Volume 10.1 August 2022

EMJ Hepatology

Interviews

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Editor's Pick

The Challenging Ethical Landscape of Non-alcoholic Fatty Liver Disease

Review of

ILC Congress 2022

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This Publication

ISSN **2513-8634**

EMJ **Hepatology** is published **once** a year. For subscription details please visit: www.emjreviews.com

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Welcome letter

Koutsouki

Evgenia Koutsouki
Editor

Welcome to this issue of *EMJ Hepatology*. Our journal brings you key highlights from this year's International Liver Congress (ILC), alongside a selection of original articles.

It was a great experience for the EMJ team to be able to immerse ourselves in four days of a full congress experience, as ILC 2022 took place a few underground stops away from the EMJ office in London. We had the great pleasure of talking to an array of experts, including some of our Editorial Board members, and to watch the fantastic presentations by key opinion leaders in the field.

This issue contains our highlights from ILC 2022, spotlighting the key research presented, including research on prevention of hepatitis C viral infection in recipients of viraemic grafts, and on dietary intervention for non-alcoholic fatty liver disease, as well as a feature on acute decompensation of cirrhosis reviewing a congress session on the topic.

In our selection of original articles, you will have the opportunity to read review articles, including one focusing on the global impact and clinical consequences of non-alcoholic steatohepatitis, as well as a review on paediatric acute-on-chronic liver failure.

I hope you have an enjoyable read through this issue, and I would like to extend a big thank you to our authors for choosing EMJ to publish their highly engaging content, to our peer reviewers and Editorial Board members for contributing to the great quality of the journal, and of course to you, our readers, for your continued support! We look forward to next year's ILC, and until then, we will continue to bring you all the key advances in hepatology.

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Foreword

Dear Colleagues,

I am happy to present to you the 2022 edition of *EMJ Hepatology*. Maybe one of the best news this year was that, after 2 years of online meetings, the International Liver Congress (ILC), European Association for the Study of Liver's (EASL) flagship annual meeting, has finally been held in person in London, UK.

While usually packed with news and interesting data from a variety of areas in liver disease, many important topics this year centred around non-alcoholic fatty liver disease, alcoholic liver disease, and liver cancer. Many studies in these fields are currently ongoing, including a lot of activity around the development of new drugs.

This year's Editor's Pick deals with non-alcoholic fatty liver disease, with a particular emphasis on the ethical challenges that this diagnosis can pose for the treating physician. This is due to the different ethnical, socioeconomic, and genetic backgrounds of these patients, and also the individualised approach and therapeutic intervention that might be required.

A great breakthrough in 2022 so far has been in the treatment of liver cancer. The positive data from the Phase III HIMALAYA trial were, for the first time, able to show superiority of all immuno-oncologic treatment (programmed cell death protein 1 and cytotoxic T lymphocyte-associated protein 4 inhibition) over a targeted therapy in advanced hepatocellular carcinoma. More interesting data will be expected later this year in the field, which could also be practice changing.

This edition is complemented with a review on the state of knowledge in paediatric acute-on-chronic-liver failure. This condition has received a lot of attention throughout the last decade in the adult population and is rare in paediatric patients. The rapid course and dismal outcome not only in adults but also in children mandates specialised care from the start, as well as ready access to all types of treatment, including liver transplantation. One of the first steps needed today would be a consensus definition that would allow the effective conduct of trials in the paediatric population, which is addressed in the contribution here.

I hope you will find this year's selection of topics interesting and enjoy the read.

Markus Peck-Radosavlijevic

Professor of Medicine, Chairman of the Department of Gastroenterology and Hepatology, Klinikum Klagenfurt am Wörthersee, Klagenfurt, Austria

ILC 2022

Review of the European Association for the Study of Liver (EASL) International Liver Congress (ILC) 2022 Congress

Location: London, UK
Date: 22nd–26th June 2022
Citation: EMJ Hepatol. 2022;10[1]:8-16. DOI/10.33590/emjhepatol/10010107. https://doi.org/10.33590/emjhepatol/10010107.

AFTER a 3-year wait to meet in-person since the 2019 congress in Vienna, Austria, the European Association for the Study of Liver (EASL) International Liver Congress (ILC) took place in London, UK, from 22nd–26th June 2022. This year marked the 57th anniversary of the annual ILC event, and welcomed over 5,300 delegates on site, and over 1,300 virtually from 112 countries. The opening ceremony, led by Thomas Berg, General Secretary of EASL, took attendees through the array of fascinating sessions that ILC 2022 had on offer this year, including exclusive online content for hybrid viewers.

This year's theme for the ILC congress centred around the association's mission to 'savour science together again'. Berg expressed the importance of coming together to inspire communities, and celebrate science in unison following the COVID-19 pandemic. With the ILC's mission firmly conveyed, Berg showcased the variety of hepatology-focused sessions taking place, including the new addition of EASL's studio sessions live from ILC 2022. The innovative format of these exclusive sessions allowed key experts in the field to interact with the audience, discussing daily data interpretations and their associated clinical consequences. Berg said, of the development of the studio sessions, "necessity is the mother of invention," providing late-breaking updates to hepatologists around the globe. The year-round online content, which consists of 23 episodes, has already had over 29,000 views in 55 countries.

Berg introduced and handed over to Mario Rizzetto, Honorary President of ILC 2022. Rizzetto, who discovered hepatitis delta in 1977, began his presentation by addressing the impact of COVID-19 on EASL. Following the challenges introduced by the pandemic, the governing board chose energy and efficiency, and made the decision to go digital for the last two congresses. With ILC 2022 almost being back to "business as usual," Rizzetto took the opportunity to reiterate the EASL mission, of ensuring that the cohesion and scientific identity of European

"Berg expressed the importance of coming together to inspire communities, and celebrating science in unison following the COVID-19 pandemic."

hepatologists remains untarnished. Rizzetto went on share the visions and successes of EASL. Their 4-year strategy was implemented to take strides in (Euorpean Union (EU)-level advocacy, with a goal of raising awareness of liver health in Europe. The EASL Campus platform has been an essential cog in this mission; with over 6,000 resources, 20,000 registered users, and 1.2 million page views, it has been a turning point in extending global digital reach. Clinical practice guideline sessions were highlighted, providing key updates to the audience in conditions, including sclerosing cholangitis, haemochromatosis and pregnancy in liver disease, and cystic disease and hepatic encephalopathy.

The stage was handed over to patient representatives affiliated with EASL. Marko Korenjak, President, European Liver Patients' Association, spoke during the ceremony of the importance and impact of patient groups, and how it is essential to retain both passion and compassion. Korenjak explained how improving patient education to be as skilled as possible can greatly improve the management of conditions, all whilst retaining patient perspective. Danjuma Adda, President, World Hepatitis Alliance (WHA), spoke of his personal experience of both living with hepatitis B, and having people close to him also diagnosed. Based in Nigeria, Adda explained how a cure for the disease is not currently affordable or accessible, which is a key factor in the WHA's goal to lead the fight against hepatitis. This impactful section gave fascinating insights, and reiterated the importance of patient perspectives and representation.

Two members of the EASL Scientific Committee, Saskia van Mil and Virginia Hernández-Gea, presented this year's award ceremony. The EASL 2022 Emerging Leader Award recognises the outstanding achievements of young fellows. This year, Salavatore Piano, Assistant Professor, University of Padua, Italy, and María Jesús Perugorria, Principal Investigator in the Liver Diseases Group, Biodonostia Health Research Institute, San Sebastian, Spain, received this award for their respective research contributions. The EASL Nurses and Allied Health Professions Rising Star Award was presented to Catherine Wood, Hepatology Clinical Nurse Specialist, Royal Cornwall Hospital NHS Trust, UK, for her dedication to improving healthcare for all patients, especially in the context of non-alcoholic fatty liver disease.

> **"With the challenges introduced by the pandemic, the governing board chose energy and efficiency, and made the decision to go digital for the last two congresses."**

Berg concluded the session with a message to all attendees, wishing them an enjoyable congress whilst reminding attendees of the most engaging and interactive sessions on offer. With numerous networking sessions, interactive ePosters, and general assembly meetings, it is safe to say that this year's ILC 2022 congress successfully provided the means for hepatologists across the globe to 'savour science together'. Expert-led symposia covered emerging topics in the discipline, including hepatitis, cirrhosis, and optimal diagnosing strategies for liver disease. Our in-house feature provides an overview of a fascinating session on the critical care management of acute decompensation of cirrhosis, alongside standout ILC press releases, and an interview with Aleksander Krag, EASL Secretary General 2022.

We were delighted to form a part of the in-person audience at this year's ILC 2022 congress, and look forward to next year's event which is taking place once again in Vienna, Austria. For now, enjoy the scientific highlights presented in our comprehensive review of this compelling congress.●

Pre-emptive Combination Therapy Can Prevent Hepatitis C Viral Infection in Recipients of Viraemic Grafts

EIGHT doses of combination therapy could prevent post-transplant complications associated with HCV transmission in patients receiving viraemic transplants. The combination therapy studied was glecaprevir/pibrentasivir (G/P) and ezetimibe, commencing on the day of surgery and continuing for 7 days after transplant of an hepatitis C virus (HCV) viraemic, non-liver solid organ into HCV seronegative recipients.

The prospective, multicentre, open-label study, presented on 23rd June 2022 by Bashar Aqel of the Mayo Clinic College of Medicine in Phoenix, Arizona, USA, at ILC 2022, assessed the efficacy and cost-effectiveness of pre-emptive combination of G/P plus ezetimibe therapy in 38 HCV-seronegative patients receiving non-liver, HCV-viraemic, solid organ transplants.

Of the 38 recipients, 63% were male and the median age was 60 years. Thirty-two patients received a kidney transplant, two received a kidney and pancreas transplant, three received a heart transplant, and one received a heart and kidney transplant.

To assess response to treatment, HCV RNA levels were monitored for 24 weeks post-transplant and patients were followed-up for 1 year to determine rates of patient and graft survival.

All recipients completed the eight-dose treatment course, which was well-tolerated. Post-operative monitoring revealed that 28 patients had transient viraemia in the initial 2 weeks post-transplant, but all 38 patients had undetectable HCV RNA levels by Week 4. These RNA levels remained undetectable at 13 weeks. One recipient died 65 days post-surgery secondary to acute subdural haematoma.

In terms of cost-effectiveness, Aqel reported that the cost of pre-emptive combination therapy was significantly less than standard therapy given in response to post-operative complications associated with HCV transmission.

> **"Aqel concluded that combination therapy with G/P and ezetimibe was effective at preventing HCV infection secondary to transplant of HCV viraemic non-liver, solid organs in 100% of HCV seronegative recipients."**

Aqel concluded that combination therapy with G/P and ezetimibe was effective at preventing HCV infection secondary to transplant of HCV viraemic non-liver, solid organs in 100% of HCV seronegative recipients. Further to this, Aqel stated that the approach is cost-effective and could potentially eliminate the risk of post-transplant complications associated with HCV transmission. These findings could increase use of HCV viraemic grafts, which could, in turn, lead to reduced patient waiting times. ●

Eliminating Viral Hepatitis C From Prisons in England

HIGH intensity test and treat (HITT) programme was a hit in English prisons. The programme, the result of a collaboration between the National Health Service (NHS) and the Hepatitis C Trust, a patient-led charity for those with viral hepatitis C (HCV), was presented at the EASL's ILC 2022, with data that highlighted the importance of the testing and treating inmates and the prevalence of the infection in different establishments in England.

Successfully completed in 34 institutions in England (7 female prisons and 27 male prisons), the HITT programme saw NHS staff, nurses, and peers who have lived experience of HCV and prison life venture into prisons. Between June 2019 and September 2021, they offered 23,388 inmates prison-wing-based testing with point-of-care antibody tests, which were followed by blood draws or dried blood spot testing for conformation of viraemia in those who tested positive for HCV antibodies.

Although the HITT programme was halted for 6–9 months due to the COVID-19 pandemic, where NHS staff, nurses, and peers could not enter prisons, 19,049 inmates agreed to testing. A total of 1,234 inmates tested positive for HCV antibodies. Of these, 175 then tested positive for the presence of HCV RNA. All individuals who were infected were offered therapy, often on the same day with HCV RNA testing and pan-genotypic medication, or with direct acting antivirals within 2 weeks of testing.

An analysis of the data showed that HCV is more prevalent in prisons for females and that different prisons had different infection rates. The programme highlighted that remand prisons had a higher prevalence of HCV than re-settlement prisons.

> **"These results indicate that the HITT programme is invaluable to providing treatment to inmates, who are more likely to test positive for HCV than the general population."**

These results indicate that the HITT programme is invaluable to providing treatment to inmates, who are more likely to test positive for HCV than the general population, and to stop the infection from becoming worse. It also provided data for the prevalence of HCV in prisons and how it varies between the establishments. ●

Genetic Variation of Hepatocellular Carcinoma in Alcohol-Related Cirrhosis

GENETIC variation in telomerase reverse transcriptase modifies the risk of patients diagnosed with alcohol-related cirrhosis (ArC) developing hepatocellular carcinoma (HCC). HCC is the most common form of liver cancer, which is often seen in patients with chronic liver diseases, such as cirrhosis.

Patients with ArC have an annual risk of up to 2.9% of developing HCC. In previous research, some host genetic risk factors have been discovered, but these do not provide a full explanation for the majority of variances in occurrence.

Presented at the EASL's ILC 2022, the aim of this study was to identify novel risk factors for HCC developing in patients with ArC.

The study was made up of a cohort of patients with ArC who developed HCC (cases: n=1,214), and another with ArC who did not have HCC (controls: n=1,866). These patients were located in Austria, Germany, Italy, Switzerland, and the UK. All patients were included in a two-stage genome-wide association study, which used a case-control design.

Researchers included a validation cohort made up of 1,520 individuals who misused alcohol, but had no evidence of liver disease. This cohort was included as a control regarding possible association effects of alcohol misuse. Researchers performed genotyping using both the Infinium®Global Screening Array (version 24v2; Illumina, San Diego, California, USA) and the OmniExpress Array (version 24v1-0a; Illumina).

> **"HCC is the most common form of liver cancer, which is often seen in patients with chronic liver diseases, such as cirrhosis."**

The study confirmed two variants previously associated with HCC in patients who have ArC at a genome-wide significance. They also identified a novel locus rs2242652 in telomerase reverse transcriptase, which continued to be significant following correction for age, ancestry, BMI, sex, and Type 2 diabetes. To conclude, rs2242652 in telomerase reverse transcriptase is a novel protective factor against developing HCC in patients who have ArC. ●

Chronic Hepatitis B and Primary Liver Cancer: Is Ultrasound an Effective Surveillance Modality?

PATIENTS with chronic hepatitis B under surveillance for primary liver cancer (PLC), who have poor Ultrasound Liver Imaging Reporting and Data System (US LI-RADS) visualisation scores, have higher false negative rates and increased risk of PLC than those with good visualisation scores.

Chronic hepatitis B is a risk factor for PLC, particularly hepatocellular carcinoma (HCC); as a result of this, regular surveillance is performed for patients considered high-risk. Ultrasound is a standard imaging technique used in surveillance.

A cohort study presented on 25th June 2022 by lead study author Min Kyung Park of The Department of Internal Medicine and Liver Research at Seoul National University College of Medicine, Korea, Republic of South Korea, at ILC 2022 highlights that ultrasound may not be the optimal imaging modality for PLC surveillance in those with poorer visualisation scores.

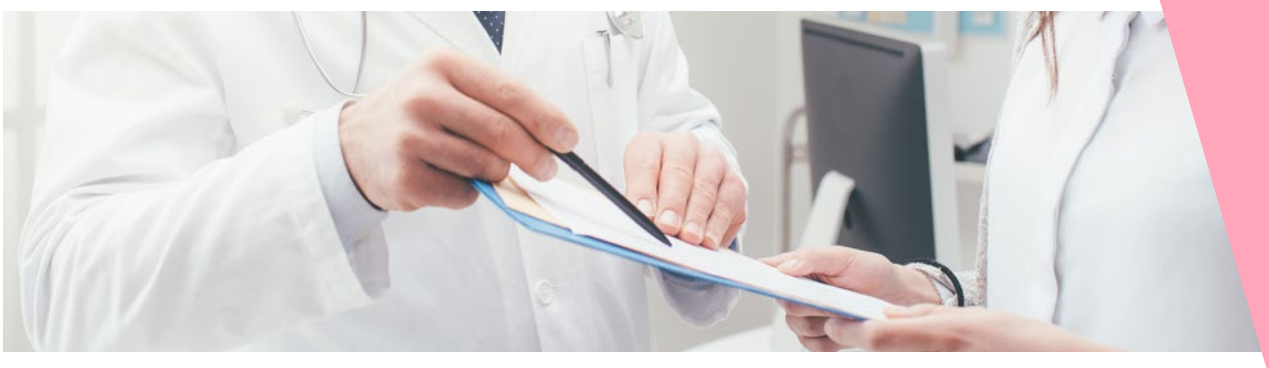
The study included 2,002 patients with chronic hepatitis B under regular HCC surveillance, with the aim of assessing the efficacy of ultrasound for detection of PLC according to US LI-RADS visualisation scores.

Patients were stratified into visualisation scores A and B/C, with visualisation score A being best and C being worst. There were 972 patients with visualisation score A, 1,003 with visualisation score B, and 27 with visualisation score C. Once stratified, the researchers analysed the incidence of PLC and ultrasound false negatives. The median follow-up period was 75 months.

> **"Those with visualisation scores B/C had a significantly higher risk (p<0.001) of developing PLC (2.41% /year) than those in visualisation group A (0.5% /year)."**

Of the 2,002 patients enrolled, 166 developed PLC (158 HCC, 8 other PLC). The researchers identified that those with visualisation scores B/C had a significantly higher risk (p<0.001) of developing PLC (2.41% /year) than those in visualisation group A (0.5% /year), as well as higher false negative rates with ultrasound surveillance (43.5% versus 20.0%). Furthermore, they found that very early-stage PLC was less likely to be picked up by ultrasound in visualisation group B/C.

The findings from this study infer that ultrasound may not be the optimal surveillance imaging modality for patients with poor US LI-RADS visualisation scores. The researchers recommended at ILC 2022 that CT or MRI could be considered as alternative surveillance techniques in this patient group. ●



Low-Carbohydrate, High-Fat Dietary Intervention for Non-alcoholic Fatty Liver Disease

OVER half (55%) of people with Type 2 diabetes also have non-alcoholic fatty liver disease (NAFLD). Glycaemic control predicts severity of hepatocyte ballooning and hepatic fibrosis in NAFLD. Although dietary interventions with low carbohydrates improve glycaemic control, the effect on NAFLD remains to be elucidated. Therefore, a team of researchers investigated the impact of a 6-month low-carbohydrate, high-fat diet on NAFLD. The effect of this dietary intervention was assessed by ≥2 points improvement in the NAFLD Activity Score (NAS). Results were presented at ILC 2022.

One hundred and eighty-five individuals with Type 2 diabetes were randomised 2:1 to a diet consisting of low carbohydrates and high fat or one comprising high carbohydrates and low fat. In both cases, non-calorie-restricted diets were used. The researchers performed liver biopsies and measured HbA1c at baseline and after 6 months.

In total, 165 of the randomised participants commenced the allocated intervention and were included in the analysis. After intervention, no significant difference was observed between the groups with respect to improvement of ≥2 points in NAS ($p=0.587$). Of note, a higher proportion of patients in the low-carbohydrate, high-fat group improved NAS with ≥1 point relative to the high-carbohydrate, low-fat group (70% and 49%, respectively; $p=0.028$). In addition, fewer in the low-carbohydrate, high-fat group experienced a worsening of NAS (1% versus 23% for the high-carbohydrate, low-fat group; $p<0.001$). Finally, those in the low-carbohydrate, high-fat group improved HbA1c with -9.5 versus -3.4 in the high-carbohydrate, low-fat group.

> **"Although dietary interventions with low carbohydrates improve glycaemic control, the effect on NAFLD remains to be elucidated."**

In conclusion, a 6-month non-calorie-restricted low-carbohydrate, high-fat diet was shown to improve NAS and HbA1c significantly more than a high-carbohydrate, low-fat diet among individuals with Type 2 diabetes. ●

The Global Burden and Aetiology of Chronic Liver Disease and Liver Cancer: Non–alcoholic Fatty Liver Disease as an Emerging Driver

THE BURDEN of chronic liver disease (CLD) and liver cancer (LC) has historically been attributed to alcohol-associated liver disease (ALD), chronic hepatitis B, and chronic hepatitis C viral infections.

However, new evidence presented at ILC 2022, 22nd–26th June, London, UK, by lead author James Paik, Betty and Guy Beatty Center for Integrated research, Inova Health System, Falls Church, Virginia, USA, and Center for Liver Disease, Department of Medicine, Inova Fairfax Medical Campus, Falls Church, Virginia, USA, reveals that non-alcoholic fatty liver disease (NAFLD) has become an emerging driver for the increasing incidence and prevalence of CLD and LC globally, between 2009 and 2019.

Using data obtained from the Global Burden of Disease Study 2019, the authors reviewed changes in incidence, prevalence, morbidity and mortality, and disability-adjusted life–years (DALYs) for LC and CLD over the preceding decade. With the data, the team calculated annual percentage change (APC) using the Joinpoint Regression Program, National Cancer Institute.

Prevalence and incidence both increased for LC and CLD during the period studied (LC: +33.7% and +30%; CLD: +22.7% and +14.8%, respectively). Deaths and DALYs also increased for both conditions. Analysis of the APC for LC death rate considered the impact of different aetiologies, with the greatest impact driven by NAFLD (APC +2.47%). NAFLD also had the greatest impact on CLD death rate (APC +1.33%), although the overall APC for CLD death rate decreased by 0.18% during the studied period.

> **"The findings from this study showed increases in NAFLD and ALD driving the increasing burden of LC and CLD."**

Geographical variations in the aetiology and burden of LC and CLD were also reported. Central Latin America showed the highest APC increase in NAFLD and hepatitis B and C virus-related LC deaths; whereas, in the North American region, the highest APC increase in LC deaths was due to ALD.

The findings from this study showed increases in NAFLD and ALD driving the increasing burden of LC and CLD. This highlights how disease aetiology can change over time and the need to continually evaluate these factors to improve understanding. ●

Critical Care Management of Acute Decompensation of Cirrhosis

Authors: Janet Nzisa, Editorial Assistant

Citation: EMJ Hepatol. 2022;10[1]:18-21. DOI/10.33590/emjhepatol/10052843. https://doi.org/10.33590/emjhepatol/10052843.

ON DAY 2 of the European Association for the Study of the Liver (EASL) International Liver Congress (ILC) 2022, which took place on 22nd–26th June 2022 in London, UK, there was a session featuring specialist insights from researchers in the field. There were discussions that focused on the critical management of acute decompensation of cirrhosis.

ILC 2022

MULTIDRUG-RESISTANT BACTERIAL INFECTIONS IN CANDIDATES FOR A LIVER TRANSPLANT

Emmanuel Weiss, Department of Intensive Care and Perioperative Medicine, Beaujon Hospital, Paris Cité University, France, opened the session on multidrug-resistant (MDR) bacterial infection in candidates for a liver transplant by emphasising that bacterial infections are a growing global healthcare problem. He presented data that demonstrated an increase in the prevalence of bacterial infection in patients with cirrhosis in Europe, from 29% in 2011 to 38% in 2018. Weiss explained that there are different types of common bacterial infections: Gram-negative *bacilli* and Gram-positive *cocci*. The most common infection is Gram-negative *bacilli* extended-spectrum β-lactamase-producing *enterobacterales*, which has a resistance mechanism of β-lactam hydrolysis. For Gram-positive *cocci*, the most common infections were from vancomycin-resistant *enterococcus* and methicillin-resistant *Staphylococcus aureus*. MDR bacterial-related infections are associated with a lower resolution rate, higher incidence of septic shock and acute-on-chronic liver failure (ACLF), and higher mortality. Weiss explained the variability in MDR rates across the world and explained that the differences between the trends of antimicrobial resistance between the north and south of Europe, detailing the importance of knowing the epidemiology of your centres as a clinician and regularly revise these analyses.

