining abstinence is a key therapeutic goal. However, there are no effective pharmacological therapies for maintaining abstinence. Brief intervention (BI) is an effective psychological tool for reducing alcohol use, but is difficult to scale widely.

**Aims:** The aims of this project:(i) to develop a smartphone app and breathalyser (AlcoChange), to facilitate self-monitoring and deliver BI in response to patient triggers, and (ii) to undertake an open-label pilot study of AlcoChange in 60 patients with ARLD, to determine compliance with the app/breathalyser and changes in self-reported alcohol consumption.

**Material and methods:** AlcoChange was developed following feedback from Camden Alcohol Service user's group. AlcoChange allows monitoring of craving, alcohol consumption and breath alcohol, and provides motivational messaging in response to patient triggers.

The pilot study involved recruitment of inpatients/outpatients at Royal Free London with ARLD and recent alcohol use. The inclusion criteria were: intent to maintain abstinence, possession of compatible smartphone. The exclusion criteria were Child-Pugh score >7, inability to provide consent. Participants were assessed at baseline and 3-months. The primary endpoint was self-reported alcohol use (units/week, timeline follow-back). Secondary endpoint was compliance with the app (monitored remotely). Paired t-test or Wilcoxon-signed rank test was used to analyse differences.

**Results:** Twenty participants completed the baseline and 3-month visits. Four subjects were lost to F/U, and one died. Self-reported alcohol intake showed a trend to reduction at 3-months (87.1±18.4 vs 46.7±15.4, p=0.09). Following sub-group analysis for compliance with the app (>20 logins over 3 months), compliant participants reduced alcohol consumption, whereas non-compliant participants increased (-52.1%±19.0% vs +30.7%±41.8%, p=0.10).

**Conclusions:** This study demonstrates that a smartphone app/breathalyser can be used for self-monitoring and BI in patients with ARLD, with a 'dose effect' amongst compliant patients. Smartphone apps are a scalable intervention to help maintain abstinence in ARLD. This study remains open, with further data to present. Future work will determine factors to predict compliance/response to smartphone interventions.

**Disclosure of Interest:** A. Nadar: : None Declared, S. Macdonald: : None Declared, M. Sheikh: : None Declared, A. Esson: : None Declared, M. Aban: : None Declared, C. Agapuyan: : None Declared, R. Jalan: Other: Founder of Cyberliver Ltd, K. Moore: : None Declared, G. Mehta: : None Declared

## P04-4

# Gene expression of miR-122, miR-217 and miR 155 in alcoholic liver disease in zebrafish

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**Introduction:** Excessive alcohol consumption remains one of the most important causes of liver disease worldwide. New tools for the diagnosis and new targets for treatment of alcoholic liver disease (ALD) they are being studied, including the miRNAs. In ALD we can highlight the role of miR-122, miR-217 and miR-155 involved in development and differentiation of hepatocytes, in lipid metabolism and in inflammatory process respectively.

**Aims:** Evaluate the gene expression of hepatic miR-122, miR-217 and miR-155 in adult zebrafish chronically exposed to ethanol.

**Material and methods:** Zebrafish adult, wild type, of both genders were kept in a light:dark cycle of 14:10h and at a temperature of 28°C–2°C. Animals were randomly assigned to one of following two groups: Ethanol Group (EG), animals exposed to ethanol at a concentration of 0.5% (vol/vol) added directly into the tank water (n=58) and Control Groups (GC) without addition of ethanol in water (n=58). After 28 days the animals were euthanized and livers collected for histological analysis (HE and Oil Red staining) and gene expression of miR-122, miR-217 and miR-155 by TaqMan assay ( $2^{-\Delta\Delta Ct}$ )

**Results:** After 28 days of treatment with ethanol, histologic analysis showed livers nucleus displacement and severe steatosis in the EG. On the other hand, the CG showed well-preserved liver cells without signs of fat deposits. The gene expression of miR-122 and miR-155 had an increase in the EG when compared de CG of 4.9 and 3.5 times respectively (P<0.001 and P<0.001). The gene expression of miR-217 did not present statistical difference.

**Conclusions:** Chronic exposure to ethanol produces an increase in the accumulation of hepatic lipids as well as an increase in hepatic gene expression of miR-122 and miR-155. This increase could be related to the ways of liver regeneration and inflammation. We observed no difference in gene expression of miR-127, provably the evaluation time.

**Disclosure of Interest:** None Declared

# Bayesian sparse regression modelling more accurately predicts mortality risk than commonly used prognostic scoring systems in patients with severe alcoholic hepatitis

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**Introduction:** Severe alcoholic hepatitis (sAH) is associated with high mortality and heterogeneity in outcomes. Understanding mortality risk is important in guiding risk-benefit analysis in clinical decision-making. Several scoring systems, derived by logistic regression, have been applied to sAH, however discrimination and calibration with regards to mortality are modest.

**Aims:** To use a state-of-the-art Bayesian variable selection algorithm to derive a predictive model of mortality in sAH with enhanced predictive performance compared to those in use.

**Material and methods:** Patients with sAH were recruited to the Steroids or Pentoxifylline for severe Alcoholic Hepatitis trial. The endpoint was 90-day mortality. Modelling was performed in patients not treated with prednisolone (n=534). A BVS algorithm R2BGLiMS was used to derive a novel prognostic model. Area under the receiver operated curve (AUROC) analysis and net reclassification index (NRI) were used to compare discrimination and calibration with the model for end-stage liver disease (MELD), Glasgow Alcoholic Hepatitis score (GAHS) and Lille under 10-fold cross-validation. High and low mortality risk were defined as <10% and >90% predicted mortality respectively. Modelling was performed first using baseline data and then incorporating day 7 data (n=391).

**Results:** At 90 days 141/534 (26.4%) of patients had died. The baseline BVS model had an AUROC of 0.78 (95% confidence interval [CI] 0.74 – 0.82), comparing favourably with MELD and GAHS scores (0.71 (95% CI 0.65 – 0.75) and 0.70 (95% CI 0.65 – 0.75), respectively). The baseline BVS model offered superior stratification by mortality risk compared to GAHS and MELD (NRI 0.19, 95% CI 0.12 – 0.25, p<0.001 and 0.18, 95% CI 0.12 – 0.24, p<0.001, respectively). Incorporation of day 7 data into the BVS model improved performance – AUROC 0.79 (95% CI 0.73 – 0.84). This was superior to the Lille score for discrimination (AUROC 0.70, 95% CI 0.64 – 0.76) and mortality risk stratification (NRI 0.25, 95% CI 0.16 – 0.35, p<0.001, Table 1). In patients with available Lille scores a BVS model using only baseline data had marginally better predictive performance (AUROC 0.73, 95% CI 0.67 – 0.77).

**Conclusions:** The use of Bayesian Variable Selection to model clinical outcomes in patients with severe alcoholic hepatitis allowed derivation of prognostic models with improved prognostic capacity compared to those already used in clinical practice. Such models could significantly enhance clinical decision-making by more accurately informing risk.

Figure:

**Table 1. Reclassification table of predicted mortality risk for Lille score against Bayesian variable selection (BVS) model including day 7 data.**

		Bayesian variable selection Day 7 model		
Mortality risk		0-10%	10-90%	90-100%
<b>Lille</b>	<i>Patients who survived (n=264)</i>			
	0-10%	21	7	0
	10-90%	64	171	1
	90-100%	0	0	0
	<i>Patients who died (n=99)</i>			
	0-10%	0	5	0
	10-90%	5	85	4
	90-100%	0	0	1

Green shading indicates more accurate mortality risk classification by BVS, red shading indicated more accurate mortality risk classification by Lille score.

Disclosure of Interest: None Declared

## P05-2

# Transcriptomics of liver tissue, PBMCs, and monocytes in alcoholic hepatitis

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**Introduction:** Alcoholic Hepatitis (AH) is an alcohol-induced inflammatory liver disease with high mortality and morbidity rates. The factors that determine the progression to AH are not well understood.

**Aims:** This study used RNA sequencing to explore gene expression profiling of human liver tissue, peripheral blood mononuclear cells (PBMCs), and monocytes from patients with AH.

**Material and methods:** The blood samples in this study were collected by the Southern California Alcoholic Hepatitis Consortium (SCAHC) from AH patients (n=15), and from normal healthy controls (n=15). For seven of the AH patients, a liver tissue biopsy was also collected at baseline before treatment. The protocol was approved by the IRB, and written consent was obtained for all participants. PBMCs and monocytes were isolated from the blood samples into cell pellets. RNA was extracted from the samples, and sequenced on an Illumina HiSeq. The RNAseq data was aligned to the human genome, followed by differential expression analysis with the Cufflinks software, using upper quartile normalization between the data files. The results were filtered to retain only those genes with fold change  $\geq 1.2$ , FPKM  $\geq 2$ , and were significant at FDR-adjusted p-value  $\leq 0.05$ . For the PBMC samples, proteomics data from a high mass accuracy LC-MS/MS platform was available for correlation. Ingenuity Pathway Analysis software was utilized to determine significant pathways.

**Results:** Differences in gene expression were observed between the AH and normal samples, with the most significantly enriched pathways related to immune and inflammatory function. The gene expression profiles of PBMCs and monocytes were similar to each other, when compared with the liver tissue samples. However, differences in gene expression and enriched pathways were also identified when focusing upon the PBMCs and monocytes. Integration of the transcriptomics and proteomics data for the PBMC samples confirmed enrichment in the inflammatory and immunity pathways and functions, and also revealed differences in several pathways.

**Conclusions:** The preliminary results suggest that there are characteristic gene expression profiles of alcoholic liver disease that may be detected by PBMCs and monocytes in the blood, in addition to that seen in liver tissue. This ability to detect differentially expressed genes may point to treatment options and disease progression monitoring for alcoholic hepatitis. (Supported by NIAAA #U01AA021838)

**Disclosure of Interest:** None Declared

## P05-3

# Transcription factor complex TRIM33-Smad2/3 is crucial for progenitor cell-mediated liver regeneration in alcoholic hepatitis

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**Introduction:** Livers with severe alcoholic hepatitis (AH) display massive expansion of liver progenitor cells (LPC), called ductular reaction (DR). In this setting, LPC frequently fail to differentiate into functional mature hepatocytes, one of the main causes of liver failure in patients with AH. Tripartite motif protein (TRIM) 33 is crucial for embryonic stem cell differentiation through formation of transcriptional complexes with phosphorylated Smads2/3, the downstream substrates of activated TGF- $\beta$  signaling.

**Aims:** We hypothesize that TRIM33-Smad2/3 complexes are critical for LPC differentiation.

**Material and methods:** Smad2 phosphorylation as well as expression of TGF- $\beta$ , TRIM33 and gooseoid, a master differentiation gene downstream of TRIM33, were examined in liver tissue specimens of 10 AH patients, who received liver transplantation, or 10 compensated cirrhosis patients by immunohistochemistry. Macrophages, monocytes, hepatic stellate cells (HSC) and intermediate hepatocyte-like cells (IHLC) were monitored by CD68, CD14/16,  $\alpha$ -SMA and CK7 staining.

**Results:** Immunohistochemical staining revealed macrophages/monocytes and activated HSC as predominant inflammatory cells surrounding DR in AH patients. Macrophages, but not HSC, produced TGF- $\beta$ . Expression of gooseoid was present in hepatocyte buds (comprising DR, IHLC and hepatocytes) from 10 patients with decompensated cirrhosis, indicating functional differentiation. LPC, IHLC and HC also displayed p-Smad2 and TRIM33 nuclear immunostaining. In contrast, no TRIM33 and gooseoid expression was found in liver cells of patients with AH, although 5 of these showed p-Smad2 positive staining in LPC.

**Conclusions:** Our preliminary clinical study suggests that lack of TRIM33-Smad2/3 complexes may result in a disturbed differentiation of LPC to mature hepatocytes. Further details of this mechanism of liver regeneration is subject matter of current investigations.

**Disclosure of Interest:** None Declared

P05-4YI

## Extracellular pro-inflammatory ASC specks released by inflammasome-mediated pyroptosis to the circulation in alcoholic hepatitis and deposition of bioactive ASC oligomers in human and murine livers are biomarkers and mediators of alcoholic hepatitis

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**Introduction:** Ethanol exposure results in NLRP3 inflammasome activation and maturation of interleukin (IL)-1 $\beta$ , a key pro-inflammatory cytokine in alcoholic liver disease (ALD). Oligomerization of the adaptor protein ASC (Apoptosis-associated speck-like protein containing CARD) is essential for NLRP3 inflammasome activation. Extracellular ASC 'specks' that retain bioactivity are released during pyroptosis, a caspase-1 mediated cell death.

**Aims:** Find the role of ethanol-induced pyroptosis and extracellular ASC to be identified in ALD.

**Material and methods:** Cell death, inflammation, and liver injury were assessed in a mouse model of alcoholic hepatitis (AH) (10 days with binge). Inhibitors for NLRP3 (MCC950), Caspase-1 (VX-765), pan-Caspases (z-VAD-fmk), and necroptosis (necrostatin-1) were administered *in vivo*. Healthy and cirrhotic human livers and plasma from patients with alcoholic hepatitis (AH) and controls were also analyzed.

