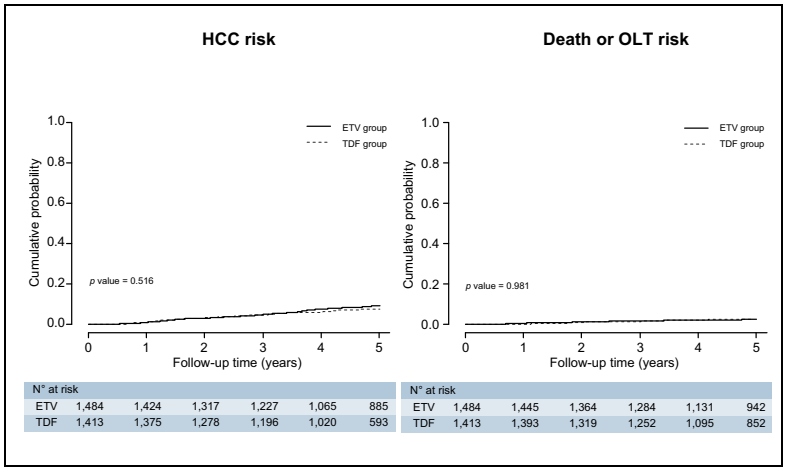
September 2019

Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

A multicenter study of entecavir *vs.* tenofovir on prognosis of treatment-naïve chronic hepatitis B in South Korea

Graphical abstract



Highlights

- The hepatocellular carcinoma risk was not statistically different between the ETV and TDF groups.
- The death or liver transplant risk was not statistically different between the 2 groups.
- These results were consistently reproduced after adjusting for confounding variables.

Authors

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Lay summary

It is currently unclear which antiviral agent, entecavir or tenofovir disoproxil fumarate, is superior for improving prognosis in patients with chronic hepatitis B virus infection. In this analysis we found that there was no difference in terms of overall prognosis, including risk of hepatocellular carcinoma, death, or the need for a liver transplant, in patients receiving either antiviral.

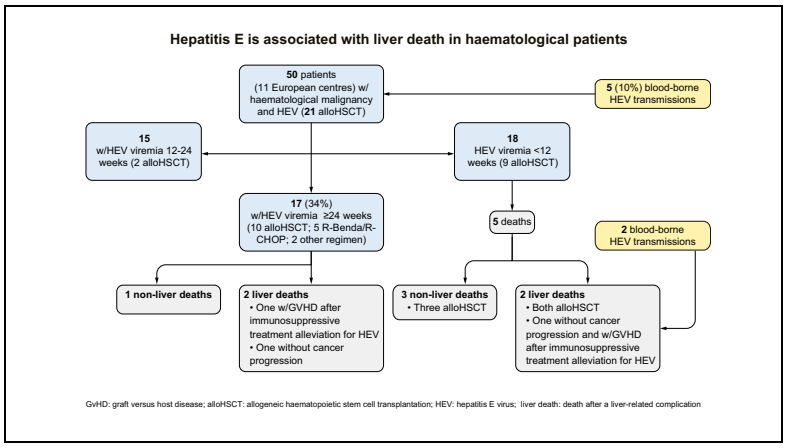
https://doi.org/10.1016/j.jhep.2019.03.028

Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

The burden of hepatitis E among patients with haematological malignancies: A retrospective European cohort study

Graphical abstract



Highlights

- Hepatitis E is associated with liver failure and mortality in haematological malignancy.
- Blood-borne transmission contributes to the burden.
- Alleviation of immunosuppressive treatment for hepatitis E requires caution.
- Ribavirin is effective and should be initiated early.

Authors

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Lay summary

Little is known about the burden of hepatitis E among patients with haematological malignancy. We conducted a retrospective European cohort study among 50 patients with haematological malignancy, including haematopoietic stem cell transplant recipients, with clinically significant HEV infection and found that hepatitis E is associated with hepatic and extrahepatic mortality, including among patients with indolent disease or among stem cell transplant recipients in complete remission. Hepatitis E virus infection evolved to chronic hepatitis in 5 (45.5%) patients exposed to a rituximab-containing regimen and 10 (47.6%) stem cell transplant recipients. Reducing immunosuppressive therapy because of hepatitis E was associated with mortality, while early ribavirin treatment was safe and effective.

