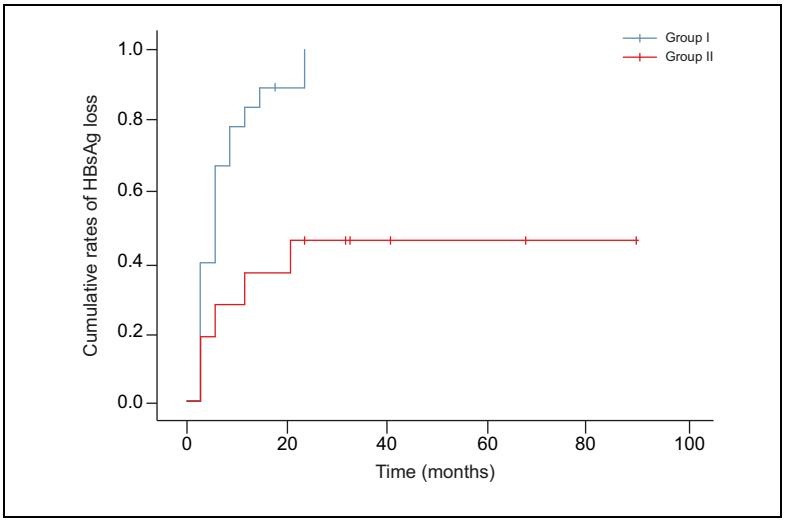
November 2019

Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

Early initiation of antiviral therapy contributes to a rapid and significant loss of serum HBsAg in infantile-onset hepatitis B

Graphical abstract



Highlights

- Infantile hepatitis B is an unusual yet serious condition which has scarcely been studied.
- No treatment options are proposed for infantile hepatitis B by expert panel consensuses or clinical practice guidelines.
- Early initiation of lamivudine can lead to a significant loss of serum HBsAg in infants with ALT $\geq 2\times$ upper limit of normal.

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Lay summary

Chronicity is a serious threat to infants infected with hepatitis B. However, no treatment measure has been recommended for infantile-onset hepatitis B in current guidelines. In order to evaluate the benefit and safety of antiviral therapy in infantile-onset hepatitis B, a real-world cohort study was conducted. Long-term follow-up results showed that early initiation of antiviral therapy with lamivudine safely led to a rapid and significant loss of serum hepatitis B surface antigen in the present subset of infants with alanine aminotransferase $\geq 2\times$ upper limit of normal. Further trials with larger cohorts are needed.

https://doi.org/10.1016/j.jhep.2019.06.009

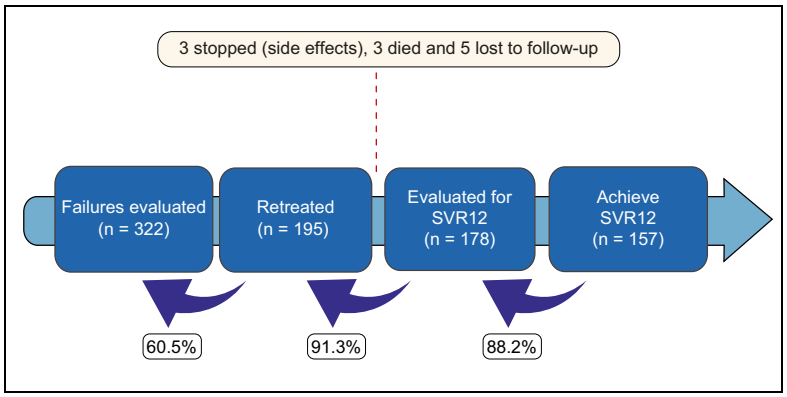
 J. Hepatol. 2019, 71, 871–875

Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

High efficacy of resistance-guided retreatment of HCV patients failing NS5A inhibitors in the real world

Graphical abstract



Highlights

- We provide recommendations on how to use resistance data and achieve 90% sustained virological response.
- If no NS5A resistance-associated substitution is found at failure, choose SOF+NS5A inhibitor with ribavirin.
- If genotype 3 and only Y93H, choose SOF+velpatasvir+ribavirin for 24 weeks.
- If both NS5A and NS3 resistance-associated substitutions, re-treat with a SOF-based 3-drug regimen+ribavirin.
- Our data may be relevant for countries with limited access to new direct-acting antiviral combinations.