**Results:** We analyzed plasma of healthy volunteers and patients with acute AH for the presence of ASC protein. Acute AH patients had increased soluble ASC protein in the circulation, as measured by ELISA and confirmed with immunoprecipitation. On immunohistochemistry, all ten livers from patients with alcohol-induced cirrhosis but none of the controls had extensive ASC aggregates in extracellular spaces. Using immunofluorescence, we observed extracellular ASC aggregates and ASC oligomers with immunoprecipitation in mouse livers with AH. We then hypothesized that extracellular ASC was dependent on liver macrophages undergoing pyroptosis, a necrotic form of inflammasome-dependent programmed cell death. Using flow cytometry, we found increased ethanol-induced pyroptosis and apoptosis indicated by a decrease in AnnexinV-positive macrophages from mice pre-treated with Caspase-1 or pan-Caspase inhibitors, respectively. Necroptosis inhibition had no effect on cell death. Finally, pre-treating mice with MCC950, an NLRP3 inhibitor, reduced Caspase-1 activity, macrophage pyroptosis and steatohepatitis in AH in mice.

**Conclusions:** Increased circulating ASC protein may serve as a new biomarker for alcoholic hepatitis in humans. Our novel findings in murine samples and human patients with AH demonstrate that ethanol-induced inflammasome activity results in Caspase-1-mediated pyroptosis and extracellular ASC aggregates in the liver and circulation. Pyroptosis can be abrogated by therapeutic inhibition of inflammasome components, NLRP3 or Caspase-1.

**Disclosure of Interest:** None Declared

P05-5YI

## Alcohol binge induces spontaneous release of neutrophil extracellular traps; however, it impairs stimulation-induced NET formation and macrophage efferocytosis in alcohol associated severe sepsis in mice

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**Introduction:** In alcoholic hepatitis (AH), increased mortality correlates with liver neutrophil infiltration and acute sepsis. Neutrophils play a major role in pathogen clearance in sepsis, however, little is known about their function in acute sepsis associated with binge drinking. Neutrophil extracellular traps (NETs) are decondensed chromatin mixed with cytoplasmic components such as neutrophil elastase. Neutrophils undergo programmed cell death (NETosis) after NET release.

**Aims:** Here we studied NET formation and its clearance by macrophages (efferocytosis) in acute sepsis following binge drinking.

**Material and methods:** Healthy volunteers consumed 2mL 40% vodka/kg body weight and blood endotoxin and 16s rDNA was measured. Peripheral neutrophils were isolated from healthy volunteers and exposed to acute alcohol (4h, 50mM) followed by phorbol myristate acetate (PMA) stimulation. Mice were treated with 3 alcohol binges followed by *i.p.* LPS to assess the dynamics of NET formation and macrophage clearance of NETs and NETosing neutrophils. *In vivo*, anti-Ly6G antibody was used for neutrophil depletion.

**Results:** We found that binge drinking in humans is associated with a rapid rise in inducers of NETs (endotoxin and bacterial DNA). *Ex vivo*, alcohol alone increased NET formation. However, alcohol attenuated NETs formation upon PMA stimulation of human neutrophils. In mouse, citrullinated histone H3, neutrophil elastase and neutrophil myeloperoxidase were decreased by alcohol binge at the early time point after LPS sepsis challenge. However, 15h after LPS, we found increased citrullinated histone H3 and TUNEL positive immunohistochemistry, suggesting decreased clearance of NETs in alcohol binge mice. This correlated with significantly higher sepsis-related cytokine levels (IL-6, MCP-1) compared to controls. *In vitro*, acute alcohol reduced phagocytosis of NETosing neutrophils by macrophages (MΦ), a process referred to as efferocytosis. Efferocytosis by alcohol-treated MΦ resulted in decreased MΦ differentiation into the M2, "repair" phenotype. Therapeutic depletion of neutrophils prior to binge-alcohol ameliorated systemic inflammation and liver injury in the acute sepsis model in mice.

**Conclusions:** Binge alcohol use prior to acute sepsis significantly diminishes NET formation by neutrophils as well as efferocytosis of NETs and NETosing neutrophils by MΦs. Therapeutic depletion of neutrophils prevents sepsis-induced liver injury after alcohol binge in mice.

**Disclosure of Interest:** None Declared

## P06-1

# Both MELD Score and Number of Organ Failures Defined by the Latest Chronic Liver Failure-Organ Failure Scoring System Effectively Select Subjects with Severe Alcoholic Hepatitis with Good Outcomes when Treated with the ELAD<sup>®</sup> System

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**Introduction:** Mortality due to severe alcoholic hepatitis (sAH) is related to organ failures (OF), MELD score, presence of Systemic Inflammatory Response Syndrome (SIRS), and concurrent infections at presentation that impact the prognosis and response to medical treatment.

**Material and methods:** A randomized, open-label, multicenter, controlled study was conducted in subjects  $\geq 18$  yrs old with a clinical or histologic diagnosis of sAH, bilirubin  $\geq 8$  mg/dL, Maddrey discriminant function (DF) score  $\geq 32$ , MELD score of 18-35 and platelets  $\geq 40,000/\text{mm}^3$ , without severe concomitant disease, uncontrolled sepsis or bleeding, hemodynamic instability or need for chronic dialysis. Subjects were randomized 1:1 to receive protocol-specified standard of care (SOC) based on AASLD and EASL guidelines alone (Control) or SOC with a 3-5 days continuous with ELAD system consisting of human C3A hepatoblastoma cells contained in a cartridge (ELAD).

**Results:** Analyses are based on an intent-to-treat population comprising 203 subjects (ELAD 96, Control 107). 76/203 subjects (32 ELAD; 44 Control) had two or more OF (liver, kidney, brain, coagulation, circulatory and/or respiratory) at baseline, based on criteria defined in the Chronic Liver Failure-OF (CLIF-OF) score system for acute-on-chronic liver failure (ACLF). 191/203 (94%) had at least one OF, of which one OF was due to liver failure. Six subjects had only one OF in other body systems (1 Brain, 4 Coagulation and 1 Circulatory) and six other subjects (ELAD 2, Control 4) did not have any OFs. Of subjects with 2 or more OFs, more ELAD than Control subjects died by d91 (20/32, 63% vs 19/44, 43%, respectively;  $p = \text{N.S.}$ ). In subjects with only one OF (ELAD 62/96, 65% vs Control 59/107, 55%), fewer ELAD (19/62, 31%) than Control subjects (21/59, 36%) died by d91 ( $p = \text{N.S.}$ ). Only one (Control) of six subjects with no OFs died by d91. 135/203 subjects (ELAD 61, Control 74) had baseline MELD  $\leq 28$ . In subjects with baseline MELD  $\leq 28$ , fewer ELAD (14/61, 23%) than Control subjects (27/74, 36%) died by d91 ( $p = 0.09$ ). 68/203 subjects (ELAD 35, Control 33) had MELD  $\geq 28$  at baseline and in this group, more ELAD (71%) than Control subjects (42%) died by d91 ( $p < 0.05$ ).

**Conclusions:** Both MELD  $\leq 28$  and restricting subjects to only liver failure are effective at predicting subjects who are likely to have a favorable response to treatment with ELAD. A new study is now enrolling that excludes subjects with evidence of secondary organ failures to exclude subjects likely to have an unfavorable response to treatment with ELAD.

**Disclosure of Interest:** R. Subramanian: Consultant: Vital Therapies, Inc., J. Thompson: : None Declared, A. Al-khafaji: : None Declared, D. Reich: Grant: Research grant by Vital Therapies, Inc., Consultant: Vital Therapies, Inc., R. MacNicholas: : None Declared, T. Hassanein: Grant: Research grant by Vital Therapies, Inc., L. Teperman: Other: Clinical Advisory Board of Vital Therapies, Inc., J. Stange: Employee: Vital Therapies, Inc., W. Frank: Employee: Vital Therapies, Inc., Z. Li: Employee: Vital Therapies, Inc., R. Ashley: Employee: Vital Therapies, Inc.

## P06-2

# Lactobacillus rhamnosus GG supplementation decreases liver steatosis in a zebrafish model of alcoholic liver disease

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**Introduction:** Alcoholic liver disease (ALD) has a complex pathogenesis, which involves an interplay between gut, immune system and the liver itself.

**Aims:** To determine an effective probiotic *Lactobacillus rhamnosus* GG (LGG) dose to promote intestinal colonization in zebrafish and to evaluate its effect on hepatic lipid accumulation in animal model of ALD.

**Material and methods:** Adult zebrafish, wild type, kept in aquariums, one cycle of light and of 14: 10h, were fed with commercial ration 4 times a day. The animals were divided in 4 groups, (n=8) according to a different concentration of probiotic LGG-ATCC 53103 (0.16, 0.4, 1 and 2 mg/day/animal) added in the diet. In addition, a control group had no probiotic in the diet. After 14 days, the animals were euthanized, aseptically opened and the intestines were collected in blocks. To confirm colonization, samples were analyzed by gram staining, microbiological analyzes and PCR. From the analyzes, a dose of 1mg/day/animal was the most effective. Defining a probiotic dose, a new experiment was conducted to evaluate the effect of LGG supplementation on ALD. Three groups (n=63) were determined: ethanol group (E), ethanol + LGG group (LGG + E) and control group (C). The (E) was submitted to an alcohol concentration of 0.5% (V / V). The probiotic was administered in the ration. After 28 days of experiment, the animals were euthanized and livers were collected for staining with oil red.

**Results:** Concentrations of 0.4, 1 and 2 mg/day/animal showed LGG Gram staining, microbiological analysis and PCR positive. However, with a dose of 1 mg/day/animal a greater homogenization was obtained and colonies were able to be counted. Through the histological evaluation, it was possible to verify the accumulation of hepatic lipid in the Ethanol group, when compared to LGG + E group the treatment with probiotics showed protective action, reducing the hepatic steatosis.

**Conclusions:** In this experimental model, LGG was able to colonize the gut and exerted protective effects on liver steatosis.

**Disclosure of Interest:** None Declared

## P06-3

# Predictors of 90-day mortality in patients with severe alcoholic hepatitis: Experience outside clinical trials with 183 patients at a tertiary care center from India

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**Introduction:** Severe alcoholic hepatitis (SAH) has very high mortality varying from 17 -40 %. There is limited data from developing countries like India on short term mortality, its predictors of mortality and comparison of various severity indices in patients of SAH.

**Aims:** To assess the short term mortality (90 days) in patients of severe alcoholic hepatitis and to determine the factors predicting the mortality along with comparison of various prognostic scores in the real world scenario.

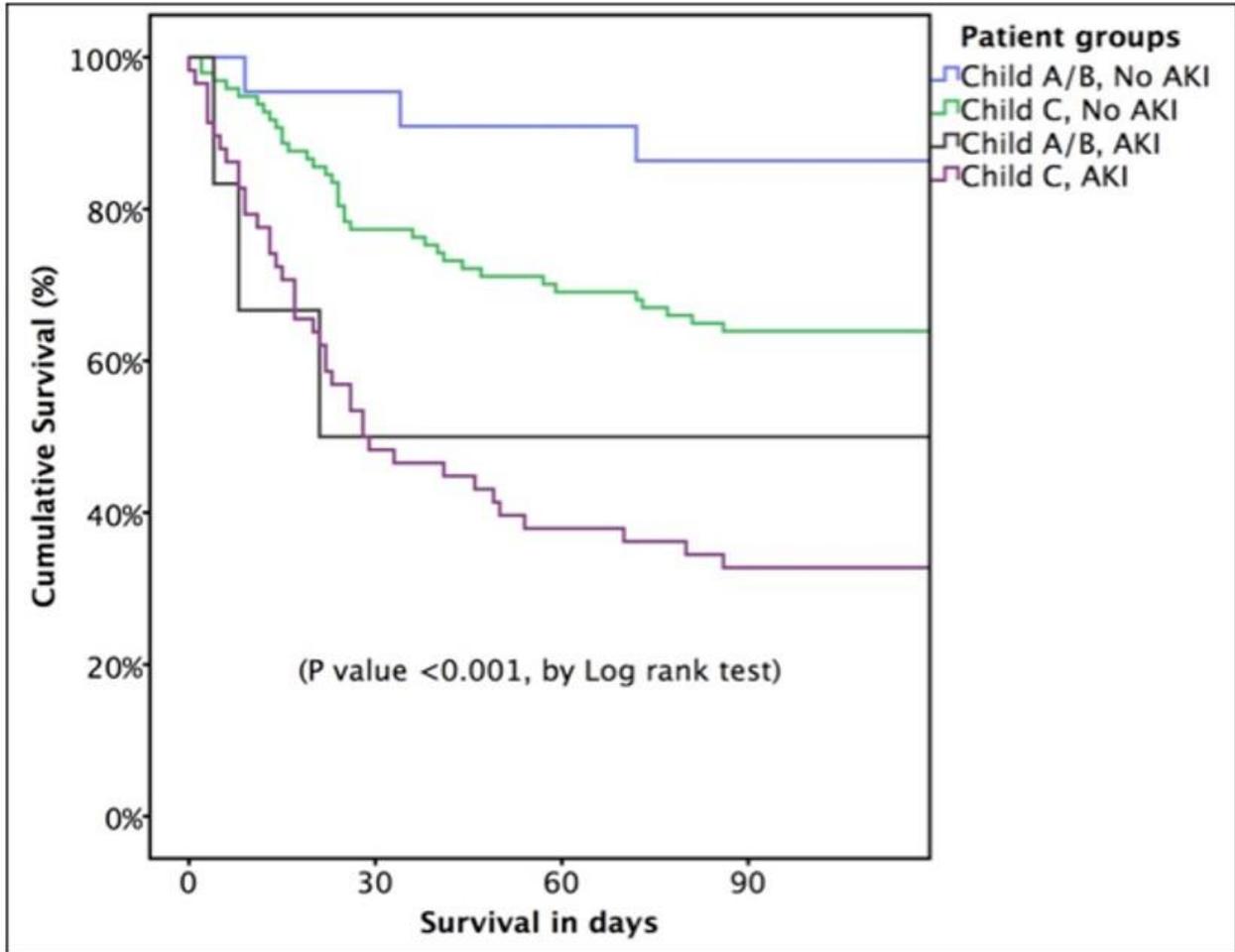
**Material and methods:** In this prospective study we analyzed patients with SAH (defined as modified discriminant function [mDF]  $\geq 32$ ) admitted from January 2015 to February 2017 at our Institute. All patients were administered standard treatment according to various established guidelines for SAH and their 90-day mortality was determined. Various hematologic, biochemical and severity indices including were compared between survivors and patients who died.