Weiss presented a study of 635 patients with cirrhosis, which demonstrated that each hour of delay in the time to introduce an effective antibiotic therapy was crucial and could increase the adjusted odds ratio of mortality in the patients due to septic shock. Weiss emphasised that clinicians should request the colonisation data in liver transplant candidates, and they should use a negative predictive value to avoid broad-spectrum antimicrobial overconsumption and use it in combination with other risk factors to have a good positive predictive value.

Weiss emphasised the importance of the specialist collaboration with a microbiologist team or infection control team to find the most appropriate treatment for the patient. The optimisation of antimicrobial treatment includes avoiding underdosing and toxicity, as well as increasing the probability of target attainment. In order to do this, the dosage should be adapted using therapeutic drug monitoring or using continuous or prolonged perfusion of β-lactams. In addition, attention should be paid to source control.

Prevention of the spread of antibiotic resistance remains the best treatment. This can be done through the promotion of antimicrobial stewardship programmes, which can limit the prescription of antibiotics. Additionally, the use of infection control policies, such as hand washing, barrier or contact precautions, and isolation of patients with cirrhosis and methicillin-resistant *S. aureus*, can also be effective strategies.

"Prevention of the spread of antibiotic resistance remains the best treatment."

In his concluding remarks, Weiss stated that in order to use the most appropriate antibiotic treatment, clinicians need to know the new molecules and emerging data in the pipeline but also optimise the pharmacokinetic–pharmacodynamic parameters, control the source, and collaborate with specialists in this field. However, the best treatment remains to prevent the spread of MDR bacteria.

BALANCING ANTICOAGULATION AND GASTROINTESTINAL BLEEDING IN DECOMPENSATED CIRRHOSIS

Annabel Blasi, Anaesthesia Department, Hospital Clinic of Barcelona, Spain, started by defining the rationale for administering anticoagulation (ACO) treatment in patients with cirrhosis. Patients with cirrhosis have a higher chance of developing deep vein thrombosis and/or pulmonary embolism compared with the general population, and the treatment of ACO is advised. In patients with cirrhosis and portal vein thrombosis, ACO treatment could assist in reducing the risk of portal hypertension and ischaemia in the superior mesenteric vein and could help avoid exclusion from a liver transplant list.

Blasi went on to outline some blind spots when it comes to ACO. According to Blasi, only 50–60% of patients with portal vein thrombosis would respond to ACO. Additionally, the efficacy of thromboprophylaxis for deep vein thrombosis or pulmonary embolism in patients with cirrhosis has not been

proved in this population, nor has the safety profile, dosing, and timing. Acute variceal bleeding accounts for 70% of all upper gastrointestinal bleeding events in cirrhosis. Blasi presented a study that showed gastrointestinal bleeding was more frequent in patients with ACLF, compared with patients with a less advanced stage of the disease.

"The decision to administer anticoagulant treatment should be considered case-by-case, based on expected benefits and risk of bleeding."

Some contributing factors for thrombosis or bleeding in patients with cirrhosis include anaemia, low haematocrit, bacterial infection, and renal injury. Infection can act as a risk factor both for anaemia and thrombosis as it can promote thrombotic complications via increasing platelet response to the agonists in patients with cirrhosis. Patients with acute kidney injury (AKI) show lower platelet aggregation, higher thrombin generation, and higher hyperfibrinolysis.

Clinicians can identify patients at high risk of thrombotic complications by analysing the clinical status of the patients to identify infections or AKIs. Additionally, a coagulation test can be carried out to identify the number of platelets and levels of fibrinogen. A low level of fibrinogen and ACLF is a high-risk factor in bleeding and thrombosis in decompensated cirrhosis.

Blasi concluded by emphasising the importance of addressing all the contributing factors for bleeding patients with cirrhosis. Additionally, the decision to administer anticoagulant treatment should be considered case-by-case, based on expected benefits and risk of bleeding, particularly in patients with higher risk factors associated with bleeding. However, further research is required to identify factors associated with a favourable response to ACO treatment in different settings in patients with cirrhosis.

PREOPERATIVE MANAGEMENT OF RENAL FAILURE AND HYPONATRAEMIA IN DECOMPENSATED CIRRHOSIS

Raj Mookerjee, Institute of Liver and Digestive Health, University College London, UK, emphasised the importance of early identification of kidney failure in order to intervene and modulate management. As Mookerjee explained,

there are three types of kidney dysfunction in cirrhosis: AKI, chronic kidney disease, and acute-on-chronic kidney disease, whereby one has repeated episodes of AKI compounding a chronic status.

Mookerjee presented studies showing that a major cause of renal failure in cirrhosis is due to precipitating factors such as bacterial infections, hypovolaemia, hepatorenal, and parenchymal nephropathy. However, the study showed that patients with bacterial infections as well as a hepatorenal syndrome prognosis had the worst outcomes and survival rates compared with patients without bacterial infections. Mookerjee stated that the presence of infection further increases portal hypertension and reduces renal perfusion, thus leading to microvascular dysfunction. Additionally, the infection promotes oxidative stress and tubular damage.

The general management of AKI in decompensated cirrhosis is to assess and confirm the AKI diagnosis by ruling out proteinuria, stopping the administration of nephrotoxins and β-blockers, withdrawal of diuretics, and correct hypovolaemia in the patient. Additionally, any underlying infection should be treated with antibiotics.

In the case of AKI including hepatorenal syndrome, Mookerjee listed some vasoconstrictors that could be useful. Terlipressin with albumin, as used in Europe, is more effective than albumin alone. Although terlipressin could be effective, he advised discontinuation after 14 days when no response or partial response is observed in the patient. Other vasoconstrictors include noradrenaline and midodrine plus octreotide, with emerging data from other countries with no access to terlipressin.

In his closing remarks, Mookerjee explained that AKI is common in acute decompensation in cirrhosis and is often associated with infections and bad outcomes. He emphasised the need for renal biomarkers other than creatinine and glomerular filtration rate values, which could precisely reflect the pathophysiology of the disease. The treatment consists of removing causative factors, volume correction, and vasoconstrictors; however, renal replacement therapy could be considered in unresponsive patients. ●

"Patients with bacterial infections as well as a hepatorenal syndrome prognosis had the worst outcomes and survival rates compared with patients without bacterial infections."

Holistic Patient Care in Primary Biliary Cholangitis: Managing Both the Disease and the Symptoms

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Disclosure:	Hirschfield has received fees for relevant consultancy or education activities from GlaxoSmithKline, Intercept Pharmaceuticals, CymaBay Therapeutics, Ipsen, Pliant, and Mirum. Lleo reports receiving consulting fees from Intercept Pharmaceuticals, Astra Zeneca, Albireo, Alfasigma, and Takeda; speaker fees from GlaxoSmithKline, AbbVie, Intercept Pharmaceuticals, Gilead, Alfasigma, and MSD; and travel expenses from Intercept Pharmaceuticals, Alfasigma, and AbbVie. Jones has received speaker fees from Abbott, Dr Falk, GlaxoSmithKline, Intercept Pharmaceuticals, and Ipsen; consultancy fees from Intercept Pharmaceuticals and Umercrine AB; and grant funding from Intercept Pharmaceuticals. Dyson has received speaker fees from Dr Falk, Intercept Pharmaceuticals, and GlaxoSmithKline, and has acted as a clinical expert for the National Institute for Health and Care Excellence.
Acknowledgements:	Medical writing assistance was provided by Eleanor Roberts, Beeline Science Communications Ltd, London, UK.
Disclaimer:	The opinions expressed in this article belong solely to the named speakers.
Support:	The publication of this article was supported by GSK.
Citation:	EMJ Hepatol. 2022;10[1]:22-31. DOI/10.33590/emjhepatol/10166227. https://doi.org/10.33590/emjhepatol/10166227.

Meeting Summary

In the progressive, immune-mediated liver disease primary biliary cholangitis (PBC), the intrahepatic bile ducts are gradually destroyed over several years. The primary biochemical means to diagnose PBC, and assess progression and treatment response, is serum alkaline phosphatase (ALP). Further diagnostic criteria depend on antimitochondrial antibody (AMA) and specific antinuclear antibody status, and histological confirmation in some patients. First-line therapy for PBC is ursodeoxycholic acid (UDCA), which has been shown to improve biochemical indices of PBC and slow disease progression. However, major quality of life (QoL)-impacting symptoms of PBC, including pruritus and fatigue, are demonstrated to be independent of disease severity. There is evidence confirming that these symptoms negatively impact a number of aspects, including emotional status, ability to work, and social life, for some patients. In a symposium as part of the European Association for the Study of the Liver (EASL) International Liver Congress™

(ILC) 2022, Gideon Hirschfield, Toronto Centre for Liver Disease, University of Toronto, Ontario, Canada; Ana Lleo, Humanitas University and Humanitas Clinical and Research Centre, Milan, Italy; and David Jones, Newcastle University and Newcastle-upon-Tyne Hospitals NHS Foundation Trust, UK, discussed the holistic treatment of patients with PBC and whether goals of such should be more or equally dependent on biochemical status or impact on QoL. This discussion was expanded on in a session moderated by Jessica K. Dyson, Newcastle University and Newcastle-upon-Tyne Hospitals NHS Foundation Trust, UK.

Introduction

PBC is an immune-mediated, chronic, progressive liver disease characterised by gradual destruction of intrahepatic bile ducts. Reflecting this, alongside cholestasis is serologic reactivity to highly-specific antinuclear antibody or AMA.[1,2] PBC more commonly occurs in females and people can live with PBC for several decades.[3-5]

Current EASL treatment guidelines recommend that PBC be stratified by disease stage and risk of liver-related complications, including death. In patients with no alternative explanation for abnormal liver blood tests, guidelines advise that 'probable' PBC can be diagnosed on the basis of elevated serum ALP and AMA at a titre >1:40, negating the need for liver biopsy in many patients.[1]

In patients who are AMA-negative with biochemical abnormalities, the diagnosis of PBC requires histological confirmation. The EASL guidelines recommend a liver biopsy if PBC-specific antibodies are absent, or if there is diagnostic uncertainty, such as the possibility of concomitant autoimmune hepatitis. If a patient has normal liver blood tests but is AMA-positive, clinical practice often consists of annual review to assess for the development of biochemical abnormality.[1]

In a symposium as part of the EASL ILC, held between 22nd and 26th June 2022 in London, UK, and online, Hirschfield discussed the possibilities of holistically treating patients with PBC, Lleo asked if the focus of treatment goals should be on ALP, Jones counterquestioned whether the focus should be on managing QoL factors, and Dyson moderated a question and answer session.

Treatment for Primary Biliary Cholangitis

PBC therapy aims to reduce morbidity, mortality, and symptom burden.[1] The only fully approved first-line medication for PBC is UDCA, using a therapeutic dose of 13–15 mg/kg/day, which should be initiated for all patients with PBC. For patients with an inadequate response to, or who are intolerant of, UDCA, obeticholic acid is approved as an adjuvant second-line therapy or monotherapy.[1,6] Also, for patients with inadequate UDCA response, the American Association for the Study of Liver Diseases (AASLD) recommends the off-label use of fibrates.[6] These are not currently recommended in EASL guidelines due to the lack of evidence from Phase III randomised clinical trials.[1] However, several studies have shown their utility with regard to biomarker response,[7] PBC progression,[8] and positive effect on pruritis[9] when combined with UDCA or as monotherapy. The use of obeticholic acid and fibrates is discouraged by the AASLD in patients with decompensated liver disease (Child–Pugh–Turcotte B or C).[6]

UDCA has been shown to improve biochemistry and long-term outcomes with a reduced need for liver transplantation and death. For instance, in one study, 90% of 4,119 UDCA-treated patients showed a 5-year transplantation-free survival rate, with rates of 78% at 10 years and 66% at 15 years. Respective survival rates in 726 non-UDCA treated patients were significantly lower: 79%, 59%, and 32%, respectively (UDCA-treated versus nontreated patients, p<0.0001).[10] UDCA has also been shown to improve the outcomes of biochemical liver tests, including ALP, bilirubin, and aminotransferases.[11] Of note though, depending on the criteria used (Table 1), inadequate response to UDCA was shown in 25–50% of patients.[17,19]

Monitoring Primary Biliary Cholangitis Progression and Treatment Response

EASL guidelines recommend monitoring response to UDCA and disease progression using biochemical means, including ALP, transaminases, and bilirubin. Response can be assessed using quantitative definitions with discrete, binary criteria or quantitative continuous scoring systems. As shown in Table 1, there are several qualitative binary criteria, including assessment of treatment response at 6, 12, and 24 months.[1] "It doesn't really matter which criteria you use," remarked Lleo, "the important concept is that you need to assess if the ALP of your patient has been reduced compared to baseline."

Although these criteria include biochemical levels predominantly still above the upper limit of normal (ULN), Lleo suggested that "it's not enough to have an ALP that is below 1.5; we should aim for normal ALP as these have been associated with better survival, and this is important when we need to evaluate if our patient is a candidate for second-line treatment." A study of 2,555 patients treated with UCDA showed that any increase in bilirubin or ALP above ULN at Year 1 was associated with an increased risk for liver transplantation or death. Moreover, a stable decrease in bilirubin to <0.63xULN was associated with an 11% improvement in 10-year survival or liver transplantation. In people with an ALP <1xULN, 10-year survival was 93.2% compared with 86.1% with ALP 1.0–1.67xULN.[20]

Approximately 8–10% of patients with PBC present with a variant that is sometimes termed PBC-autoimmune hepatitis overlap. Here, the Paris diagnostic criteria include at least two of ALP >2xULN or γ-glutamyltranspeptidase >5xULN, AMA >1:40, and florid bile duct lesion, as well as two of alanine aminotransferase >5xULN, serum IgG >2xULN or smooth muscle autoantibody-positive, and moderate–severe interface hepatitis on histology.[21] In these cases, liver biopsy is considered mandatory.[1] In patients with a true overlap syndrome, adding immunosuppressants to UDCA therapy may be beneficial.[1]

Continuous scoring systems can also help stratify disease risk and predict transplantation-free survival. The GLOBE score is a validated risk assessment tool specific to UDCA-treated

Table 1: Criteria for assessing biochemical response in primary biliary cholangitis.[1]

Criteria	Time (months)	Indicators of treatment failure
Rochester[12]	6	ALP ≥2×ULN or Mayo score ≥4.5
Ehime[13]	6	Decrease in GGT ≤70% and GGT ≥1×ULN
Barcelona[14]	12	Decrease in ALP ≤40% and ALP ≥1×ULN
Paris-I[15]	12	ALP ≥3×ULN or AST ≥2×ULN or bilirubin ≥1 mg/dL
Paris-II[16]	12	ALP ≥1.5×ULN or AST ≥1.5×ULN or bilirubin >1 mg/dL
Rotterdam[17]	12	Bilirubin ≥1×ULN and/or albumin <1×ULN
Toronto[18]	24	ALP >1.67×ULN

ALP: alkaline phosphatase; AST: aspartate aminotransferase; GGT: γ-glutamyltranspeptidase; ULN: upper limit of normal.

patients that, according to Lleo, provides a reliable estimate of prognosis. The risk score includes Year 1 scores for ALP, total bilirubin, serum albumin, and platelets, and also considers age at therapy initiation.[6,19,22,23] The study that helped define this score showed that patients with risk scores >0.30 had significantly shorter times of transplant-free survival than matched healthy controls.[19] The GLOBE score is of particular use, said Lleo, as the biomarkers used should be universally available.

The UK-PBC score is another validated risk assessment tool for UDCA-treated patients. It can help predict liver transplant or liver-related death occurring within 5, 10, or 15 years.[6,24] Serum albumin, ALP, platelet count, alanine aminotransferase, aspartate aminotransferase, and total bilirubin scores can be used to identify patients who would benefit most from further risk reduction with second-line therapy.[24]

Additionally, transient elastography (TE) tools, such as FibroScan® (EchoSens, Paris, France), are noninvasive means to assess liver fibrosis and cirrhosis via measurement of the degree of liver stiffness. Such tools can provide a high degree of accuracy in patients with PBC for diagnosis of advanced fibrosis, which is important as liver stiffness progression is predictive of poor outcome.[25,26] A recent study utilising vibration-controlled TE found that a liver stiffness measurement cut-off of ≤6.5 kPa could diagnose the absence and >11.0 kPa the presence of advanced fibrosis, with a negative predictive value of 0.94, positive predictive value of 0.93, and error rate of 5.6%.[27] TE, discussed Lleo, "is an easy to obtain exam, you can repeat it over time, and the variation can give you an idea of the prognosis of your patient."

Several other indices have also been used to help predict outcomes in PBC. For instance, in patients without cirrhosis, according to the AASLD guidelines, ductopenia and inflammation severity are strongly related to ALP elevation, ductopenia and biliary piecemeal necrosis severity are related to hyperbilirubinaemia, and lobular necrosis and inflammation are reflected by increases in aminotransferase activity and IgG levels. Early indicators of cirrhosis and portal hypertension development include increased serum bilirubin, hyaluronic acid, and globulins, together with decreased serum albumin and platelet counts.[6,28,29]

As hyperbilirubinaemia is only seen in the late stages of PBC, bilirubin levels are considered less discriminatory for the detection of early disease progression and clinical outcome prediction.[23,30] However, some data suggest that any increase in bilirubin level, even within the normal range, should highlight high-risk patients with prompt consideration for optimal management, including potentially second-line therapies.[23]

Quality Of Life in Patients with Primary Biliary Cholangitis

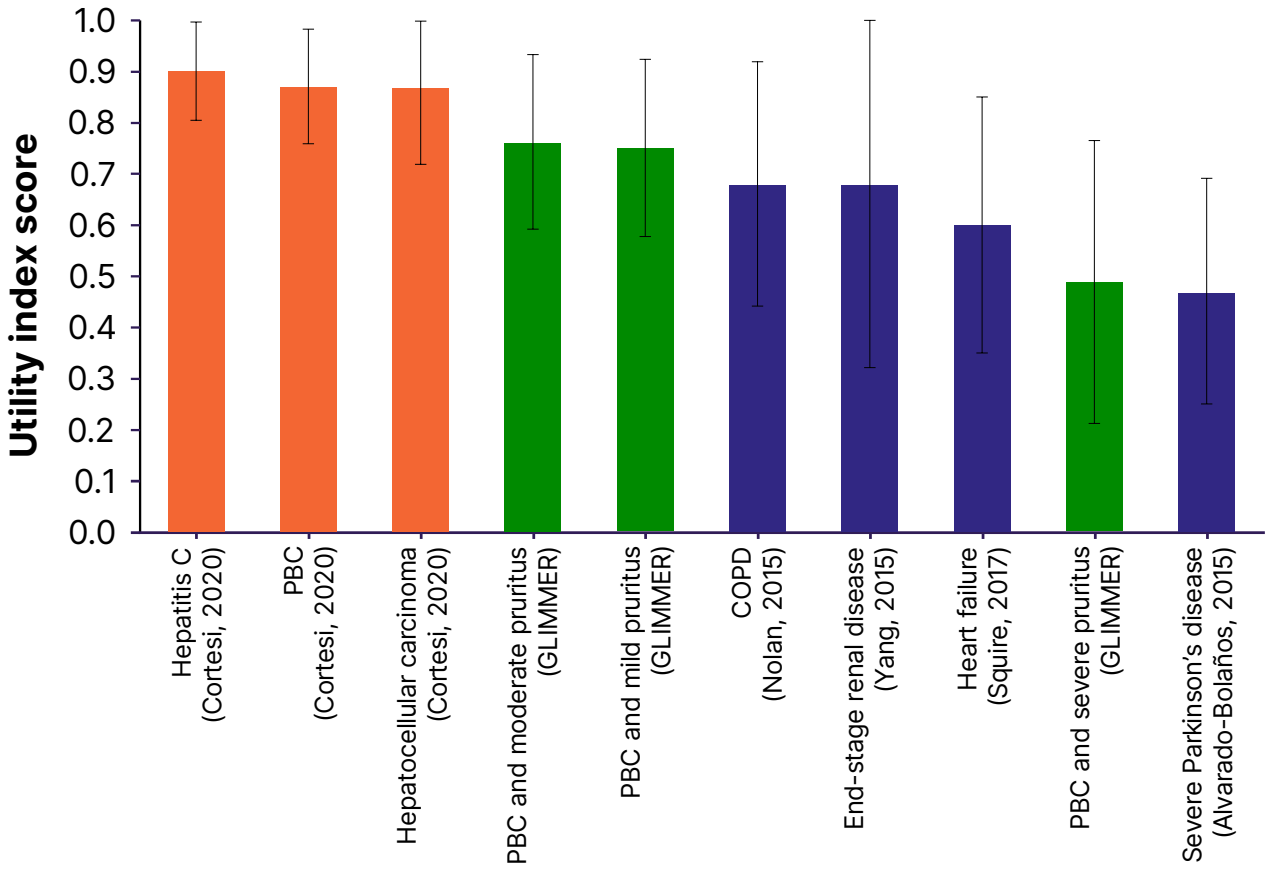
"Biochemical liver tests can help healthcare professionals identify the best therapy option for patients with PBC," said Hirschfield. "However, biochemistry will not necessarily be tackling symptom burden. We think about PBC very clinically," he continued, "but our patients have to live with it every day." Jones agreed that "both prognosis and symptoms are equally important. However, although we talk about symptoms in practice, our patients feel that we perhaps don't do as much as we could."

In patients with PBC presenting moderate–severe symptoms, impacts include pruritus, fatigue, cognitive problems, social impairment, and emotional dysfunction.[31] Jones explained that "when you have one bad symptom with PBC, you tend to have several of them." These domains can be assessed using the PBC-40 QoL, a six domain, 40 question instrument that asks patients to rate the frequency of factors associated with symptoms (e.g., I had dry eyes), itch (e.g., itching disturbed my sleep), fatigue (e.g., I felt worn out), and cognition (e.g., I found it difficult to concentrate on anything), and how much they are bothered by social (e.g., I can't plan holidays because of having PBC) and emotional (e.g., having PBC gets me down) factors.[32]

Cholestatic Pruritus

Cholestatic pruritus is one of the major symptoms of PBC,[6] with around half of all patients experiencing this to some degree at

Figure 1: Health utility mean (standard deviation) of patients with cholestatic pruritus compared with liver-related and other conditions.[42-47]



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COPD: chronic obstructive pulmonary disorder; PBC: primary biliary cholangitis.

any given time.[33-35] One survey of 238 patients showed that approximately 70% of respondents experienced this at any time,[36] with another survey, including 2,194 patients, showing similar rates of 73.5%.[37] As PBC is a chronic disease, pruritus can persist for years, with 34.5% of patients reporting persistent pruritus over the survey period of 8 years and 11.7% of patients reporting this pruritus was severe.[37]

Pruritus can impact all domains on the PBC-40, which can be increased relative to the degree of itching.[38] "If you itch all the time," added Hirschfield, "you don't sleep, you can't control your executive functions and how can you cope with life and work, and all the things you're trying to balance in addition to your health?" Patients also reported that scratching due to cholestatic pruritus can impact their self-esteem[39] and contribute to social isolation.[40] Further, the GLIMMER study of 147 predominantly female (94%) patients with PBC who also experienced severe pruritus compared administration of linerixibat (an ileal bile acid transporter inhibitor) or a placebo.[41] As seen in Figure 1, analysis of participants at baseline found that health utility value (EuroQol 5-dimension measure of health-related QoL) scores[42] were similar to people with severe Parkinson's disease,[43] and lower than people with heart failure,[44] end-stage renal disease,[45] and chronic obstructive pulmonary disorder.[46] "These are catastrophically bad levels of QoL," said Jones.

In a survey of 281 people with PBC, respondents were asked to confirm descriptors of pruritus. Here, 35.0% agreed it was like 'bugs crawling', 29.2% said the pruritus was 'deep and relentless', 17.6% said it made them 'want to tear my skin off', and 15.2% agreed that it was 'prickly/like needles'.[36] Interviews with patients with PBC presented as part of this symposium asked patients to describe pruritus in their own words. Descriptions included "it's relentless [...] it's like a life sentence of just being uncomfortable," "it starts to mess with your head mentally. You start thinking of ways to escape it, but you can't," and "I've gotten to the point of bleeding that it is so itchy."[48]

Despite these findings, Jones reported that "people struggle to get their clinicians to take it seriously. Clinicians think that if the liver biochemistry is good, then perhaps pruritus cannot be anything to do with the liver disease." Indeed, some studies have not shown a correlation between pruritus and biological indicators of PBC severity.[49] However, others have shown that severe itch occurs more frequently in patients with cirrhosis and higher ALP levels.[50] These studies also found pruritus was more common in younger patients,[37,50] with other studies showing pruritus may wane with disease progression.[6] As such, Jones advised that "if you do get control of the itch with improved biochemical tests, it's a bonus, but do not assume it will happen."