https://doi.org/10.1016/j.jhep.2019.04.022

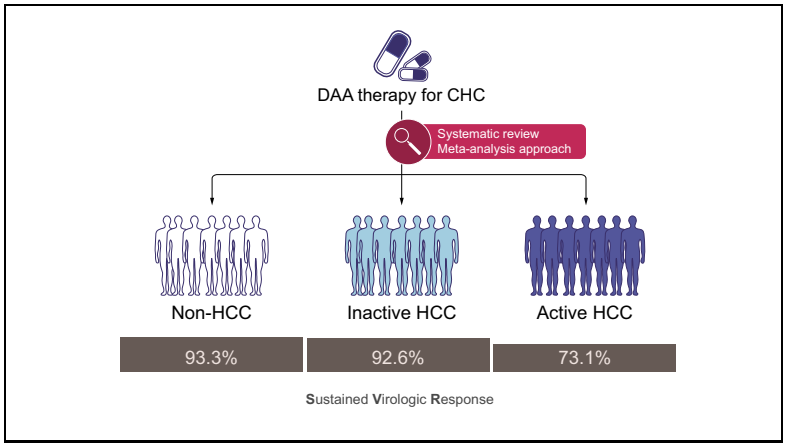
J. Hepatol. 2019, 71, 465–472

Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

Sustained virologic response to direct-acting antiviral therapy in patients with chronic hepatitis C and hepatocellular carcinoma: A systematic review and meta-analysis

Graphical abstract



Highlights

- The present study summarizes the SVR rate in patients with/without liver cancer treated with all oral DAAs.
- The cure rate was lower in patients with liver cancer, especially those with active cancer.
- Additional controlled studies are needed to study the impact of liver cancer on HCV cure rate in DAA-treated patients.

Authors

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Lay summary

There are now medications (direct-acting antivirals or "DAAs) that can "cure hepatitis C virus, but patients with hepatitis C and liver cancer may be less likely to achieve cure than those without liver cancer. However, patients with liver cancer are also more likely to have advanced liver disease and risk factors that can decrease cure rates, so better controlled studies are needed to confirm these findings.

https://doi.org/10.1016/j.jhep.2019.04.017

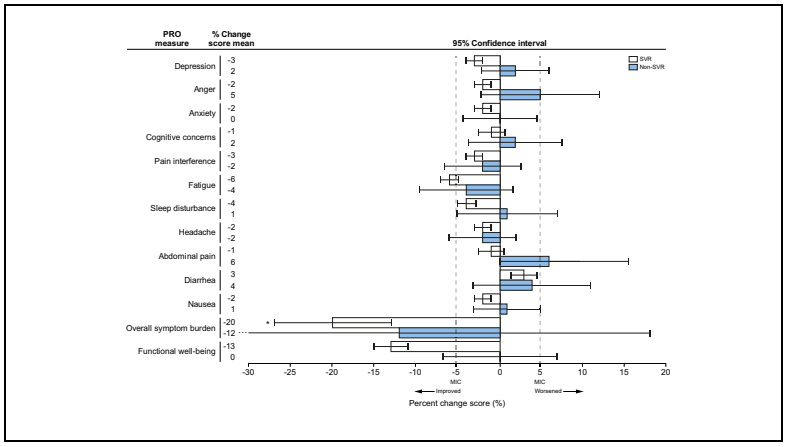
 J. Hepatol. 2019, 71, 473–485

Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

Patient-reported symptoms during and after direct-acting antiviral therapies for chronic hepatitis C: The PROP UP study

Graphical abstract



Highlights

- Overall change in symptoms and functioning on DAAs was not clinically meaningful.
- Patient experiences are very heterogeneous.
- Patients prescribed one DAA regimen experienced the worst symptoms.
- Patients that were cured had clinical improvements in fatigue, sleep, and functioning.
- Patients who were not cured had minimal improvements.

Authors

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Lay summary

Patients who received direct-acting antiviral medications for hepatitis C at several liver centers in the US did not generally experience significant changes in baseline symptoms during treatment. We observed a full range of patient experiences with some patients experiencing substantial symptom improvements, yet others experiencing less improvements and some even experiencing a worsening of symptoms. The 1,346 patients who were cured of hepatitis C experienced improvements in fatigue, sleep disturbance, and functional well-being, and trends for improved pain and depression; whereas the 64 who were not cured experienced minimal improvements.