**Results:** A total of 183 patients (98% males, median age 41 years [range 20-70 years]) were included in our study. The median (range) values of severity scores at baseline were as follows: DF 70 (32-320); GAHS 9 (6-12); ABIC 7.6 (4.7-12.0); MELD 26 (15-40); MELD-Na 30 (14-40); and CTP 11 (7-14). Ascites was present in 83% and hepatic encephalopathy (HE) in 38%. Only 21 (12%) could be offered steroid therapy, due to contraindications in the remaining. By 90 days, only 103 (56%) patients survived while 80 (44%) patients had died. All patients died due to progressive liver failure or its complications. On multivariate analysis presence of ascites, hepatic encephalopathy, high bilirubin, low albumin, high creatinine, high INR, and low potassium independently predicted 90-day mortality. All the scores performed significantly in predicting 90-day mortality with no statistically significant difference between them. MELD score had maximum area under the curve 0.76 for 90-day mortality. A combination of Child class and presence of acute kidney injury (creatinine  $\geq 1.35$ ) was good in predicting 90-day mortality.

**Conclusions:** SAH in India has 44% 90-day mortality. Most patients (only one fifth of the patients are eligible) are not eligible for steroids. Presence of Child C and high creatinine ( $\geq 1.35$  mg/dL) accurately predicts mortality.

Figure:

Figure : Comparison of four groups of patients according to Child class and presence of acute kidney injury (serum creatinine  $\geq 1.35$  mg/dL)



Disclosure of Interest: None Declared

## P06-4YI

# Extracellular vesicles from subjects with alcoholic liver disease are increased in number, enriched in sphingolipids and correlated with the severity of the disease

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**Introduction:** Alcoholic liver disease (ALD) is a major cause of morbidity and mortality. The role of released nanosized membrane vesicles, termed extracellular vesicles (EV), has become increasingly recognized as disease biomarkers which carry signaling cargos. In this regard, diverse sphingolipid molecules have been implicated as functional EV cargo and biomarkers but not explored in ALD.

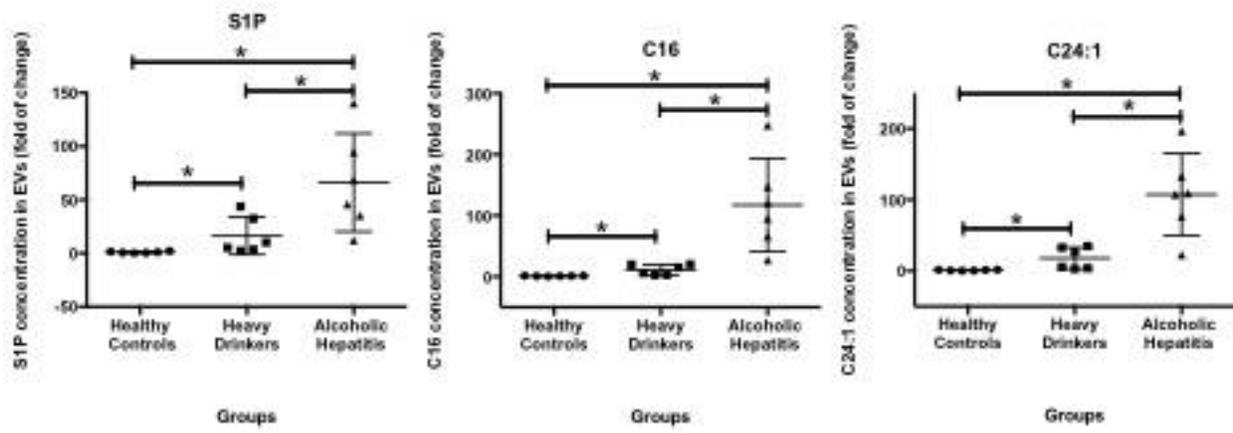
**Aims:** We tested the hypothesis that ALD may increase EV release, modify its sphingolipid content, and correlate with severity of the disease.

**Material and methods:** We performed an observational study of well characterized alcoholic hepatitis (AH) patients, heavy drinkers without clinical evidence of AH (HD) and healthy controls (HC). Accepted criteria were used for diagnosis of AH. Participants were evaluated at baseline, 6 and 12 months. Plasma EVs were isolated by differential ultracentrifugation and quantified with nanoparticle tracking analysis (NTA), clinical evaluation and biochemical analyses were done to calculate Child-Pugh and MELD scores. EV sphingolipid composition was determined by tandem mass spectrometry.

**Results:** A total of 21 subjects were evaluated, mean age  $48.4 \pm 12.6$  years, 38.1% female, mean Child-Pugh score  $6.8 \pm 2.4$ , mean MELD score  $13.2 \pm 8.4$ , mean ALT  $65 \pm 68.8$  IU/L, and mean total bilirubin  $5.8 \pm 9.4$  mg/dL. Relative EV release was  $7.7 \pm 1.0$ -fold higher in HD subjects compared to HC and  $36.6 \pm 4.6$ -fold higher in AH subjects compared to HC ( $p=0.005$ ). EVs from patients with AH were enriched in specific sphingolipids (predominantly sphingosine-1-phosphate [S1P], and ceramides C16 and C24:1) compared to HC, meanwhile HD had an intermediate content. Figure 1 depicts the relative EV concentration of S1P, C16 and C24:1 ceramides, which are enriched in AH subjects compared to HD and HC, being C16 ceramide the most enriched. EV count was positively correlated with MELD score ( $r=0.89$ ,  $p=0.03$ ). EV count decreased over time in patients with AH, reaching statistical difference at day 360 of follow-up ( $p=0.0397$ ).

**Conclusions:** EV from subjects with AH are increased in number and enriched in sphingolipids, especially S1P, C16 and C24:1 ceramides, which correlate with disease severity. Ceramide containing EVs may represent a pathogenesis based biomarker in AH.

Figure:



Disclosure of Interest: None Declared

P06-5YI

## Three treatment options in severe alcoholic hepatitis

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**Introduction:** Severe alcoholic hepatitis (AH) is dangerous liver disease with high mortality rate even among patients treated with steroids. In this study we compare efficacy and safety of three different therapeutic regimens: prednisolone, prednisolone plus S-adenosilmethionine (SAME) and budesonide.

**Material and methods:** The data from fifty five patients with severe AH were analyzed retrospectively. Group 1 (n = 20) patients received prednisolone 40 mg/daily per os, group 2 patients were given prednisolone 40 mg/daily per os plus SAME 800 mg i.v. and group three were treated with budesonide 9 mg/daily per os. Treatment duration was 28 days.

**Results:** Mortality at 28 days was 10% (2 of 20 patients) in prednisolone group, 13.3% (2 of 15 patients) in budesonide group and 0% in prednisolone plus SAME group. The response rate assessed by Lille model was highest in prednisolone plus SAME group (95%, 19 of 20 patients), lowest in prednisolone group (65%, 13 of 20 patients) and in budesonide group it reached 80% (12 of 15 patients). Serious infections occurred in 35% (7 of 20 patients) in prednisolone group, 30% (6 of 20 patients) in prednisolone plus SAME group, while only in 13.3% in budesonide group. Hepatorenal syndrome (HRS) occurred in 20% (4 of 20 patients) in prednisolone group, with no cases in prednisolone plus SAME ( $p = 0.035$ ) and budesonide group ( $p = 0.003$ ).

**Conclusions:** Therapy with prednisolone plus SAME showed better response rate according to Lille model. Both treatment options (prednisolone plus SAME and budesonide) appeared to be protective against HRS development. However none of the regimens improved 28-days survival in patients with alcoholic hepatitis

**Disclosure of Interest:** None Declared

## P07-1

# Impact of the Systemic Inflammatory Response Syndrome on 3-month Mortality Rates in Subjects with Severe Alcoholic Hepatitis Treated with the ELAD System

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**Introduction:** Systemic Inflammatory Response Syndrome (SIRS) is a major predictor of multi-organ failure (MOF) and mortality in subjects with severe alcoholic hepatitis (sAH).

**Material and methods:** A randomized, open-label, multicenter, controlled study was conducted in subjects  $\geq 18$  yrs old with a clinical or histologic diagnosis of sAH, bilirubin  $\geq 8$  mg/dL, Maddrey discriminant function (DF) score  $\geq 32$ , MELD score of 18-35 and platelets  $\geq 40,000/\text{mm}^3$ , without severe concomitant disease, uncontrolled sepsis or bleeding, hemodynamic instability or need for chronic dialysis. Subjects were randomized to either protocol-specified standard of care (SOC, Control group) or SOC plus 3-5 days continuous treatment with an investigational extracorporeal human allogeneic cellular liver system (ELAD) consisting of human C3A hepatoblastoma cells contained in a cartridge (ELAD group). SOC protocol was implemented based on AASLD and EASL guidelines.

**Results:** 203 subjects were enrolled in the study. Of the 203 subjects, 122 had a white blood cell count  $>12$  or  $<4 \times 10^3/\text{mL}$ , 93 had a pulse  $>90$  beats/min, 13 had a temperature  $>38^\circ\text{C}$  or  $<36^\circ\text{C}$ , and 22 had a respiratory rate  $>20$  breaths/min. In the ELAD group, 36 subjects compared with 31 subjects in the Control group had 2 or more of these criteria and had SIRS at randomization (14 and 13 subjects were receiving steroids in the ELAD and Control groups, respectively). In subjects with SIRS and MELD  $<28$ , the 3-month mortality rate in the ELAD group was 3/20, 15% compared with 7/17, 41% in the Control group ( $p=0.07$ ). However, in subjects with SIRS and MELD  $\geq 28$ , the 3-month mortality rate in the ELAD group was 12/16, 75% compared with 5/14, 36% in the Control group ( $p=0.03$ ).

**Conclusions:** In sAH subjects with SIRS and MELD  $<28$ , lower 3-month mortality rates were observed when treated with ELAD plus SOC compared to SOC alone. However, in subjects with SIRS and MELD  $\geq 28$ , 3-month mortality rates were higher in the ELAD group when compared to SOC. A current prospective randomized controlled clinical study in subjects with sAH and MELD  $<30$ , including subjects with SIRS, is underway.

**Disclosure of Interest:** A. Al-khafaji: : None Declared, R. Subramanian: Consultant: Vital Therapies, Inc., J. Thompson: : None Declared, D. Reich: Grant: Research grant by Vital Therapies, Inc., Consultant: Vital Therapies, Inc., R. MacNicholas: : None Declared, Z. Li: Employee: Vital Therapies, Inc., J. Stange: Employee: Vital Therapies, Inc., W. Frank: Employee: Vital Therapies, Inc.

## P07-2

# SALVE data base and inventory: a multinational effort to increase case numbers in cohorts of people with ALD

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**Introduction:** Monocentric studies in alcoholic liver disease (ALD) may be limited by small patient numbers. The EASL-endorsed Study of Alcoholic Liver Disease in Europe (SALVE) Consortium is currently involved in studies on the natural history of ALD, a survey on clinical management of alcoholic hepatitis (AH), and the development of a histopathologic grading/staging system, efforts supported by the multinational pro- and retrospective SALVE data base at the University of Lille, France.

**Aims:** An inventory was performed among SALVE centers to gather retrospective information for the data base.

**Material and methods:** Clinical stages of ALD collected included alcoholic subjects (AS) with normal liver function, AS without or with fibrosis/cirrhosis of compensated/decompensated stage, severe and mild AH, and transplant recipients. The centers also provided information on patient/sample numbers, follow up and availability of DNA, liver, saliva, and stool samples.

