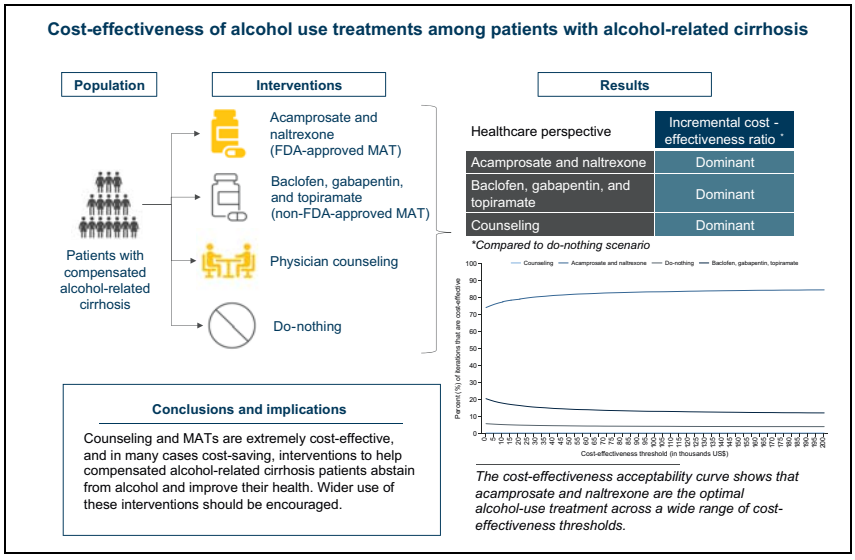
June 2021

Research Article
NAFLD and Alcohol-Related Liver Diseases

JOURNAL OF HEPATOLOGY

Cost-effectiveness of alcohol use treatments in patients with alcohol-related cirrhosis

Graphical abstract



Highlights

- Alcohol use treatments improve outcomes in patients with alcohol-related cirrhosis.
- Medication-assisted therapies and counseling are cost-effective or cost-saving.
- Different assumptions on costs and effectiveness do not shift main findings.
- Wider use of these interventions should be encouraged.

Authors

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Lay summary

Alcohol use treatments, including physician counseling and medication-assisted therapies (MATs), improve the outcomes of patients with compensated alcohol-related cirrhosis, though use and access have remained suboptimal. In this study, we found that counseling and MATs are extremely cost-effective, and in some cases cost-saving, interventions to help patients with alcohol-related cirrhosis abstain from alcohol and improve their health. Wider use of these interventions should be encouraged.

https://doi.org/10.1016/j.jhep.2020.12.004

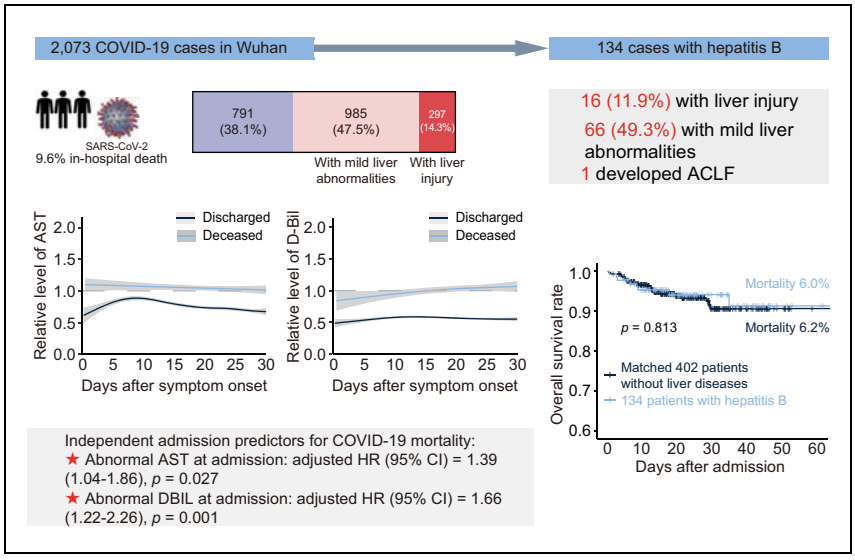
 J. Hepatol. 2021, 74, 1286–1294

Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

Association of liver abnormalities with in-hospital mortality in patients with COVID-19