Authors

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Lay summary

Hepatitis C infection can be cured with currently available antiviral agents. Only a small proportion of patients experience treatment failure, however, in absolute numbers, a high number of patients may require retreatment. Highly effective combinations of antivirals are also available for retreatment. However, these antivirals might not be available in resource-limited settings. Herein, we show how, by analyzing the cause of resistance, retreatment efficacy with old drugs can get very close to the efficacy of new drug combinations.

https://doi.org/10.1016/j.jhep.2019.06.022

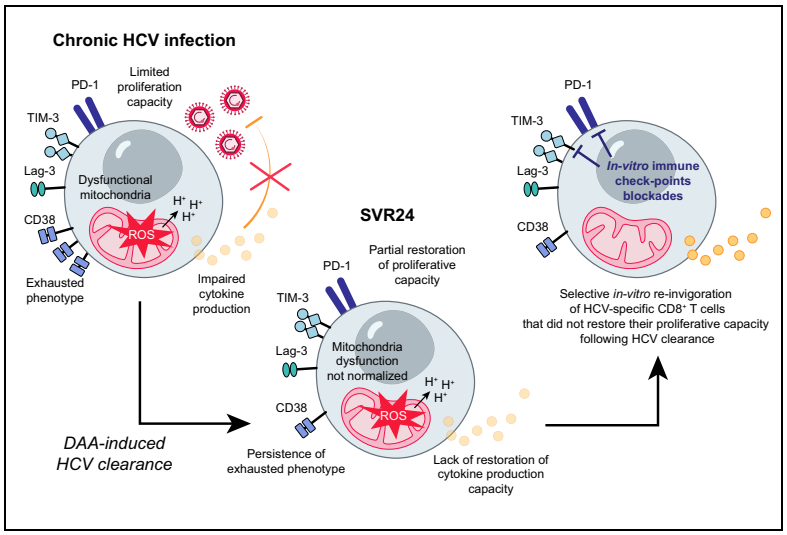
 J. Hepatol. 2019, 71, 876–888

Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

Elimination of hepatitis C virus has limited impact on the functional and mitochondrial impairment of HCV-specific CD8+ T cell responses

Graphical abstract



Highlights

- HCV-specific CD8+ T cell phenotypes and functional responses are not universally restored during DAA-induced HCV clearance.
- Mitochondrial fitness of virus-specific CD8+ T cells unaltered by cessation of persistent HCV replication.
- *In vitro* immune check-point inhibition mediated selective revival of *in vitro* DAA unresponsive HCV-specific CD8+ T cells.

Authors

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Lay summary

Direct-acting antiviral therapy results in cure of hepatitis C virus (HCV) in almost all treated patients. However, the impacts of HCV cure on immune responses remain controversial. Whether immune responses to HCV recover is important in cases of re-exposure, or for the resolution of extrahepatic manifestations. The main finding of our study was that HCV-specific T cells remain functionally impaired despite HCV clearance. This finding could explain the fact that HCV cure does not lead to protective immunity and that re-infections have frequently been observed.

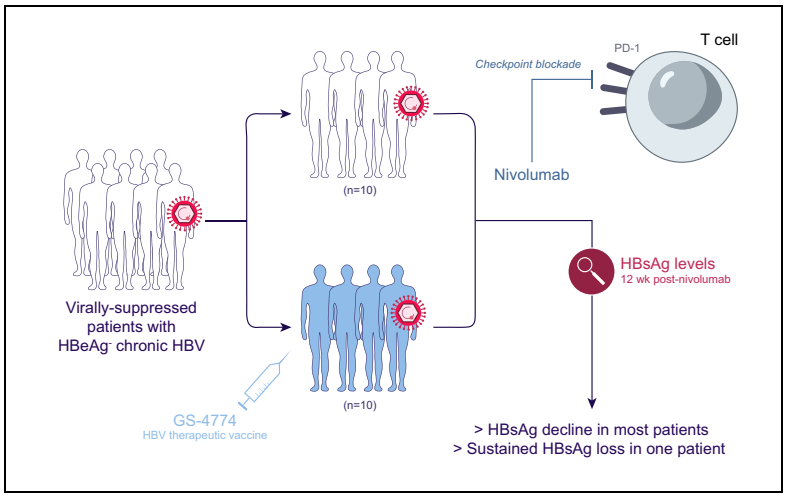
https://doi.org/10.1016/j.jhep.2019.06.025

Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

Anti-PD-1 blockade with nivolumab with and without therapeutic vaccination for virally suppressed chronic hepatitis B: A pilot study

Graphical abstract



Highlights

- In patients with chronic HBV infection, T cell responses are inhibited, leading to an inability to control the virus.
- One of the most common inhibitors present on exhausted T cells is PD-1, which likely contributes to T cell dysfunction.
- A single dose of either 0.1 or 0.3 mg/kg of nivolumab, with or without GS-4774, was well tolerated and effective.