**Results:** Eleven out of 22 SALVE centers contributed to this inventory (results shown in Table1). With respect to the clinical stages of ALD, cohorts ranging approximately from 100 to 1000 patients were collected. In 16 to 100% of cases serum and DNA samples, in 14 to 83% and in 13 to 37% FFPE and frozen liver samples were available, respectively. Finally, in up to 3% saliva and in up to 44% of AS stool had been sampled.

**Conclusions:** Multinational and multicenter combination of patient cohorts substantially increases patient and sample numbers of all clinical settings of ALD and may be a valuable approach to foster studies of adequate statistical power.

**Figure:**

Table1. Results of the SALVE inventory

Clinical setting	Number of AS* with	Biological materials					
		follow up	Serum	DNA	Liver tissue FFPE** biopsy/surgical	Liver tissue frozen	Saliva
		Number					
Healthy subject	650	650	650	0	0	0	0
AS normal liver function test	630	366	366	264/0	0	15	279
AS without fibrosis/cirrhosis	97	0	0	40/0	0	0	0
AS with fibrosis/cirrhosis	775	0	0	130/0	0	0	0
AS with fibrosis/cirrhosis Compensated	1360	1140	1140	250/0	273	0	150
Decompensated	1262	427	451	180/0	170	30	30
Severe AH	392	520	520	320/0	145	0	30
AH with MDF<32 or MELD<18	339	229	229	136/0	115	0	71
Transplant recipient	1025	168	168	855/1025	168	0	0
<b>Contributors:</b> Santa Maria Hospital, Univ. de Lisboa, Portugal; La Fe University Hospital, Valencia Spain; Padua University Hospital, Padua, Italy; Hippokration Gen. Hospital, Athens, Greece; 1st Moscow State Medical University, Moscow, Russian Federation; Newcastle University, Newcastle upon Tyne, United Kingdom; Hopital Claude Huriez, Lille, France; C.U.B. Erasme Hospital, Brussels, Belgium; Hopital Saint Eloi, Montpellier, France; University Hospital and Faculty of Medicine, Geneva, Switzerland, Medical University of Graz, Austria;							

\*Alcoholic subject

\*\* Formalin-fixed paraffin-embedded

Disclosure of Interest: None Declared

P07-3YI

## Accurately defining infection as a clinical trial endpoint in patients with alcohol induced chronic liver disease: results from a multicentre feasibility study

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**Introduction:** Infection is a common complication in alcohol-induced cirrhosis and often carries a poor prognosis, however it is often difficult to definitively diagnose. A standardized criteria for the diagnosis of infection in liver cirrhosis trials exists, but in real life practice clinicians are unlikely to adhere to a rigid criteria and will use their own clinical judgment prior to the initiation of therapy for suspected infection. Microbiology culture represents the current gold standard diagnostic test however these cultures are positive in only 40-50% of patients that are diagnosed and treated clinically. Therefore clinical trials aimed at reducing infection rates face a significant challenge in recording this information accurately.

**Aims:** To assess antibiotic prescription as an objective surrogate marker of infection diagnosis in a feasibility trial of targeted 20% human albumin infusions.

**Material and methods:** This prospective multicentre, single arm, open label feasibility trial recruited 79 patients with albumin < 30 g/L from 10 centres over 6 months. There was daily recording of drugs prescriptions plus biochemical, radiological, clinical and microbiological markers of infection. A blinded panel of microbiologists considered the documented evidence for infection at the time of antibiotics initiation.

**Results:** 41/79 patients were prescribed antibiotics at recruitment with 27/41 of these recorded as having an infection diagnosis by the treating clinicians. During the treatment period 21/79 (27%) were diagnosed with a new infection. Infection case report forms were completed for 35 of these antibiotic prescriptions (at baseline/after recruitment). Blinded microbiology review revealed 4/35 (>11%) did not fulfill infection predefined criteria. Table 1 details types of infection.

**Conclusions:** A robust diagnosis of infection in patients with decompensated cirrhosis is challenging due to high rates of presumed culture-negative sepsis. The on-site clinician-reported infection rate on admission was 34%, in line with other studies; however antibiotics were prescribed in 52%. This perhaps reflects a tendency to over prescribe and therefore using new/change in antibiotic prescription as a surrogate for infection diagnosis appeared subject to potential bias and this cannot be standardized across multiple sites. Therefore we propose defining infection according to clinician, validated by an infection report form to be blindly scrutinized by a microbiology panel. This approach appeared feasible in a subset of 35 patients.

Figure:

Table 1: Details from infection data matched to 35/62 antibiotic prescriptions

Classified Infection	Number of times confirmed <sup>b</sup>	Antibiotic sensitivity		
		Resistant	Sensitive <sup>a</sup>	Unknown
Spontaneous bacterial peritonitis	4	0	1	3
Pneumonia	6	0	1	5
Cellulitis	4	0	1	1
Bacterial enterocolitis	1	1	0	0
Fungal infection	1	0	0	1
Spontaneous bacteraemia	7	2	2	3
Other infection	8	3	0	5
Urinary tract infection	0	n/a		
Other intra abdominal infection	0			
C.Difficile	0			
<b>TOTAL</b>	<b>31</b>	<b>6</b>	<b>5</b>	<b>18</b>

Disclosure of Interest: None Declared

## P07-4YI

# A study of predictors of 90-day mortality in patients with severe alcoholic hepatitis: experience outside clinical trials with 183 patients at a tertiary care center from India

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**Introduction:** Severe alcoholic hepatitis (SAH) has very high mortality varying from 17 -40 %. There is limited data from developing countries like India on short term mortality, its predictors of mortality and comparison of various severity indices in patients of SAH.

**Aims:** To assess the short-term mortality (90 days) in patients of severe alcoholic hepatitis and to determine the factors predicting the mortality along with comparison of various prognostic scores in the real-world scenario

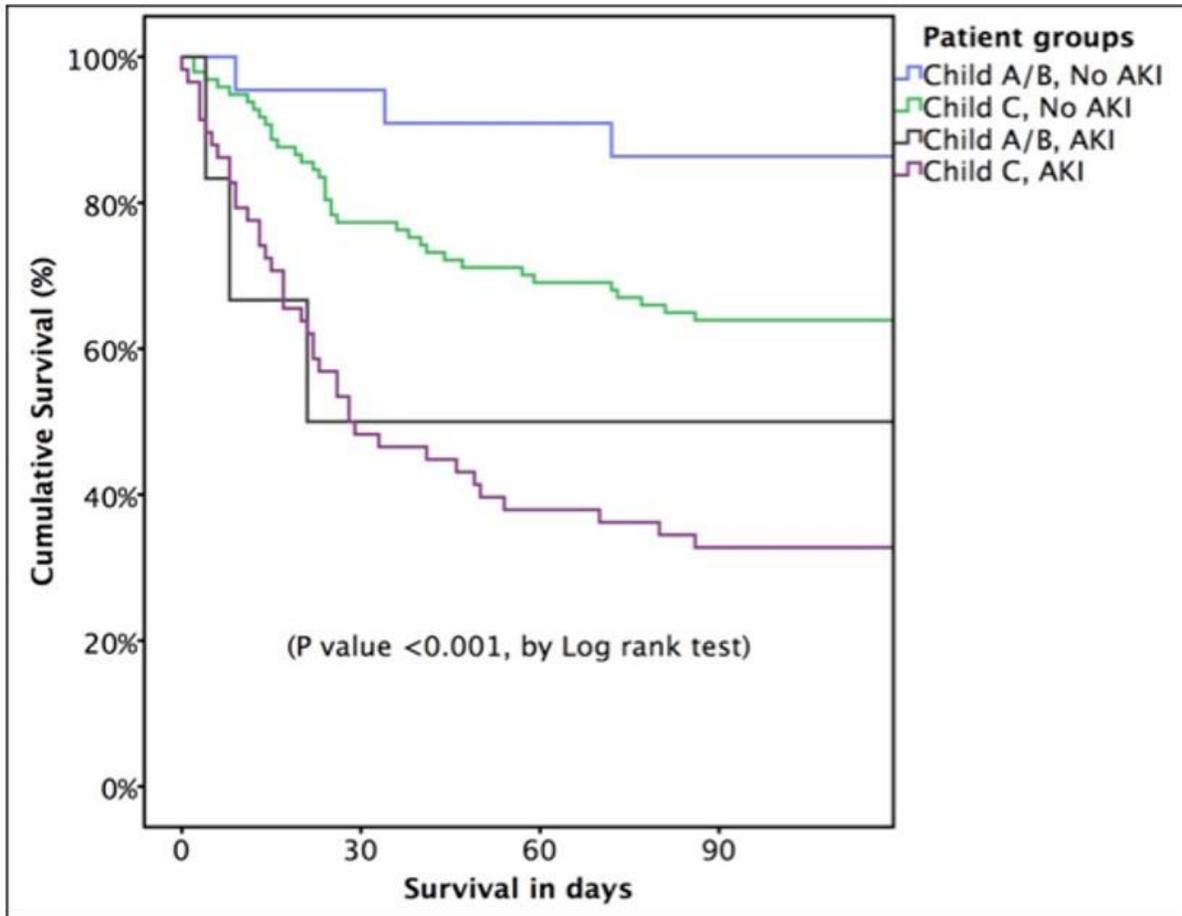
**Material and methods:** In this prospective study, we analysed patients with SAH (defined as modified discriminant function [mDF]  $\geq 32$ ) admitted from January 2015 to February 2017 at our Institute. All patients were administered standard treatment according to various established guidelines for SAH and their 90-day mortality was determined. Various hematologic, biochemical and severity indices including were compared between survivors and patients who died.

**Results:** A total of 183 patients (98% males, median age 41 years [range 20-70 years]) were included in our study. The median (range) values of severity scores at baseline were as follows: DF 70 (32-320); GAHS 9 (6-12); ABIC 7.6 (4.7-12.0); MELD 26 (15-40); MELD-Na 30 (14-40); and CTP 11 (7-14). Ascites was present in 83% and hepatic encephalopathy (HE) in 38%. Only 21 (12%) could be offered steroid therapy, due to contraindications in the remaining. By 90 days, only 103 (56%) patients survived while 80 (44%) patients had died. All patients died due to progressive liver failure or its complications. On multivariate analysis presence of ascites, hepatic encephalopathy, high bilirubin, low albumin, high creatinine, high INR, and low potassium independently predicted 90-day mortality. All the scores performed significantly in predicting 90-day mortality with no statistically significant difference between them. MELD score had maximum area under the curve 0.76 for 90-day mortality. A combination of Child class and presence of acute kidney injury (creatinine  $\geq 1.35$ ) was good in predicting 90-day mortality

**Conclusions:** SAH in India has 44% 90-day mortality. Most patients are not eligible for steroids. Presence of Child C and high creatinine ( $\geq 1.35$  mg/dL) accurately predicts mortality.

Figure:

Figure : Comparison of four groups of patients according to Child class and presence of acute kidney injury (serum creatinine  $\geq 1.35$  mg/dL)



Disclosure of Interest: None Declared

## The rising healthcare burden of alcoholic cirrhosis in the United States

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**Introduction:** Alcoholic cirrhosis is a major cause of liver-related morbidity and mortality both in the United States and worldwide, and rising rates of alcohol use disorders are predicted to lead to further increases. Recent studies have focused on the economic and healthcare burden of liver disease due to HCV and NAFLD.

**Aims:** We aimed to use a nationally-representative cohort to determine prevalence, healthcare utilization and costs of alcoholic cirrhosis in the United States.

**Material and methods:** We collected data on the prevalence, admissions, and costs from patients aged 18-65 with alcoholic cirrhosis (identified by ICD-9/ICD-10 codes) enrolled in the Truven Analytic MarketScan Commercial Claims and Encounters database (2008-2015). We determined yearly prevalence trends, weighted to the national employer-sponsored insured population (approximately 120 million people). Using competing risk analysis, we estimated event rates for portal hypertensive complications and determined the effect of alcoholic cirrhosis on total and per-person costs as well as admissions and readmissions.

**Results:** 294,561 enrollees had cirrhosis in 2015 (0.27% prevalence nationally), with 43% attributed to alcohol (0.12% prevalence). Mean age at diagnosis was 54 years. National prevalence of cirrhosis and alcoholic cirrhosis rose from 0.20% to 0.27% between 2008 and 2015 for cirrhosis overall, and 0.09% to 0.13% for alcoholic cirrhosis. Compared to non-alcoholic cirrhosis, alcoholic cirrhosis patients were significantly more likely to be decompensated at diagnosis (ascites: 20% vs. 7%; hepatic encephalopathy 6% vs. 1%; variceal bleeding: 4% vs. 1%;  $p < 0.05$  for all). Cirrhosis and alcohol-related admissions were higher for alcoholic cirrhosis patients (22.8 excess cirrhosis admissions per 100 patients) as were 30-day readmissions (29.2 excess readmissions per 100 patients). Per-person healthcare costs in the first year after index diagnosis were nearly double for alcoholic cirrhosis (per-person: 69,489 US\$ vs. 37,129 US\$,  $p < 0.05$ ). Total direct healthcare costs for the first year after diagnosis for all ALD were 11 billion US\$.