https://doi.org/10.1016/j.jhep.2019.04.016

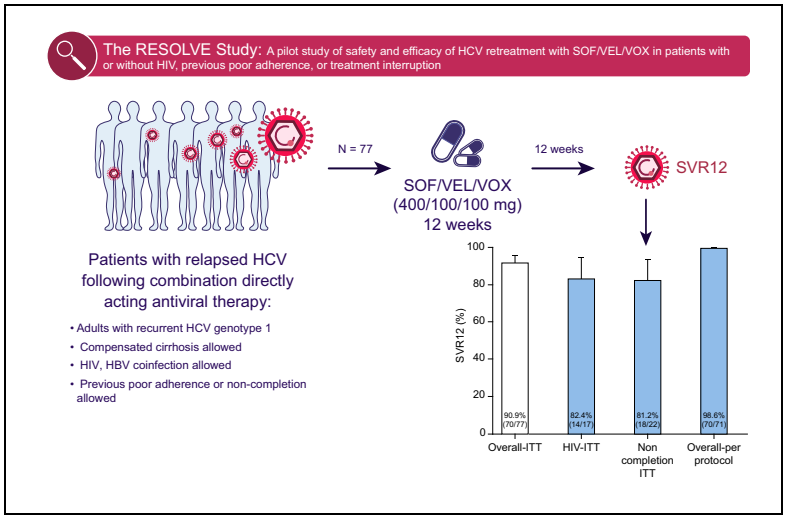
 J. Hepatol. 2019, 71, 485–497

Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

A pilot study of safety and efficacy of HCV retreatment with sofosbuvir/velpatasvir/voxilaprevir in patients with or without HIV (RESOLVE STUDY)

Graphical abstract



Highlights

- This study included 77 patients with relapsed HCV genotype 1, who were treated with 12 weeks of SOF/VEL/VOX.
- >90% of patients achieved sustained virologic response 12 weeks after the end of treatment in an intention-to-treat analysis.
- Treatment responses were similar in patients with HIV, poor adherence or non-completion of therapy.
- SOF/VEL/VOX is a safe, effective, and well-tolerated option for the retreatment of relapsed HCV genotype 1.

Authors

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Lay summary

Twelve weeks of the combination of direct-acting antivirals (SOF/VEL/VOX) was safe and effective in patients with relapsed hepatitis C virus infection who had previously received combination therapy with direct-acting antivirals. Treatment response was not diminished by HIV coinfection, or non-completion of previous direct-acting antiviral-based therapy.

https://doi.org/10.1016/j.jhep.2019.05.021

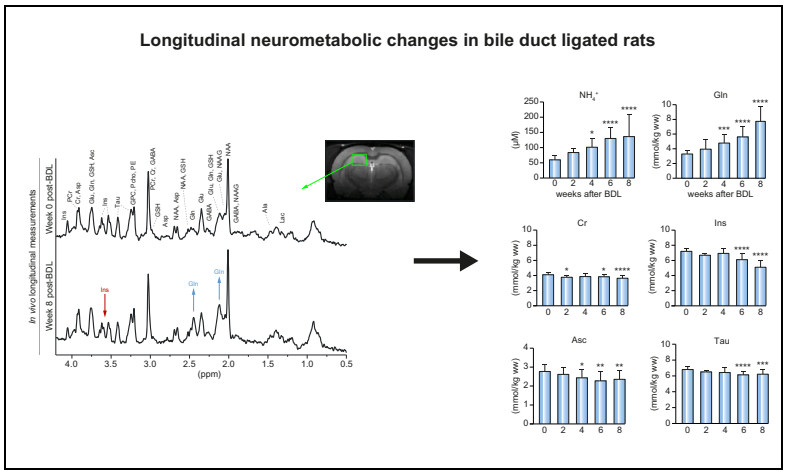
 J. Hepatol. 2019, 71, 498–504

Research Article
Cirrhosis

JOURNAL
OF HEPATOLOGY

Longitudinal neurometabolic changes in the hippocampus of a rat model of chronic hepatic encephalopathy

Graphical abstract



Highlights

- In hepatic encephalopathy, early neurometabolic changes occur 2–4 weeks post-bile-duct ligation.
- In hepatic encephalopathy, brain glutamine increases, but creatine and ascorbate decrease.
- Changes in astrocyte morphology are observed 4 weeks after bile-duct ligation.
- Early changes in hepatic encephalopathy are suggestive of osmotic/oxidative stress.
- Early changes in hepatic encephalopathy are accentuated 6–8 weeks after bile-duct ligation.