According to Hirschfield, "there is an imbalance in the consultation between the patient and the doctor." This was reflected in a patient survey where 69.8% said their doctor had not evaluated them for pruritus.[36] Reasons for this lack of evaluation may not only be because pruritus is not necessarily related to disease stage,[51] but also because pruritus can be difficult to quantify as there is considerable inter- and intraindividual variation and severity can fluctuate.[52] Lleo pointed out that "itching is not easy to treat, so sometimes physicians get discouraged and they don't want to ask because they don't want to deal with the problem."

With this in mind, Jones emphasised that every patient with PBC should be asked at every clinic visit whether or not they have pruritus and should be educated about the connection between the two. However, he said, "don't over-elicit these symptoms because if you push too hard, everyone in life has pruritus. You're trying to understand the nature of the impact. Don't just ask, 'have you got the itch?' because people will say yes, but often they are not troubled by it. Instead, ask, 'have you got an itch that's bad enough to need treatment?'"

Pruritus scores can be used to assess severity (e.g., on a 1–10 scale from minimum to maximum) and impact on QoL. Body location should be noted, as well as descriptions of how pruritus feels. Specific questions can also be asked regarding factors that may exacerbate itch, whether it is worse at any particular time of day, and whether any medications are taken to relieve the pruritus.[48]

Addressing pruritus symptoms is essential, highlighted Jones, because "if you can roll the

itch back, you can start to roll back several other difficult symptoms." Although there are some general medications that can help pruritis, specific treatment for PBC-related pruritus is not well developed and bile acid-binding resins are the only licenced therapy for such.[1] While UDCA can improve liver biochemistry measures and histological progression, it does not significantly improve PBC symptoms, including pruritus in many cases.[1,11] EASL guidelines discuss several off-label treatments, including rifampicin, opiate antagonists, selective serotonin uptake inhibitors, and gabapentin.[1]

Jones discussed how patients should be educated regarding lifestyle measures that might help pruritus. These are reflected in EASL guidelines and include bathing in tepid water, using ice packs, applying moisturisers and oatmeal extract, and avoiding tight or sticky clothing.[1] However, in the above-mentioned survey, respondents reported that while for 65% applying something cool to the skin helped pruritus, only 14% said it was relieved by scratching, and 22% said that nothing relieved it.[36]

Fatigue In Primary Biliary Cholangitis

Fatigue as a symptom of PBC can also greatly impact a patient's QoL,[6,53,54] with one study showing this occurred in 68.0% of patients.[53] This is an important symptom to recognise, as, according to Hirschfield, it can significantly affect wellbeing. For instance, studies have shown that fatigue in PBC is associated with diminished emotional reactions, social isolation, a lack of mobility,[53] and excessive daytime somnolence.[55] Fatigue is also linked to incidences of depression[56] and cited as having a negative influence on family life and work.[4]

In a published testimony, one patient with PBC recounted how their fatigue was "mind-numbing," and left them feeling like they were "in a fog," and could "hardly lift one foot in front of the other," making everything difficult. The patient also discussed that one of the problems with fatigue is that "it is hidden. I don't look different from other people." The patient recalled how "when I say [to people] I am tired, they tell me how tired they are, and if I try to explain the difference they do not understand what I am talking about."[57]

"It's important to quantify fatigue," said Jones, "as it's more of a difficult concept for people to understand." His clinic assesses fatigue at each appointment so they can track it. There are several simple assessment tools to do this, including the Fatigue Severity Score[56] and a Visual Analogue Scale.[58] The Fatigue domain of the PBC-40 assessment tool can also be used. This asks a person to rate how often (never, rarely, sometimes, most of the time, or always) they feel worn out, how much fatigue interferes with their daily routine, how often fatigue 'just hit me', and how often PBC 'drained every ounce of energy out of me'.[32,59]

Jones recommended that fatigue is discussed with patients at every clinic visit. It is crucial, he stressed, that it is explained that fatigue is a common symptom of PBC. He emphasised that people may feel uncomfortable discussing fatigue and not mention it without prompting. "Try to avoid abstract concepts," said Jones, "like asking how bad is your fatigue as it depends on what you mean by fatigue. Talk about the things they struggle with like can they do the shopping, go out to work, or socialise with friends." Jones also discussed how it is essential for patients to identify natural fluctuations in energy levels each day and 'listen to their body', and emphasised the importance of maintaining social structures.

Recommendations concerning managing fatigue include drawing up an energy-management plan and encouraging energy pacing to help conserve energy for important tasks. Patients may also be referred to a fatigue management specialist, such as an occupational or physical therapist, and patient support groups.[60] Additionally, there are smartphone applications available from the PBC Foundation, of which Jones is a trustee, where patients can view the latest research information, take part in surveys, and access self-management tools.[61]

Once a management plan is in place, Jones encouraged people to "look for change over a long time frame, you're not going to make people better next week or the week after but Christmas to Christmas, birthday to birthday, you're looking for a pattern of improvement over time."

As discussed by Jones, treating comorbidities and factors contributing to fatigue may also help lessen the symptom and its impact. "These

are all things that don't cause PBC fatigue, but they cause fatigue in the sort of people that get PBC." For instance, treating depression, sicca syndrome, obstructive sleep apnoea, restless leg syndrome, vitamin D deficiency, and autonomic dysfunction if present.[62]

Conclusions

The primary therapy for PBC is UDCA, the biochemical response to which can be monitored using liver blood tests such as ALP. Such tests can be used to assess response to treatment and risk stratify patients, improving identification of patients who may benefit from second-line therapies.

A patient-centred approach to PBC requires symptom assessment and treatment rather than focusing only on biochemical indices, particularly given that symptom burden does not correlate with disease severity. Pruritis and fatigue are two common PBC symptoms that significantly impact patient QoL and are under-recognised by physicians. When PBC is accompanied by severe pruritus, health-related QoL can be as negatively impacted as people with severe Parkinson's disease. These symptoms can significantly affect a patient's emotional health and lead to embarrassment and social isolation. As such, recognition and active management of pruritus and fatigue are vital for patients with PBC.

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Abstract Reviews

The following abstracts share the latest insight, research, and expert knowledge from the International Liver Congress (ILC) 2022, covering topics such as steroid hepatotoxicity, liver injury, and hepatocellular carcinoma.

Prescription Event Monitoring of Checkpoint Inhibitor-Induced Liver Injury and Outcomes of Rechallenge: A 10-Year Experience

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Checkpoint inhibitor-induced liver injury (ChILI), checkpoint inhibitors, drug-induced liver injury, incidence rate, liver toxicity, prescription event monitoring.

Citation: EMJ Hepatol. 2022;10[1]:32-34. DOI/10.33590/emjhepatol/10057736. https://doi.org/10.33590/emjhepatol/10057736.

BACKGROUND AND AIMS

The definition and severity of checkpoint inhibitor-induced liver injury (ChILI) have been reported using the Common Terminology Criteria for Adverse Events (CTCAE) used in cancer therapy.[1] Among patients with melanoma receiving checkpoint inhibitors (CPI), alanine aminotransferase elevation >5-fold (Grade 3) occurs in 1–16%.[2] However, the incidence rate of ChILI by treatment duration (time at risk) per type of cancer and CPI regime has not been accurately assessed. The authors estimated the risk and incident rate of ChILI in patients with melanoma or renal cell carcinoma who received CPI at Nottingham University Hospitals, UK, from 2011 to 2021.

MATERIALS AND METHODS

Using a prospective oncology prescribing database, the authors identified all adult patients who received CPI for adjuvant or metastatic melanoma or metastatic renal cell carcinoma over 10 years (2011–2021). The authors performed prescription event monitoring using patient-related records and digital records to identify ChILI, other immune-related adverse events, and response to rechallenge. International Expert Working Group (EWG) for drug-induced liver injury case definitions were used to define ChILI cases and grade severity.[3] Causality was assessed using Roussel Uclaf Causality Assessment Method (RUCAM).[4] Duration at risk for each patient was calculated, and the risk and incidence rate of ChILI were measured.

RESULTS

Out of 432 patients, 47 patients met the criteria and were identified as possible ChILI. After causality assessment, 9/47 (19.1%) were excluded due to other aetiologies. Overall, ChILI occurred in 38 patients (8.8%) and the highest risk of ChILI was noted in patients with

Table 1: Risk and incidence rate of checkpoint inhibitor-induced liver injury.

Cancer	CPI regime	Total person-time at risk (months)	ChILI cases (N)	Risk (%)	IR per 1,000 patient-months	95% CI
Melanoma (n=359)	Ipilimumab (n=88)	200.5	2	2.3	10.0	1.2–36.0
	Ipilimumab plus nivolumab followed by nivolumab (n=102)	761.1	29	28.4	38.1	25.5–54.7
	Nivolumab (n=22)	281.2	0	0.0	0.0	0.0–13.1
	Pembrolizumab (n=108)	1,035.4	3	2.8	2.9	0.6–8.5
	Adjuvant pembrolizumab (n=39)	343.3	1	2.6	2.9	0.1–16.2
RCC (n=73)	Ipilimumab plus nivolumab followed by nivolumab (n=19)	149.1	2	10.5	13.4	1.6–48.5
	Nivolumab (n=54)	524.7	1	1.9	1.9	0.0–10.6
Total (N=432)	All regimes	3,295.3	**38**	**8.8**	**11.5**	8.2–15.8

ChILI: checkpoint inhibitor-induced lung injury; CI: confidence interval; CPI: checkpoint inhibitor; IR: incidence rate; RCC: renal cell carcinoma.

melanoma who received combination therapy (28.4%). RUCAM was possible in nine, probable in 22, and highly probable in seven cases. The overall incidence rate of ChILI was 11.5 (95% confidence interval: 8.2–15.8) per 1,000 patient-months, with most cases occurring in patients with melanoma treated with dual checkpoint inhibition (38.1; 95% confidence interval: 25.5–54.7), as shown in Table 1. The pattern of liver injury was hepatocellular in 22 cases (57.9%), mixed in 11 (28.9%), and cholestatic in five (13.2%). Although nine patients (23.7%) were classified with Grade 4 hepatitis according to CTCAE (life-threatening), ChILI severity was mild in 11 (29%) and moderate in 27 (71%) based on EWG grading. Only two patients developed jaundice, and none progressed to acute liver failure. Thirty-six of 38 patients (94.7%) received corticosteroids, with two requiring second-line therapy with mycophenolate mofetil. Mean time to resolution of ChILI was 82±65 days following steroid therapy compared with 49±21 days in those untreated. Of 38 ChILI cases, 15 (39.5%) were retreated with a single CPI, and only one patient developed recurrent ChILI (6.7%). However, three developed colitis (20%), and one each developed hypophysitis and severe neuropathy (6.7%).

CONCLUSION

Incidence rate of ChILI was 11.5 per 1,000 patient-months, with the highest incidence in patients receiving combination therapy for melanoma (38.1). Most cases were hepatocellular in pattern. Jaundice was rare, with no severe cases developing acute liver failure or requiring

liver transplantation. Rechallenge with single CPI was feasible and most cases didn't experience recurrence of ChILI; however, they were at risk of other immune-related adverse events, especially colitis. The risks and benefits of corticosteroid therapy need to be evaluated in a larger cohort of patients with ChILI. ●

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Management of Severe, Steroid-Resistant and Steroid-Refractory Hepatotoxicity in Patients Treated with Checkpoint Inhibitor Immunotherapy

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Disclosure: Cunningham has received honoraria from Janssen and AbbVie. Iafolla has consulted for Novartis; received research (clinical trials) support from Astellas Pharma Global Development Inc., AstraZeneca, Bristol-Myers Squibb, and Seagen; and received honoraria from Bayer, Canadian Urologic Association, Compass-MD, Ipsen, MD Analytics, Merck, Sanofi, Save Your Skin, and Sermo Team. Kanjanapan has consulted for Novartis. Butler has consulted for Bristol-Myers Squibb, EMD Serono, GlaxoSmithKline, Immunocore, Immunovaccine, Merck, and Novartis; and has received grant/research support from Merck and Takara Bio. Siu has consulted for Arvinas, AstraZeneca/MedImmune, Celgene, GeneSeeq, GlaxoSmithKline, Loxo, Merck, Morphosys, Navire, Oncorus, Pfizer, Roche, Seattle Genetics, Symphogen, Tessa, Treadwell Therapeutics, and Voronoi; has received grant/research support from AbbVie, Amgen, Astellas, AstraZeneca/Medimmune, Avid, Bayer, Boerhinger-Ingelheim, Bristol-Myers Squibb, Celgene, GlaxoSmithKline, Intensity Therapeutics, Karyopharm, Merck, Mirati, Novartis, Pfizer, Roche/Genentech, Shattucks, and Symphogen; and has spousal shareholder interests in Agios and Treadwell Therapeutics. Bedard has consulted for BMS, Pfizer, and Sanofi; and has received grant/research support from AstraZeneca, Bristol-Myers Squibb, Genentech/Roche, GlaxoSmithKline, Immunomedics, Lilly, Merck, Mersana, Nektar, Novartis, PTC Therapeutics, Sanofi, Seattle Genetics, Servier, and SignalChem. Spreafico has consulted for Bristol-Myers Squibb, Janssen, Merck, Novartis, and Oncorus; and has received grant/research support from Alkermes, Array Biopharma, AstraZeneca/Medimmune, Bayer, Bristol-Myers Squibb, Janssen Oncology/Johnson & Johnson, Merck, Novartis, Northern Biologics, Regeneron, Roche, Surface Oncology, and Symphogen. Feld has consulted for Abbott, AbbVie, Entanta, Gilead, and Roche; and has received grant/research support from AbbVie, Eiger, Gilead, Janssen, and Wako/Fujifilm. Hamdan and Patel have declared no conflicts of interest.

Keywords: Checkpoint inhibitor, drug-induced liver injury, hepatitis, immune-mediated adverse event.

Citation: EMJ Hepatol. 2022;10[1]:34-36. DOI/10.33590/emjhepatol/10082046. https://doi.org/10.33590/emjhepatol/10082046.

BACKGROUND AND AIMS

Checkpoint inhibitor immunotherapy (ICI) has revolutionised cancer care but is associated with immune-related toxicities, which may require ICI discontinuation and immunosuppressive therapies (IST). Severe ICI hepatotoxicity is treated with high-dose corticosteroids; however, 30% of patients may be steroid-refractory (no response after 48–72 hours) or steroid-resistant (rebound alanine aminotransferase [ALT] upon steroid taper).[1,2] Further management for these patients is not well defined. The authors sought to better understand management of severe ICI hepatotoxicity and responses to IST.

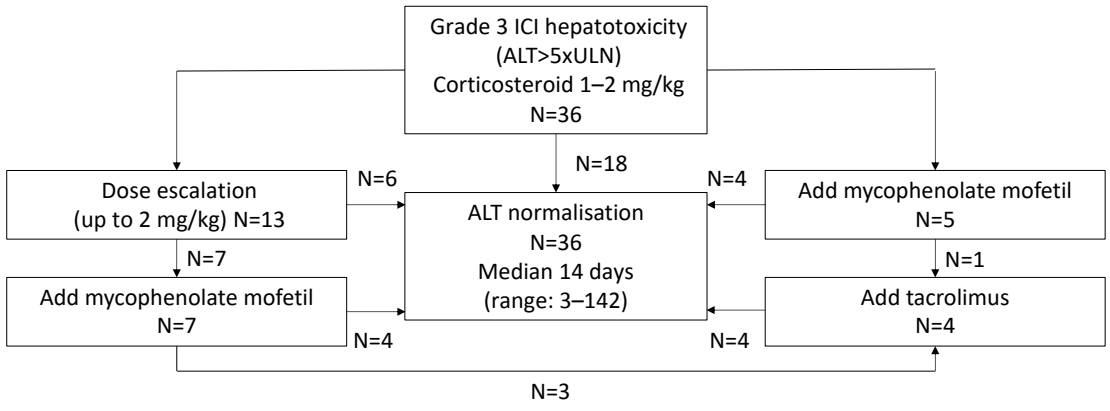
MATERIALS AND METHODS

Patients receiving ICI in early phase clinical trials at Princess Margaret Cancer Centre, University Health Network, Toronto, Canada, or treated at the Toronto Centre for Liver Disease, Ontario, Canada, for ICI hepatotoxicity were included. Patients with Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 ICI hepatotoxicity (ALT >5 times the upper limit of normal) were identified and clinical records reviewed for management and outcomes. Patients with an alternate cause for ALT elevation, who did not receive corticosteroids, or with HCC or viral hepatitis were excluded.

RESULTS

Between August 2012 and December 2021, 36 patients with Grade 3 ICI hepatotoxicity were identified. Most (23; 64%) had metastatic melanoma. Thirteen received anti-CTLA-4/PD-1, 18 received anti-PD-1 or anti-PD-L1, and five received anti-CTLA-4 monotherapy. All patients initially received corticosteroids (1–2 mg/kg/day prednisone equivalent). Figure 1 shows response to corticosteroids and sequence of additional IST. Eighteen patients (50%) were poor corticosteroid responders, either steroid-refractory (four; 11%) or steroid-resistant (14; 39%). Age, sex, liver metastases, prior ICI exposure, or peak ALT did not predict steroid response, although poor responders were more likely to have been treated with combination anti-CTLA-4/PD-1 (10 [55%] of poor responders versus three [17%] of responders; p=0.04). Thirteen received steroid dose escalation (up to 2 mg/kg/day), with response in eight. Overall, 12 patients (66%) required treatment with mycophenolate (MMF) as second-line IST. Five were transitioned directly to MMF, and seven after failure of steroid escalation. Four (33%; 11% of total cohort) did not respond to MMF and required third-line IST (tacrolimus). Age, sex, liver metastases, prior ICI exposure, or peak ALT did not predict need for second- or third-line IST. ALT normalised in all, after median 14 days (range: 3–142 days). Total time on IST was shorter in steroid responders than poor responders (medians of 45 days [range: 9–177 days] and 104 days [range: 30–371 days], respectively; p<0.01). Amongst patients with poor response to initial corticosteroids, there was no difference in peak ALT or time to normalisation of ALT between patients treated with steroid escalation relative to MMF. The MMF group showed numerical trends towards shorter duration of corticosteroids (medians of 61 days [range: 32–86 days] and 97 days [range: 21–275 days], respectively) and reduced need for additional lines of IST (one patient [20%] versus seven [54%]), although not reaching statistical significance in this small cohort. Steroid-related adverse events occurred in two patients (vertebral fracture;

Figure 1: Sequence of treatment with immunosuppressive therapies in patients with severe immune checkpoint inhibitor-related hepatotoxicity.



ALT: alanine aminotransferase; ICI: immune checkpoint inhibitor; ULN: upper limit of normal.

hyperglycaemia); both were poor steroid responders treated with steroid escalation. Over median follow-up of 14.1 months (range: 2.3–81.5 months), 14 patients died. Ten patients were rechallenged with ICI, and none developed recurrent hepatotoxicity. No patients died of complications of hepatotoxicity.

CONCLUSION

Poor steroid response is common in patients with severe ICI hepatotoxicity. Earlier introduction of second-line IST (MMF) may be associated with equivalent outcomes to steroid escalation and reduce total time on IST. Tacrolimus is effective as third-line therapy, if required. These results will assist development of treatment algorithms for severe ICI hepatotoxicity, for further prospective evaluation. ●

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Pre-transplant Changes in Serum Protein Glycosylation Relates to Risk of Hepatocellular Carcinoma Recurrence After Liver Transplantation and Provide a Potential Prognostic Biomarker: A Proof-of-Concept Study

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Disclosure: Verhelst and Van Vlierberghe declare that they have a patent licensed as WO2021191372A1. The other authors have declared no conflicts of interest.

Keywords: Glycan, glycomics, hepatocellular carcinoma (HCC), liver transplantation (LT), precision medicine, prediction, recurrence.

Citation: EMJ Hepatol. 2022;10[1]:36-37. DOI/10.33590/emjhepatol/10020546. https://doi.org/10.33590/emjhepatol/10020546.

BACKGROUND AND AIMS

Hepatocellular carcinoma (HCC) recurs after liver transplantation (LT) in approximately 10% of patients. Changes in protein glycosylation have been described during the development of HCC and are associated with progressive disease and early mortality.[1] The authors' study goal was to assess the risk of HCC recurrence after LT, according to changes in serum protein glycosylation before LT.

MATERIALS AND METHODS

A prospective study was performed in patients receiving LT between July 2011 and September 2018 at the Liver Transplant Unit of Ghent University Hospital, Belgium. A whole serum protein N-glycan profile was assessed using a DNA sequencer assisted by fluorophore and capillary electrophoresis, and validated high-throughput protocol.[2] For every sample, 13 glycans were quantified. Patients were followed until HCC recurrence or death. Specific changes in serum protein glycosylation profiles were analysed in patients with HCC recurrence compared with patients without.

RESULTS

Amongst 225 consecutive patients with LTs, 76 patients had a diagnosis of HCC before LT. The main indications were related to alcoholic cirrhosis (47.4%), hepatitis C virus infection (21.1%), and non-alcoholic steatohepatitis (15.8%). Eight patients (10.5%) developed HCC recurrence after a median follow-up time of 9.5 months after LT. Seventy-four patients (97.0%) fulfilled the Milan criteria. Significant differences in the relative abundance of five serum glycans were present in patients with HCC recurrence compared with patients without (through Cox regression analysis).

Based on these changes, a composite biomarker was developed (Glyco HCC Recurrence Score). This score integrates an increased presence of tri-antennary glycans (NA3) with and without branch and core fucosylation (NA3Fc and NA3Fbc), and a decreased presence of under-galactosylated glycans (NGA2F and NGA2FB) in patients with HCC recurrence. This biomarker panel showed an area under the curve of 0.855 (p=0.001; 95% confidence interval: 0.731–0.979) for association with HCC recurrence. Using an optimised cut-off (-4.24), sensitivity was 87.5% and specificity 67.6%. Only 2.1% of patients with a value below this cut-off showed HCC recurrence compared with 24.1% of patients with values above this cut-off (p=0.011). The positive predictive value was 72.98% and negative predictive value was 84.39%.

CONCLUSION

A glycomics-based serum biomarker panel is strongly associated with tumour recurrence in a cohort of patients who have had a LT with HCC, even if adhering to Milan criteria. In a multivariate analysis, this biomarker was the only pre-transplant discriminative parameter of HCC recurrence in this cohort. The biomarker could potentially increase the prediction of HCC recurrence and improve allocation strategies in LT candidates with HCC. A prospective validation study will start soon.

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Congress Interview

Aleksander Krag

Professor, Department of Clinical Research, University of Southern Denmark; Chair of Health Sciences, Danish Institute of Advanced Studies (DIAS), University of Southern Denmark; Head of Hepatology, Odense University Hospital, Denmark; Director, Odense Liver Research Centre, Odense University Hospital, Denmark

Q1 What initially sparked your interest in the field of hepatology?

Hepatology is an exciting and challenging clinical discipline with many great research opportunities and a vibrant international community. This field is rich, and there are moments where you will feel more like a detective. Diagnosing liver diseases can be very challenging. Thus, there is always more to learn, and nobody knows it all.

Q2 What are the main goals of the European Association for the Study of the Liver (EASL) congress, and what has your role as vice-secretary been like thus far?

EASL is a medical association dedicated to pursuing excellence in liver research, clinical practice of liver disorders, and in the provision of the best-in-class education for all those interested in hepatology. The EASL Congress is the incarnation of all we do; bringing people interested in liver diseases from across the world together to learn, to share, and to exchange knowledge and new data that can advance the field from clinical care to basic science. My first year in the leadership of EASL has already passed. Lots of learning, things achieved, things to celebrate, and much more to do. What a journey! When I started, I was concerned by the 4-year term; now, 4 years seems short. I enjoy it immensely. When I think about what EASL stands for, values like unites, advances, share, collaborative, innovative, diverse, and friends come to my mind. That is basically my motivation to join the EASL governing board: something valuable and worth supporting, that resonates with my values in life.