**Conclusions:** In a nationally representative cohort of privately insured cirrhosis patients, almost half had alcoholic cirrhosis. Patients with alcoholic cirrhosis were sicker at presentation, had more admissions, and total healthcare costs were nearly twice that of non-alcoholic cirrhosis. Early diagnosis and aggressive alcohol cessation efforts may help improve outcomes and healthcare utilization in these patients.

**Disclosure of Interest:** None Declared

P08-2YI

## Bile acids and intestinal dysbiosis in alcoholic hepatitis

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**Introduction:** Alcoholic liver disease is associated with dysbiosis, impaired gut barrier and inflammation. Intestinal microbiota (IM) plays an important role in bile acids (BA) homeostasis and impact the gut barrier and promotes inflammation.

**Aims:** The aim of our study was to study the structure of the IM and its function in BA homeostasis in alcoholic patients according to the severity of alcoholic liver disease.

**Material and methods:** We included in a prospective study 4 groups of active alcoholic patients (N=109): two non-cirrhotic (nc) without or with alcoholic hepatitis (AH) (noAHnc, N=60 or AHnc N=14, respectively) and two cirrhotic groups without or with AH (noAHc, N=18 or sAHc, N=17, respectively). Serum and fecal BA profiles, as well as IM composition, using high-throughput 16s sequencing, were assessed.

**Results:** In sAHc patients compared to noAHc patients, there was an increase in serum total BA, primary BA (total CA and total CDCA), conjugated BA and tauro-glycoconjugated ratio and a decrease in the UDCA/total BA and secondary/primary ratio. In feces, there was a decrease in total BA and an increase in secondary BA (total LCA and DCA). These 2 groups had a different IM structure. At the phyla level, there was an increase in Actinobacteria and a decrease in Bacteroidetes; 7 genera were increased and 4 were decreased. Moreover, in sAHc patients compared to noAHc patients, there was an increase in 4 and a decrease in 11 metabolic pathways (eg increase in glutathion and nucleotid metabolism, phosphotransferase system). In AHnc patients as compared to noAHnc, there was an increase in serum total conjugated BA. The IM of AHnc patients was characterized by an increase in *Wolbachia* and *Dorea* as compared to noAHnc.

**Conclusions:** Disruption of BA homeostasis associated with alcoholic hepatitis is correlated to a specific IM signature that may lead to liver disease progression.

**Disclosure of Interest:** D. Ciocan: Grant: Biocodex, C. Voican: None Declared, L. Wrzosek: None Declared, C. Hugot: None Declared, G. Perlemuter: Consultant: Biocodex, Gilead, Servier, and Pileje, Other: Elsevier-Masson, John Libbey Eurotext and Solar, A.-M. Cassard: Other: Biocodex, Elsevier-Masson and John Libbey Eurotext

P08-3

## Characterization of alcoholic hepatitis using proteomics of PBMCs

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**Introduction:** Alcoholic hepatitis (AH) is a serious type of alcoholic liver disease with high short term mortality. Although corticosteroids and other therapies are used, they are often inadequate to halt the systems-wide disturbances that can lead to death. To better understand the pathophysiology of AH we are utilizing advanced liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods to provide a systems-wide evaluation of plasma, peripheral blood mononuclear cells (PBMCs), and liver tissue.

**Aims:** The aim is to present data on the proteomic analysis of PBMCs from AH patients compared longitudinally, corticosteroid treatment, and cross-sectionally to alcoholic cirrhosis (AC), non-alcoholic fatty liver disease (NAFLD), and healthy controls.

**Material and methods:** PBMCs were freshly isolated from 21 patients with biopsy proven severe AH (discriminant function score >32), 13 patients with stable AC (abstinent or recently drinking), 12 NAFLD patients, and 21 healthy controls. AH treatment consisted of 40 mg of prednisolone per day for up to 28 days. PBMC proteins were processed into peptides and analyzed utilizing a high mass accuracy LC-MS/MS platform. Data was searched utilizing MSGF+ with identification thresholds set at <0.1% FDR. Statistical comparisons were performed using the proteomics analysis tool Inferno.

**Results:** Analysis identified and quantified >6K proteins from the isolated PBMCs. Comparison of baseline AH versus normal and related liver disease patients revealed large systematic differences in protein abundance/pathways, i.e., >3K and >1.9K proteins differentially regulated compared to healthy and disease controls respectively. Regulated proteins mapped to apoptotic signaling, Erk kinase, fibrinolysis, and integrin signaling pathways among others. Comparison of corticosteroid treated patients identified regulation of MAPKinase signaling, toll-like receptor, and TNFR1 related pathways. Correlation with transcriptomic analysis from the same PBMCs using Ingenuity helped identify corresponding pathways, i.e., TREM1, ephrin receptor and integrin signaling, for further targeted study.

**Conclusions:** Application of proteomics on isolated PBMCs helped identify protein/pathway alterations specific to AH that differentiate from other liver diseases. Longitudinal analysis of corticosteroid treatment provided insights into the molecular mechanisms correlated with outcome. Integration with transcriptomic analysis of the same samples further strengthened the investigations into changes in PBMCs in AH.

**Disclosure of Interest:** None Declared

P08-4YI

## The STOPAH trial has altered clinical practice: results of a UK national survey

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**Introduction:** The recent STOPAH trial conducted in the UK was intended to resolve the uncertainty around best pharmacological therapy for severe alcoholic hepatitis (SAH). It demonstrated no difference of pentoxifylline over placebo and only a modest short-term survival benefit from corticosteroids at the expense of increased mortality from infection.

**Aims:** We aimed to document the current variation in clinical management of patients with AAH in the UK and determine whether the results of the STOPAH trial have changed practice.

**Material and methods:** An anonymised online survey of gastroenterologists, hepatologists and trainees in the UK was conducted which was distributed via the British Association for the Study of the Liver and the British Society of Gastroenterology. Data was analysed descriptively.

**Results:** There were 182 respondents of which 31% were hepatologists, 18% gastroenterologists with an interest in hepatology and 14% general gastroenterologists. Acute hospitals, liver transplant centres and district general hospitals were equally represented by respondees. Pentoxifylline is no longer used as first line therapy (1%) while corticosteroids remain the most common pharmacological therapy either used alone (68%) or in combination with pentoxifylline (4%) or N-acetylcysteine (8%). No pharmacological therapy was used in 19%. The majority (74%) intended to complete 28 days of treatment with corticosteroid but 92% applied steroid discontinuation rules either based on the Lille score (42%), early change in bilirubin (24%) or a combination of other factors (37%). 76% felt that the STOPAH trial had altered their practice either by changing their choice of treatment (68%) or by discontinuing corticosteroids in patients with infection (26%). However, no respondent was satisfied with the current management options for SAH and suggested clinical trials of novel therapy (73%), improved access to alcohol liaison services (59%), development of an updated clinical guideline (54%) and improved methods to determine corticosteroid responsiveness (42%) as strategies to improve care.

**Conclusions:** The STOPAH trial has altered clinical practice in the UK with more judicious use of corticosteroids. Although still the most popular pharmacological therapy, the vast majority of clinicians apply a stopping rule based on dynamic biochemical changes or development of infection. There remains a need to improve methods of patient stratification to enable accurate selection of patients who derive the most benefit from corticosteroids.

**Disclosure of Interest:** None Declared

## Carriage of rs738409 in PNPLA3 is positively associated with the severity of histological damage in patients with alcoholic hepatitis

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**Introduction:** In people who misuse alcohol carriage of the risk allele of rs738409:G in *PNPLA3* plays an important role in determining risk for the development of cirrhosis and influences several important aspects of disease progression and outcome. In patients with severe alcoholic hepatitis homozygosity for rs738409:G in *PNPLA3* confers significant additional risk of mortality.

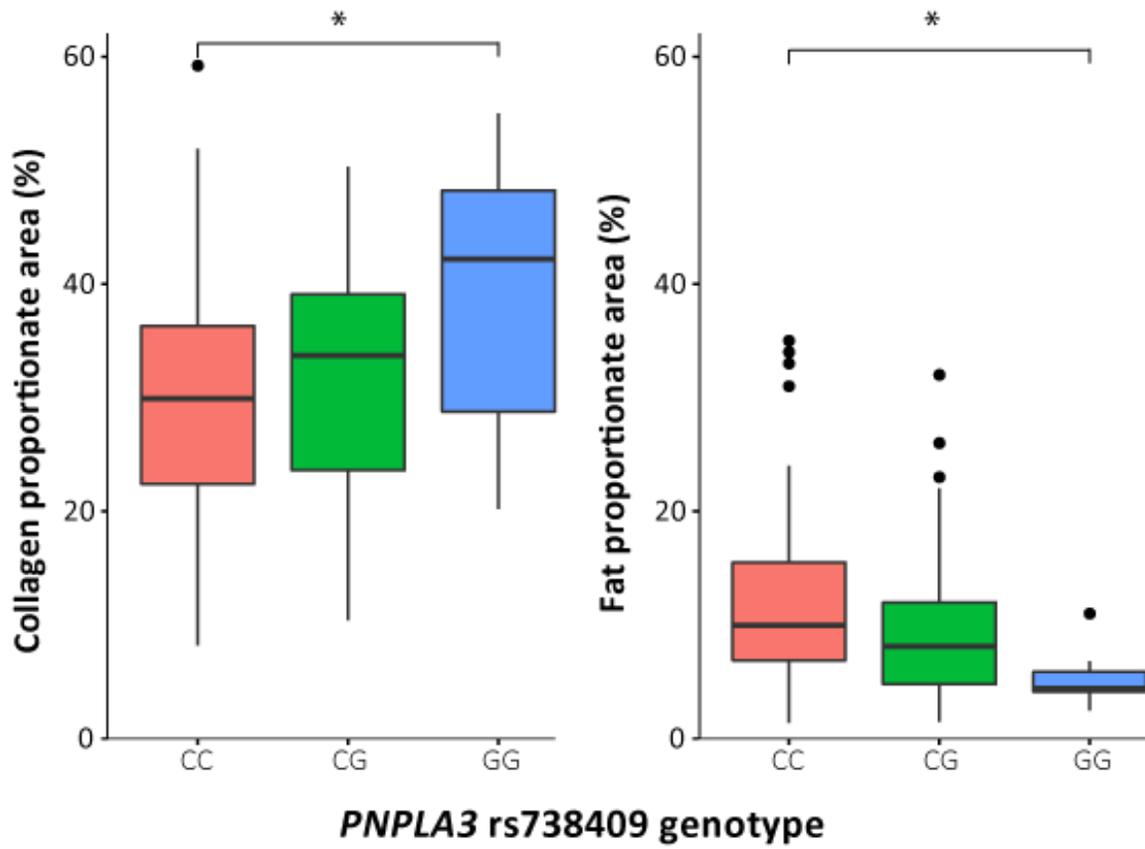
**Aims:** The aim of this study was to determine whether carriage of rs738409:G is associated with histological severity of alcoholic hepatitis at presentation.

**Material and methods:** The study population comprised participants in the *Steroids or Pentoxifylline for Severe Alcoholic Hepatitis* trial with available DNA in whom liver histology of sufficient quality and adequately timed with respect to the start of treatment (+/- 28 days), was available. Liver biopsy material was stained with haematoxylin & eosin and Sirius red. The slides were assessed by two histopathologists using the alcoholic hepatitis histological scoring system. Images were also digitally scanned and the collagen (CPA) and fat proportionate areas (FPA) quantified. Baseline, pre-treatment serum levels of the M30 and M65 subtypes of cytokeratin-18 were measured by ELISA. Associations with the rs738409 genotype were examined.

**Results:** A total of 129 participants (men: 89 (69%); mean age: 49(IQR 42 - 56)) were included, median time to biopsy was 4 days after start of treatment. There was a significant positive association between carriage of rs738409:G and severe inflammation (CC: 4/53 (7.5%); CG 16/50 (32%); 4/12 (33%),  $p=0.003$ ) but not severe hepatocyte ballooning (CC: 29/53 (55%), CG: 31/50 (62%), GG: 5/12 (42%),  $p=0.43$ ). Severe inflammation and ballooning were significantly positively associated with serum levels of both CK18-M30 ( $p<0.01$ ) and CK18-M65 ( $p<0.01$ ). Carriage of rs738409:G was associated with higher serum levels of both CK18-M30 ( $p=0.01$ ) and CK18-M65 ( $p=0.07$ ). Carriage of the risk allele was associated with greater CPA (CC: 30% (IQR 22-36%), CG: 33% (24 – 38%), GG: 42% (29 – 48%),  $p=0.01$ , Figure 1A) but lower FPA (CC: 13.6% (10.0 – 21.5%), CG: 11.5% (8.0 – 17.5%), GG: 8.5% (6.4 – 14.1%),  $p=0.02$ , Figure 1B).

**Conclusions:** In patients who present with alcoholic hepatitis carriage of rs738409:G in *PNPLA3* is associated with greater hepatic fibrosis, inflammation and serum markers of hepatocyte death. These findings may explain, in part, the slower recovery in liver function and higher medium-term mortality seen in carriers of this risk allele.