Authors

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Lay summary

The sequence of events in chronic hepatic encephalopathy (HE) remains unclear, therefore using the advantages of *in vivo* proton magnetic resonance spectroscopy at 9.4T we aimed to test the hypothesis that neurometabolic changes are detectable very early in an established model of type C HE, offering insight into the primary events underpinning HE, before advanced liver disease confounds the findings. These early, previously unreported neurometabolic changes occurred as early as 2 to 4 weeks after bile-duct ligation, namely an increase in plasma ammonium and brain glutamine, a decrease in brain creatine and ascorbate together with behavioural and astrocyte morphology changes, and continued to progress throughout the 8-week course of the disease.

https://doi.org/10.1016/j.jhep.2019.05.022

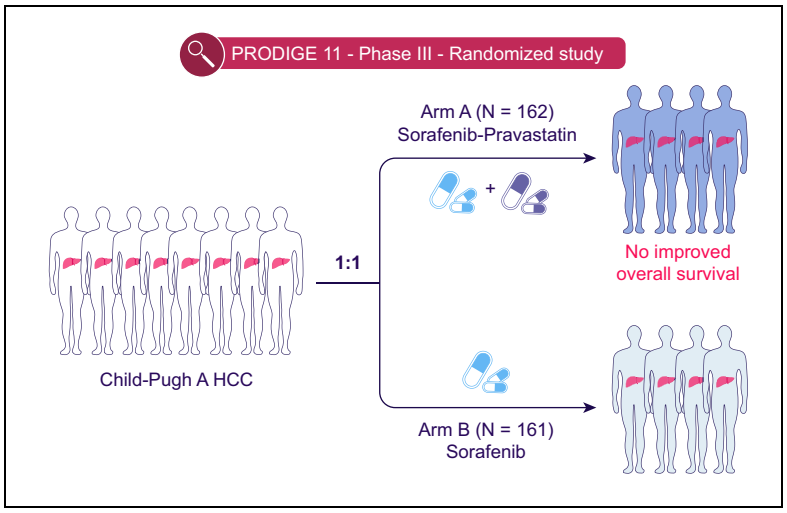
 J. Hepatol. 2019, 71, 505–515

Research Article
Cancer

JOURNAL
OF HEPATOLOGY

Pravastatin combination with sorafenib does not improve survival in advanced hepatocellular carcinoma

Graphical abstract



Highlights

- Phase III, multicenter study, comparing sorafenib + pravastin to sorafenib alone in Child-Pugh A patients with HCC.
- The sorafenib-pravastatin combination did not improve overall survival in our study population.
- Significant prognostic factors for overall survival were CLIP score, performance status, and QoL scores.
- In multivariate analysis, only CLIP score was a prognostic factor for overall survival.
- The anticancer effect of statins may be more evident in the adjuvant setting, or in the early stages of carcinogenesis.

Authors

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Lay summary

Sorafenib has proven efficacy for the treatment of patients with advanced hepatocellular carcinoma. However, overall survival remains poor in these patients, so we were interested to see if the addition of a statin, pravastatin, improved outcomes in patients with advanced HCC. This randomized-controlled trial demonstrated that the sorafenib-pravastatin combination did not improve overall survival in this study population compared to sorafenib alone.

https://doi.org/10.1016/j.jhep.2019.04.021

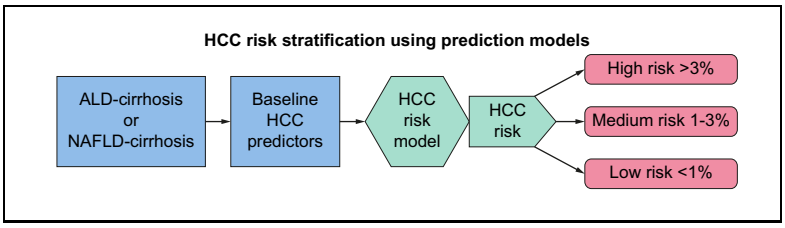
 J. Hepatol. 2019, 71, 516–522

Research Article
Cancer

JOURNAL
OF HEPATOLOGY

Models estimating risk of hepatocellular carcinoma in patients with alcohol or NAFLD-related cirrhosis for risk stratification

Graphical abstract



Highlights

- HCC risk varies dramatically in patients with cirrhosis.
- We developed models estimating HCC risk in patients with NAFLD-cirrhosis or ALD-cirrhosis.
- The models use simple, readily available predictors.
- The models are available as web-based tools at www.hccrisk.com.