Graphical abstract



Highlights

- Levels of AST and D-Bil elevated early after the symptom onset in deceased patients and showed disparity compared with that in discharged patients throughout the clinical course of COVID-19.
- Abnormal admission AST and D-Bil levels were independent predictors of COVID-19 mortality.
- A novel nomogram was built based on admission AST and D-Bil levels as well as other baseline characteristics to predict the in-hospital mortality of COVID-19.
- Hepatitis B infection was not found to be associated with the risk of lethal outcome in patients with COVID-19.

Authors

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Lay summary

Liver test abnormalities (in particular elevations in the levels of aspartate aminotransferase [AST] and direct bilirubin [D-Bil]) were observed after symptom onset in patients who went on to die of coronavirus disease 2019 (COVID-19). Abnormal levels of AST and D-Bil at admission were independent predictors of COVID-19-related mortality. HBV infection in patients did not increase the risk of poor COVID-19-associated outcomes.

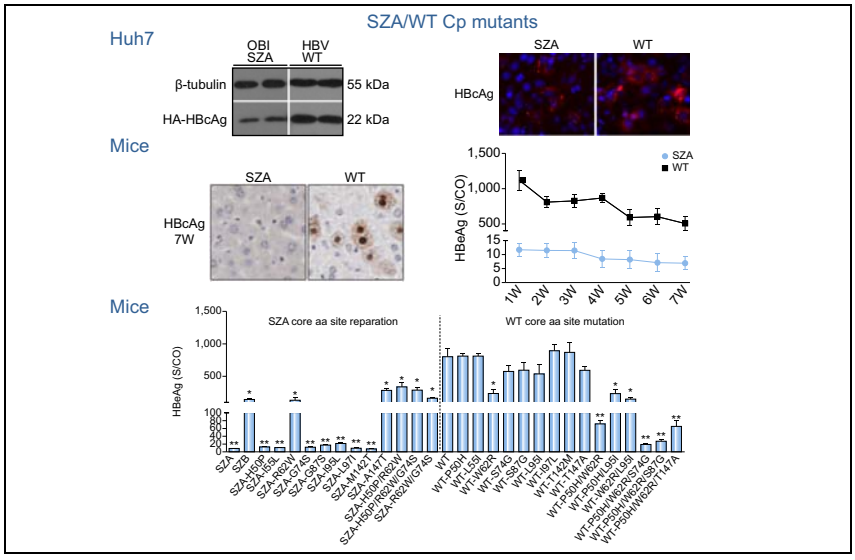
https://doi.org/10.1016/j.jhep.2020.12.012

Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

Role of core protein mutations in the development of occult HBV infection

Graphical abstract



Highlights

- Amino acid (aa) substitutions in the core protein (Cp) of occult HBV infection (OBI) strains were identified.
- An OBI mutant strain (SZA) carrying 9 aa substitutions in Cp was characterised *in vitro* (cells) and *in vivo* (mice).
- The functional impact of individual aa substitutions in pHBV1.3-SZA Cp replicons was assessed *in vitro* and *in vivo*.
- The Cp W62R mutation significantly reduced HBV protein production.
- The Cp W62R and its combination mutations might contribute to the occurrence of OBI.

Authors

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Lay summary

Occult hepatitis B virus infections (OBIs) have been found to be associated with amino acid mutations in the S region of the HBV, but the role of mutations in the core protein (Cp) remains unclear. In this study, an OBI strain (SZA) carrying 9 amino acid substitutions in Cp has been examined comprehensively *in vitro* and *in vivo*. The W62R mutation in Cp majorly reduces HBcAg and HBeAg production during HBV replication, potentially contributing to the occurrence of OBI.