Authors

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Lay summary

Chronic hepatitis B virus infection (CHB) is characterized by a dysfunctional immune response. In patients with CHB, inhibitory receptors, such as programmed death receptor 1 (PD-1) are overexpressed on T cells, leading to an ineffective immune response in the liver. Herein, we show that the PD-1 inhibitor, nivolumab, is safe and effective for the treatment of virally suppressed patients with CHB.

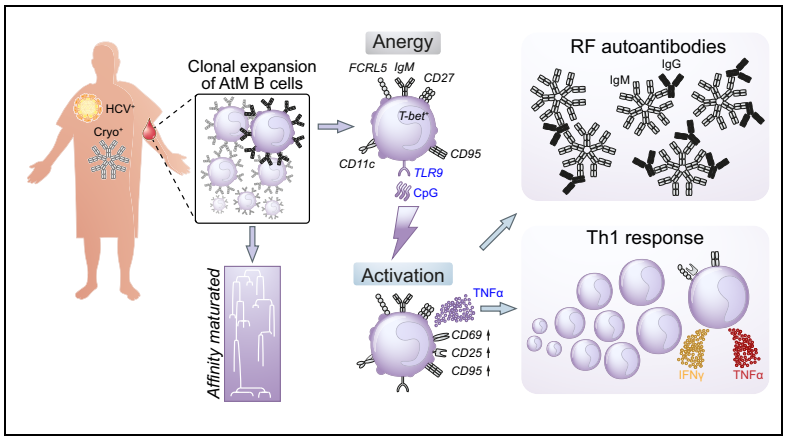
https://doi.org/10.1016/j.jhep.2019.06.028

Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

TLR9 signalling in HCV-associated atypical memory B cells triggers Th1 and rheumatoid factor autoantibody responses

Graphical abstract



Highlights

- TLR9 activation of atypical memory B cells (AtMs) has a central role in breaking tolerance in patients with HCV-CV.
- TLR9 signaling on AtMs stimulates proliferation and activation of effector Th1 cells by secreting TNFα.
- Rheumatoid factors produced by AtMs recognized distinct IgG-Fc epitopes and did not cross-react against HCV proteins.
- AtMs largely disappear after antigen removal by DAA therapy.

Authors

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Lay summary

B cells are best known for their capacity to produce antibodies, which often play a deleterious role in the development of autoimmune diseases. During chronic hepatitis C, deleterious B cells proliferate and can be responsible for autoimmune symptoms (arthritis, purpura, neuropathy, renal disease) and/or lymphoma. Direct-acting antiviral therapy clears the hepatitis C virus and eliminates deleterious B cells.

https://doi.org/10.1016/j.jhep.2019.06.029

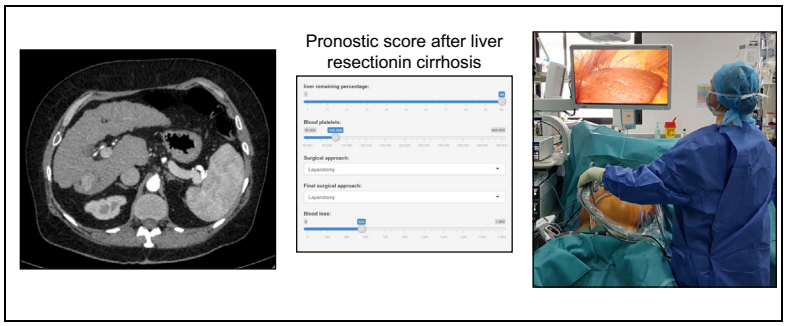
 J. Hepatol. 2019, 71, 908–919

Research Article
Cirrhosis

JOURNAL
OF HEPATOLOGY

An ordinal model to predict the risk of symptomatic liver failure in patients with cirrhosis undergoing hepatectomy

Graphical abstract



Highlights

- Laparoscopy reduces the risk of liver failure after resection in a cirrhotic liver.
- Remnant to total liver volume and platelets are other predictors of liver failure.
- Intraoperative blood loss is a postoperative predictor of liver failure.
- Predictive models are available at: https://prodeau.shinyapps.io/shiny/.

Authors

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Lay summary

In patients with liver cirrhosis, the risk of a hepatectomy is difficult to appreciate. We propose a statistical tool to estimate this risk, preoperatively and immediately after surgery, using readily available parameters and on online calculator. This model could help to improve the selection of patients with the best risk-benefit profiles for hepatectomy.