Figure:



Disclosure of Interest: None Declared

## P09-IYI

# Risk factors for alcohol relapse after liver transplantation: a 9-year retrospective study

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**Introduction:** Relapse to harmful alcohol intake following orthotopic liver transplantation (OLT) for alcohol-related chronic liver disease occurs in 10-20% of patients. Detrimental consequences include graft dysfunction, increased morbidity and mortality, and negative public perceptions counterproductive to organ donation. No consistent predictive factors for alcohol relapse have been shown.

**Aims:** We evaluated the predictive risk of alcohol relapse using demographic, psychosocial and addiction-related variables both in isolation and in conjunction as a novel risk-assessment scoring system. We assessed the impact of relapse on post-OLT survival.

**Material and methods:** Consecutive patients (n=181) with a history of alcohol excess who underwent OLT in a tertiary centre (2004-2013) were included. Demographic variables, alcohol history, substance misuse, psychiatric comorbidities and family alcohol dependence were recorded. The Relative Risk Factors for Relapse (RRFR) score consists of abstinence history, dependence diagnosis, acceptance of diagnosis, willingness to engage in treatment, social network, drug misuse, and replacement activities, and has a numerical scale of 0-27, higher values indicating greater relapse risk. Relapse outcomes, 1-year and 5-year survival after OLT were evaluated.

**Results:** Patients were predominantly male (88%), mean age 54±7 years, mean MELD score 15.7±5.8. 18.8% remained abstinent, with a high rate of slips (68.5%) and few lapses (4.4%). Relapse to harmful alcohol intake occurred in 8.3% of patients (15/181), lower than published rates of 10-20%. 1-year and 5-year survival after OLT was 93.3% and 86.7% respectively, compared to European Liver Transplant Registry survival rates of 86% and 74%. Relapse did not have a significant effect on 1-year (p=1.0) or 5-year survival (p=0.43). In univariate analysis, units of alcohol per week (p=0.04), past treatment for alcohol (p=0.046), and total RRFR score (p=0.03) were associated with relapse. Multivariate analysis revealed no independent predictive factors.

**Conclusions:** The low rate of relapse to harmful alcohol intake and high survival rate in our cohort compares favourably to existing literature. While no individual factors, including abstinence time, independently predicted harmful alcohol relapse post-OLT, comprehensive pre-assessment incorporating the RRFR score contributed to improved outcomes. Further study is required to elucidate reliable criteria for relapse risk stratification to assist OLT selection in patients with previous alcohol excess.

**Disclosure of Interest:** None Declared

# IgA antibodies against filamentous-actin are frequently detected in patients with cirrhosis and indicate a progressive disease course

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**Introduction:** Gut barrier failure and pathological bacterial translocation (BT) are characteristic features of cirrhosis and play an important role in the progression of liver disease.

**Aims:** To investigate, whether hallmarks of gut barrier failure are associated with accelerated development of complications and liver-related death in cirrhosis.

**Material and methods:** Sera from 260 outpatients with cirrhosis (male: 129, age: 56±11 yrs, alcohol: 167 [64.2%]) and from 155 healthy subjects were assayed for antibodies against filamentous actin [AAA IgA and IgG] and gliadin [AGA IgA and IgG] and for intestinal fatty acid-binding protein (I-FABP) by ELISA. Association of gut failure markers with disease specific characteristics was assessed at baseline. BT was assessed based on the presence of anti-microbial antibodies (anti-OMP Plus IgA and/or endotoxin core antibody IgA [EndoCab]). We evaluated decompensating events (ascites, variceal bleeding, hepatic encephalopathy, bacterial infections) and liver-related death in a 5-year follow-up, observational study.

**Results:** Elevated concentrations of the gut failure markers IgA-AAA (62.7 vs. 4.4%) and IgA-AGA (27.7 vs. 2.6%) were more often observed in cirrhosis as compared to healthy controls ( $p < 0.001$  for both). In addition, serum I-FABP was increased in cirrhosis as compared to controls (741 vs. 244 pg/mL,  $p < 0.001$ ) and correlated with serum levels of IgA-AAA and IgA-AGA. IgA-AAA positivity was associated with alcoholic liver disease, liver disease scores and decompensated clinical stage (all  $p < 0.001$ ). Serological markers of BT were more often found in patients with elevated IgA AAA compared to those without (72.3 vs. 13.5 % for IgA-EndoCab and 85.2 vs. 20.5% for IgA anti-OMP,  $p < 0.001$  for both). In patients with compensated disease stage ( $n = 131$ ) the risk of decompensation was higher in patients with elevated IgA-AAA (HR [95%CI]: 1.85 [1.06-3.24]), as was the risk of liver-related mortality (HR: 2.66 [1.27-5.56]). Such associations were not observed for IgG-AAA and IgA/IgG-AGAs. In the overall cohort, IgA-AAA remained an independent predictor of liver-related death (HRadj: 1.96 [1.08-3.55]) when adjusting for important clinical variables (MELD score, etiology, clinical stage, see Table 1).

**Conclusions:** Presence of IgA antibodies against filamentous-actin indicate patients with an unfavourable outcome in cirrhosis, which may be related to intestinal damage beyond being related to bacterial translocation. IgA-AAA might be considered as a novel serologic marker of disease progression.

Figure:

	Wald	Hazard ratio	95% confidence interval	P-value
AAA IgA positivity ( $\geq 35$ U)	4.83	1.96	1.08-3.58	0.028
MELD score (per 1 point increase)	11.71	1.10	1.04-1.17	0.001
Etiology (alcohol)	1.63	0.70	0.40-1.21	0.202
Clinical stage (decompensated)	1.73	1.38	0.86-2.22	0.188

**Disclosure of Interest:** T. Tornai : None Declared, B. Balogh : None Declared, N. Sipeki : None Declared, Z. Vítális : None Declared, I. Tornai : None Declared, P. Antal-Szalmás : None Declared, G. Norman: Employee: Inova Diagnostics Inc., T. Bruns : None Declared, M. Papp : None Declared

P09-3YI

## Determinant of decompensation and death in patients with alcoholic liver disease and longitudinal follow-up

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**Introduction:** Alcoholic liver disease (ALD) is the most prevalent cause of advanced liver disease in Europe and is responsible for most of alcohol-related deaths.

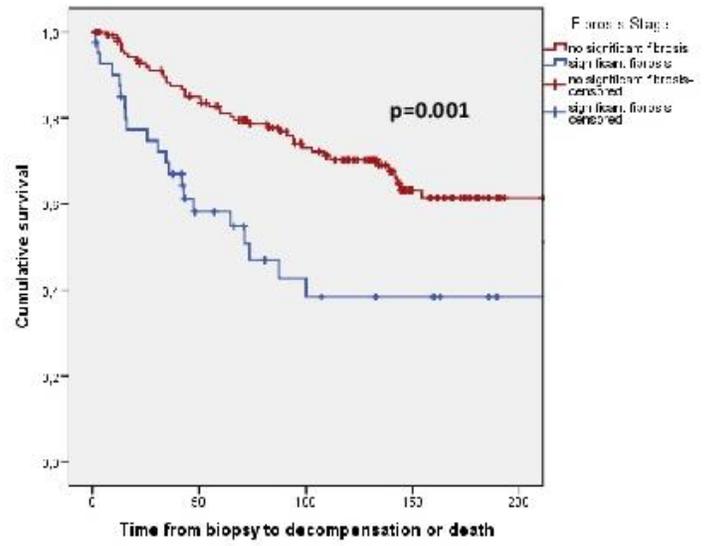
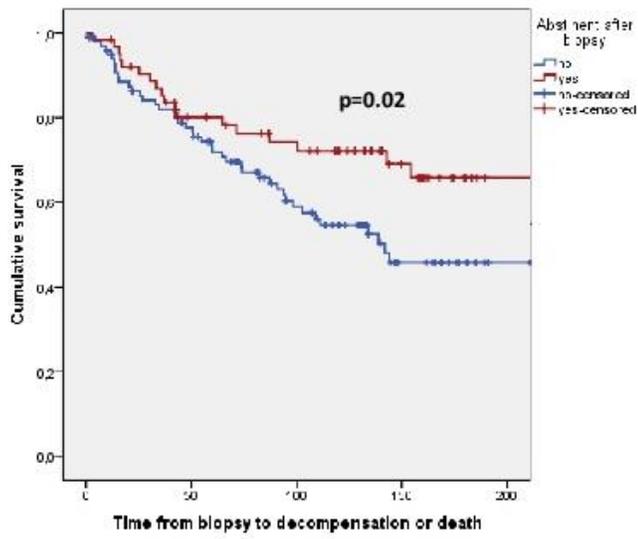
**Aims:** We evaluated the characteristics and predictors of decompensation and/or death in consecutive patients with ALD and available liver histology in our centre

**Material and methods:** We retrospectively included a cohort of 187 patients with biopsy-proven ALD, irrespective of fibrosis stage. All patients with concomitant primary cause of liver disease were excluded. Clinical details and laboratory parameters at the time of liver biopsy were collected. Follow-up data were collected at the time of the last clinical follow-up or death. Hepatic decompensation and liver-related mortality were considered as the combined primary outcome

**Results:** We included 187 patients, 75.4% were male with a mean age of 51.1 years. Most of the patients were Caucasian (75.4%). Fifty patients (26.7%) had also features of metabolic syndrome. The mean alcohol intake was 166 grams per day. 63 patients were abstinent (33.7%) after the biopsy with a median abstinence period of 14.5 (IQR 217) months. The distribution of fibrosis (METAVIR score) in our population was as follows: F0=77 (41.2%) patients, F1=44 (23.5%) patients, F2= 25 (13.4%), F3=7 (3.7%) and F4=34 (18.2%). Sixty-six patients (35.3%) had at least one episode of hepatic decompensation and/or died during a median follow-up of 133.6 (IQR 316) months. The development of new hepatic decompensation and/or death was higher in patients with significant fibrosis (F3-F4) (22.7% at 24 months and 33% at 36 months) than in patients with non-significant fibrosis (F0-F2), (7.3% at 24 months and 11.9% at 36 months);  $p=0,001$ . Abstinent patient had a lower rate of new hepatic decompensation and/or mortality compared to patients with active drinking (8% at 24 months and 14.7% at 36 months in the abstinent group vs. 14% at 24 months and 18% at 36 months in patient with active drinking;  $p= 0.02$ ). A Cox-regression analysis was performed to identify predictors of hepatic decompensation and/or liver-related mortality. Presence of advance fibrosis (OR 4.17, 95% CI 2.0-8.7), and abstinence (OR 0.334, 95% CI 0.15-0.73) were independent predictors of clinical outcome

**Conclusions:** The degree of fibrosis and maintained abstinence are independent predictors of death and/or decompensation in patients with ALD. Long term abstinence is therefore the main objective in the management of this patients

Figure:



Disclosure of Interest: None Declared

P09-4YI

## Innate T cells are significantly altered in the livers of patients with alcoholic liver disease

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**Introduction:** Innate T cells include natural killer T (NKT) cells, mucosa-associated invariant T (MAIT) cells, and gamma delta ( $\gamma\delta$ ) T cells. Innate T cells are enriched in the human liver, with MAIT cells alone making up to 50% of hepatic T cells. Innate T cells are key players in liver immunity with the ability to promote and regulate both innate and adaptive responses. Each subset responds to a different group of antigens, all of which are non-protein in nature and presented to MHC class I-like molecules such as CD1 and MR1. It has been reported recently that the frequencies of innate T cells was reduced in the liver of mixed chronic liver disease cohort compared to healthy controls (HC). However, little is known about the effects of alcoholic liver disease (ALD) on liver-resident human innate T cells.

**Aims:** We aimed to characterize innate T cells in the liver of patients with ALD.

**Material and methods:** Intrahepatic mononuclear cells (HMC) from liver perfusates of 10 explanted ALD livers and 10 healthy controls (HC) were analysed by flow cytometry for the expression of CD3, Va24-Ja18, Va7.2, CD161,  $\gamma\delta$ -TCR, CD19, CD4, CD8, CD40, MHC-II, and CD1d.

**Results:** The frequency of T cells within HMC was significantly reduced in patients with ALD compared to HC (ALD: 12%, HC: 46%,  $P=0.0036$ ). The frequencies of MAIT cells and  $\gamma\delta$  T cells as a proportion of total T cells were significantly reduced (ALD: 3%, HC: 16%,  $P=0.004$ ) and (ALD: 4%, HC: 11%,  $P=0.01$ ) respectively. An insignificant reduction in NKT cells was observed in ALD patients (ALD: 0.01, HC: 0.3,  $P=0.1$ ). The proportions of total T cell subsets based on CD4 and CD8 expression were significantly skewed in patients with ALD. CD4<sup>+</sup> T cells were significantly increased (ALD: 50%, HC: 26%,  $P=0.0001$ ), while CD8<sup>+</sup> T cells and CD4<sup>+</sup>CD8<sup>-</sup> T cells were significantly reduced (ALD: 42%, HC: 59,  $P=0.01$ ) and (ALD: 4%, HC: 13%,  $P=0.0003$ ) respectively. B cells and monocytes from ALD patients showed a significant up regulation of the co-stimulatory molecule CD40 and antigen-presenting molecule CD1d, but not MHC class II compared to HC.