Q3 Which advancements have occurred in the discipline of hepatology since you began your career?

There are many. At the EASL Congress in London, UK, we celebrated one, the invention of the transjugular intrahepatic portosystemic shunt, and awarded Martin Rössle the EASL Innovation Award. His invention has improved care among thousands of patients. But also, better diagnostics, such as the introduction of elastography, have changed and improved clinical practice.

Q4 You set up the Fibrosis Fatty Liver and Steatohepatitis (FLASH) Research Centre in Odense, Denmark, which focuses on clinical and translational research. Can you tell us more about FLASH and its aims, and what has been achieved thus far?

The overall aim is to help reduce the burden of alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) on health and healthcare costs by scientific means; to generate

clinically relevant and usable biomarkers and interventions for management of ALD and NAFLD. FLASH is involved in four Horizon consortia, and several active projects. On the biomarkers front, we have shown how elastography and the enhanced liver fibrosis test hold strong prognostic value in early alcohol-related liver disease. In June, we published an article about how proteomics biomarkers can potentially outperform all current diagnostic and prognostic biomarkers in ALD. At the EASL Congress in London, we presented two randomised controlled trials: one on the effects of rifaximin in early ALD, and one on a low-carb, high-fat diet for patients with NAFLD and Type 2 diabetes.

"This field is rich, and there are moments where you will feel more like a detective."

Q5 What would you say are the benefits of belonging to EASL, and what is the impact of the association on both hepatologists and patients?

EASL is sort of a gateway to the international community. EASL unites hepatology; it brings together all stakeholders including patients and patients' organisations and works towards a shared goal: improving care of liver patients across the world through science, education, policy, and awareness.

Q6 You are co-ordinator of the GALAXY project, the aim of which is to optimise personalised healthcare for patients. Why do you feel that personalised healthcare is so important, and what are some of the benefits it can offer to patients?

Humans are different. People who have a disease are not alike, and the current 'one size fits all' approach is becoming

obsolete. In many situations, we need to treat 10 individuals for one to benefit. But we do not know who is most likely to benefit. Personalised care is when you know who is likely to benefit or not, and only treat those who are likely to benefit.

"People who have a disease are not alike, and the current 'one size fits all' approach is becoming obsolete."

Q7 In 2022, you co-authored a paper entitled 'The negative bidirectional interaction between climate change and the prevalence and care of liver disease'. What conclusions did this paper reach, and how do you feel climate change will impact healthcare on a more general level in future?

The association between climate change and liver health and disease, and the need for sustainable hepatology services, must be recognised. This is a key concern for EASL. We all need to do our part, take responsibility, and act. The four main domains of sustainable healthcare are prevention, patient empowerment and self-care, lean service delivery, and provision of low-carbon alternatives.

Q8 How has the COVID-19 pandemic affected your work? Has the shift to online teaching and virtual congresses brought any unforeseen benefits?

COVID-19 has propelled innovations in how we interact and work together with very effective online platforms for communication and education. Many processes have been sped up, and we have become even more effective. There has also been less travel, with a positive effect on the climate.

Q9 Which recent advances and innovations in the field of hepatology excite you the most?

There are many. The emergence of novel biomarkers to guide clinical decision will change clinical practice. Yet, this is just the beginning. Artificial intelligence and omics technologies are picking up speed, and will soon translate into clinical medicine. The introduction of direct-acting antivirals to treat hepatitis C was a revolution. Currently, we have several very exciting new drugs for the large disease groups such as hepatitis B, hepatitis D, and non-alcoholic steatohepatitis in late-phase testing. But we also see early breakthroughs in the rare disease field, such as with alpha-1 antitrypsin deficiency, Wilson's disease, and primary biliary cirrhosis.

Q10 Which advice would you offer to someone beginning a career in hepatology?

Join EASL, the international community; be inspired, see and learn from others. It will bring learning and a nice contrast to your day-to-day business. It's an ecosystem where you have the chance to capture the bigger picture of where the field is moving, and widen your horizon. I would encourage young hepatologists to join EASL because of the various programmes the association offers to young investigators to develop their skills, and push their research further; this is a unique opportunity. Use the EASL network to stay connected, or to take the next step to pursue your dreams and grow. EASL supports the younger generation of hepatologists by offering different programmes such as Schools, Masterclasses, Mentorships, and Awards. The next generation of hepatologists can take advantage of this, to carry our field forward into the future, into the next discoveries.

EMJ Interviews

Virginia Hernández-Gea and Charlotte Scott spoke to EMJ Hepatology about the driving forces which led them to their influential positions within the field of hepatology, also sharing first-hand experiences, research insights, and how they see the clinical landscape changing in the near future.

Featuring: Virginia Hernández-Gea and Charlotte Scott

Virginia Hernández-Gea

Interventional Hepatologist, Hospital Clínic de Barcelona, Spain; Secretary, Vascular Liver Disease Group (VALDIG); Recipient of the Rising Star in Gastroenterology Award and Young Investigator Award, United European Gastroenterology (UEG); Scientific Committee Member, European Association for Study of the Liver (EASL).

Q1 Was there a particular person or event that encouraged you to pursue a career in hepatology?

I guess it was a combination of different things. Firstly, hepatology is a very wide specialty that combines internal medicine with interventional procedures, and I liked that very much; secondly, I had an excellent group of medical school teachers who instilled in me their passion for the liver and encouraged me to choose the specialty. But it was during my residency that I really realised the challenges, the complexity, and the research opportunities that hepatology offers, and I decided to dedicate my career to this field.

Q2 Where have you gained the most valuable experience to date in your career: the Hospital de Sant Pau, Barcelona, Spain; Mount Sinai School of Medicine, New York, USA; the Hospital Clínic de Barcelona, Spain, where you are currently; or elsewhere?

Undoubtedly, all of them intensely contributed to my career in a unique manner; being trained in diverse institutions with several mentors has been a very valuable experience that has had a large positive impact on my training. Adapting to different working environments gives you a broad perspective so you can perceive various ways of facing and solving problems and challenges. I became a hepatologist at the Hospital de Sant Pau and it has had a huge impact on my way of practising medicine, solving clinical challenges, and appreciating clinical research. Mount Sinai, and especially Dr Scott Friedman, really influenced my interest in translational research, and it was at Hospital Clínic where I became an independent investigator and expanded my expertise in liver

catheterisation and vascular liver diseases.

Q3 A lot of your research and work centres around managing patients with portal hypertension and vascular liver diseases. How have you seen this field change over the course of your career?

The field of portal hypertension has evolved significantly in the last decades due to a better understanding of the physiology and the development of new therapeutic strategies, which has significantly improved the survival of patients. These changes have transformed recent research to focus on the prevention of decompensation, the identification of patients at high risk of complications, and more personalised management and treatment. Moreover, the cure of the hepatitis C virus, together with the emergence of new aetiologies such as fatty liver disease, has also changed the clinical scenario and brought new challenges to the field.

In the field of rare vascular liver diseases, advances in recent years have been very remarkable. The creation of interest groups, such as the Vascular Liver Disease Group (VALDIG), together with the endorsement of scientific societies, has substantially raised awareness and fostered international research studies, which have contributed to advances in the field and stimulated the interest of the scientific community.

Q4 How do you keep up to date with developments in liver catheterisation procedures, and how do you see these changing in the near future?

The field of liver haemodynamics and catheterisation was born due to an intimate collaboration of hepatologists with cardiologists trying to adapt their knowledge and techniques to liver diseases. In the last few decades, however, interventional radiologists have moved the field forward. As a hepatologist performing liver catheterisation, I think it is essential to work in a multidisciplinary team to share knowledge about the disease and technical skills, and solve clinically relevant problems in a less invasive way. As said before, changes in the epidemiology of the disease and new challenges also require the modernisation of techniques and expanded indications.

While diagnostic procedures may end up being replaced by non-invasive techniques, therapeutic procedures will play a predominant role in the future, i.e., earlier indications in patients with portal hypertension, personalised treatments, and new indications, such as the recanalisation of the splanchnic territory.

Q5 As an educator, where should we expect to see your focus lie in the coming years? Will you publish more work in a similar field to your recent research on liver fibrosis?

We have advanced a lot in the management of patients with liver diseases, but we still have many areas that need extensive research, meaning that hepatology is a super interesting field for new generations. The search for an antifibrotic treatment remains one of the top areas of interest where exciting findings will be revealed in the next few years, but still there is a lot to do. A better understanding of the mechanisms leading to hepatic regeneration is, in my opinion, another promising field that may lead to the discovery of new therapeutic targets and the development of new drugs.

Q6 You have been recognised by both United European Gastroenterology (UEG) and the European Association for Study of the Liver (EASL). How important are these organisations as platforms for networking and sharing

knowledge in the hepatology community?

It really means a lot! Getting international recognition for my work and achievements was nicely overwhelming. Both prizes are dedicated to young scientists and bring attention to your work, which exponentially increases your network opportunities. This is something that is essential to progress in the field, but is difficult to gain when you are young. Moreover, it boosts your motivation, encourages you to continue pursuing your goals, and facilitates your active involvement in scientific societies.

Q7 What does your role as a scientific committee member for EASL involve? Is there anything in particular you are hoping to achieve whilst serving in this position?

My main task is to help EASL to achieve its main aims of pursuing excellence in liver research and clinical practice, promoting education to all stakeholders interested in liver disease, and actively contributing to the diffusion of the latest scientific breakthroughs. During my time working on the Governing Board, I will do my best to raise awareness and make visible the main challenges in my field of expertise to, ideally, encourage future public health policies and increase funding dedicated to the field. I will try to contribute as much as possible to the EASL goals of uniting and collaborating with other scientific societies and reinforce the training of professionals working in hepatology at all stages of their career. And lastly, I hope to contribute to the identification of future challenges in the field in order to anticipate innovative solutions and guarantee that EASL continues to be relevant in the hepatology community.

Q8 Have you encountered any great successes or challenges whilst running your translational laboratory, which aims to study and understand the role of liver endothelium in liver diseases?

Research is full of challenges and trying to overcome or solve them sometimes gives you success, and this is what I've found since starting my career as a principal investigator. I am very proud of my team's contribution to the understanding of liver endothelial dysfunction during liver injury. In the last few years, we discovered how autophagy regulates the phenotype of liver endothelial cells upon injury and orchestrates the response to the liver microenvironment and liver fibrosis. More recently, we have demonstrated how supplementation with spermidine (an autophagy enhancer) in the early phases of liver disease protects the liver endothelium from oxidative stress and delays disease progression.

Charlotte Scott

Group Leader, Scott Lab, VIB-UGent Center for Inflammation Research, Ghent, Belgium; Associate Professor, Department of Biomedical Molecular Biology, Ghent University, Belgium.

Q1 Was there any specific person or event that inspired you to pursue a career in molecular and biomedical biology, particularly with a focus on hepatology?

I have always been curious, wanting to understand how and why everything works. My interest in biology began in secondary school in Ireland, where I had a very energetic teacher, Mr Whisker. This, coupled with some family illnesses and a desire to understand the mechanisms at play, drove me to study Biochemistry as an undergrad, where I fell in love with Immunology. Wanting to further understand the immune system after graduating with my BSc, I was lucky enough to be selected for a 4-year Wellcome Trust PhD program at the University of Glasgow in Scotland, UK. It was there that I met my PhD supervisor and mentor, Prof Allan Mowat, who further inspired and encouraged me down this path. My transition to hepatology was not planned as such, but rather because I followed my favourite immune cells, the mononuclear phagocytes! During my PhD, we were limited in the functional studies we could do, due to the lack of specific tools with which we could specifically target our cell types of interest; for me, intestinal dendritic cells. When looking for a postdoc, I met Prof Martin Guilliams, who had just developed a mouse model to specifically deplete liver resident macrophages (Kupffer cells [KC]). This was a unique opportunity to really be able to specifically target one cell type, and I jumped at it, leading to my transition to hepatic immunology. While these mice did not work out as we expected (the KCs return very quickly after depletion, making it difficult to study their function), these cells quickly captured my attention. For example, their high expression of lipid metabolism-related genes, is what prompted me to start researching non-alcoholic fatty liver disease (NAFLD). Since then, the research has taken a lot of often unexpected, but very interesting turns, and I am very happy to follow the data wherever it leads us. This is the most fun part, getting an unexpected result and trying to understand it!

Q2 The laboratory that you lead aims to understand macrophage functional heterogeneity in non-alcoholic fatty liver disease (NAFLD). How extensive is the clinical burden of this disease, and what drives your continued research?

With the current obesity epidemic, NAFLD places a huge burden on society. This is probably best illustrated by the prediction that in just 8 years, in 2030, NAFLD will become the leading cause of liver transplantation in the Western world. This stems from the fact that currently we have no treatment for patients with NAFLD, and often diagnosis comes too late. This is because the initial stages of disease are often asymptomatic, and the procedures required to confirm diagnosis are quite invasive. As mentioned above, we first started to study this because we noticed that the transcriptional profile of KCs was enriched for genes associated with lipid metabolism, leading us to ask whether they would then contribute to NAFLD development. However, we

quickly realised that KCs were not the only macrophages present in the fatty liver. Rather we found that these cells start to die and are, in part, replaced by monocyte-derived KCs, and in part by another distinct population of macrophages called lipid-associated macrophages (LAMs). LAMs specifically reside in regions of steatosis and fibrosis, but their precise roles remain unknown. This is our main focus right now, understanding what these different populations do and how they contribute to disease progression. We are looking at this in the context of NAFLD, but also other hepatic injury models where we have also identified these cells (unpublished). If we can understand this, perhaps we can develop methods to manipulate the macrophage populations in patients to improve disease outcome.

Q3 Since you were appointed as an associate professor at Ghent University, what has been your proudest achievement?

I have been very lucky since becoming independent, and have been awarded a couple of young investigator prizes recently, and a European Research Council (ERC) starting grant, which allowed me to get the lab off the ground, and for which I am very grateful. Nevertheless, I think what I am most proud of since establishing my independent lab is that I have been able to recruit a team of highly motivated and talented scientists (PhDs, postdocs and technicians) to work with to answer these questions. The fact that these mostly international people saw something interesting in the research questions I was proposing, and were willing to move country and, let's face it, take a risk on a Junior Principal Investigator, to join my lab is a real honour for me. I'm sure they would be the first to tell you that I still learning about how to be a good Principal Investigator in terms of people management! It's certainly not always easy and I still have a lot to learn, but to me this is so important. I get as much joy from seeing them succeed as I do from answering the scientific questions. My first PhD student (as main supervisor), Anneleen Remmerie, has just defended her thesis, and while I only played a small part in her scientific successes, this is something that I am very proud of.

> **"In just 8 years, in 2030, NAFLD will become the leading cause of liver transplantation in the Western world."**

Q4 How has our knowledge of hepatic macrophages advanced in recent years? Are there any significant updates that we can expect to see affecting clinical practice in the near future?

So I should start by saying that our research is definitely fundamental in nature. I think as a field, we have come a long way in recent years regarding our understanding of which macrophages are present in murine and crucially human liver in different disease settings but right now, what we really lack is functional data. What are all these macrophage populations doing in the different settings? Once we know this, then I think we can start to develop ways to manipulate these cells for clinical benefit, but I don't think we are there yet!

Q5 Where do you feel that you have gained the most valuable experience in your career to date? Was it during your time training in Scotland, your experience working in Belgium, or elsewhere?

I will have to sit on the fence with this one, sorry! I don't think there is any one place where I have gained the most. I've gained a lot of different experience,

both during my PhD and postdoc, and the great thing about science is that I am still learning and gaining experience now. All of these experiences I keep with me now to keep moving my lab forward. Moving was illuminating for me, both from Ireland to Scotland from BSc to PhD, and from Scotland to Belgium for my postdoc. I learnt a lot just from looking at things from a different perspective at each location. However, even though I did not move institute after my postdoc to set up my own lab, I have still learnt a lot in these last years, again with much of this coming from diversity of experiences within my team!

Q6 You recently co-authored a study that investigated evolutionary conserved hepatic macrophage niches. What are the key findings that this research aimed to demonstrate?

In this publication, we have profiled all of the cells of the liver using spatial proteogenomic approaches (cellular indexing of transcriptomes and epitopes by sequencing, nucleus RNA sequencing, and spatial transcriptomics). We did this in mouse and human in the context of both healthy and obese livers, and have further supplemented this data with healthy livers from five additional species (macaque, pig, chicken, hamster, and zebrafish). This was a massive collaborative effort, led by my lab and the lab of Martin Guilliams, and including Hans Van Vlierberghe's and Lindsey Devisscher's teams at the University Hospital Ghent, which enabled us to investigate human livers; and multiple other teams to profile the other species. We also benefitted immensely from collaboration with Wouter Saelens, Bart Deplancke, Robin Browaeys, and Yvan Saeys for the novel bioinformatics algorithms used to analyse the data. By combining all of these techniques, species, and expertise, we were able to identify the conserved macrophage populations in the healthy and obese liver. Moreover, we were able to identify the local environments (niches) and the cell-cell interactions driving the development of these macrophage subtypes, which is crucial if we think of manipulating these cells in the future. This led us to determine that the LAM phenotype is for a large part driven by the presence of local lipid content rather than cell-cell interactions, whereas KCs require BMP9/BMP10 signalling from hepatic stellate cells (through ALK1 on the KC surface) to develop. This allowed us to generate a mouse model which constitutively lacks KCs, by removing ALK1 from all macrophages. Thus, now we finally have a mouse that always remains devoid of KCs, enabling the study of their function.

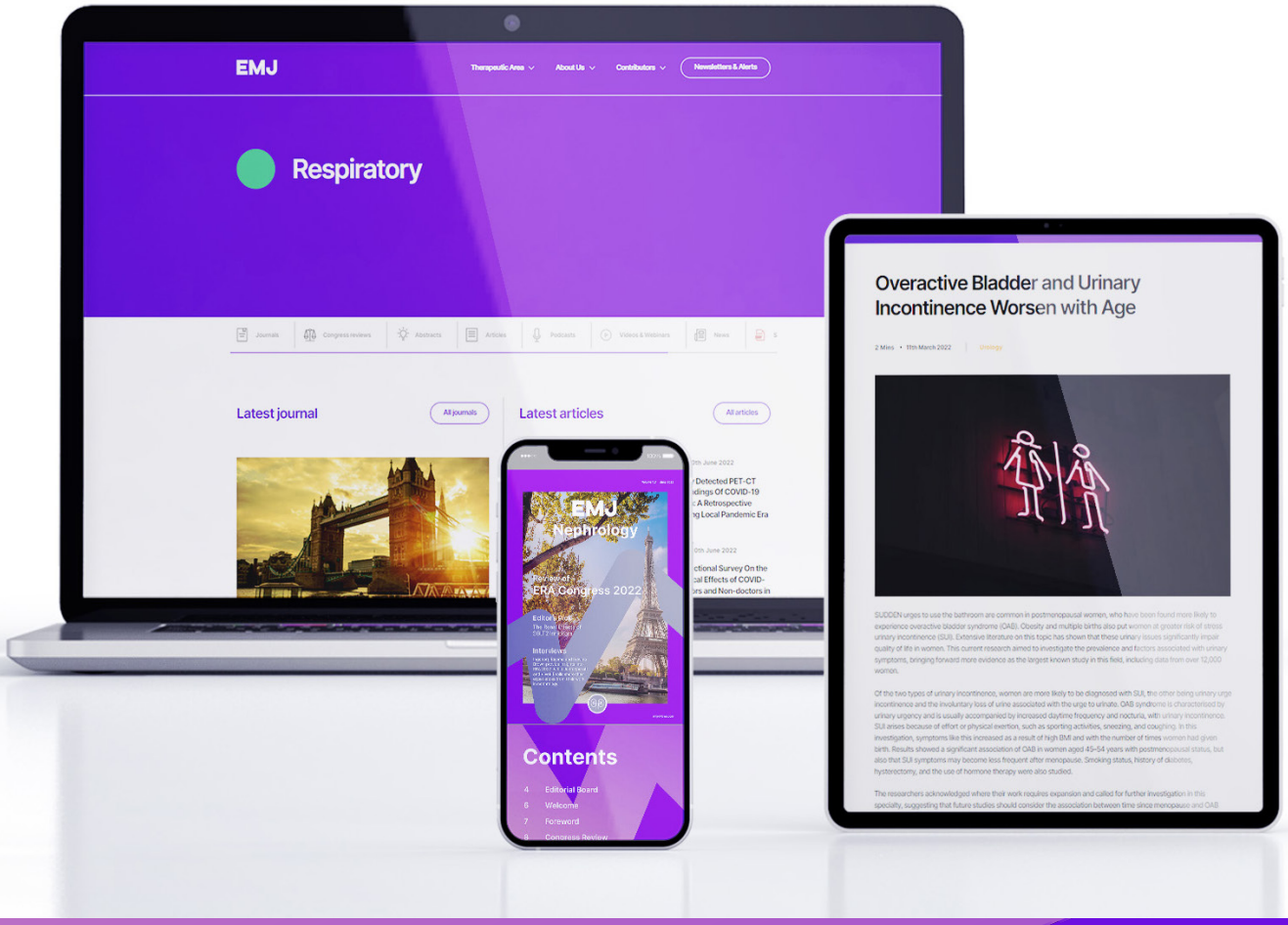
Q7 In 2021, you received a European Association for Study of the Liver (EASL) Emerging Leader Award. Could you please explain what this was awarded in reference to, and the implications of your work that were recognised in this achievement?

The EASL emerging leader award is awarded yearly to young investigators (<40 years) based on their international liver research achievements to date. I was really honoured to receive this award last year. While I do not know the precise reasons the selection committee chose me for this award, personally I feel this award is reflective of my collective work on understanding liver macrophages both during my postdoc and since launching my own independent lab. During my postdoc, one of my most exciting findings was that despite being largely of embryonic origin in the adult liver, bona fide KCs can be generated from bone marrow-derived monocytes if the niche becomes available (e.g., upon depletion/loss of the macrophage population). This led us to put forward the macrophage niche hypothesis, stipulating that there are a restricted number of niches for macrophages in any given tissue, and that it is the local environment in these niches which govern macrophage

phenotype but not origin, as had been previously proposed. This hypothesis then led us to investigate the signals regulating KC development, and led us to determine a role for the transcription factors Zeb2 and liver X receptor alpha (LXRa) in maintaining KC identity. Moreover, this work led us to ask what happens to the macrophages when the niche is altered due to injury and inflammation. This led me to start my independent lab, which focusses on hepatic macrophage functional heterogeneity in inflammation and injury. In terms of NAFLD, we determined that KCs were lost from zones of steatosis and fibrosis, which were then instead populated by the LAMs. This work which was published back-to-back with two similar reports demonstrated that we need to distinguish between these populations when studying macrophages functions in NAFLD.

Q8 Finally, what advice would you give to a younger self, or to an aspiring young clinician?

Follow the data and the questions that interest you the most, and enjoy it! If you had asked me 10 years ago what would I working on today, I am confident I would not have said NAFLD; I'm not even sure I would have predicted I would be working on the liver! However, this is where the data led us, and I'm very grateful to be here and working on this topic right now. Science is not easy, there are ups and downs, but by following the data, you can go places you never even thought of! It's hard work, but as long as you enjoy what you do, it's so worth it!



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The Challenging Ethical Landscape of Non-alcoholic Fatty Liver Disease

Editor's Pick

As one of the most common chronic liver disorders globally, it is essential that healthcare professionals are aware of the ethical challenges associated with non-alcoholic fatty liver disease. In this timely review, Berry and Kotha outline the issues surrounding late and invasive diagnostic strategies, the current lack of effective treatment options, and the stigmas surrounding obesity in the context of healthcare. The authors also discuss the hesitancy to engage in population-wide screening programmes, providing readers with a comprehensive review of the available information on non-alcoholic fatty liver disease.

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Disclosure:	The authors have declared no conflicts of interest.
Received:	05.10.21
Accepted:	21.01.22
Keywords:	Ethics in non-alcoholic fatty liver disease, fibrosis, non-alcoholic fatty liver disease (NAFLD), transplantation.
Citation:	EMJ Hepatol. 2022; DOI/10.33590/emjhepatol/21-00217. https://doi.org/10.33590/emjhepatol/21-00217.