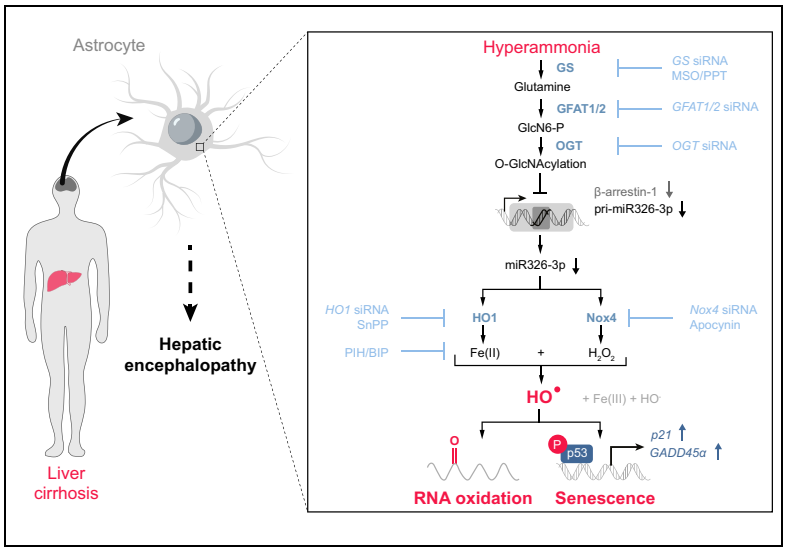
https://doi.org/10.1016/j.jhep.2019.06.003

 J. Hepatol. 2019, 71, 920–929

JOURNAL
OF HEPATOLOGY

O-GlcNAcylation-dependent upregulation of HO1 triggers ammonia-induced oxidative stress and senescence in hepatic encephalopathy

Graphical abstract



Highlights

- Ammonia triggers protein O-GlcNAcylation in astrocytes via synthesis of GlcN.
- O-GlcNAc-dependent upregulation of HO1 + Nox4 induces RNA oxidation and senescence.
- Protein O-GlcNAcylation is increased in the brains of cirrhotic patients with HE.

Authors

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Lay summary

Patients with liver cirrhosis frequently exhibit hyperammonemia and suffer from cognitive and motoric dysfunctions, which at least in part involve premature ageing of the astrocytes in the brain. This study identifies glucosamine and an O-GlcNAcylation-dependent disruption of iron homeostasis as novel triggers of oxidative stress, thereby mediating ammonia toxicity in the brain.

https://doi.org/10.1016/j.jhep.2019.06.020

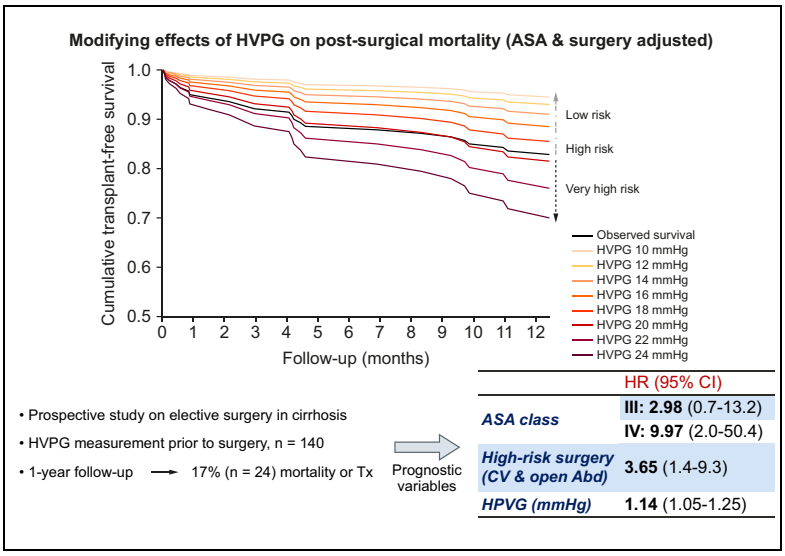
 J. Hepatol. 2019, 71, 930–941

Research Article
Cirrhosis

JOURNAL
OF HEPATOLOGY

The prognostic role of hepatic venous pressure gradient in cirrhotic patients undergoing elective extrahepatic surgery

Graphical abstract



Highlights

- Hepatic venous pressure gradient is a prognostic factor in cirrhotic patients undergoing surgery.
- ASA class and the type of surgery are the other main prognostic factors.
- Hepatic venous pressure gradient values >16 mmHg are independently associated with higher mortality.
- Hepatic venous pressure gradient values ≥20 mmHg identify the patients at highest risk.
- The potential of pre-surgery TIPS in high-risk patients deserves further study.