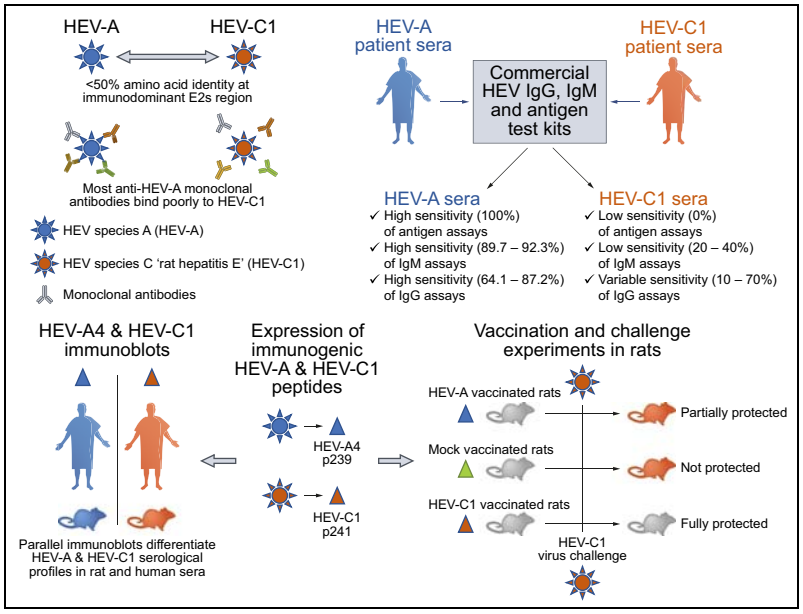
https://doi.org/10.1016/j.jhep.2020.12.023

Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

Multimodal investigation of rat hepatitis E virus antigenicity: Implications for infection, diagnostics, and vaccine efficacy

Graphical abstract



Highlights

- Rat HEV (HEV-C1) is antigenically distinct from human HEV genotypes.
- Human HEV-based antigen and antibody assays may not diagnose HEV-C1 infection.
- Prior exposure to human HEV genotypes is not protective against HEV-C1 infection.
- An HEV-C1 peptide can be used for specific HEV-C1 sero-diagnosis and vaccination.

Authors

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Lay summary

Rat hepatitis E virus (HEV-C1) is a new cause of hepatitis in humans. Using a combination of methods, we showed that HEV-C1 is highly divergent from the usual cause of human hepatitis (HEV-A). This divergence reduces the capacity of existing tests to diagnose HEV-C1 and also indicates that prior exposure to HEV-A (via infection or vaccination) is not protective against HEV-C1.

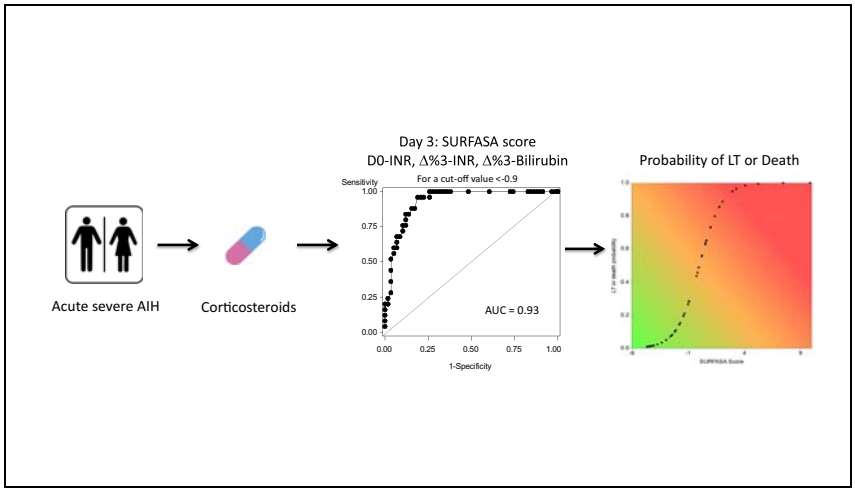
https://doi.org/10.1016/j.jhep.2020.12.028