Abstract

Non-alcoholic fatty liver disease presents a number of ethical dilemmas. These relate to the potential harms of diagnosing the disease in health, diagnosing a condition for which there is no effective treatment, and variability in specialists' attitudes to discussing and managing obesity. Erroneous homogenisation of a patient group that is extremely varied in terms of risk factors such as ethnic background, socioeconomic status, and genetic predisposition may result in inappropriate uniformity of approach when counselling patients as to underlying causes. This article will explore these challenges from the perspective of the gastroenterologist or hepatologist who must navigate them. Each section starts with questions posed by patients or comments made by doctors. Caution is suggested before widespread population-based screening is established, and the need for good adherence to referral algorithms is emphasised. Physicians are urged to engage with the condition's hidden complexities and reflect on their own communication strategies.

Key Points

1. Ethical dilemmas in the management of non-alcoholic fatty liver disease (NAFLD) stem from the potential harms of diagnosing the disease in health, diagnosing a condition for which there is no effective treatment, and variability in specialists' attitudes to discussing and managing obesity.

2. The patient group affected by NAFLD are diverse, in terms of risk factors such as ethnic background, socioeconomic status, and genetic predisposition, so communication strategies should be tailored to each patient.

3. Without straightforward management options, NAFLD screening, referral, and investigation should be carefully considered and outlined at the health service level.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), the most common hepatological condition in the Western world, is associated with late diagnosis in those who progress to cirrhosis; yet there is no consensus on how to treat it when diagnosed at an early stage.[1-4] NAFLD is the hepatological manifestation of metabolic syndrome and is associated with obesity, Type 2 diabetes, and dyslipidaemia; therefore, its diagnosis also has implications for long-term cardiovascular mortality and morbidity. Self-management of obesity, which often drives NAFLD, frequently fails.[5] It is a common scenario for a patient to be seen in clinic after having an ultrasound that shows steatosis, and for them to be told about the risk of progression to advanced fibrosis, but for no effective management plan to be offered other than long-term monitoring (the authors' experience and personal communications). In cases where advanced fibrosis or cirrhosis is identified, surveillance for hepatocellular carcinoma or other complications is considered, but these do not change the patient's trajectory. In cases of early or moderate fibrosis, the importance of addressing the underlying problem of obesity (if present) can be explored and strategies for losing weight discussed. Referral to bariatric services may be undertaken in selected cases; however, access to surgical treatment is limited and waiting lists are long. The only other avenue is entry into a research study. Many studies involve novel pharmacological agents, are placebo controlled, and last for >2 years; therefore, a large proportion of patients will receive either no or limited treatment (although the placebo effect itself has been shown to reduce alanine aminotransferase by around 10 U/L in trials).[6] Though NAFLD is increasingly diagnosed, unified global strategies for management and treatment options are sparse.[7] Going forward, tackling the rising epidemic of NAFLD requires a multidisciplinary approach, with hepatologists working closely with primary care physicians, cardiologists, and diabetologists.

For such a common condition, and one with few troublesome early symptoms, NAFLD presents a surprising number of ethical dilemmas, largely derived from our failure to adequately treat the majority of cases.[8] This article explores these challenges from the perspective of the gastroenterologist or hepatologist who must navigate them.

"I ONLY HAD THE BLOOD TEST BECAUSE OF A MEDICATION I TAKE; I DIDN'T THINK THERE WAS ANYTHING WRONG WITH MY LIVER...": DIAGNOSING DISEASE IN HEALTH

Liver disease is largely silent until symptoms associated with decompensation occur. Although there is evidence to suggest many patients with NAFLD go undiagnosed, there a danger of failing to discriminate between the liver that contains fat (NAFL) and the liver in which fat may be mediating a degree of permanent harm (NAFLD or NASH).[9-11] Historically, it has been accepted that NAFL is largely benign, but there are emerging data to suggest there may be progression of fibrosis.[12] It is difficult to predict this progression as it is dependent on numerous factors such as genetics and environment.[13]

Age, presence of diabetes, and BMI also play significant roles.[14] Despite this reservation, diagnosis of definite disease in all patients with fat in their livers, without reference to strict criteria, may lead to overdiagnosis and its associated harms.[15]

For example, patients who are given the label of NAFLD may encounter problems when seeking life insurance; others may come away with the impression they are heading towards liver failure (patient communications). A recent meta-analysis shows patients with NAFLD have a high prevalence of depression, and discussions around diagnosis need to be nuanced in order to prevent unnecessary anxiety.[16] Studies in another liver condition, hepatitis C infection, have shown that awareness of viraemia negatively impacts quality of life over decades, even when hepatic- or virus-related symptoms are not the cause.[17] The reasons for this were unclear, but were felt to relate to anxiety due to the diagnosis, alcohol use, social deprivation, having been homeless at any stage, older age, and methadone treatment.

If, following diagnosis, there are no well-developed guidelines or algorithms to rationalise the pathway, patients may continue to attend specialist clinics for monitoring of liver function, thus increasing the burden on hospital services. The continued referral of patients with simple steatosis to specialist services is costly and may detract from the management of patients who are at higher risk of liver fibrosis and require more intensive monitoring. In order to avoid this, strict referral criteria are required. These have been developed and are based on the exclusion of patients who appear at low-risk, based on non-invasive markers such as Fibrosis-4 (FIB-4) or Enhanced Liver Fibrosis (ELF) test; nevertheless, these are not yet universally embedded.[18,19]

The danger of overdiagnosis may be increased if population-based screening is adopted. Health systems have different incentives and reimbursement arrangements for the management of conditions that are detected during health screens, and this has to be considered when offering screening tests to whole populations. Several initiatives using community based FibroScans® (Echosens, Waltham, Massachusetts, USA) have been developed and, although these may benefit the minority who have advanced fibrosis, the advice given to attendees who are found to have liver steatosis must be clear in order to avoid undue anxiety.[20] An economic evaluation of a screening programme in Nottingham, UK, using a Markov model, was predicated on the likelihood that pioglitazone, when widely used, would reduce disease progression and morbidity.[21] This drug is not in wide use, and the evidence for its efficacy is weak (see below). Moreover, a large observational studies of patients with Type 2 diabetes taking this drug found signals towards bladder malignancy and osteoporosis.[22] The paper does not explore potential harms due to false positive diagnosis. Increasing access to mobile FibroScan technology has allowed informal 'roadshow' screening, where patients receive an immediate assessment of fatty infiltration and fibrosis. Hepatologists may be in two minds about this. In the one hand, they increase the awareness of silent liver disease; however, on the other, they risk previously healthy men and women walking away with a diagnosis but no clearly defined forward plan other than advice to adopt a healthy lifestyle and visit their GP.

"SO IT'S JUST A BIT OF FAT IN THE LIVER, DOCTOR?": THAT DOESN'T SOUND TOO BAD!

Patients may leave the consultation thinking NAFLD is not significant unless there is inflammation and subsequent fibrosis. This is a simplistic view as NAFLD is the hepatological manifestation of metabolic syndrome and is associated with obesity, Type 2 diabetes, and dyslipidaemia, with implications for long-term cardiovascular mortality and morbidity. There has been a recent international expert consensus statement to change the terminology from NAFLD to metabolic-associated fatty liver disease.[23] Unless patients understand this, efforts to make meaningful lifestyle changes to modify risks may not be successful. Recent meta-analysis have shown patients with NAFLD have significantly high risks for cardiovascular events,[24,25] which is the main cause of mortality in these patients, whereas mortality due to liver events only accounts for a third of the causes.[26]

In addition to associations with metabolic syndrome, other extrahepatic manifestations

include chronic kidney disease, polycystic ovary disease, malignancies, obstructive sleep apnoea, osteoporosis, depression, and cognitive impairment.[27,28] There is indeed new evidence to suggest the association between NAFLD and Type 2 diabetes is bidirectional, and NAFLD could be a precursor of diabetes.[29] The theory is that hepatokines such as fetuin-B impair metabolic control, leading to diabetes.[30] These considerations raise an important question: should NAFLD be managed by hepatologists alone, or does it need a multidisciplinary clinic?

"THAT DOESN'T SOUND VERY NICE, DOCTOR": ARE INVASIVE INVESTIGATIONS LIKE LIVER BIOPSY JUSTIFIED?

Although liver biopsy is the 'gold standard' investigation to differentiate NAFL from NASH, its role has been controversial, especially in the absence of specific treatment options. It is a useful tool when there is diagnostic uncertainty regarding concomitant liver pathology, borderline non-invasive markers, or to permit inclusion in clinical trials. However, many patients having a liver biopsy for inclusion in clinical trials may not have significant fibrosis and may have undergone an unnecessary invasive procedure. In the context of metabolic associated fatty liver disease, when there is definitive evidence of metabolic associations of fatty liver disease, is a liver biopsy justified for diagnosis unless the purpose is inclusion in clinical trials? Furthermore, biopsies taken for research and clinical trials raise ethical questions about voluntary consent, and patients misunderstanding that there is a requirement to undergo a biopsy for an intervention.

Though guidelines from various societies like the European Association for the Study of the Liver (EASL), American Association for the Study of Liver Diseases (AASLD), and Asian Pacific Association for the Study of the Liver (APASL) differ slightly in their recommendations for liver biopsy in NAFLD. The general consensus is that it is reserved in cases with uncertain diagnosis or to confirm advanced liver fibrosis.[31,32] Liver biopsy is associated with risks such as bleeding, infection, and pain. A recent meta-analysis of liver biopsies reported an overall risk of bleeding of around 2%.[33] Patients report significant anxiety associated with biopsy, and studies show this is associated with higher reported pain.[34] Clear discussion about indications, risks, and procedure can help patients make an informed decision and alleviate anxiety.

"SO, WHAT CAN YOU DO ABOUT IT?": DIAGNOSING DISEASE WHEN THERE IS NO TREATMENT

Patients diagnosed with NAFLD, NASH, and fibrosis will ask what can be done. The reasonable expectation, as in other areas of medicine, is that some form of treatment will be prescribed. In NAFLD, although many agents have been trialled, and some are included in guidelines, there is no highly effective pharmacological intervention. A meta-analysis of 77 trials including 6,287 participants concluded that: "Due to the very low quality evidence, we are very uncertain about the effectiveness of pharmacological treatments for people with NAFLD including those with steatohepatitis."[35] Vitamin E and pioglitazone feature on many guidelines, but their use in secondary care is not routine. Indeed, vitamin E (with other antioxidants) has been associated with increased overall mortality.[36] A recent trial of the farnesoid X receptor obeticholic acid found a high incidence of side effects among patients who took the dose required to reverse fibrosis;[37] the U.S. Food & Drug Administration (FDA) did not approve the drug. Research into other agents that interrupt the pathway to fibrosis continue; however, the underlying problem, obesity, appears to be the area where interventions will be most fruitful. Weight loss of 5–10% is associated with improvements in liver function and histological features of NASH, and weight loss following bariatric interventions have shown great promise.[38-41] However, non-surgical weight loss is often difficult to achieve, with many patients unable to adhere to diets, while musculoskeletal problems related to previous injuries, or as a result of excess body weight, can restrict options for exercise (personal communications). Surgery, while effective, is implicitly riskier in the short-term, with longer-term complications that are being recognised as decades pass since techniques were refined.[42,43] Waiting times for bariatric surgery for those who are selected may be ≥2 years. Less invasive bariatric procedures such as endoscopic sleeve gastroplasty or duodenal ablation appear to be promising alternatives but are not yet widely

available. NAFLD, arguably more than any other condition, represents a paradox. Its prevalence is hugely disproportionate to the available effective management options. This means that many patients will leave the clinic unsure about what to do.

"MAYBE HE WAS BEING CRUEL TO BE KIND, BUT I FELT FAT SHAMED...": ATTITUDES TO OBESITY AMONG PHYSICIANS

The fact that obesity is stigmatised is well established. In studies dating back over a decade, patients with obesity may have been assumed to be "lazy, unmotivated, lacking in self-discipline, less competent, noncompliant, and sloppy."[44] Discrimination of people with obesity is as prevalent discrimination based on race or gender.[45] How then, does the average physician view patients with obesity and liver disease?

Physicians' attitudes to obesity vary greatly, and this can have measurable effects on patient outcome in terms of weight loss.[46] For physicians do judge and often do harbour negative attitudes.[46,47] Even professionals who specialise in obesity have been found to show "very strong weight bias, indicating pervasive and powerful stigma."[48] Ringle and Ditto showed that moralisation (the assumption that obesity reflects weakness or diminished responsibility for one's own body) by physicians was associated with presumptions that patients should be able to control the condition, and with stronger opinions about the possible harms.[49]

Empathy for patients with obesity is not elicited automatically, but can vary according their perceived success in self-management.[50] If simplistic attitudes prevail, and these are communicated to patients (albeit unconsciously), the therapeutic relationship is likely to deteriorate. Hearing that weight gain is a simple mathematical imbalance between calories in and calories out is unlikely to engage a patient constructively. It is very unlikely that patients attending clinic with significant liver disease related to obesity will not have understood the importance of body weight on their lives previously, and the vast majority will have tried to address this, albeit ineffectively. Patients in clinic who request assistance with weight loss are not necessarily shifting the onus of responsibility onto their physician. In one survey, only 20% of patients felt that their doctor should actively contribute to their weight loss management.[51] However, general gastroenterologists and hepatologists are not dietitians or psychological therapists, and their skills in counselling patients on how to address their weight are unlikely to be well developed. Large studies of primary care physicians have shown low levels of confidence in their ability to manage this condition, and this could reasonably be extrapolated to doctors working in secondary care.[52]

Peckham[53] observed: "Obesity is becoming increasingly stigmatised as 'scientific' health information is incorporated into a pre-existing set of cultural beliefs that fat people are either gluttonous or slothful (or both), and that their lack of self-control and moral fibre is costing millions of pounds each year in medical treatment and lost earnings."

Encouragingly, Budd et al.,[54] in their review of 15 studies on physician attitudes, found that they may have improved between 1990 and 2007. Conversely, studies have shown that the theme of control is important to patients, and that this can be increased or renewed following bariatric surgery.[55] The moral complexity of performing surgery on 'healthy organs', purely to treat a condition that is secondary to 'lack of self-control' opens up a legion of difficult questions regarding choice, utility, and resource allocation.[56] Outside of this review of adult medicine, but worthy of comment, bariatric surgery performed on children with obesity highlights the moral dilemmas even more clearly. Children do not have independent medical capacity, but the intervention may well be lifesaving.[57]

Hepatologists, perhaps more than other medical specialists, see several conditions that are ostensibly related to lifestyle. These include alcoholic liver disease and viral hepatitis acquired through intravenous drug use. There is bound to be variability related to physicians' personal attitudes, backgrounds, and education, as has been described in relation to people with alcohol or drug dependence.[58] Moral responsibility, deservingness of medical attention, and de-prioritisation for scarce resources have been studied extensively in relation to alcoholism

and liver failure; it would not be surprising if judgmental attitudes crossed over into NAFLD.[59] One way of approaching this tendency is to reflect on the fact that many patients were pushed onto the path of obesity, metabolic syndrome, and liver disease long before they had responsibility for their own health.

"I've been overweight for as long as I can remember…": Hereditary and social determinants of disease

Clinically significant NAFLD is associated with numerous genetic, hereditary, ethnic, and social determinants, over which patients have no control. It has parallels with alcoholic liver in this regard.[60] At the genetic level, polymorphisms in PNPLA3, *TM6SF2*, and MBOAT7 have major impacts in both; this is unsurprising, as the mechanism of both diseases involves lipid dysregulation.[60,61] In a study correlating liver biopsies to genetic status, fibrosis was associated with MBOAT7 and PNPLA3 polymorphisms.[62] Recent evidence has suggested that gut microbiota dysbiosis may also predispose to liver damage.[63] While it is hoped that identifying such underlying factors could allow us to tailor management and surveillance, for physicians facing patients in the present, these associations may serve to remind them that the scarred liver is not just a manifestation of weak will.[64]

More complex still, and less well understood, are the influences of race and wealth. The influence of deprivation is felt at a young age, as shown in studies of paediatric populations with confirmed liver disease on MRI or biopsy.[65] Alarmingly, socioeconomic status may extend its influence to the post-transplant period, one study showing that graft survival was negatively affected among children from poorer areas.[66] Underlying risks driving racial and socioeconomic disparities in obesity prevalence may be poor education, unemployment, greater access to poor quality foods, poor access for physical activity, targeted marketing of unhealthy foods, and poor access to healthcare or referrals.[67] In the UK, Sir Michael Marmot's[68] report 'Fair Society Healthy Lives' clearly showed that obesity prevalence correlates to socioeconomic quintile. Ethnicity and NAFLD and its complications are clearly linked; it is unclear how much of this is due to genetic profiles and dietary changes resulting from urbanisation. From high to low, incidence varies across the Middle East, South America, Asia, North America, Europe, and Africa; globally, it affects approximately 25% of the population.[69]

"I'll refer you, but I can't guarantee they'll put you on the list…": Transplantation in older patients with comorbidity

NASH cirrhosis is diagnosed later in life than other forms of cirrhosis, and patients are more likely to have other cardiovascular comorbidities.[70,71] When hepatocellular carcinoma is found, it tends to be at a later stage.[72,73] Transplanted patients are older (typically over 65), and early complications are more common.[74,75] One-year survival is lower compared to other indication, according to one report.[76] The patient with end-stage liver disease from NASH, therefore, presents a management challenge as movement onto the liver transplant waiting list may be impeded by concerns about perioperative risk and graft utility. Referring for transplantation is therefore a complex decision. In the authors' experience, patients are often declined.

Then, there is the issue of disease recurrence. Unlike alcohol-related liver disease or viral hepatitis, where lifestyle or medical treatment are assured to reduce the risk of de novo disease in the graft, NAFLD is likely to return. A meta-analysis showed that the incidence of recurrent NAFLD was 82% at 5 years.[76] Cirrhosis related to recurrent NASH was 11–14%. An expert group that convened to discuss the phenomenon post-transplant fatty change agreed that NASH in this context was more aggressive but that, thus far, evidence was lacking to show that graft failure is more common, or overall patient survival is impaired.[77] These concerns have not led to reduced rates of transplantation for NASH on the basis of reduced utility. However, much thought is being given to strategies to reduce disease recurrence. Potential post-liver transplant treatments (beyond lifestyle and diet) include liraglutide, a glucagon-like peptide 1 receptor antagonist, and bariatric surgery.[78,79]

From the standpoint of the general hepatologist, it is clear that considerable thought needs to be

given before referring patients for transplantation, and that false hope should not be given to the older patient with overt, or a high chance of covert, comorbidity.

The ethical issues and challenges associated with NAFLD and potential solutions are presented in Table 1.

CONCLUSION

Management of NAFLD is not as straightforward as it first looks. There is no virus to supress, no single behaviour to modify, no easy prescription, and no straightforward route to transplantation. For gastroenterologists and hepatologists who see patients with NAFLD, a good understanding of hereditary factors, significant uncertainties around management, and their own potential biases or presumptions is required. Services should strive to design and embed clear criteria for referral, investigation, and subsequent discharge, if appropriate. More broadly, careful thought should be given to population screening, for there is a danger that healthy people, or those with mild disease who are unlikely to suffer liver-related morbidity, will acquire the label of disease without a clear forward plan.

Table 1: Ethical issues and challenges associated with non-alcoholic fatty liver disease and potential solutions.

Ethical Issues	Challenges	Potential Solution
'I don't have any symptoms...': diagnosing disease in health	Overdiagnosis Anxiety Insurance issues Pressure on specialist services	Open and honest conversations with patients regarding diagnosis Streamlining referral process
'Just a bit of fat in the liver': communicating pathogenesis	Explaining complex pathophysiology Addressing wider impact of disease, e.g., cardiovascular, malignancies	Multidisciplinary clinics addressing metabolic syndrome rather than just hepatological issues
Invasive investigations	Justifying biopsies: will the result change management? Ethical issues around biopsies for clinical trials	Liver biopsy in appropriately selected cases Rational use of serological markers and elastography Adequate discussion about purpose, risks, and benefits
"So, what can you do about it?": diagnosing disease when there is no effective treatment	Lack of large trials proving effectiveness of pharmacological treatments Long waiting times for bariatric surgical options	Multidisciplinary approach to obesity, including psychological support Develop bariatric endoscopy options Increase access to trials and expand evidence base
"I felt fat shamed...": attitudes to obesity among physicians	Obesity is stigmatised Conscious and unconscious bias	Empathy Psychological and dietary support
"I've been overweight for as long as I can remember...": hereditary and social determinants of disease	Socioeconomic aspects	Recognising genetic, hereditary, ethnic, and social determinants
"I can't guarantee they'll put you on the list...": transplantation in older patients with comorbidity	Transplantation challenges due to older age and cardiovascular comorbidity Recurrence	Avoid false hope and keep patients informed New treatments to prevent recurrence needed

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Primary Sclerosing Cholangitis in a Paediatric Patient: An Atypical Presentation

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Disclosure:	The authors have declared no conflicts of interest. Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.
Received:	09.08.21
Accepted:	19.01.22
Keywords:	Bile ducts, biliary obstruction, biliary stricture, cholangiography, liver, primary sclerosing cholangitis.
Citation:	EMJ Hepatol. 2022; DOI/10.33590/emjhepatol/21-00172. https://doi.org/10.33590/emjhepatol/21-00172.

Abstract

Primary sclerosing cholangitis (PSC) is an autoimmune chronic liver disease that studies have shown is rare in children. Here, a challenging case of PSC in a 13-year-old male, without preceding manifestations of inflammatory bowel disease and with evidence of biliary obstruction, is reported. The patient presented with progressive scleral icterus; their total bilirubin and alkaline phosphatase levels were raised, with negative autoimmune work-up, and an ultrasound scan of their abdomen was unremarkable. Magnetic resonance cholangiopancreatography revealed marked dilatation of the intra- and extrahepatic bile ducts, with strictures in the hepatic duct and proximal common bile duct (CBD). Endoscopic retrograde cholangiopancreatography revealed a very narrow CBD with high-grade severe biliary stricture at the common hepatic duct. A cholangiogram revealed the beaded appearance of the intrahepatic ducts, and a left percutaneous external biliary drainage tube was placed. Overall, the findings were suggestive of PSC with high-grade CBD strictures. This case is unique due to the absence of preceding clinical manifestations of inflammatory bowel disease and predominantly obstructive symptoms at the time of presentation, which is highly unusual in the paediatric population.

Key Points

1. Primary sclerosing cholangitis (PSC) usually presents in young and middle-aged males and is rare in children.

2. Paediatric patients with PSC usually experience an insidious disease course, and initially present with inflammatory bowel

3. PSC is one of the widest unmet needs in hepatology, and although some therapies show promise, trials are yet to agree on an effective treatment for the disease.

INTRODUCTION

Primary sclerosing cholangitis (PSC) is an autoimmune chronic liver disease that is mostly prevalent in young and middle-aged males, less common in females, and rare in children. Morbidity and mortality rates are high for PSC due to its progression to end-stage liver disease (ESLD), which often requires a liver transplant. Epidemiology of PSC is not well-defined in the paediatric population: studies have shown that it is an extremely rare disease in children, with a reported incidence rate that is 20% less than that of adults.[1] Most paediatric patients initially present with inflammatory bowel disease (IBD) and are found to have underlying PSC coincidentally. Unlike the adult population, PSC in paediatrics have an insidious course, with <5% of the paediatric population having dominant biliary strictures (DBS) or ESLD at the time of their diagnosis.[2] Here, an unusual and challenging case of PSC in a 13-year-old male, without preceding manifestations of IBD and with evidence of biliary obstruction at the time of diagnosis, is presented.

CASE PRESENTATION

A 13-year-old male with no significant past medical history presented to the clinic with progressive yellow discoloration of the eyes for 3 weeks, associated with multiple episodes of non-bilious, non-bloody vomiting; fever; intermittent, generalised body itching; and significant weight loss. Their initial vital signs showed a blood pressure of 93/65 mmHg, heart rate of 112 beats per min, respiratory rate of 16 breaths per min, body temperature of 37 °C, and a pulse oximetry that was 98% on room air. Physical examination was significant for scleral icterus and a non-tender, non-distended abdomen with normal bowel sounds.