Authors

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Lay summary

The hepatic venous pressure gradient is associated with outcomes in patients with cirrhosis undergoing elective extrahepatic surgery. It enables a better stratification of risk in these patients and provides the foundations for potential interventions to improve post-surgical outcomes.

https://doi.org/10.1016/j.jhep.2019.07.007

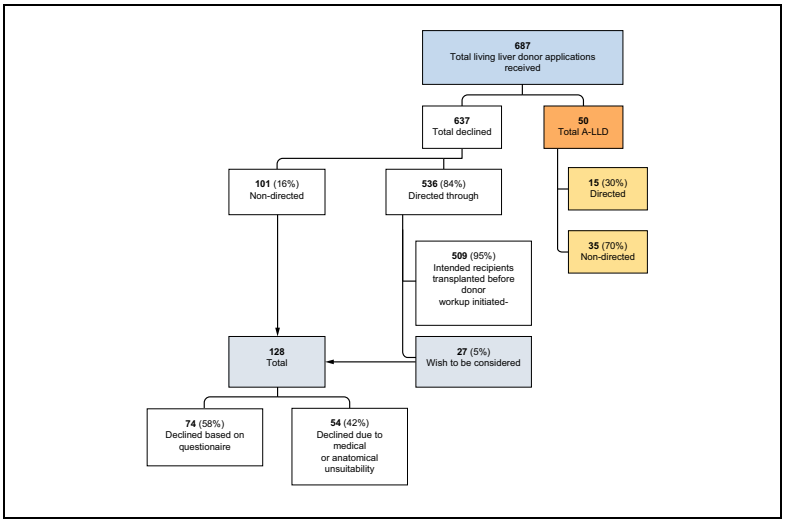
 J. Hepatol. 2019, 71, 942–950

Research Article
Transplantation

JOURNAL
OF HEPATOLOGY

Donor outcomes in anonymous live liver donation

Graphical abstract



Highlights

- Anonymous liver donors can successfully contribute to the donor organ pool.
- Social media can be used to educate communities about this opportunity.
- Anonymous donors are motivated by their values and beliefs and are very satisfied with their experience.

Authors

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Lay summary

We report a unique experience with 50 living donors who volunteered to donate to a recipient with whom they had no biological connection or prior relationship (anonymous living donors). This report is the first to discuss motivations, strategies and facilitators that may mitigate physical, social and ethical risk factors in this patient population. With rigorous protocols, anonymous liver donation and recipient outcomes are excellent; with appropriate clinical expertise and system facilitators in place, our experience suggests that other centers may consider the procedure for its significant potential to reduce the gap between transplant organ demand and availability.

https://doi.org/10.1016/j.jhep.2019.06.027

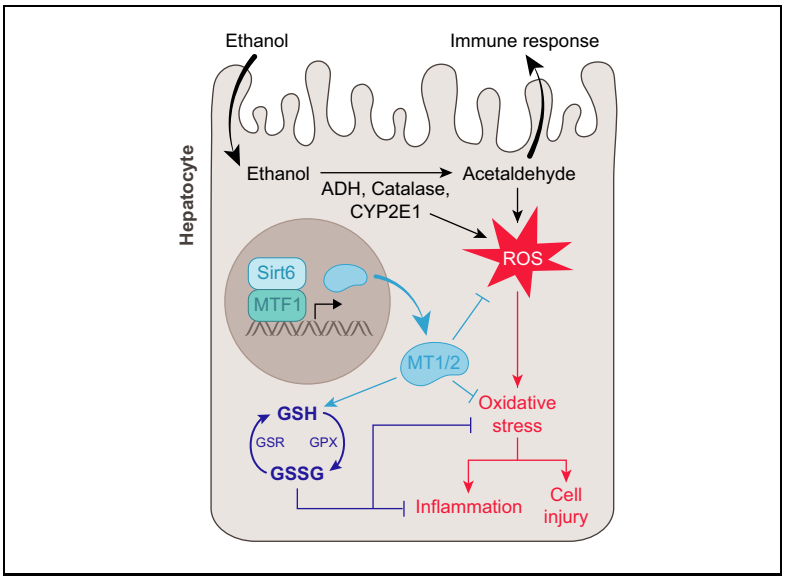
 J. Hepatol. 2019, 71, 951–959

Research Article
Molecular and Cell Biology

JOURNAL
OF HEPATOLOGY

The epigenetic regulator SIRT6 protects the liver from alcohol-induced tissue injury by reducing oxidative stress in mice

Graphical abstract



Highlights

- SIRT6 deficiency predisposes mice to the development of alcohol-related liver disease.
- SIRT6 overexpression ameliorates alcohol-related liver disease.
- SIRT6 induces metallothionein genes to protect against oxidative stress.
- SIRT6 coactivates metal regulatory transcription factor 1.