Authors

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Lay summary

Patients with cirrhosis of the liver are at risk of getting hepatocellular carcinoma (HCC or liver cancer) and therefore it is recommended that they undergo surveillance for HCC. However, the risk of HCC varies dramatically in patients with cirrhosis, which has implications on if and how patients get surveillance, how providers counsel patients about the need for surveillance, and how healthcare systems approach and prioritize surveillance. We used readily available predictors to develop models estimating HCC risk in patients with cirrhosis, which are available as web-based tools at www.hccrisk.com.

https://doi.org/10.1016/j.jhep.2019.05.008

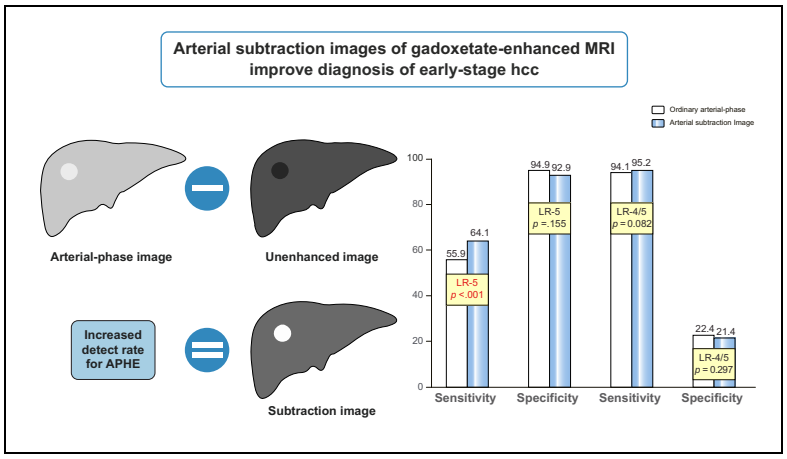
 J. Hepatol. 2019, 71, 523–533

Research Article
Cancer

JOURNAL
OF HEPATOLOGY

Arterial subtraction images of gadoxetate-enhanced MRI improve diagnosis of early-stage hepatocellular carcinoma

Graphical abstract



Highlights

- Arterial subtraction images show more arterial hyperenhancement than arterial images.
- Arterial subtraction images significantly increase sensitivity for the diagnosis of HCC.
- Arterial subtraction images do not significantly decrease specificity.
- Arterial subtraction images can be useful for diagnosing early-stage HCC.

Authors

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Lay summary

Gadoxetate disodium-enhanced magnetic resonance imaging is an imaging technique with a high sensitivity for the diagnosis of hepatocellular carcinoma. However, arterial-phase images may be unsatisfactory because of weak arterial enhancement. We found that using arterial subtraction images led to clinically meaningful improvements in the diagnosis of early-stage hepatocellular carcinoma.

https://doi.org/10.1016/j.jhep.2019.05.005

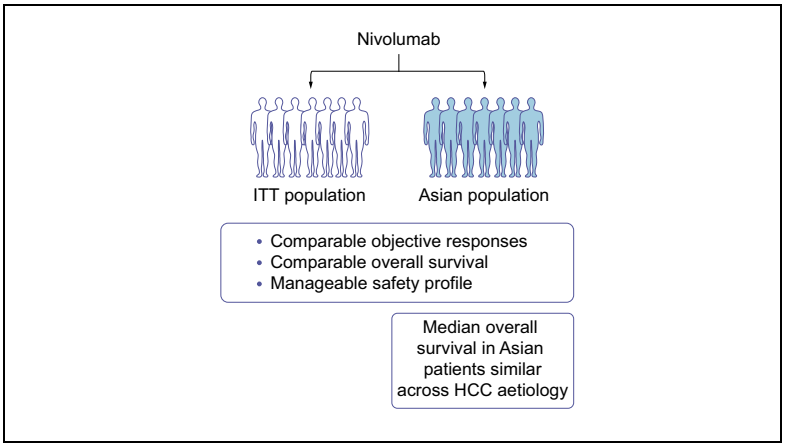
 J. Hepatol. 2019, 71, 534–542

Research Article
Cancer

JOURNAL
OF HEPATOLOGY

Nivolumab in advanced hepatocellular carcinoma: Sorafenib-experienced Asian cohort analysis

Graphical abstract



Highlights

- Objective responses and survival were comparable between intent-to-treat (ITT) overall population and Asian cohort.
- Median overall survival in Asian patients was similar across HCC aetiologies.
- Nivolumab had a manageable safety profile in both the ITT overall population and Asian cohort.