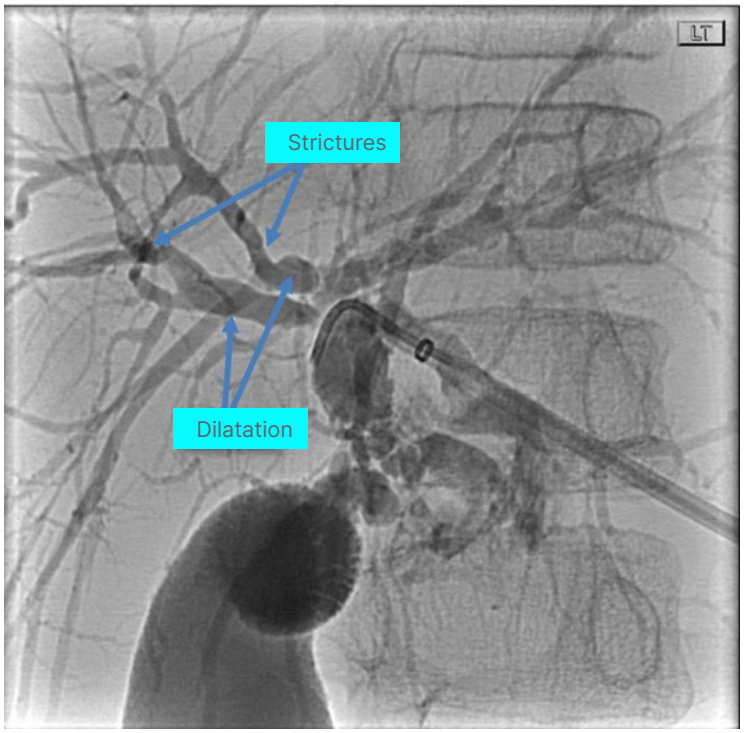
Initial lab work-up showed white blood cells: 6.70×10^3 /µL; red blood cells: 5.07×10^6 /µL; haemoglobin: 14.10 mg/dL; haematocrit: 43.3%; platelets: 441×10^3 /µL; total bilirubin: 3.80 mg/dL; direct bilirubin: 1.91 mg/dL; gamma-glutamyl transpeptidase (GGT): 96 U/L; alanine aminotransferase: 66 U/L; aspartate transaminase: 57 U/L; and alkaline phosphatase (ALP): 196 U/L. Further laboratory tests were negative for the hepatitis A antibody IgM, the hepatitis B core antigen IgM, and the hepatitis B surface antigen, and found that the level of liver–kidney microsomal antibody was <1.0 U, mitochondrial M2 antibody was <20.0 U, and smooth muscle antibody was 6.0 U.

An abdominal ultrasound revealed gallbladder wall thickening, with no shadowing calculus or pericholecystic fluid and with no common bile duct dilation. Magnetic resonance cholangiopancreatography revealed marked dilatation of the intra- and extrahepatic biliary duct, as well as areas of strictures seen in the hepatic duct and the proximal common bile duct (CBD). There was no evidence of pericholecystic fluid or a filling defect, which would suggest cholelithiasis or choledocholithiasis.

Endoscopic retrograde cholangiopancreatography (Figure 1) revealed a very narrow CBD with a high-grade severe biliary stricture in the common hepatic duct. A cholangiogram revealed areas with a beaded appearance in the intrahepatic ducts. A papillotomy was performed, but the procedure was terminated as the guidewire could not bypass the severe obstruction of the biliary stricture in the common hepatic duct. A percutaneous transhepatic cholangiogram was performed by an interventional radiologist, which demonstrated a high-grade stricture in the mid CBD with pre-stenotic dilatation. A left percutaneous external biliary drainage tube was placed, resulting in an improvement in total bilirubin and ALP levels. An ultrasound-guided liver biopsy revealed liver parenchyma with focal and loose concentric fibrosis around the bile ducts and focal periportal fibrosis, confirmed by trichrome stain.

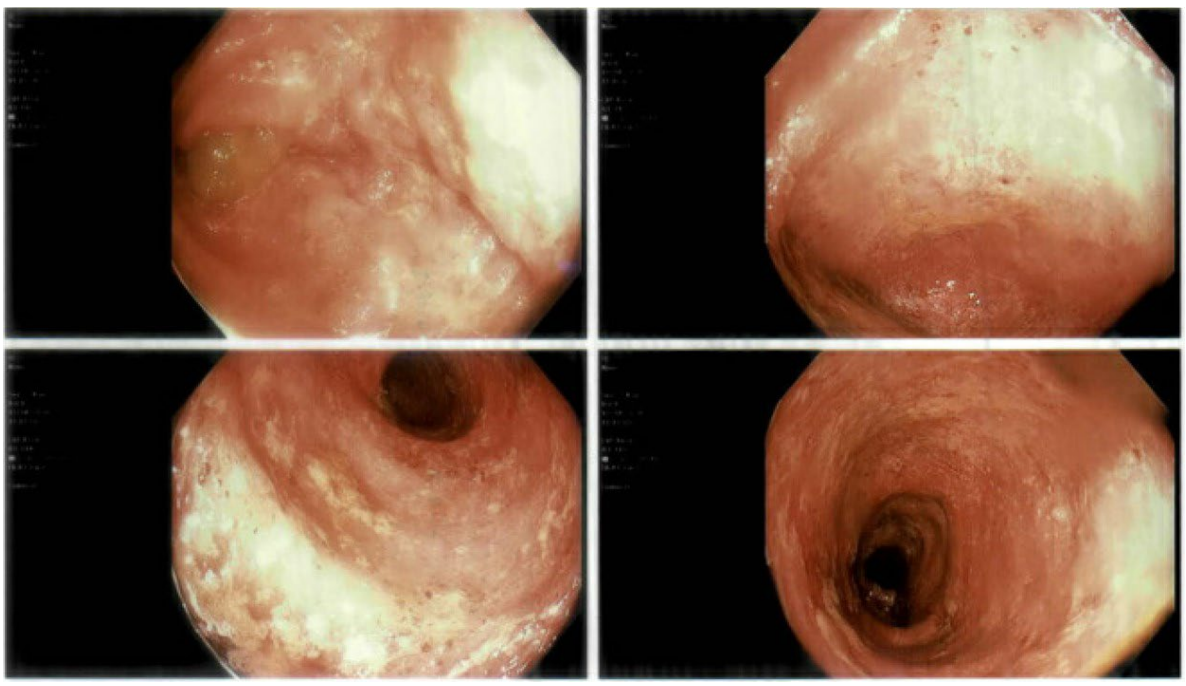
Overall, the findings were suggestive of PSC with high-grade CBD stricture. The patient was started on the fat-soluble vitamins A, D, E, and K,

Figure 1: Fluoroscopy image demonstrates dilatation of the intra- and extrahepatic biliary ductal system.



Portions of the hepatic duct and proximal common bile duct demonstrate areas of stricture.

Figure 2: Colonoscopy images revealing erythematous and ulcerated colonic mucosa.



and ursodiol (13 mg/kg daily). Their faecal occult blood test was positive, and an oesophago-gastro-duodenoscopy and colonoscopy were performed since PSC is mostly associated with IBD, specifically ulcerative colitis (UC). An endoscopy showed normal oesophageal, gastric, and duodenal mucosa; a colonoscopy (Figure 2) with biopsy revealed colonic mucosa with chronic focally active colitis with crypt distortion in both the ascending and descending colon, confirming a diagnosis of UC. The patient was started on delayed-release oral mesalamine (4 g/day).

DISCUSSION

PSC in paediatrics has an insidious course, mild symptoms, and most cases initially present without complications. The most reported symptoms are fatigue, itching, weight loss, and right upper quadrant pain. Jaundice and obstructive biliary symptoms are highly unusual at the time of the patient's presentation.[2-4] Less than 5% of the paediatric population have DBS or ESLD at the time of diagnosis. The natural course is usually progressive, with 50% of children developing clinical complications and 30% requiring liver transplantation (LT) within 10 years from the time of diagnosis.[5]

A review of the literature indicated that 60–80% of cases of patients with PSC have associated IBD, an incidence that is thought to be higher in the paediatric population. The most common phenotype of IBD is UC, and at least 10% of children with UC are affected with PSC. Diagnosis of IBD usually precedes PSC by many years. Children with PSC-IBD often have more severe mucosal inflammation compared to those who have IBD without PSC.[2,5] This case is unique due to the absence of preceding clinical manifestations of IBD and predominantly obstructive symptoms at the time of presentation, which is highly unusual in the paediatric population. This highlights the importance of considering PSC in children with features of cholestasis or abnormal liver function tests, even in the absence of IBD manifestations.

Most children with PSC have elevated levels of GGT and ALP early in the course of disease, but GGT is more specific in the paediatric population.[1,3] The gold standard imaging is magnetic resonance cholangiopancreatography, with 89% sensitivity in children,[6] and typical findings from this are dilated intra- and extrahepatic biliary ducts, with multiple areas of narrowing. The presence of dominant strictures of extrahepatic biliary tree is unusual at the time of diagnosis. As seen in this patient, DBS are most often found at the bifurcation of the hepatic duct.[7,8] In the presence of typical cholangiography changes and negative autoimmune serologic markers, a liver biopsy is not typically required for the diagnosis of PSC.[9]

PSC is recognised as having one of the largest unmet needs in hepatology, as currently there is no proven medical therapy available to delay the progression of liver disease or the onset of complications.[10] Management is mainly supportive and geared toward treating complications and palliating symptoms. The normalisation of ALP levels has been associated with improved prognosis,[11] and LT has been proven to prolong survival in patients with PSC.[12]

Transhepatic and endoscopic balloon dilatation of strictures has been shown to be useful in the palliation of symptoms. Surgical drainage procedures (e.g., portoenterostomy and choledochoenterostomy) are associated with an increased risk of cholangitis and could make the subsequent liver transplantation technically challenging.[8,13]

There have been conflicting results regarding the role of ursodeoxycholic acid (UDCA). Multiple paediatric studies have shown that UDCA is more effective than a placebo in lowering serum ALP, serum bilirubin, symptoms of pruritis, and potentially the incidence of cholangiocarcinoma, but it consistently showed no survival benefit.[8] A double-blind randomised controlled trial in adults assessing the efficacy of high-dose UDCA further complicated the use of this therapy, as significantly higher rates of death, LT, and other serious adverse events were seen in the drug-treated group, despite biochemical improvement observed.[14] The current consensus is to avoid UDCA at doses >20 mg/kg/day, and that it could be beneficial in a subset of patients with PSC who tolerate it well and have normalisation of ALP.[3,10]

The gut microbiome and PSC dysbiosis (reduced microbiota diversity) has been implicated in the

pathogenesis of the disease.[15] Oral vancomycin therapy (OVT) has shown very promising results in two previous pilot studies in the paediatric population, as 6 weeks of OVT induced sustained remission in 14 patients with non-cirrhotic PSC, resulting in the improvement of symptoms and a reduction in biochemical markers, although there was no consistent improvement in liver histology.[16,17] Similar effects in the reduction of liver biochemistry were reported in small-scale prospective adult studies. On the contrary, the largest retrospective study to date in paediatric patients by Deneau et al.[18] showed that neither patients treated with OVT nor those treated with UDCA had outcome benefits compared to the non-treatment group, and the rate of progression to ESLD was similar between the clinical groups.[18]

PSC has a waxing and waning course of inflammation. During the early stages of disease, the spontaneous normalisation of biochemical markers is common in children.[11] This characteristic feature in the natural history of PSC is likely to have contributed to the conflicting data and challenges in inferring results from the predominantly small and underpowered studies that are currently available in the literature.

CONCLUSION

Specifically in the paediatric group, PSC is a rare disease with poor prognosis. Major concerns for patients with PSC include the progression to ESLD and an increased risk of developing malignancies such as cholangiocarcinoma, gallbladder cancer, and colorectal cancer.[13] Further prospective and long-term follow-up studies are necessary to expand the current literature in order to better understand and manage this disease.

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Paediatric Acute-on-Chronic Liver Failure: A Review of Current Evidence in Children

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Disclosure: The authors have declared no conflicts of interest.

Received: 09.03.22

Accepted: 13.06.22

Keywords: Cirrhosis, chronic liver disease, liver failure, multiorgan failure, paediatric.

Citation: EMJ Hepatol. 2022;10[1]:64-73. DOI/10.33590/emjhepatol/22-00084. https://doi.org/10.33590/emjhepatol/22-00084.

Abstract

Acute-on-chronic liver failure (ACLF) is a syndrome that describes acute decompensation of chronic liver disease with differing definitions worldwide, but is universally associated with high short-term mortality. This is becoming increasingly recognised as a unique entity that affects both adults and children. This narrative review summarises the current available evidence from paediatric studies on definition, incidence, pathophysiology, and outcome, with reference to data on ACLF from adult literature. Paediatric data remain scarce, and study groups have used differing inclusion criteria that have limited generalisability of data. There is a crucial need for a consensus definition for paediatric ACLF so that future collaborative research may provide better understanding on the epidemiology, pathophysiology, risk factors, and outcome of this clinical entity.

Key Points

1. The underlying causes of paediatric acute-on-chronic liver failure (ACLF) are varied, with Wilson's disease, autoimmune liver disease, and hepatitis B contributing to its aetiology.

2. While the only possible treatment for paediatric ACLF is transplantation, the condition can be supported through therapies to manage hepatic and extrahepatic complications.

3. Studies have shown the importance of monitoring ACLF in order to prevent short-term mortality through emergency transplantation in a 'golden window' of time.

INTRODUCTION

There is growing recognition of acute-on-chronic liver failure (ACLF) as a distinct clinical syndrome that portends excessively high short-to-medium term mortality rates in patients with chronic liver disease (CLD).[1] ACLF is characterised by severe, acute hepatic decompensation in patients with underlying CLD, with or without cirrhosis, resulting in liver failure and failure in

one or more extrahepatic organs, and associated with increased risk of death within 28 days–3 months from onset. The definitions proposed by the Asian Pacific Association for the Study of the Liver (APASL)[2] and the European Association for the Study of the Liver–Chronic Liver Failure (EASL-CLIF) Consortium[3] are most frequently used in studies on adult patients. However, it remains that there is no universally accepted consensus on the definition or diagnostic criteria for ACLF. Moreover, paediatric data is significantly lacking, and ACLF in children remains poorly defined. In recent years, there has been greater awareness and interest in this topic, and new studies have emerged that provide better understanding of ACLF in paediatric patients with CLD.

In this review, the authors aim to highlight and summarise current and latest evidence on definition, epidemiology, pathophysiology, management, and outcome of ACLF in children.

DEFINITION AND DIAGNOSTIC CRITERIA

There are different definitions proposed by various international hepatology societies, with the main distinction being the inclusion of extra-hepatic organ failure as a major criterion (Table 1). The definition provided by the APASL in 2009,[2] and subsequently updated in 2014[4] and 2019,[5] characterises ACLF as an acute hepatic insult manifesting as jaundice and coagulopathy complicated within 4 weeks by ascites and/or hepatic encephalopathy (HE) in a patient with previously diagnosed or undiagnosed chronic liver disease (CLD) or cirrhosis. Notably, the APASL definition excludes patients with prior decompensation, focuses primarily on liver dysfunction, and considers only intrahepatic insults as precipitating factors, and extrahepatic factors such as bacterial infections as a consequential complication.

On the other hand, the European Association for the Study of Liver–Chronic Liver Failure (EASL–CLIF) consortium defined ACLF in the CANONIC study in patients with compensated cirrhosis and/or prior episode(s) of decompensation based on the failure of one or more organs including the liver, and included patients with hepatic and/or non-hepatic insults.[3] The CLIF-SOFA (sequential organ failure assessment) and its simplified version, CLIF Consortium Organ Failure (CLIF-C OF) scores are calculated based on severity of organ failure in hepatic, renal, neurologic, haematology, circulatory, and respiratory systems, and mortality in ACLF correlates with the ACLF grade that is based on number of

Table 1: Comparison of current definitions for acute on chronic liver failure.

Society	Definition
APASL	Acute hepatic insult with jaundice and coagulopathy complicated within 4 weeks by ascites and/or encephalopathy in a patient with chronic liver disease or cirrhosis. Patients with known, prior decompensation (existing jaundice, encephalopathy or ascites) are excluded.
EASL	Acute deterioration of pre-existing compensated or decompensated cirrhosis, usually related to a precipitating event which can be hepatic or systemic (extrahepatic), and associated with organ failure in one or more of six major organ systems based on CLIF-SOFA scale.
NASCELD	Acute deterioration of cirrhosis, with or without prior episode(s) of decompensation, with two or more extrahepatic organ failures.

APASL: Asian Pacific Association for the Study of the Liver; EASL: European Association for the Study of the Liver; NASCELD: North American Consortium for the Study of End Stage Liver Disease.

organ failures.[6] In the EASL-CLIF definition, precipitating disorders may include intrahepatic, extrahepatic (including infection, gastrointestinal haemorrhage), or both.

Similarly, the North American Consortium for the Study of End-Stage Liver Disease's definition of acute-on-chronic liver failure (NACSELD-ACLF)[7-9] involves acute deterioration of cirrhosis with failure in two or more extrahepatic organs.

Although these definitions have been derived from adult populations, they have also been adapted for use in children by various paediatric groups. The APASL definition was used as a basis for several paediatric studies,[10,11] whereas Godfrey et al.[12] and Bolia et al.[13] adapted the CLIF-C OF and CLIF-SOFA scores by modifying creatinine derangements and classifying cardiorespiratory failure according to age-appropriate cut-offs. One recent North American single-centre study by Banc-Husu et al.[14] identified paediatric ACLF cases using the NACSELD-ACLF criteria.

With such heterogeneity in definitions and inclusion criteria, it is virtually impossible to generalise the findings and draw meaningful conclusions from current paediatric studies. In the updated 2019 APASL consensus,[5] major limitations were acknowledged in existing definitions derived from adult populations, among which clinical identification of HE and ascites may often be difficult in young children, and some paediatric liver diseases can present with hepatic failure without significant hyperbilirubinaemia. There is a pressing need to develop and validate the definition of paediatric ACLF to allow early identification and treatment, accurate prognostication, and facilitate global collaborative research efforts.[15,16]

PATHOPHYSIOLOGY

The concept of 'predisposition, injury, response, organ failure' (PIRO) in explaining the pathophysiological basis of ACLF has been very elegantly described by Jalan et al.[17] in their 2012 review paper. To briefly summarise this concept, predisposition refers to the underlying chronic liver disease or cirrhosis and severity of hepatic dysfunction and extra-hepatic organ involvement. A precipitating injurious event such as drug-induced liver injury, superimposed viral hepatitis, variceal bleeding, or sepsis may then exacerbate liver injury, leading to acute decompensation in hepatic function. An abnormal systemic inflammatory response syndrome ensues which may then lead to an over-compensatory anti-inflammatory response and 'immune paralysis' in both the innate and adaptive immune systems. Although the exact mechanism of this immune dysregulation is unclear, infections are recognised as common triggers and complications of ACLF, which further heighten the pro-inflammatory response in a vicious cycle and are associated with complications such as HE, renal dysfunction, rebleeding and increased mortality. Ongoing infection, endotoxaemia, pro-inflammatory state and systemic inflammatory response syndrome result in dysregulation of systemic and hepatic haemodynamics, each factor variably contributing to end-organ dysfunction including decreased hepatocyte function with cholestasis and coagulopathy, HE and cerebral oedema, acute kidney injury, subclinical myocardial injury and circulatory failure, and acute respiratory distress syndrome.

EPIDEMIOLOGY

Epidemiological data on ACLF in children are limited to single-centre studies using different inclusion criteria, and comprising very heterogeneous patient groups. The incidence of ACLF, as defined by APASL criteria, was reported by Lal et al.[11] and Alam et al.[18] to be 11–14% of paediatric patients with chronic liver disease from two single-centre studies in India. A single-centre study from the USA using an adapted NACSELD reported an incidence of 14% among 144 children with chronic liver disease listed for transplant, and found that ACLF accounted for 12% of hospitalisations for decompensated cirrhosis.[14] By contrast, using a modified paediatric-CLIF definition, ACLF made up 2.3% of all children listed for liver transplantation on the Organ Procurement and Transplantation Network.[12] There has also been published data on incidence of ACLF among specific patient sub-populations. For example, ACLF, diagnosed based on EASL-CLIF criteria, was reported to occur in 20% of patients with biliary atresia, which is the most common cause of chronic liver disease in children.[19] Other studies have

also found that ACLF accounted for nearly 18% of patients with liver cirrhosis admitted to the paediatric intensive care unit.[20]

In the adult population, the incidence of ACLF similarly differs based on the definition used. A study of 72,316 patients with decompensated cirrhosis has shown that the prevalence of ACLF was 26.4% and 9.8% based on the European and North American definitions, respectively.[21,22] In another study of 80,383 adult patients with cirrhosis, 783 patients developed ACLF that fulfilled both EASL-CLIF and APASL criteria; 4296 developed EASL-CLIF ACLF alone; and 574 developed APASL ACLF alone. The overall incidence rate of ACLF in adult patients with liver cirrhosis using APASL criteria was 5.7 per 1,000 person-years, whereas the incidence rate of ACLF using EASL-CLIF criteria was 20.1 per 1,000 person-years.[23]

UNDERLYING AETIOLOGY OF CHRONIC LIVER DISEASE

While alcoholic cirrhosis, non-alcoholic steatohepatitis, and chronic hepatitis B have been reported consistently as the predominant aetiologies of chronic liver disease in adults,[3,7-9] the aetiology of primary liver disease in children with ACLF is more varied among studies. Paediatric studies from Asia using the APASL criteria have found Wilson's disease (41–52%) and autoimmune liver disease (13–42%) to be the most common underlying liver disorders, followed by viral hepatitis B accounting for around 5.6–6.5%.[10,11,18,24] These were in contrast to findings from a limited number of North American studies that have used the adapted EASL-CLIF and NACSELD criteria for ACLF, which found biliary atresia to be the predominant aetiology of chronic liver disease, accounting for approximately half of cases that presented with ACLF.[12,14] This disparity may be explained with the following reasons. The APASL definition includes patients with only intrahepatic insults, such as acute flare of underlying liver disease and superimposed or reactivated viral hepatitis; hence, this may explain the higher representation of autoimmune hepatitis and Wilson's disease, as well as viral hepatitis triggers in the Asian cohorts. To support this point, Jagadisan et al.[25] explained in their study that the small number of biliary atresia cases in their series was due to the the premature follow-up of young patients with biliary atresia, which did not allow sufficient time to assess exposure to acute insults specifically from infection with hepatotropic viruses. The gradual progressive nature of liver dysfunction in biliary atresia also meant that majority of these children with chronic, progressive cholestasis and decompensation would be excluded from APASL definition. By contrast, the European and North American criteria provide broader definitions of acute triggers of decompensation that include intra and extrahepatic events such as bacterial infections. Studies using these criteria may include a wider variety of liver disorders, including biliary atresia. Moreover, geographic factors may influence the prevalence of specific liver disorders and hepatotropic viruses. Nonetheless, until a standardised criteria is used across studies, it will be impossible to draw any conclusion on aetiologic factors associated with paediatric ACLF.

PRECIPITATING TRIGGERS

Data on the precipitating triggers of ACLF in children are mostly from studies from India using the APASL criteria. Superimposed viral hepatitis (majority hepatitis A and E viruses) accounted for 22–81% of acute insults leading to ACLF, while poor control of underlying autoimmune liver disease or Wilson's disease (13–48%) and drug induced liver injury (6–11%) were other common triggers.[10-12,18,25,26] Although, the APASL definition includes only hepatic insults as a cause of ACLF, Jagadisan et al.[25] reported that the concomitant presence of bacterial sepsis with hepatotropic virus in 41% of children with ACLF (7 out of 17) was associated with a higher mortality rate of 71%, as compared to 59% without bacterial sepsis. Compared to 20 children with biliary atresia from the UK described by D'Souza et al.[19] using the EASL-CLIF criteria, ACLF was precipitated by sepsis (45%) and gastrointestinal bleeding (40%). Similarly, gastrointestinal bleeding (30%) was found to be an important triggering event leading to decompensation in North American children with ACLF from Banc-Husu et al.'s study.[14] It is noteworthy that distinct geographic backgrounds of the different populations that were studied do play a significant role, as hepatitis A and E are highly endemic in India, but are not as prevalent in Western countries.