Authors

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Lay summary

The liver, the primary organ for ethanol metabolism, can be damaged by the byproducts of ethanol metabolism, including reactive oxygen species. In this study, we have identified a key epigenetic regulator SIRT6 that plays a critical role in protecting the liver from oxidative stress-induced liver injury. Thus, our data suggest that SIRT6 may be a potential therapeutic target for alcohol-related liver disease.

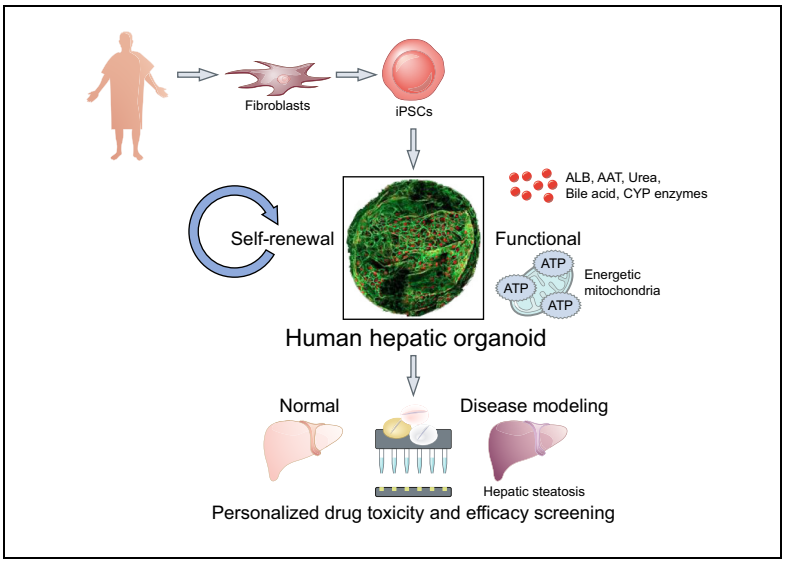
https://doi.org/10.1016/j.jhep.2019.06.019

Research Article
Molecular and Cell Biology

JOURNAL
OF HEPATOLOGY

Generation of expandable human pluripotent stem cell-derived hepatocyte-like liver organoids

Graphical abstract



Highlights

- Pluripotent stem cell (PSC)-derived expandable human hepatocyte-like liver organoids were generated.
- PSC-derived human hepatic organoids are capable of long-term expansion with competent liver functionality.
- PSC-derived human hepatic organoids provide a robust hepatic model for toxicity prediction and drug screening.

Authors

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Lay summary

A functionally mature, human cell-based liver model exhibiting human responses in toxicity prediction and drug evaluation is urgently needed for pre-clinical drug development. Here, we develop a novel human pluripotent stem cell-derived hepatocyte-like liver organoid that is critically advanced in terms of its generation method, functional performance, and application technologies. Our organoids can contribute to the better understanding of liver development and regeneration, and provide insights for metabolic studies and disease modeling, as well as toxicity assessments and drug screening for personalized medicine.

https://doi.org/10.1016/j.jhep.2019.06.030

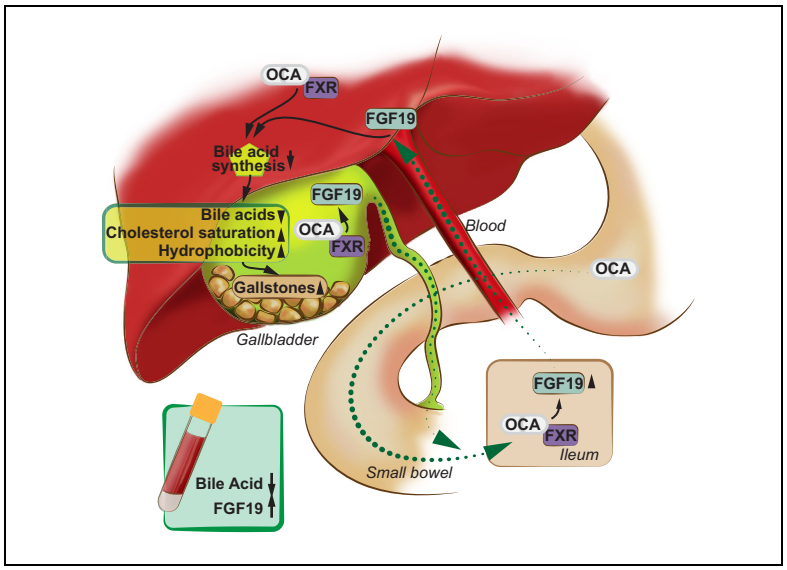
 J. Hepatol. 2019, 71, 970–985

Research Article
Cholestasis and Autoimmune Diseases

JOURNAL
OF HEPATOLOGY

Obeticholic acid may increase the risk of gallstone formation in susceptible patients

Graphical abstract



Highlights

- In humans, FXR activation with obeticholic acid decreases gallbladder bile acids.
- FXR activation with obeticholic acid increases the biliary cholesterol saturation index.
- It also increases the bile acid hydrophobicity index and formation of cholangiocellular FGF19.
- All of these effects are potential risk factors for gallstone formation.