Authors

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Lay summary

The CheckMate 040 study evaluated the safety and efficacy of nivolumab in patients with advanced hepatocellular carcinoma who were refractory to previous sorafenib treatment or chemotherapy. This subanalysis of the data showed that treatment responses and safety in patients in Asia were similar to those of the overall treatment population, providing support for nivolumab as a treatment option for these patients.

https://doi.org/10.1016/j.jhep.2019.05.014

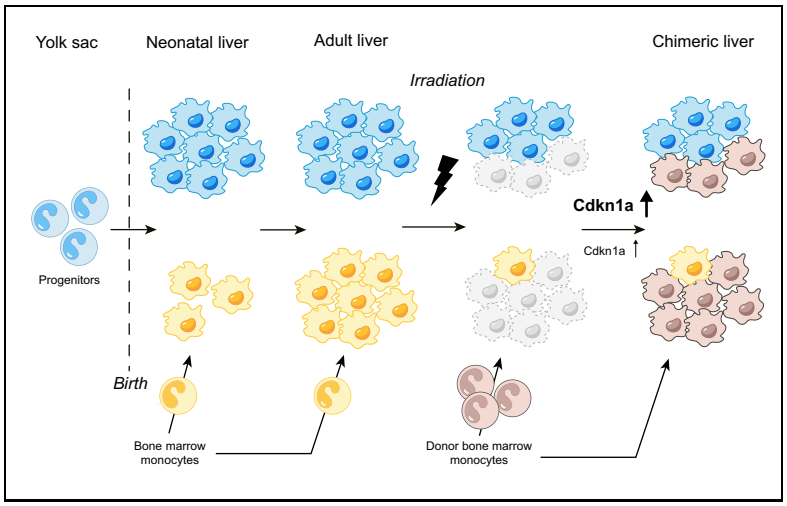
 J. Hepatol. 2019, 71, 543–552

Research Article
Molecular and Cell Biology

JOURNAL
OF HEPATOLOGY

Fetal origin confers radioresistance on liver macrophages via p21$^{cip1/WAF1}$

Graphical abstract



Highlights

- Kupffer cell-specific Cre-driven RiboTag reporter allows translatome analysis.
- Fetal-derived Kupffer cells are relatively radioresistant.
- Adult monocyte-derived Kupffer cells are sensitive to lethal irradiation.
- p21$^{Cip/WAF1}$ regulates the radioresistance of the fetal subset.

Authors

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Lay summary

Kupffer cells (KCs) are the tissue-resident macrophages of the liver. KCs can be originated from fetal precursors and from monocytes during the fetal stage and post-birth, respectively. Most immune cells in mice are sensitive to lethal-irradiation-induced death, while a subset of KCs resists radiation-induced death. These radioresistant KCs continue to live in the irradiated mice. We discovered that this relatively radioresistant KC subset are the fetal-derived KCs, and they achieve this through cell-cycle arrest. Understanding the radiobiology of KCs will provide valuable insights into the mechanisms that elicit radiation-induced liver disease.

https://doi.org/10.1016/j.jhep.2019.04.015

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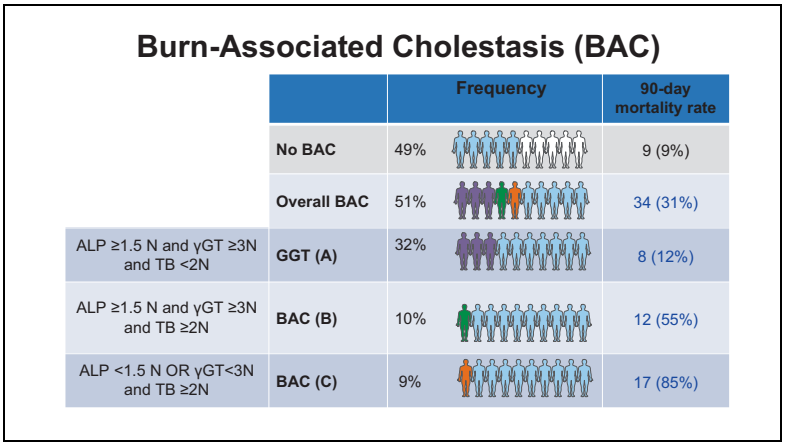
Research Article
Cholestasis and Autoimmune Diseases

JOURNAL
OF HEPATOLOGY

Contributing factors and outcomes of burn-associated cholestasis

Graphical abstract



Highlights

- In this cohort study, intrahepatic cholestasis was found in half of patients suffering from severe burn injuries.
- The presence of burn-associated cholestasis doubled the risk of death during the burn unit stay.
- There was a strong association between burn-associated cholestasis, bacteraemia and extrahepatic organ failure.
- Patients with elevated bilirubin levels without elevated ALP and GGT levels had the highest risk of mortality.
- Burn-associated cholestasis was associated with a long-term risk of sclerosing cholangitis.