In adults, the main triggers are bacterial infections, relapse of hepatitis B, active alcoholism, and gastrointestinal bleeding.[21,27] Interestingly in 20–50% of cases of adult ACLF, the trigger remains unknown,[21,28] and this is similarly reflected in a paediatric study where no cause was found in 23% of ACLF.[10]

OUTCOME AND PROGNOSTIC SCORES

Across all definitions and population groups, mortality rates for both paediatric and adult ACLF are universally high, emphasising the need for early recognition and expedited treatment of ACLF. The overall mortality rate without transplantation in children is 25% at 28 days, rising to 30–50% within 90 days,[12,24] which are relatively consistent with mortality rates derived from adult studies that quote a mortality rate of 25–40% at 28 days[6,22,27] and 40% at 90 days.[22]

In adult studies, the CLIF-C OF score has been shown to have higher predictive accuracy than model for end stage liver disease in predicting survival.[29] The score takes into account the number of organ failures, and incorporates age and white cell count to calculate an ACLF score with a predicted mortality rate. However, this has not been validated for use in children. For children, a paediatric adaptation of the chronic liver failure sequential organ failure assessment (pCLIF-SOFA) score has been created that scores six impairments (respiratory, neurologic, circulatory, haematological, renal, and liver) based on paediatric-appropriate cut-offs (Table 2). A pCLIF-SOFA score of ≥11 identified 28-day mortality with a sensitivity of 94.9% and specificity of 91.5%.[13] When comparing the pCLIF-SOFA to the paediatric end stage liver disease (PELD) score, both pCLIF-SOFA and PELD scores at cut-off values >8 and >30 respectively on admission predicted death in children with acute liver failure (ALF) with high sensitivity, with pCLIF-SOFA demonstrating superior specificity, positive predictive value, and negative predictive value as compared to PELD.[30] Claude et al. also showed that a pCLIF-SOFA score of >9 was predictive of mortality within 28 days with a sensitivity of 87.8% and a specificity of 77.3%, while a pCLIF-SOFA score of >7 was associated with increased odds of liver transplantation on day-60.[20]

Lal et al.[24] evaluated the APASL ACLF Research Consortium (AARC) acute-on-chronic liver failure (AARC-ACLF) score and its paediatric-adapted version (Table 2) in prognosticating ACLF in children. The authors found that AARC-ACLF and CLIF-SOFA scores were superior to other prognostic scores in paediatric ACLF, and paediatric modifications of AARC-ACLF and CLIF-SOFA did not perform better than their original scores, all having AUROC of greater than 0.9 for predicting poor outcome in paediatric ACLF. A cut-off of 11 or more in these scores, and/or an increasing score at Day 4, were found to be predictive of death or liver transplantation.

Table 3 summarises and compares the differences between paediatric and adult ACLF.

MANAGEMENT

The mainstay of treatment is early diagnosis of ACLF to treat the precipitating event and then provide supportive therapy to hepatic and extrahepatic complications. Whilst there are several therapeutic options to help delay progression of ACLF, the only definitive life-saving therapeutic option is liver transplantation.

Based on paediatric studies,[10,18,25] suggested investigations to identify the trigger such as bacterial cultures from blood, urine, and stool; testing for hepatotropic viruses such as hepatitis A–E, cytomegalovirus, Epstein–Barr virus, herpes simplex virus, parvovirus, human herpes virus-6 and enterovirus; fungal studies; and toxicology studies should be considered. For the underlying cause of liver cirrhosis if not yet diagnosed, screening for autoimmune hepatitis, Wilson's disease, as well as other metabolic liver disorders may be performed. Hepatobiliary imaging such as with ultrasonography may confirm features related to cirrhosis and portal hypertension, and also allows objective assessment of ascites. To assess hepatic function, the prothrombin time, international normalised ratio, serum glucose, ammonia, lactate, bilirubin, albumin, ammonia, and liver transaminases should be checked. Initial antimicrobial coverage for patients with ACLF should include broad spectrum antibiotics and antifungals.

Depending on the complications of liver failure, supportive treatment would include fluid and

Table 2: Paediatric adaptations of the chronic liver failure sequential organ failure assessment (pCLIF-SOFA) score and Asian Pacific Association for the Study of the Liver (APASL) acute-on-chronic liver failure (ACLF) Research Consortium (AARC) acute on chronic liver failure (AARC-ACLF-Paediatric) score.

pCLIF-SOFA					
	0	1	2	3	4
Respiratory (PaO2/FiO2)	>400	<400	<300	<200	<100
Neurologic (Grade of HE)	No HE	1	2	3	4
Circulatory	No hypotension	Systolic BP <5th centile for age	Dopamine <5 µg/kg/min	Dopamine >5 µg/kg/min or epinephrine ≤0.1 µg/kg/min or norepinephrine ≤0.1 µg/kg/min	Dopamine >15 µg/kg/min or epinephrine ≥0.1 µg/kg/min or norepinephrine ≥0.1 µg/kg/min
Haematological (INR)	≤1.1	>1.10–<1.25	≥1.25–<1.50	≥1.50–<2.50	≥2.50
Renal (serum creatinine)	Normal for age	1–≤2 ULN	>2–≤3 ULN	>3 ULN	Use of renal replacement therapy
Liver (serum bilirubin mg/dL)	<1.2	≥1.2–<2.0	≥2.0–<6.0	≥6.0–<12.0	≥12.0
AARC-ACLF-Paediatric					
Points	Total bilirubin (mg/dl)	HE grade	INR	Lactate (mmol/l)	Creatinine (rise from baseline)
1	<15	0	<1.8	<1.5	<1.5x
2	15–25	1–2	1.8–2.5	1.5–2.5	1.5–≤3x
3	>25	3–4	>2.5	>2.5	>3x or need for renal replacement therapy

HE: hepatic encephalopathy; INR: international normalised ratio; ULN: upper limit of normal.

electrolyte management, intravenous Vitamin K supplementation, fresh frozen plasma and/or platelet infusion for active clinical bleeding, albumin replacement, diuretics and/or paracentesis for ascites, vasoactive drug therapy and/or gastroscopy for variceal bleeding, neuroprotective measures for encephalopathy, dextrose infusions for hypoglycaemia, and/or dialysis for hepatorenal syndrome.

In view of the high short-term mortality rate, it is suggested that patients who show no clinical improvement at 3–7 days after ACLF is diagnosed should be considered for emergency liver transplantation (LT).[31] The majority of patients achieved their final grade of ACLF within the first week. A paper published by the APASL ACLF Research Consortium[32] also proposed a 7-day threshold, or the 'golden window' for organ support, or prioritisation for definitive organ

Table 3: Comparison between paediatric and adult acute-on-chronic liver failure.

	Paediatric	Adult
Incidence of ACLF: acute-on-chronic liver failure	11–20%[11,14,18-20]	10–26%[21-23]
Underlying aetiology of chronic liver disease	Wilson's disease, autoimmune hepatitis, hepatitis B, biliary atresia[10-12,14,18,24]	Alcoholic cirrhosis, non-alcoholic steatohepatitis, and chronic hepatitis B[3,7-9]
Pathophysiology	Systemic inflammation resulting in single or multiple organ failure[17]	
Triggers	Acute viral hepatitis, flare of underlying disease, sepsis, gastrointestinal bleed, drugs[10-12,25,26,28]	Alcohol, drugs, bacterial infection, massive gastrointestinal haemorrhage[21,27,28]
Outcome/survival rates	25% mortality at 28 days and 30–50% at 90 days[12,14]	25–40% mortality at 28 days and 40% at 90 days[6,22,27]

Table 4: Summary of relevant paediatric studies on acute-on-chronic liver failure.

Study	Country	Number of subjects	Definition used	Aetiology of CLD	Trigger	Outcome
Lal et al. (2011)[10]	Chandigarh, India (December 2007–May 2009)	31 children with ACLF	APASL	AIH (41.9%) WD (41.9%) Hepatitis B (6.5%)	Hepatitis A (41.9%) Hepatitis E (9.7%) Flare of underlying disease (12.9%) Drugs (6.5%) Cholangitis (3.2%) Gastrointestinal bleed (3.2%) Indeterminate (22.6%)	19.4% mortality
Jagadisan et al. (2012)[25]	Lucknow, India (January 2000–January 2010)	17 out of 36 (47%) children with CLD	APASL	WD (41.0%) AIH (18.0%) Cryptogenic (35.0%)	Hepatitis E (81.0%) Other hepatotropic viruses (19.0%)	59.0% mortality without bacterial sepsis; 71.0% with bacterial sepsis
Lal et al. (2015)[26]	New Delhi, India (December 2010–February 2015)	41 out of 439 children with CLD (9.2%)	APASL	WD (52%) AIH (29.7%) Cryptogenic (11.1%)	Viral infection (22.2%) Drugs (14.8%) Flare of underlying disease (44.0%)	34.0% mortality; 5.0% received LT
Alam et al. (2016) [11]	New Delhi, India (January 2011–December 2014)	56 (11.2%) out of 499 children with CLD	APASL	WD (42.8%) AIH (32.1%) Cryptogenic (12.5%) BA (5.6%) Hepatitis B (5.6%) Hepatic venous outflow tract obstruction (1.8%)	Flare of underlying disease (48.2%) Viral hepatitis: Hepatitis A, E, and EBV (30.0%) Drugs (10.7%) Cholangitis (3.6%)	30.4% mortality; 8.9% received LT

Table 4 continued.

Study	Country	Number of subjects	Definition used	Aetiology of CLD	Trigger	Outcome
D'Souza et al. (2019)[19]	London, UK (1999–2003)	20 out of 99 children with biliary atresia (20.0%)	EASL	BA only	Gastrointestinal bleed (40.0%) Viral sepsis (22.0%) Bacterial sepsis (22.0%)	20.0% mortality
Lal et al. (2018)[24]	New Delhi, India (January 2011–January 2018)	86 out of 640 children with CLD (13.4%)	APASL	WD (46.5%) AIH (34.9%) Hepatitis B (5.8%) BA (3.5%) Hepatic vein outflow tract obstruction (1.1%) Cryptogenic (8.1%)	N/A	25% mortality at 28 days; 66.7% native liver survival at 28 days. 29.8% mortality at 90 days; 61.9% native liver survival at 90 days
Lal et al. (2018)[18]	New Delhi, India (August 2011–December 2014)	84 out of 602 children with CLD (14.0%)	APASL	WD (45.2%) AIH (35.7%)	Viral hepatitis: Hepatitis A, B, E, and EBV (34.5%)	N/A
Banc-Husu et al. 2020[14]	USA (January 2007–December 2017)	20 out of 144 children listed for liver transplantation (14.0%)	NACSELD	BA (55.0%)	Cholangitis 4.0% Gastrointestinal bleed 30.0%	22.0% mortality; 57.0% received LT
Sharma et al. (2020)[38]	Chandigarh, India (January 2017–March 2018)	35 children with ACLF	APASL	WD (45.2%) AIH (13.0%) Alagille syndrome (6.4%) Mitochondrial disease (3.2%)	Hepatitis A (25.8%) Hepatitis E (12.9%) CMV (2.8%) Parvovirus B19 (16.1%)	N/A
Claude et al. (2020)[20]	Four European paediatric ICUs (2011–2016)	23 children out of 130 children with cirrhosis admitted into ICU (17.7%)	EASL	N/A	Sepsis (26.0%)	N/A
Godfrey et al. (2021)[12]	USA (March 2002–2017	264 out of 11,300 children on liver transplant waitlist (2.3%)	pCLIF	BA (48.1%) AIH (1.1%) PSC (0.8%) Genetic/metabolic (11.0%), PN-associated liver disease (13.2%)	N/A	46.6% 90-day mortality from listing

ACLF: acute-on-chronic liver failure; AIH: autoimmune hepatitis; APASL: Asian Pacific Association for the Study of the Liver; BA: biliary atresia; CLD: chronic liver disease; CMV: cytomegalovirus; EASL: European Association for the Study of the Liver; EBV: Epstein–Barr virus; LT: liver transplantation; N/A: not applicable; NASCELD: North American Consortium for the Study of End Stage Liver Disease; pCLIF: paediatric chronic liver failure; PN: parenteral nutrition; PSC: primary sclerosing cholangitis; WD: Wilson's disease.

transplant prior to onset of sepsis to improve survival.

Extracorporeal liver support systems (ECLS) are used to prolong the window of opportunity while awaiting LT in both adults and children with liver failure. An effective ECLS system should perform three primary hepatic functions: detoxify, stimulate liver regeneration, and prevent further injury to the liver.[33] Numerous systems have been investigated, but no system has demonstrated improvement to mortality in ACLF in prospective trials. Molecular adsorbent recirculating system has shown significant improvement to serum bilirubin and creatinine levels within 4 days, and reduction in the proportion of patients with clinically significant hepatic encephalopathy.[34]

Granulocyte colony-stimulating factor (GCSF) has shown promising results in improving survival rate and prognosis of patients with liver failure.[35] GCSF has been reported to reduce the rate of complications such as sepsis and multiorgan failure, possibly from improved neutrophil function and immunomodulation.[36] The mechanism of GCSF in the treatment of ACLF remains unclear, but has been proposed to involve the promotion of hepatocyte regeneration and facilitation of migration, proliferation, and differentiation of stem cells into the damaged liver. A meta-analysis of six clinical studies by Huang et al.[35] suggested that GCSF may optimise the efficacy of medical treatment or ECLS in patients with ACLF, hence preventing progression of multiple complications and multiorgan failure. However, a multicentre, prospective, open-label Phase II study[37] that was published just after the aforementioned meta-analysis, reported no significant benefit in patients with ACLF versus standard medical therapy alone. The 90-day transplant-free survival rate in the GCSF patient group was 34.1% compared with 37.5% in the standard medical therapy group. Transplant-free and overall survival rates, liver function scores, and infection rates at 360 days did not differ between the two groups. The aforementioned studies were mainly conducted in adult patients, but a study investigating the benefits of GCSF in paediatric ACLF patients also reported ineffectiveness in improving the survival outcome on Days 30 and 60 of therapy.[38]

LT remains the only definitive therapeutic option in patients who do not recover from ACLF. Numerous studies have shown good 1-year survival rates (81–92%) in ACLF patients post-LT.[39-41] Identification of patients with ACLF who would benefit from early liver transplantation and organ allocation remains unclear in both the adult and paediatric populations.[42,43]

CONCLUSION

ACLF is increasingly recognised as a clinical syndrome of critical importance in patients with chronic liver disease and cirrhosis associated with significant mortality. Current paediatric literature remains scarce, and study groups have used differing inclusion criteria that have limited generalisability of data (Table 4). There is a pressing need for international paediatric groups and societies to develop and validate the diagnostic criteria for paediatric ACLF, so that further collaborative research may provide greater understanding on the epidemiology, pathophysiology, risk factors, and outcome of this clinical entity.

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Non-alcoholic Steatohepatitis: Global Impact and Clinical Consequences

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Disclosure: Younossi has received research funds or served as consultant to Bristol Myers Squibb, Gilead Sciences, Intercept Pharmaceuticals, Madrigal, Merck, NovoNordisk and Siemens. Henry has no conflict of interest to disclose. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Received: 16.05.22

Accepted: 01.07.22

Keywords: Non-invasive tests, progression, regression, treatment.

Citation: EMJ Hepatol. 2022;10[1]:74-83. DOI/10.33590/emjhepatol/22-00150. https://doi.org/10.33590/emjhepatol/22-00150.

Abstract

Non-alcoholic steatohepatitis (NASH) is the potentially progressive form of non-alcoholic fatty liver disease (NAFLD). NAFLD and NASH are very common in most regions of the world and are on trajectory to become the most common liver disease at a global scale. Risk for high prevalence and progressiveness include visceral obesity and Type 2 diabetes. The conundrum of NAFLD is related to the rapid increase in its global burden with very low awareness among most general providers, as well as a lack of widespread availability of fully validated non-invasive diagnostic and prognostic tests and limited treatment options. Currently, lifestyle modification with diet and exercise are the best options. A large number of clinical trials are being developed to provide drug therapeutic options with patients with NASH and moderate to advanced fibrosis.

Key Points

1. There is limited knowledge about non-alcoholic fatty liver disease (NAFLD) in general healthcare settings, despite a rapid increase in global diagnoses.

2. There exist limited treatment options for NAFLD, and a lack of widespread availability of diagnostic testing.

3. Researchers are developing clinical trials in order to provide therapeutic drug options for patients with non-alcoholic steatohepatitis (NASH), the potentially progressive form of the disease.

EPIDEMIOLOGY

Changing socioeconomic conditions around the world have led to environmental changes promoting major chronic diseases.[1] In this context, there has been a rapid increase in the prevalence of obesity and Type 2 diabetes (T2D). While these disease states are associated with many chronic diseases, they are also the drivers for one of the leading causes of chronic liver disease, specifically non-alcoholic fatty liver disease (NAFLD).[2-8] NAFLD, a biologically and clinically heterogeneous disease, is an umbrella term used to describe a broad spectrum of histological conditions that are characterised by hepatic fat accumulation. A subtype of NAFLD or non-alcoholic steatohepatitis (NASH) is histologically diagnosed with hepatic fat in conjunction with liver cell injury. NASH is associated with an increase in both hepatic and non-hepatic morbidity and mortality, as well as impairment of health-related quality of life and substantial economic burden.[9-19]

Currently, 25–30% of the adult population are estimated to have NAFLD, while 8–10% of children and young adolescents are reported to have NAFLD. These prevalence rates are higher in populations with obesity and diabetes.[20] In contrast, it is important to recognise that NAFLD can be found in those who are not obese (sometimes referred to as lean NAFLD).[21-24] In fact, up to 40% within the NAFLD adult population can be considered to be non-obese.[24] Despite the non-lean terminology, most of these patients have insulin resistance and may have visceral obesity.[22-24]

It is estimated that about 15–20% of patients with NASH can progress, leading to the development of cirrhosis, hepatocellular carcinoma (HCC), end-stage liver disease, and death.[2,3] In fact, NASH is the second most common indication for liver transplantation in the USA.[25] From all cancers globally, HCC is now the second leading cause of years of life lost, and NASH is a growing cause of HCC.[2]

Within the younger population, NAFLD can be diagnosed around the age of puberty (11–13 years old) and about a quarter of these children may already have NASH.[26-28] In addition, it has been reported that for each 1-unit gain in BMI Z-score among children aged 7–13 years, the risk for cirrhosis is increased by 16% in adulthood.[28] These data are worrisome as it indicates the potential growing wave of NASH-related liver disease in the decades to come.

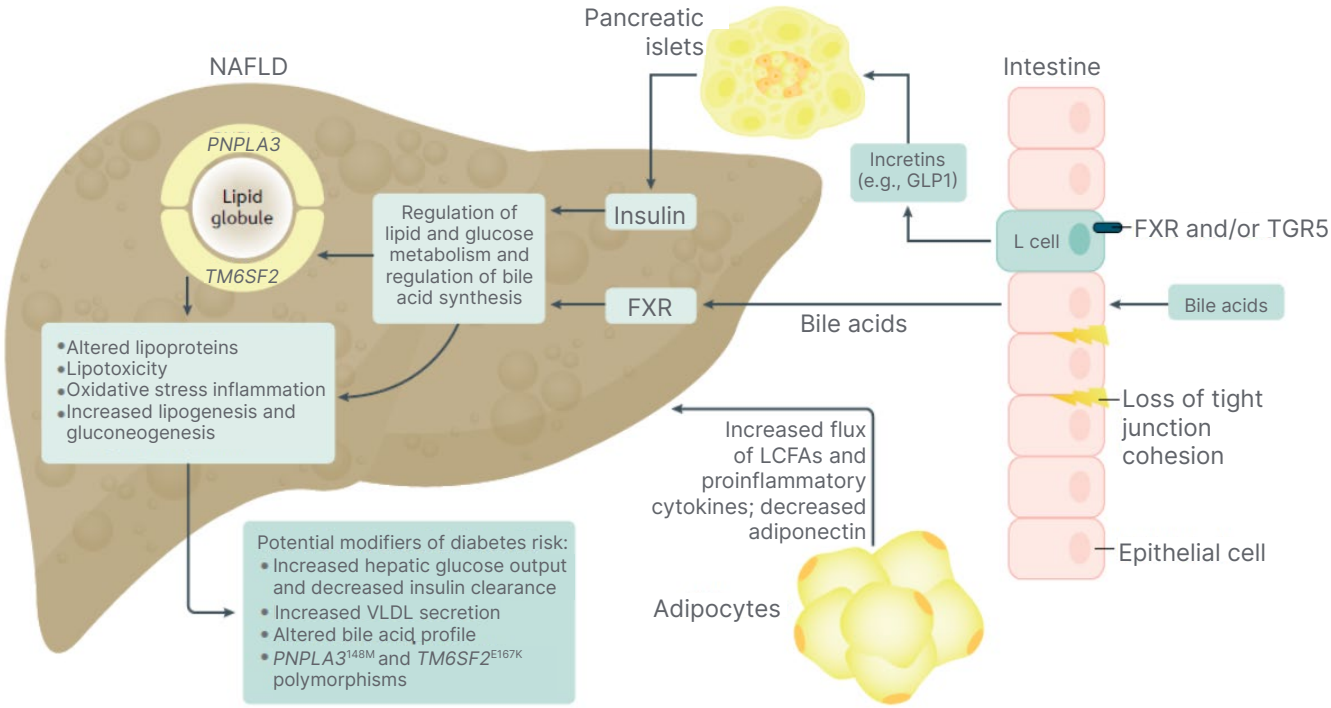
Finally, the consensus is that the prevalence of NAFLD increases with age. The peak prevalence of NAFLD for males is between the ages of 50–60 years (29.3%),[29] while for females the peak time is noted for those over the age of 65 (25.4%).[30,31] Based on NHANES III data, the prevalence rates for males by age have been cited as 16.1% in those aged 30–40 years old; 22.3% in those aged 41–50 years old; and 27.6% in those over 60 years old.[30] For females, the prevalence of NAFLD was 12.5% in those aged 30–40 years old; 16.1% in those aged 41–50 years old; and 21.6% for those 51–60 years.[30] During assessment of disease burden according to gender, researchers found that females aged 50 years and older were 17% more likely to develop NASH, and 56% more likely to develop advanced fibrosis compared with males of similar ages.[31]

PATHOPHYSIOLOGY OF NON-ALCOHOL FATTY LIVER DISEASE NON-ALCOHOLIC STEATOHEPATITIS

As noted, NASH is part of the systemic disease that is multifactorial with complex metabolic associations. Insulin resistance, T2D, and visceral obesity appear to be key pathogenic drivers for the development of NASH.[1,21] They contribute to increased levels of free fatty acids and carbohydrates, which then places excess lipotoxic and metabolic loads on the liver leading to hepatic lipid accumulation, liver cell injury, inflammation, activation of Stellate cells, and fibrosis (Figure 1).[32-34]

Importantly, a significant amount of focus has been given to the pathophysiology of NAFLD and T2D.[35] NAFLD is thought to be associated with hepatic and peripheral insulin resistance, which causes the systemic release of pro-inflammatory cytokines and hepatokines, which promote the development of T2D.[35] Another recent study demonstrated that the presence of a fatty liver drives the liver–pancreatic α-cell axis increases glucagon production, which then contributes to the diabetes pathophysiology.[36] In this context, the risk of T2D incidence has also been reported to increase as the severity of NAFLD

Figure 1: Pathophysiology of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis.