Authors

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Lay summary

Obeticholic acid increased human gallbladder cholesterol saturation and bile acid hydrophobicity, both decreasing cholesterol solubility in bile. Together with increased hepatobiliary levels of fibroblast growth factor 19, our findings suggest that pharmacological activation of the farnesoid X receptor increases the risk of gallstone formation.

https://doi.org/10.1016/j.jhep.2019.06.011

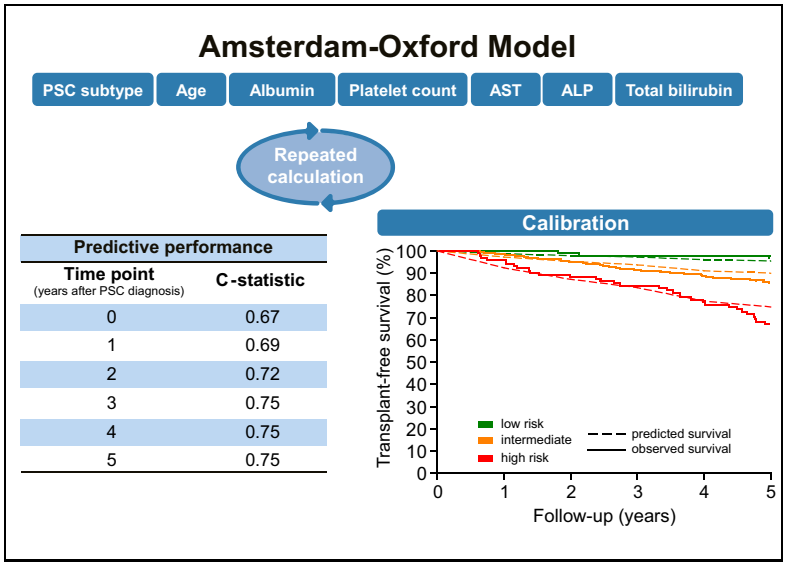
 J. Hepatol. 2019, 71, 986–991

Research Article
Cholestasis and Autoimmune Diseases

JOURNAL
OF HEPATOLOGY

Validation, clinical utility and limitations of the Amsterdam-Oxford model for primary sclerosing cholangitis

Graphical abstract



Highlights

- Reliable estimates of survival are pivotal to optimize clinical management of patients with PSC.
- The Amsterdam-Oxford model (AOM) was recently introduced to estimate survival for patients with PSC at diagnosis.
- The AOM has adequate discriminatory performance and good predictive accuracy at PSC diagnosis.
- It maintains this performance and accuracy at other time points during follow-up.

Authors

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Lay summary

In our study we assessed whether the Amsterdam-Oxford model (AOM) is able to correctly estimate the risk of liver transplantation or death in patients with primary sclerosing cholangitis (PSC). This model uses 7 objective and readily available variables to estimate prognosis for individual patients at the time of PSC diagnosis. The AOM may aid in patient counselling and timing of diagnostic procedures or therapeutic interventions for complications of liver disease. We confirm that the model works well at PSC diagnosis, but also when the AOM is recalculated at different timepoints during follow-up, greatly improving the applicability of the model in clinical practice and for individual patients.