**Conclusions:** MAIT cells and  $\gamma\delta$  T cells, the most abundant T cells in human liver, are reduced in frequency in the liver of patients with ALD. The selective up regulation of CD1d and CD40, relevant for innate T cell stimulation, provides some indication that innate T cells may be depleted by mechanisms of activation-induced cell death. These findings warrant further investigation into the role of MAIT and  $\gamma\delta$  T cells in the pathogenesis of ALD.

**Disclosure of Interest:** None Declared

P09-5YI

## Liver-brain axis in alcoholic liver disease: Chronic alcohol induces recruitment of peripheral macrophages with different inflammatory gene expression profile into the liver and brain

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**Introduction:** Alcohol-induced changes occur in the liver and the brain, where both cell damage and inflammation are profound. While it is known that alcohol-induced alterations occur in both organs, the extent to which these changes are congruous or not is yet to be defined. The contribution of infiltrating macrophages to these changes is of particular interest for potential therapeutic interventions.

**Aims:** We aimed to study the infiltrating macrophages in the brain and liver and the effect of chronic alcohol inflammation in the liver-brain axis.

**Material and methods:** WT C57BL6 mice were fed Lieber DeCarli (PF and 5% EtOH) diet for 6 weeks and resident and infiltrating macrophages were quantified by flow cytometry from livers and brains. Some mice received a small molecule inhibitor of CCR2/5 to block infiltration of peripheral macrophages. RNA from the liver and cerebellum was analyzed using Nanostring nCounter Inflammation Panel. To distinguish resident microglia (CX<sub>3</sub>CR1<sup>+</sup>) from infiltrating macrophages (CCR2<sup>+</sup>) we studied heterozygous CCR2-RFP and CX<sub>3</sub>CR1-GFP mice.

**Results:** We found a 2-fold increase in infiltrating peripheral macrophages by flow cytometry in the total brain (CD11b<sup>+</sup>, CD45<sup>hi</sup>) as well as in the liver (CD11b<sup>hi</sup>, F4/80<sup>lo</sup>) of alcohol-fed mice compared to pair-fed controls. CCR2 blockade inhibited the increase in peripheral macrophages in both organs. Using CCR2-RFP and CX<sub>3</sub>CR1-GFP heterozygous mice, we confirmed macrophage recruitment in the cortex, hippocampus and cerebellum of the brain. Of 256 inflammation-related genes 59 genes were either up- or downregulated in the liver, while only 17 genes were changed in the cerebellum by alcohol feeding. Five common genes were changed in both liver and cerebellum including intracellular enzymes involved in signal transduction, alarmins and extracellular signals on inflammation. qPCR confirmed many of these gene changes in larger sample sets (n=6 PF; n=6 EtOH). Importantly, *in vivo* blockade of CCR2 signaling eliminated the alcohol-induced increase of these genes and reduced proinflammatory proteins in both organs, including TNF $\alpha$  and IL-6.

**Conclusions:** Our findings provide novel evidence that infiltrating macrophages enter the brain as well as the liver following chronic alcohol use. However, the spectrum of inflammatory gene changes is broader in the liver compared to the brain with 5 common genes between the two organs. These data indicate organ-specific inflammatory cell activation after chronic alcohol feeding and offer unique insights into the liver-brain axis.

**Disclosure of Interest:** None Declared

## PIO-I

# “You gotta want it”: Misconceptions, preferences, and barriers to alcohol use treatment in alcoholic liver disease

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**Introduction:** While alcohol cessation improves mortality in alcoholic liver disease (ALD), many patients struggle to achieve abstinence. The hepatology clinic visit may be a teachable moment for more effective referrals to alcohol treatment

**Aims:** Our aim was to characterize ALD patients' preferences, misconceptions, and knowledge of alcohol use treatment options.

**Material and methods:** We performed semi-structured interviews of 22 outpatients with a history of alcoholic cirrhosis or alcoholic hepatitis recruited from a US tertiary care hepatology clinic. We purposefully sampled men and women, compensated and decompensated patients to ensure adequate representation of gender and severity of liver disease. Interviews were performed by a professional interviewer. Interview transcripts were analyzed and coded in an iterative fashion with coding agreed upon by investigator consensus.

**Results:** 22 ALD patients (10 women, 12 men) completed interviews. Median age was 59 years (range 27-74). 16 had a history of decompensated cirrhosis or alcoholic hepatitis. 14 subjects (6 women, 8 men) self-reported alcohol abstinence. All participants had engaged in some form of alcohol treatment but over half felt that they did not need treatment (n = 13) with several characterizing it as ineffective or a “waste of time.” Misconceptions about alcohol treatment included inaccurate perceptions of relapse medication side effects, beliefs that advanced liver disease symptoms meant it is too late to treat alcohol use, and a lack of understanding about the chronicity of alcohol use disorders. Alcoholics Anonymous was well-known, but other treatment modalities were poorly understood. Many (14) had heard of relapse prevention medications, while only 5 had used them. Participants expressed a range of preferences for treatment options, though there was skepticism about Alcoholics Anonymous/group therapies, to which many patients had their most vocal reactions. Barriers to treatment were varied. The most common barriers were unwillingness to be in treatment, financial/insurance and transportation barriers. Medical providers were the most common source for knowledge about alcohol use and liver disease, with many participants stating they trusted and listened to their medical providers.

**Conclusions:** Knowledge of alcohol treatment options was limited and preferences for alcohol use treatments were varied. Efforts to engage in preference-sensitive alcohol treatment discussions may result in more effective referrals and increased alcohol abstinence.

**Disclosure of Interest:** None Declared

# Patatin-like phospholipase domain-containing protein 3(PNPLA3) gene polymorphism in Alcoholic Liver disease in India

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**Introduction:** Various western studies have shown that carriage of “G” allele in Patatin-like phospholipase domain-containing protein 3(PNPLA3) gene polymorphism is associated with an increased risk of developing alcohol-related cirrhosis. Significant correlation has been observed between severity of the Alcoholic Liver Disease and single nucleotide polymorphism in PNPLA3 gene.

**Aims:** To study the PNPLA3 polymorphism in patients with Alcoholic liver disease (ALD) in western Indian population and compare frequency of G allele amongst cirrhotic ALD and non-cirrhotic ALD.

**Material and methods:** In a prospective study, we recruited 109 patients with ALD. PNPLA3 gene polymorphism was analyzed in all patients by Polymerase Chain Reaction using specific primers; subsequently Restriction Fragment Length Polymorphism technique was employed for genotyping. The frequency of C/G and G/G genotype of PNPLA3 in non-cirrhotic ALD and cirrhotic ALD were compared using chi square test. The cirrhotic and non-cirrhotic ALD were differentiated on the basis of biochemistry, imaging, endoscopy and liver biopsy if required.

**Results:** Total 109 patients with ALD were enrolled (51 and 58 patients with non-cirrhotic ALD and cirrhotic ALD respectively). Mean age of patients was 45±11 in non-cirrhotic ALD and 52±11 in cirrhotic ALD. Of the 51 patients with non-cirrhotic ALD, PNPLA3 C/G or G/G genotype was seen in 25(49%). Of the 58 patients with cirrhotic ALD, PNPLA3 C/G or G/G genotype was seen in 36(62%). The difference between both the groups was statistically significant ( $p < 0.05$ ).

**Conclusions:** “G” allele of PNPLA3 gene more common in patients with Alcoholic cirrhosis than non-cirrhotic ALD in western Indian population. It may be a predictor of severity of ALD.

**Disclosure of Interest:** None Declared

## PIO-3

# Early Liver Transplantation for Acute Alcoholic Hepatitis: Pilot Program in a single Transplant Centre

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**Introduction:** Acute alcoholic hepatitis (AAH) is characterized by high mortality rates, especially in patients with severe forms and not responding to medical therapy. Despite AAH is still considered an absolute contraindication to liver transplantation (LT) in most liver transplant centres, there is increasing evidence that early liver transplantation within strict and standardized protocols can improve survival.

**Aims:** The aims of the study were: a) to evaluate demographic, clinical and biochemical features of patients with severe AAH; b) to assess survival in patients with severe AAH non-responding to medical-therapy who underwent early LT; d) to compare outcomes of these patients with those patients with severe AAH non-responding to medical therapy excluded from LT.

**Material and methods:** We included patients admitted for severe AAH at Multivisceral Transplant Unit of Padua University Hospital (January 2013 - June 2017). Demographic, biochemical and clinic characteristics were evaluated at the admission. Patients were stratified according to the response to medical therapy predicted by Lille score. Patients not responding to medical therapy were placed on the waiting list for LT only if they were considered suitable candidates by a strict selection process.

**Results:** 20 patients with severe AAH were evaluated (50% women and 90% white non-Hispanics), with a median age of 45.5 years (range: 33-61). Thirteen out of 20 (65%) were not responders to medical therapy (median Lille score: 0.92; range: 0.65-0.98) and underwent the selection process. Amongst these, 6 patients were considered suitable candidates for liver transplantation and were placed on the waiting list. The median time from admission to placement on the waiting list was 28.5 days (6-41 days). Survival at 6 months after liver transplantation was significantly higher in patients with severe AAH who underwent liver transplantation compared with patients who were considered to suitable for liver transplantation (100% vs. 43%;  $p=0.0339$ ). Median hospitalisation time after liver transplantation was 18.5 days (range: 9-36 days). None of liver transplanted patients experience alcohol relapse during the follow-up (median: 19.7 months, range 2-51).

**Conclusions:** Early liver transplantation significantly improve survival in severe AAH non-responding to medical therapy, when a strict selection process is applied. Further studies are needed in order to properly assess the rate of alcohol relapse in this special population with a longer follow-up.

**Disclosure of Interest:** None Declared

# Healthy donor fecal microbiota transplantation for severe alcoholic hepatitis related acute on chronic liver failure - Short term outcomes from a tertiary center in South India

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**Introduction:** Severe alcoholic hepatitis (SAH) leading to acute on chronic liver failure (ACLF) especially with  $\geq 3$  organ failures (OF) portends poor prognosis in the absence of treatment options that have good long-term outcomes and transplant free survival. Corticosteroid (CS) could cause severe infections and only short-term benefits. Liver transplantation (LT) is curative at the cost of controversy with regards to deceased donor programs, infections and risk of recidivism.