FXR: farnesoid-X receptor; GLP1: glucagon-like peptide-1; LCFA: long-chain fatty acid; NAFLD: non-alcoholic fatty liver disease; TGR: G protein-coupled receptor; VLDL: very-low-density lipoprotein.

increases. In fact, the presence of NAFLD has been associated with a 2.2 times greater chance of developing T2D, and patients with more advanced stages of liver fibrosis are at even a higher risk of T2D; however, if NAFLD improves or resolves, the risk for diabetes is reduced.[37] In fact, another study found that the presence of NAFLD increased the risk of metabolic syndrome to almost the same degree.[38]

There also appears to be a genetic predisposition involved in the development of NASH. Specifically, the polymorphisms of *PNPLA3* and *TM6SF2* genes predispose these patients to NASH, and potentially adverse outcomes.[34] Environmental factors such as a poor food environment (easy availability of calorie dense processed food), lack of easy access to safe areas for physical activity, poor sleep, and stress may all influence the onset and severity of NAFLD and NASH.[39-43]

NASH DIAGNOSIS

Hepatic steatosis is defined as an accumulation of triglycerides in >5% of hepatocytes is the first step required for diagnosing NAFLD and NASH. In this light, ultrasound is recommended for those at high-risk for NAFLD (e.g., those with components of metabolic syndrome but especially obesity and T2D).[44] In fact, a recent meta-analysis determined that the use of conventional ultrasound has greater diagnostic accuracy than originally thought, especially for those with mild as well as moderate-severe hepatic steatosis (≥30% steatotic hepatocytes).[45] In contrast, the diagnosis of NASH and stage of hepatic fibrosis are established through a liver biopsy sample that shows hepatic steatosis, lobular inflammation, and hepatocellular ballooning.[46-49] It is important to note that the histology of NASH may differ between young patients and adults. Young patients with NASH are noted to have periportal zone (acinar

zone 1) or azonal distribution of steatosis (Type 1) compared with the perivenular zone (acinar zone 3) of steatosis among adults (Type 2).[50-52] In regard to inflammation, portal inflammation is more common during youth, whereas lobular inflammation is more common in adults. Ballooning Mallory's hyaline bodies are infrequent, and hepatocyte ballooning is also rare in young patients, while ballooning degeneration can be present in adults. Finally, fibrosis in the youth is seen as portal fibrosis while, in adults, fibrosis is seen as perisinusoidal fibrosis.[50-52]

There are major limitations of liver biopsy due to its invasiveness, risks, and costs.[53] These limitations have led to significant efforts for establishing validated non-invasive tests (NIT) that can determine the presence and stage of fibrosis.[54-59] The NITs can be simple biomarker blood tests such as Fibrosis Score 4 (FIB-4), AST-Platelet Ratio Index (APRI), and NAFLD fibrosis score (NFS). These NITs incorporate 'indirect' markers of liver fibrosis, such as aminotransaminases accompanied with clinical parameters (age, sex, presence of insulin resistance/T2D, and andromorphic assessments). There are also 'complex' serum biomarker blood tests (e.g., the Enhanced Liver Fibrosis Score [ELF], which incorporates some of the direct markers of fibrogenesis and fibrinolysis such as serum tissue metalloproteinases and hyaluronic acid). Simple NITs and serum biomarkers may be best used in combination as a part of clinical algorithms.[57-59]

Finally, assessment of liver stiffness through elastography (transient elastography, magnetic resonance elastography, etc.) is also being established as important radiologic NITs.[55] Again, the use of these tests is optimised in the context of algorithms that use risk stratification and simple NITs.[57-59] As more work continues in the field of NITs, it is important to establish validated algorithms to accurately risk stratify patients at risk, who are seen in primary care and endocrinology practices.[57]

NASH FIBROSIS, FIBROSIS PROGRESSION, AND MORTALITY

Stage of hepatic fibrosis, presence of T2D, and increasing number of components of metabolic syndrome as well as *PNPLA3* can play an important role for determining prognosis of patients with NASH.[1,21,39,60] In this context, a recent prospective study of 1,773 persons with NAFLD, where 1,330 persons had NASH, conducted over a median of 4 years, found that all-cause mortality increased with increasing fibrosis stages, which increased from 0.32 deaths per 100 person-years for stage F0–F2 to 0.89 deaths per 100 persons-years for stage F3, and 1.76 deaths per 100 person-years for stage F4.[60] Such findings validated prior results that came from retrospective data. The investigators also noted that the incidence of liver-related complications such as variceal haemorrhage, ascites, encephalopathy, and hepatocellular cancer increased with fibrosis stage. Other notable findings included that compared with patients with stage F0–F2 fibrosis, patients with stage F4 fibrosis had a higher incidence of T2DM (7.53 versus 4.45 events per 100 person-years), and experienced a decrease in their estimated glomerular filtration rate of more than 40%.[60] On the other hand, investigators reported that the incidence of cardiac events and non-hepatic cancers were similar across all the fibrosis stages. Finally, they reported that in their multivariable analysis controlling for age, sex, race, diabetes status, and baseline histologic severity, all-cause mortality was increased almost seven times (average hazard ratio: 6.8; 95% confidence interval [CI]: 2.2–21.3) following an incidence of any hepatic decompensation event and the overall all cause death rate was higher in this group than the expected death rate (0.57 deaths per 100 person-years versus 0.40 deaths per 100 person-years, respectively).

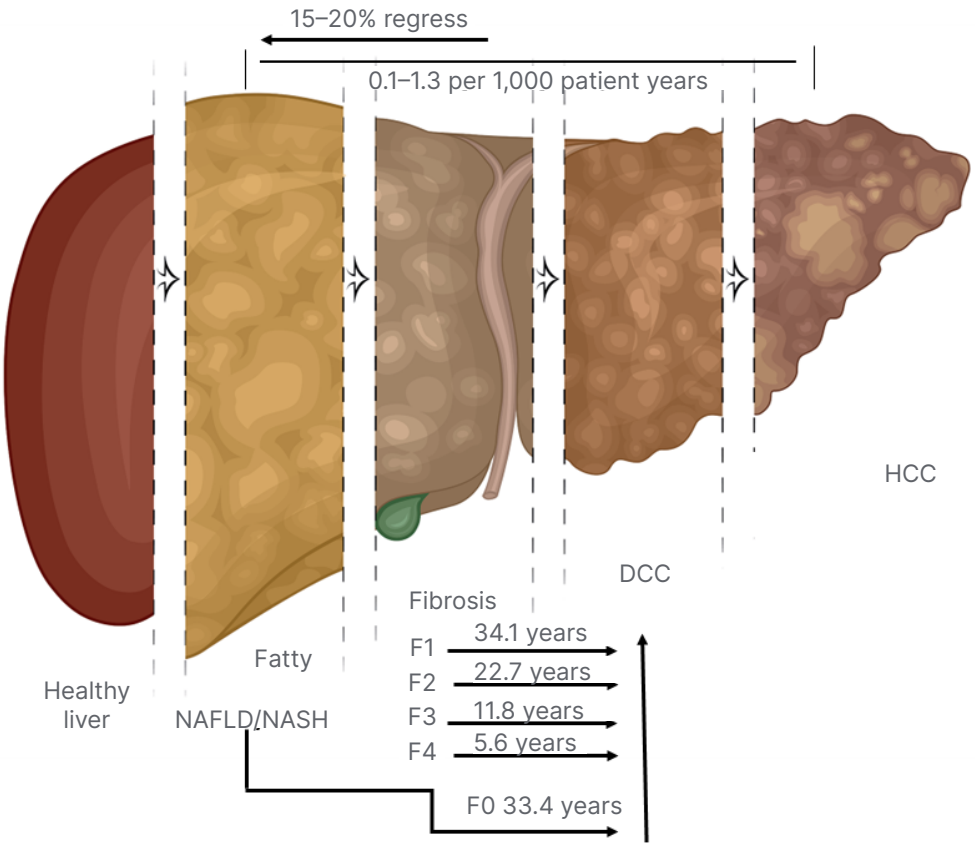
Another study conducted in the USA had similar findings. In this study, investigators estimated that in the USA there are 9.8 million people living with NASH, where 6.5 million were living with fibrosis stages F0–F2; 2 million were living with NASH and fibrosis stage F3; and 1.3 million were living with NASH and cirrhosis (F4). These investigators also reported the incidence rate and the numbers of annual deaths attributable to NASH and NASH fibrosis such that the mortality rate for F3 and F4 fibrosis was 0.89 and 1.76 deaths per 100 person-years, respectively, with 17,800 annual deaths for F3 and 22,800 annual deaths for F4.[4] These same investigators also provided forecasts for other countries reporting the relatively similar results.[61-63]

Another study attempted to discern time to the development of severe liver disease.[64] These investigators found that regardless of having NAFL or NASH, it was the presence and the stage of fibrosis that dictated the time to severe liver disease and mortality. In this study, with a mean follow up of 20 years (range 0–40 years), the researchers reported that the median time until 10% of the patients developed liver decompensation was 33.4 years for F0 (95% CI: 24.2–42.6); 34.1 years for F1 (95% CI: 25.1–43.2); 22.7 years for F2 (95% CI: 13.7–31.7); 11.8 years for those with F3 (95% CI: 4.3–19.4), and 5.6 years for those with F4 (95% CI: 0.9–10.3 [Figure 2]).[64]

Other studies have also described the natural history of NASH and NASH fibrosis.[65-69] One such study found that approximately 14% of patients with stage F0–F2 fibrosis progressed to stage F3, and 2% progressed to stage F4 over a mean duration of 4.5 years.[65] When the investigators actualised these rates, they suggest that there will be 15,000 additional deaths annually among persons whose disease transitions to stage F3 or F4. As mentioned, one of the more common risk factors for progressive liver disease among NAFLD was the presence of T2D. In fact, T2D has been shown to be an independent risk factor for the liver-related mortality in patients with NAFLD and NASH.[70-72]

Using data from the Global Burden of Disease investigators found that, from 1990–2017, the global disability-adjusted life years from HCC due to NASH increased from 0.71 million to 1.46 million. Geographically, Australasia experienced the largest increase in the burden of HCC due

Figure 2: Non-alcoholic steatohepatitis fibrosis progression and regression.



DCC: decompensated cirrhosis; HCC: hepatocellular carcinoma; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis.

to NASH, with the age-standardised disability-adjusted life years rate increasing by 143.54%. The global prevalence of HCC due to NASH peaked at 60–64 years in males and at 65–69 years in females, and a heavier burden in males compared with females.[73]

Finally, despite the stage of hepatic fibrosis being a major predictor of mortality, cardiovascular disease is the number one cause of death among those with NAFLD. This is most likely due to the presence of components of metabolic syndrome being associated with mortality among those with NAFLD, and the risk of mortality increasing with each component of metabolic syndrome present.[74] However, due to a possible bi-directional relationship between NAFLD and various components of metabolic syndrome, particularly T2D and hypertension, work continues on discerning which disease component precedes what, and whether NAFLD is an independent predictor of cardiovascular mortality or an intermediary step along the cardiometabolic disease trajectory.[75]

NASH PROGRESSION AND REGRESSION

It is important to note that the natural history of NASH is not linear. Increasing evidence suggests that patients with NASH can progress for a period of time, followed by a period of regression or stability. One small study using paired liver biopsies reported on the progression and regression of patients with NAFLD.[66] At baseline, 26 (72%) patients had NAFL (steatosis without liver cell injury) and 10 (28%) patients had NASH. At follow-up, 27% of those with NAFL had progressed to NASH, while 50% of patients with NASH appeared to have regressed as they no longer met the criteria of NASH. Fibrosis was found to progress in 15 (42%), regress in 9 (25%), and remain stable in 12 (33%) patients. They also found that the incidence of T2D was significantly higher in those that had progressed.[66]

In another study, Wong et al.[67] showed that among patients with NASH at baseline, 59% continued to have NASH after 3 years of follow-up while 35% had borderline NASH and 6% of patients regressed to simple steatosis. Additionally, 27% of patients showed fibrosis progression, 48% remained stable, and 25% had fibrosis regression. While another study reported that of the patients who had NASH on baseline biopsy, 93% still had NASH at follow-up (median of 6.6 years); however, 7% had regressed to NAFL, while among those with NAFLD 42% progressed, 40% remained stable, and 18% regressed.[68] In a meta-analysis of 11 cohort studies that included 150 persons with biopsy proven NAFL and 261 persons with biopsy proven NASH, investigators found that at baseline 35.8% had fibrosis stage F0; 32.5% had F1; 16.7% had F2; 9.3% had F3; and 5.7% had cirrhosis. When they studied what happened over time, they reported that, over 2,145.5 person-years of follow-up, 33.6% had fibrosis progression, 43.1% remained stable, and 22.3% experienced regression, which translated to an annual fibrosis progression rate in patients with NAFL F0 at baseline to 0.07 stages (95% CI: 0.02–0.11 stages), while for those with NASH experienced an annual progression of 0.14 stages (95% CI: 0.07-0.21 stages). These findings corresponded to one stage of progression over 14.3 years for patients with NAFL (95% CI: 9.1–50.0 years) and 7.1 years for patients with NASH (95% CI: 4.8–14.3 years).[66] It is important to note that discrepancies among these results could be due to the length of time of the follow-up, more disease activity at baseline noted in those that progressed, underestimation of the presence of advanced fibrosis due to the limitations of liver biopsies, as well as the risk factors present in the patient populations (Figure 2).[64,66-69]

THERAPEUTIC INTERVENTIONS

Understanding the natural history of NASH is also important in the development of therapeutic interventions that may ultimately be effective in changing the trajectory of patients' long-term outcomes. Currently, the main treatment for NASH is lifestyle management, which involves the loss of body weight of at least 10%, which may be required to have resolution of NASH and improvement of fibrosis.[62,63] However, accomplishing and maintaining this weight loss is a challenge due to the multitude of factors that are barriers for sustained weight loss.[64] In addition, vitamin E for those without T2D and pioglitazone for patients with pre-diabetes and diabetes have also been recommended.[76-80]

As such, numerous clinical trials have been ongoing to determine which medications can reach the agreed upon endpoints for a successful trial (either a regression of fibrosis of at least one stage without the progression of NASH or NASH resolution without worsening of fibrosis).[81-84] In addition, it appears from a compilation of prior clinical trials that improvement in histologic features (hepatocyte ballooning, Mallory–Denk bodies, and portal inflammation) may also be associated with improvement in fibrosis, which may, in the future, be considered as surrogates for the established clinical trial endpoints.[84]

However, given that NASH can regress and progress, very few clinical trials have met these clinical trial endpoints that some have suggested that a trial duration should last from 5 to 7 years in order to capture the true efficacy of these medications.[56-69] Despite this drawback, several medications are showing promising results such as glucagon-like peptide-1 receptor agonists and sodium–glucose co-transporter 2 inhibitors, which decrease hyperglycaemia and improve cardiovascular health; modulators of bile acid and metabolism, including farnesoid-X receptor agonist obeticholic acid and liver X receptor α inhibitor dithiolethione oltipraz; fibroblast growth factor 19 analogue aldafermin; fibroblast growth factor 21 analogue pegbelfermin; modulators of lipid metabolism (e.g., acetyl-CoA carboxylase inhibitors, stearoyl-CoA desaturase-1 inhibitors, diacylglycerol acyltransferase 2 inhibitors, thyroid hormone receptor-β agonists); and antifibrotic drugs (chemokine receptor inhibitors).[35]

In addition, it is also important to acknowledge basic science work that may inform future clinical trials.[85-87] One study investigated the use of dandelion to prevent the progression of hepatic fibrosis among albino male rats.[87] Investigators noted that the use of dandelion did have an antifibrotic effect through the carbon tetrachloride (Chemokine [C-C motif] ligand 4) liver fibrosis system through its ability to be a free radical scavenger and attenuate inflammatory cell activation. Another study using Wister rats investigated the use of olive leaf extract in providing cardiac protection while increasing the effectiveness (decreasing inflammation and oxidative stress) of an antineoplastic drug for HCC (doxorubicin), and found that olive leaf extract may be a useful adjuvant treatment.[88] Work on non-invasive tests is also being conducted in conjunction with these basic science studies. One study investigating the effects of *Moringa oleifera* against fibrosis used MRI textured analysis to determine the antifibrotic effects of Moringa oleifera. MRI textured analysis performed excellently in identifying histological changes when compared with conventional histopathological and liver function tests.[89]

Bariatric surgery can be a viable alternative for those who are morbidly obese, although bariatric surgery should not be considered the first treatment choice for patients with NASH.[90] Efforts must also continue on improving the living environment of many to provide healthy food options and the availability of safe places to exercise.[91] Finally, low awareness and recognition of this disease plagues the field of NAFLD/NASH.[92] Therefore, efforts must continue to raise awareness of this disease through educating providers and the general population.

SUMMARY

The global burden of NASH, the progressive form of NAFLD, is on the rise. Although many patients may not progress, the sheer number of people with NAFLD across the globe creates a potential tsunami of patients that need to be assessed for risk of progressive liver disease and linked to appropriate care. In this context, lifestyle management with diet and exercise should be the first step. In addition, several drugs are entering into Phase III clinical trials and could potentially provide future therapeutic options. The ongoing research in basic science in both therapeutic and diagnostic areas is encouraging, and may help advance the understanding and treatment of NASH. Raising awareness among providers, patients, and policy makers continues to be of utmost importance as the awareness of NASH increases.

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Post-traumatic Isolated Right Hepatic Duct Injury: A Case Report

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Disclosure: The authors have declared no conflicts of interest. The patient provided their consent to publish their case and identifiers have been taken out of the case to protect their interests.

Received: 06.02.22

Accepted: 27.04.22

Keywords: Endoscopic retrograde cholangiopancreatography, extra-hepatic injury, focused assessment with sonography in trauma, geriatric patient, post-operative, post-trauma, right hepatic duct injury.

Citation: EMJ Hepatol. 2022;10[1]:84-86. DOI/10.33590/emjhepatol/22-00042. https://doi.org/10.33590/emjhepatol/22-00042.

Abstract

A 73-year-old female presented with a rare presentation of extrahepatic ductal injuries post-trauma in the form of a right hepatic duct injury. Such injuries go undetected despite normally advised imaging, presenting a few to several days post-trauma. Taking into consideration the risk of biliary leakage, biliary strictures, or recurrent cholangitis, it is imperative to keep a lookout for this differential diagnosis. Given the scarce literature on post-traumatic right hepatic duct injuries, the authors felt that this case could be a beacon in the discussion of the same issue among the surgical community.

Key Points

1. While the primary cause of biliary tract injury is surgical procedures, trauma may also lead to biliary tract injuries through several pathogenic mechanisms including compression which can lead to ruptures.

2. The point of bifurcation between the left and right pancreatic ducts and the pancreaticoduodenal junction is the most common anatomical site of post-traumatic biliary tract injury.

3. Prematurely ruling out biliary tract injuries may result in complications, including biliary leakage, biliary strictures, or recurrent cholangitis.

INTRODUCTION

Biliary tract injuries are mainly caused by iatrogenic procedures, which account for a major risk factor, and trauma is a relatively rare cause.[1] These usually present with clinical features such as abdominal pain and distension, nausea and vomiting, or fever if biliary peritonitis sets in. An ultrasound or a CT scan is the initial diagnostic modality, depending on the haemodynamic condition of the patient, whereas magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography (ERCP) are performed in cases that remain undiagnosed.[1] The management of the injuries can be done either endoscopically (the various treatment options include sphincterotomy; nasobiliary tube insertion; or plastic stent placement, according to the European Society of Gastrointestinal Endoscopy [EGSE])[2] or surgical ligation, depending on the clinical scenario.[1] The authors' case adds to the scarce epidemiological pool regarding right hepatic duct injuries in cases of blunt trauma.

CASE REPORT

A 73-year-old female reported to the emergency department of a tertiary care institute in Northern India, with a history of assault by a stranger. The patient reported that she was attacked unannounced and had suffered multiple stab injuries to the body and suffered a fall from the chair an hour before the initial presentation to the hospital. There were two stab injuries present in the abdominal region: one above the umbilicus (size: 2.5×0.5 cm) and the other below the umbilicus (size: 3.0×0.5 cm). A laceration was located on the interdigital space between the right hands thumb and index finger. There was active bleeding from the wounds but no other complaints. The patient had a history of hypertension and diabetes but no other history of illnesses, surgery, or trauma.

On examination, the patient was calm, conscious, co-operative, and well-oriented to time, place, and person. The patient had mild tachycardia (120 /min) and normotension (100/66 mmHg), with the other vitals in the normal range. On physical examination, the abdomen was tender and resonant on percussion with normal bowel sounds. Respiratory, cardiovascular, and neurological examinations were normal. After providing first aid to the patient and conducting an abdominal ultrasound according to FAST protocol, which did not yield any significant results, the patient remained hemodynamically stable and was shifted to the operating room for repair of the stab wounds. The patient underwent the advised routine laboratory investigations such as complete blood count, renal function test, liver function test, electrocardiogram, and more. The results were insignificant, and the patient was kept under observation.

On the second-day post-operation, an oral contrast CT abdomen and pelvis was advised, which was normal and showed no visceral injury. The patient's condition was improving well until three days after the operation, when the patient reported diffuse pain, guarding, and distension in the abdominal region. There was a greenish-yellow discharge on the dressings, which was further expressed by applying pressure to the abdomen or on exertion by the patient. The fluid was confirmed to be biliary in origin on complete biochemical analysis.

A circumferential laceration in the right bile duct was seen on ERCP. The patient was taken to the operating room for exploratory laparotomy and duct repair through a duct-to-duct anastomosis. A drain was placed in the abdominal cavity to monitor any further leakage of fluids and the patient was observed over the following week. The patient's health gradually improved, and the patient was discharged five days after their operation.

DISCUSSION

Surgical procedures are the leading cause of biliary injuries, while abdominal trauma holds a much less proportion of the pathology. There have been various pathophysiological mechanisms proposed for traumatic biliary tract injuries such as the compression of portions of the extrahepatic bile ducts against the vertebral column or the liver; the compression of a full gallbladder against the liver, hence leading to a blowout rupture of the biliary tract; or the application of non-uniform shearing forces on the biliary system, ultimately producing the same injuries.[3] As the authors' case was the result

of assault and an associated fall, they believe that the most probable mechanism for the right hepatic duct could have been the non-uniform shearing forces.

The most common anatomic locations of traumatic biliary injuries are the origin of the left hepatic duct; the point of bifurcation of the left and right hepatic ducts and the pancreaticoduodenal junction.[4] Pereira et al.[5] conducted a systematic review of a total of 66 cases of traumatic bile duct injuries. They reported that complete transection of the common bile duct (suprapancreatic and intrapancreatic) were the most common injuries reported followed by partial laceration of the left hepatic duct; partial laceration of the right hepatic duct; and complete laceration of the right hepatic duct.[5] What makes the authors' case rare was an isolated laceration of the right hepatic duct, which is usually protected in patients post-trauma due to the duct being located deeper below the liver.[1]

Extrahepatic bile duct injuries due to trauma may generally go unnoticed in the initial period and be diagnosed in the later part of the clinical course of the patient.[1] Zago et al.[6] reported two cases of traumatic biliary duct injuries. One was diagnosed as left hepatic duct injury on the sixteenth day after a motor vehicle collision, while the other patient suffered from multiple lacerations of the extrahepatic biliary duct after a fall from a height of 7 m and was diagnosed at the time of laparotomy.[6] In comparison, the suspicion of biliary tract injury started on the third day post-trauma in the authors' patient, based on the presence of biliary discharge on the dressings. The diagnosis and treatment of a patient developing a biliary injury broadly depends on the haemodynamic state of the patient, with the patients who are haemodynamically unstable generally getting diagnosed earlier compared with patients who are haemodynamically stable, like in this case.

On ERCP, right hepatic duct injury without continuity associated with bile leak was seen, so the authors arrived at a diagnosis of a circumferential right hepatic duct injury. As the right hepatic duct injury was circumferential, repair through endoscopic stenting, a procedure which is utilised only for partial lacerations, was not possible. The patient had recently undergone a penetrating stab wound to her abdomen, which was repaired. As a result of the recent abdominal surgery, a laparoscopic procedure was considered out of the question and the duct-to-duct anastomosis for the right hepatic duct injury was completed through open surgery instead. A monofilament interrupted 5-0 prolene suture was used.

The authors' case suffered a laceration of the right hepatic duct, which itself is a rare presentation amongst the various extrahepatic ductal injuries post-trauma. The absence of any significant features on the CT scan of the abdomen on the day after the initial trauma did not rule out biliary tract injuries in this case. So, despite adequate imaging, one should always keep a differential diagnosis of biliary tract injury in the back of one's mind as the failure to do the same might result in the development of various complications such as biliary leakage, biliary strictures, or recurrent cholangitis.[7]

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