Authors

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Lay summary

Cholestasis is common after burn injuries and is associated with burn severity, sepsis, organ failure and mortality. Patients with hyperbilirubinemia without elevated alkaline phosphatase and gamma-glutamyltransferase levels after the burn injury have a poor prognosis. Patients with burn-associated cholestasis may develop sclerosing cholangitis and secondary biliary cirrhosis.

https://doi.org/10.1016/j.jhep.2019.05.009

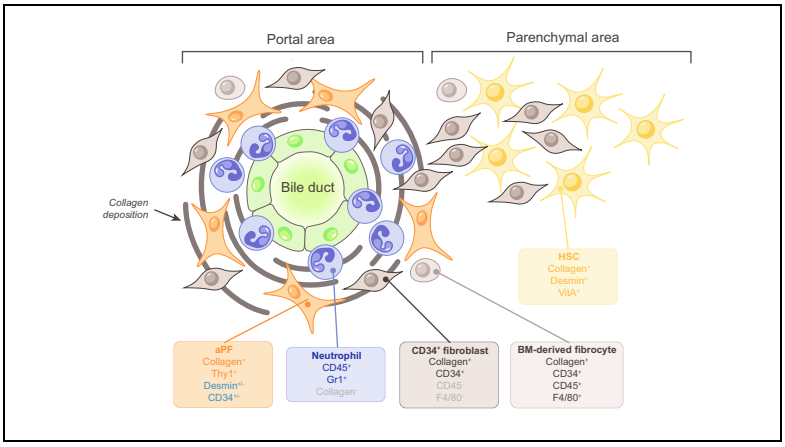
 J. Hepatol. 2019, 71, 563–572

Research Article
Genetic and Metabolic Diseases

JOURNAL
OF HEPATOLOGY

Activated hepatic stellate cells and portal fibroblasts contribute to cholestatic liver fibrosis in *MDR2* knockout mice

Graphical abstract



Highlights

- Hepatic myofibroblasts progressively accumulate in the livers of *Mdr2*$^{-/-}$ mice.
- Myofibroblasts mostly originate from hepatic stellate cells or portal fibroblasts.
- Meanwhile, fibrocytes minimally contribute to myofibroblasts in *Mdr2*$^{-/-}$ mice.
- In addition to collagen production, myofibroblasts serve as a source of NADPH oxidase (NOX).
- Therapeutic blocking of NOX1/4 ameliorates cholestatic fibrosis in *Mdr2*$^{-/-}$ mice.

Authors

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Lay summary

Activated portal fibroblasts and hepatic stellate cells, but not fibrocytes, contributed to the production of the fibrous scar in livers of *Mdr2*$^{-/-}$ mice, and these cells can serve as targets for antifibrotic therapy in cholestatic injury. Therapeutic inhibition of the enzyme NADPH oxidase (NOX) in *Mdr2*$^{-/-}$ mice reversed cholestatic fibrosis, suggesting that targeting NOXs may be an effective strategy for the treatment of cholestatic fibrosis.