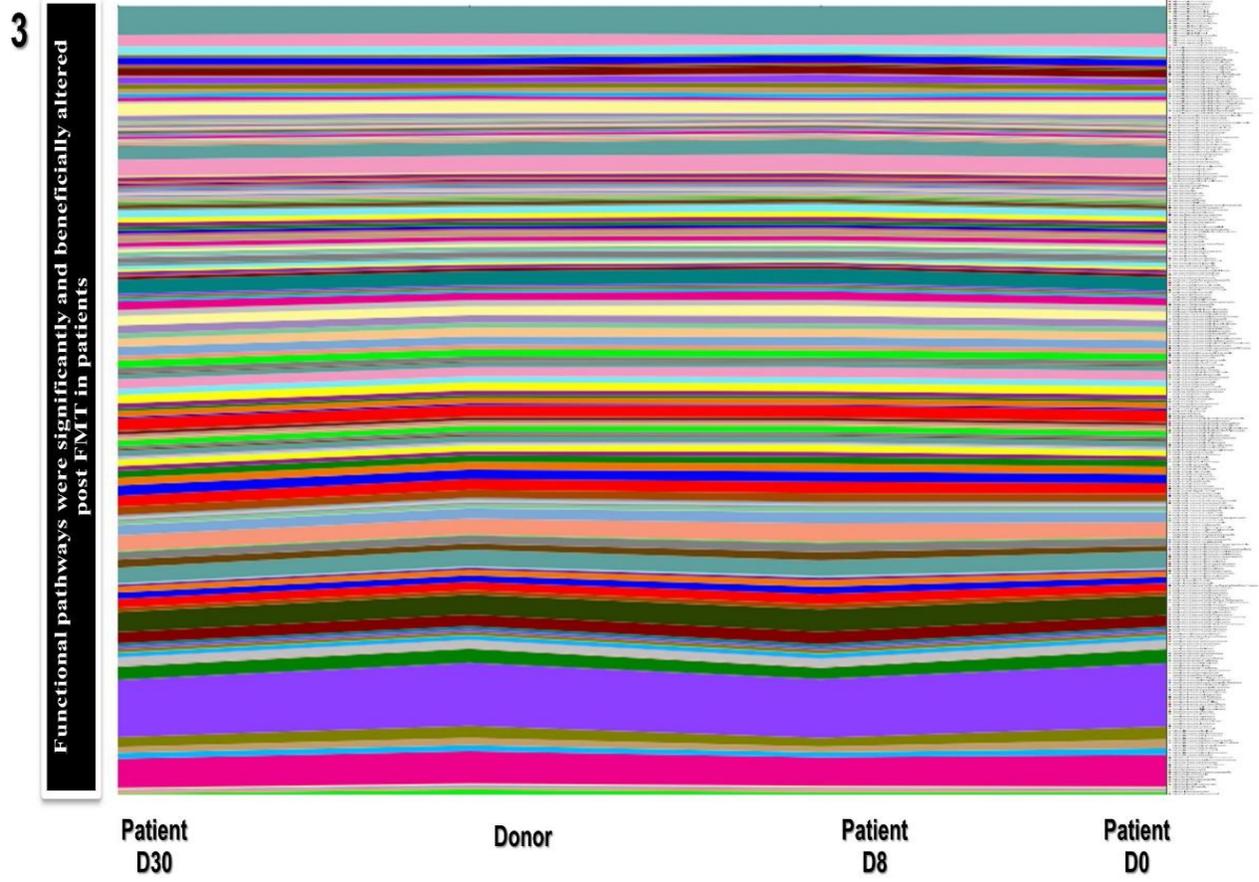
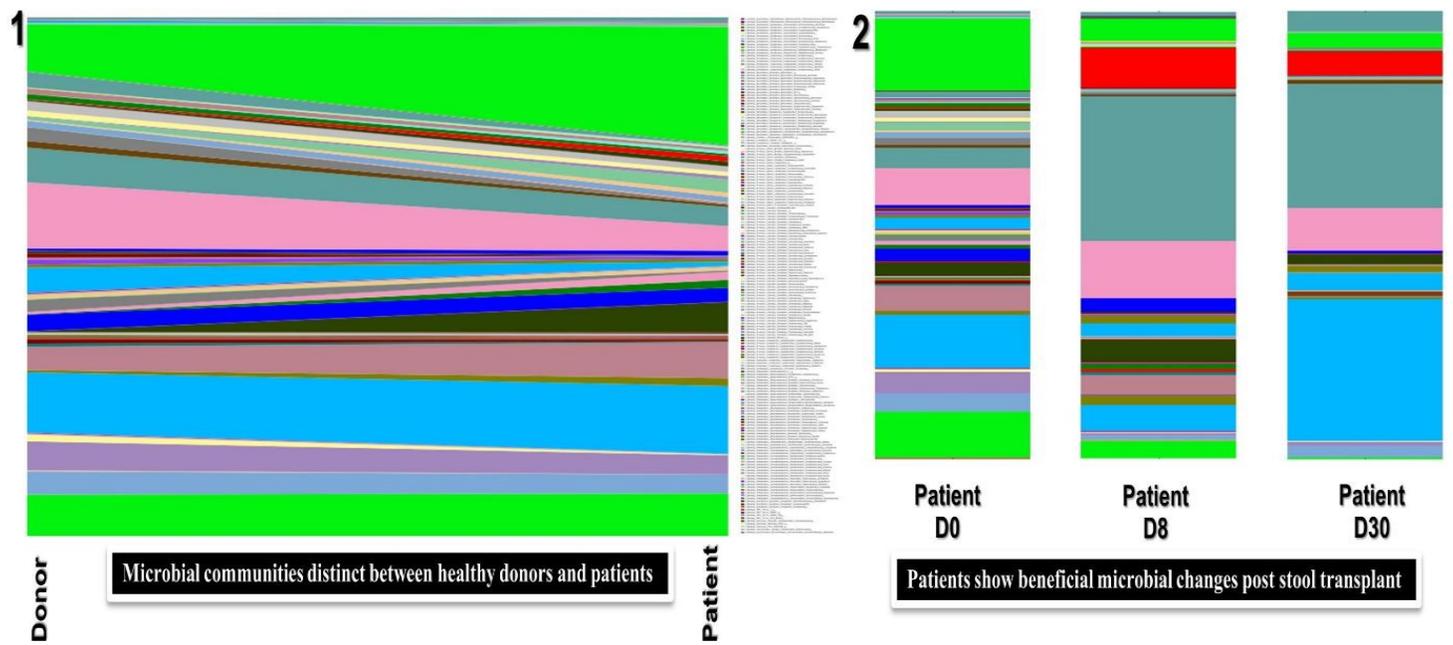
**Aims:** We studied SAH-ACLF patients who were not candidates for CS or LT, undergoing healthy donor fecal microbiota transplantation (FMT) as salvage therapy.

**Material and methods:** Out of 562 ACLF patients (Dec 2016 – Apr 2017), 348 (62%) were diagnosed with SAH. Eighteen patients ineligible for CS and unwilling for LT underwent FMT (ILBS-FMT protocol) after informed consent and Ethical clearance. Clinical, biochemical follow up done at baseline, day 8 and day 30 post FMT; stool microbiota and functional profiling as per standard protocols.

**Results:** All were males with mean age  $49 \pm 8.6$  yrs. 12 (66.7%) survived at end of 1 month. Total bilirubin, prothrombin time, INR, ammonia, discriminant function, Child score, MELD and MELDNa at baseline -  $13.9 \pm 6.7$  mg/dl,  $23.1 \pm 4.4$  sec,  $1.97 \pm 0.4$ ,  $163.4 \pm 56.1$  mcg/dL,  $68.9 \pm 19.9$ ,  $13 \pm 0.9$ ,  $25.4 \pm 4$ ,  $29.7 \pm 3.1$ ; at D8 -  $13.2 \pm 8.7$ ,  $20.7 \pm 5.5$ ,  $1.78 \pm 0.5$ ,  $105.8 \pm 29.5$ ,  $58.7 \pm 26.1$ ,  $11 \pm 1.3$ ,  $22 \pm 3.1$ ,  $25.6 \pm 3.4$ ; D30 -  $8.6 \pm 5.6$ ,  $16.8 \pm 4.1$ ,  $1.4 \pm 0.4$ ,  $72.2 \pm 14.1$ ,  $35.3 \pm 20.6$ ,  $8 \pm 0.9$ ,  $17 \pm 3.6$ ,  $21.7 \pm 3.5$  which were statistically significant ( $p < 0.001$ ). Donors (more *Ruminococcus*, *Fecalibacterium*, *Veillonella*) showed distinct microbiota profile from patients (*Catenibacterium*, *Megasphaera*, *Enterococcus*). Post FMT, distinct and significant changes in patient microbial and associated functional communities was noted from day 8 onwards ( $p < 0.05$ ; increase in relative abundance of *Fecalibacterium*, *Lachnospirae*; decrease in *Enterobacteriaceae*, *Collinsella*; decrease then increase - *Bacteroides*, increase then decrease - *Ruminococcae*). Patients who died post FMT, had disparate microbiota profiles at baseline (predominant *Clostridiales*, *Bifidobacterium*) in contrast to survivors.

**Conclusions:** ACLF patients with  $\geq 3$  OF have 92% mortality at 1 month. FMT improved 1 month survival by beneficially altering pathogenic microbial communities in patients with SAH-ACLF who were not candidates for CS or LT and is a cost-effective modality as salvage therapy in this very sick group of patients in developing countries that lack centralized liver transplant allocation systems in place.

Figure:



Disclosure of Interest: None Declared

# Persistence of decompensation despite abstinence in alcoholic cirrhosis is associated with poor outcomes and lower survival

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**Introduction:** Alcohol withdrawal is a main prognostic factor in alcoholic cirrhosis. However, it has not been explored whether the effect of abstinence is homogeneous along the whole spectrum of alcoholic disease

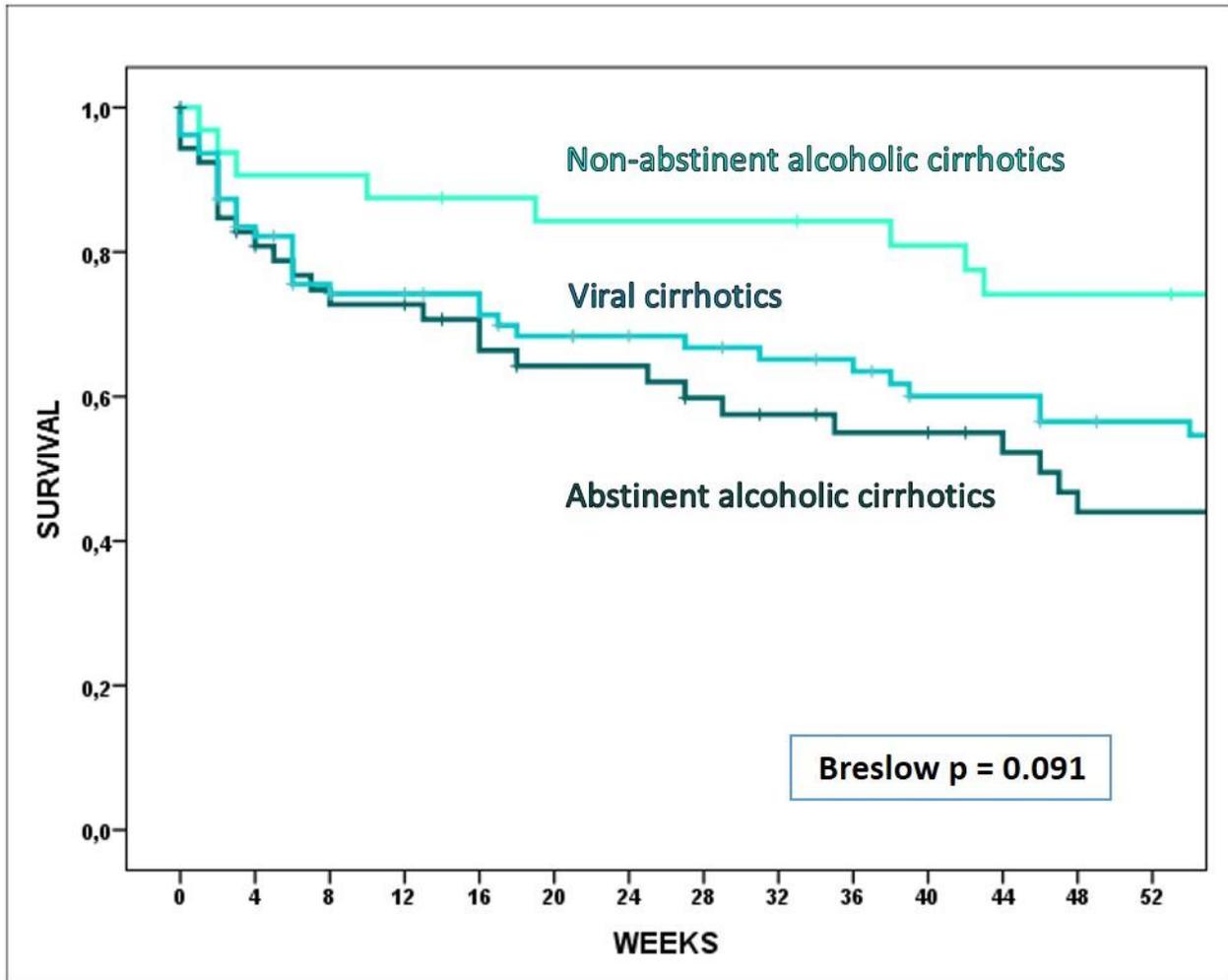
**Aims:** To analyze whether alcohol abstinent patients who remain decompensated have a worse evolution as compared to non-abstinent alcoholic or viral cirrhotic patients

**Material and methods:** 190 cirrhotic decompensated patients consecutively admitted to our Liver Unit were included (viral cirrhosis n=106; abstinent alcoholic cirrhosis n=54; non-abstinent alcoholic cirrhosis n=30). Patients with suspected or confirmed alcoholic hepatitis were excluded. Baseline and epidemiologic features were compared by ANOVA. Kaplan Meier curves were used to compare survival among the groups

**Results:** Median age was 59 years (36-87). 74% were male. MELD score was significantly higher in abstinent alcoholic patients compared to the other groups (16 Vs 12 in active alcoholic and 11 in viral cirrhosis, p=0.002). Abstinent patients had higher leukocyte count at admission than non-abstinent and viral ( $8.9 \times 10^3$  Vs  $8.2 \times 10^3$  Vs  $6.5 \times 10^3$ , p=0.004). Moreover, CRP was also greater in abstinent patients (3.2 Vs. 2.2 mg/dl in both non-abstinent and viral patients, p=0.1). Bacterial infection at admission was similar among the three groups. Previous decompensations such as ascites or encephalopathy were more frequent in abstinent alcoholic patients (76% Vs 60% Vs 60%; p=n.s, and 45% Vs 23% Vs 26%; p=n.s, respectively). However, cause of admission was similar among groups. ACLF at admission was more frequent in alcohol abstinent patients (35% Vs 11% in non-abstinent patients and 8% in viral, p=0.004). Fifty-two weeks survival was higher in active alcoholic than in abstinent patients with a trend towards statistical significance (figure 1, Log-Rank 0.19, Breslow 0.091). No statistically significant differences were found in the proportion of patients who received liver transplantation during follow-up (5.3% non-abstinent Vs 24% abstinent Vs 19% viral, p=n.s)

**Conclusions:** Alcoholic cirrhotic patients who remain decompensated despite alcohol withdrawal seem to have a more severe disease and a decreased survival as compared to non-abstinent alcoholic or viral cirrhotics. Therefore, this subgroup of patients could benefit from more intensive clinical management as well as prioritization strategies on liver transplant list

Figure:



Disclosure of Interest: None Declared