https://doi.org/10.1016/j.jhep.2019.06.012

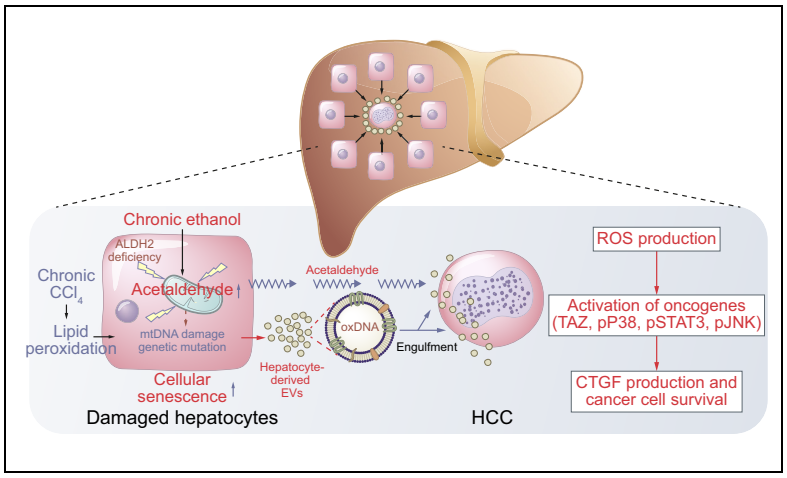
 J. Hepatol. 2019, 71, 992–999

Research Article
Genetic and Metabolic Diseases

JOURNAL
OF HEPATOLOGY

ALDH2 deficiency promotes alcohol-associated liver cancer by activating oncogenic pathways via oxidized DNA-enriched extracellular vesicles

Graphical abstract



Highlights

- ALDH2 deficiency is associated with an increased risk of HCC from cirrhosis in those who drink alcohol.
- Chronic CCl_4+EtOH treatment induces greater hepatic mitochondrial DNA damage in *Aldh2*-deficient mice than WT mice.
- Oxidized mitochondrial DNA is delivered to HCC cells via hepatocyte-derived extracellular vesicles.
- Oxidized mitochondrial DNA and acetaldehyde synergistically promote ROS production and multiple oncogenic pathways.

Authors

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Lay summary

Alcoholics with an *ALDH2* polymorphism have an increased risk of digestive tract cancer development, however, the link between ALDH2 deficiency and hepatocellular carcinoma (HCC) development has not been well established. In this study, we show that ALDH2 deficiency exacerbates alcohol-associated HCC development both in patients and mouse models. Mechanistic studies revealed that after chronic alcohol exposure, *Aldh2*-deficient hepatocytes produce a large amount of harmful oxidized mitochondrial DNA via extracellular vesicles, which can be delivered into neighboring HCC cells and subsequently activate multiple oncogenic pathways, promoting HCC.

https://doi.org/10.1016/j.jhep.2019.06.018

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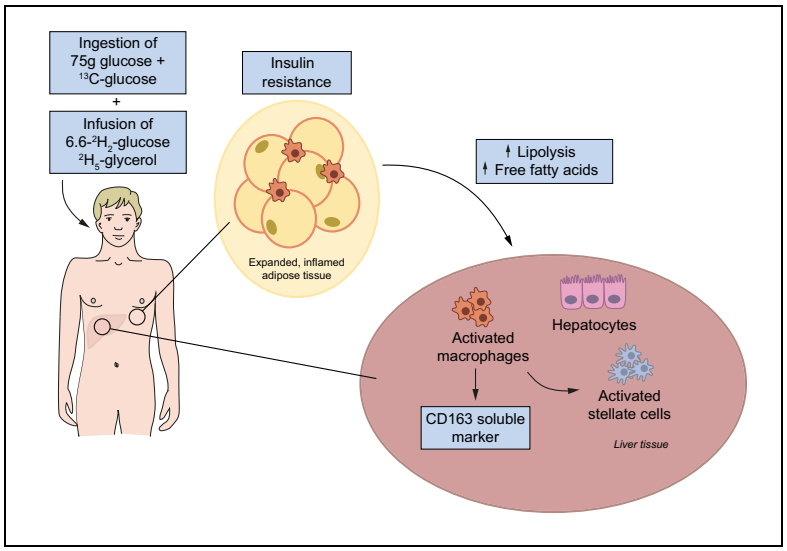
Research Article
Genetic and Metabolic Diseases

JOURNAL
OF HEPATOLOGY

Crosstalk between adipose tissue insulin resistance and liver macrophages in non-alcoholic fatty liver disease

Graphical abstract



Highlights

- Insulin resistance (IR) plays a pivotal role in the onset and progression of NAFLD.
- Adipose tissue IR seems to be the main metabolic determinant of the presence and degree of liver fibrosis in NAFLD.
- sCD163 is a specific macrophage activation marker that increases according to the degree of hepatic fibrosis in NAFLD.
- This study suggests a link between activation of resident macrophages in the liver and alterations in adipose tissue.

Authors

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Lay summary

The pathogenesis of non-alcoholic fatty liver disease (NAFLD) and steatohepatitis (NASH) is likely due to the interaction between a deranged metabolic milieu and local mediators of hepatic inflammation and fibrosis in the insulin resistant state. This study provides *in vivo* support for a possible link between deranged metabolism in the adipose tissue and activation of hepatic macrophages in patients with NAFLD, most likely in response to free fatty acid overflow and independent of obesity and diabetes.

https://doi.org/10.1016/j.jhep.2019.06.031

 J. Hepatol. 2019, 71, 1012–1021