https://doi.org/10.1016/j.jhep.2019.04.012

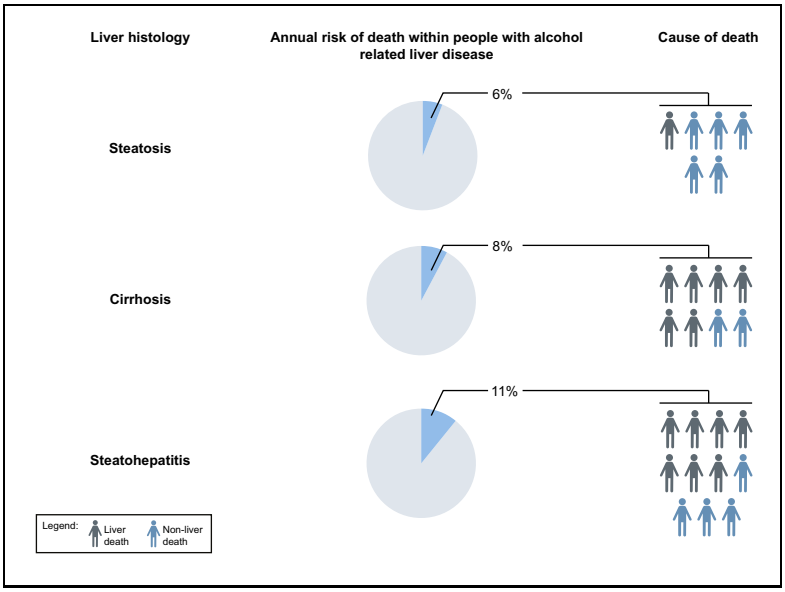
 J. Hepatol. 2019, 71, 573–585

Research Article
Genetic and Metabolic Diseases

JOURNAL
OF HEPATOLOGY

Natural history of histologically proven alcohol-related liver disease: A systematic review

Graphical abstract



Highlights

- Approximately 15% of hazardous drinkers may have normal liver histology.
- Progression to cirrhosis is most common in people with steatohepatitis (10% per year).
- Liver-related factors are the predominant cause of death in people with steatohepatitis or cirrhosis.
- Hepatic steatosis is not benign, with an annual mortality rate of ~6%/year, but deaths are mainly non-liver related.

Authors

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Lay summary

Knowledge of the natural history of a disease allows clinicians and patients to understand the risks that are associated with a medical condition. In this study we systematically gathered all the published data regarding the natural history of alcohol-related liver disease in people who had a liver biopsy. We used this data to define the prevalence of the disease, the annual risk of progression to cirrhosis and the annual risk of death at each stage of the disease.

https://doi.org/10.1016/j.jhep.2019.05.020

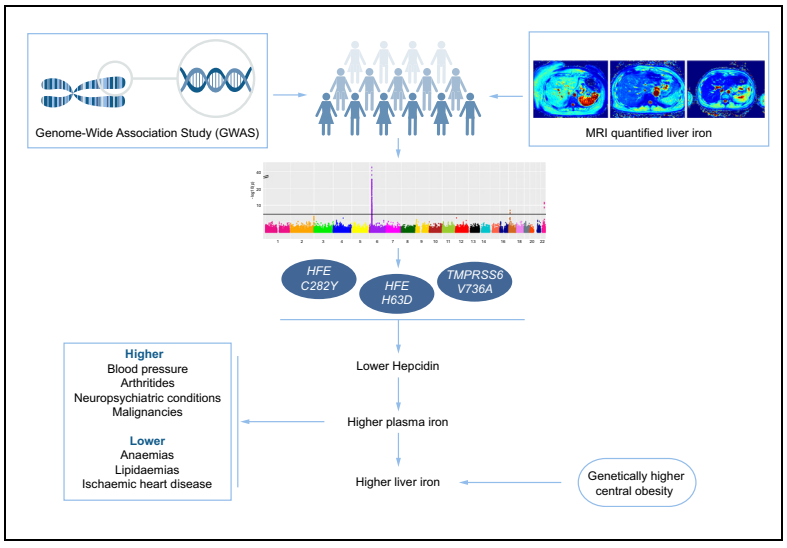
 J. Hepatol. 2019, 71, 586–593

Research Article
Genetic and Metabolic Diseases

JOURNAL
OF HEPATOLOGY

Genetic studies of abdominal MRI data identify genes regulating hepcidin as major determinants of liver iron concentration

Graphical abstract



Highlights

- Variants in *HFE* and *TMPRSS6* are associated with higher liver iron.
- There is genetic evidence that higher central obesity causes higher liver iron.
- Liver iron variants are not organ specific and associate with multiple diseases.

Authors

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Lay summary

Excess liver iron content is common and is associated with liver diseases and metabolic diseases including diabetes, high blood pressure, and heart disease. We identified 3 genetic variants that are linked to an increased risk of developing higher liver iron content. We show that the same genetic variants are linked to higher risk of many diseases, but they may also be associated with some health advantages. Finally, we use genetic variants associated with waist-to-hip ratio as a tool to show that central obesity is causally associated with increased liver iron content.

https://doi.org/10.1016/j.jhep.2019.05.032

 J. Hepatol. 2019, 71, 594–602