Research Article
DILI, Autoimmune, Cholestatic and Genetic Diseases

JOURNAL
OF HEPATOLOGY

Early liver transplantation for corticosteroid non-responders with acute severe autoimmune hepatitis: The SURFASA score

Graphical abstract



Highlights

- In patients with acute-severe autoimmune hepatitis treated with corticosteroids, the LT-free survival rate is 66%.
- INR at the introduction of corticosteroids and the evolution of INR and bilirubin values after 3 days of therapy are highly predictive of LT or death.
- The SURFASA score [-6.80+1.92*(D0-INR)+1.94*(Δ%3-INR)+1.64*(Δ%3-bilirubin)] combines these 3 variables.
- The SURFASA score can rapidly identify non-responders to corticosteroid therapy who require referral for LT.

Authors

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Lay summary

The management of patients with acute severe autoimmune hepatitis is highly challenging, particularly regarding their early referral for liver transplantation. We found that international normalized ratio at the initiation of corticosteroid therapy and the evolution of international normalized ratio and bilirubin values after 3 days of therapy were highly predictive of liver transplantation or death. We are thus proposing a score that combines these variables and identifies patients in whom liver transplantation is urgently required.

https://doi.org/10.1016/j.jhep.2020.12.033

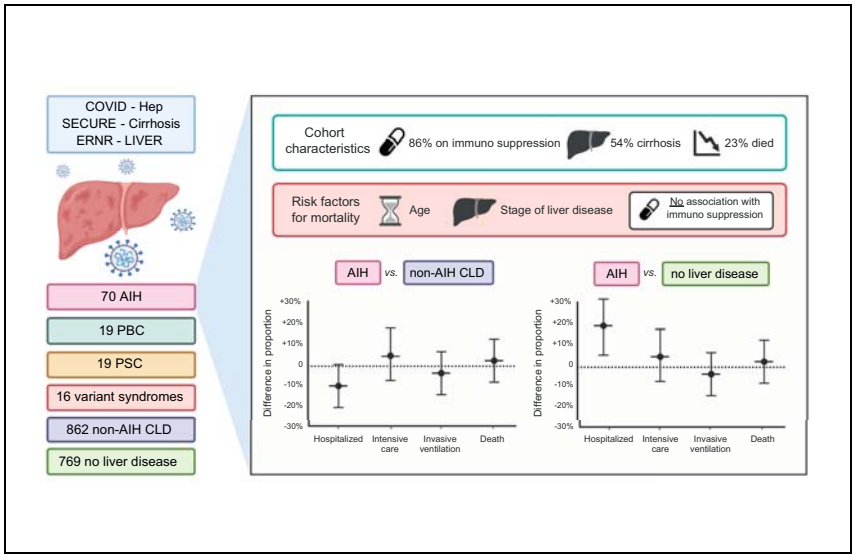
 J. Hepatol. 2021, 74, 1325–1334

Research Article
DILI, Autoimmune, Cholestatic and Genetic Diseases

JOURNAL
OF HEPATOLOGY

SARS-CoV-2 infection in patients with autoimmune hepatitis

Graphical abstract



Highlights

- This is the largest cohort of patients with autoimmune hepatitis and laboratory proven SARS-COV-2 infection reported to date.
- There were no differences in rates of major adverse COVID-19 outcomes between patients with AIH and those with other liver diseases.
- Patients with AIH had higher rates of hospitalization than patients without liver disease, but no increased risk of ICU admission or death.
- Independent risk factors for death in AIH patients were age and baseline liver disease severity, but not the use of immunosuppression.

Authors

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Lay summary

Little is known about the outcomes of COVID-19 in patients with autoimmune hepatitis (AIH), a rare chronic inflammatory liver disease. This study combines data from 3 large registries to describe the course of COVID-19 in this patient group. We show that AIH patients do not appear to have an increased risk of death from COVID-19 compared to patients with other forms of liver disease and compared to patients without liver disease, despite the use of medications which suppress the immune system.

https://doi.org/10.1016/j.jhep.2021.01.021

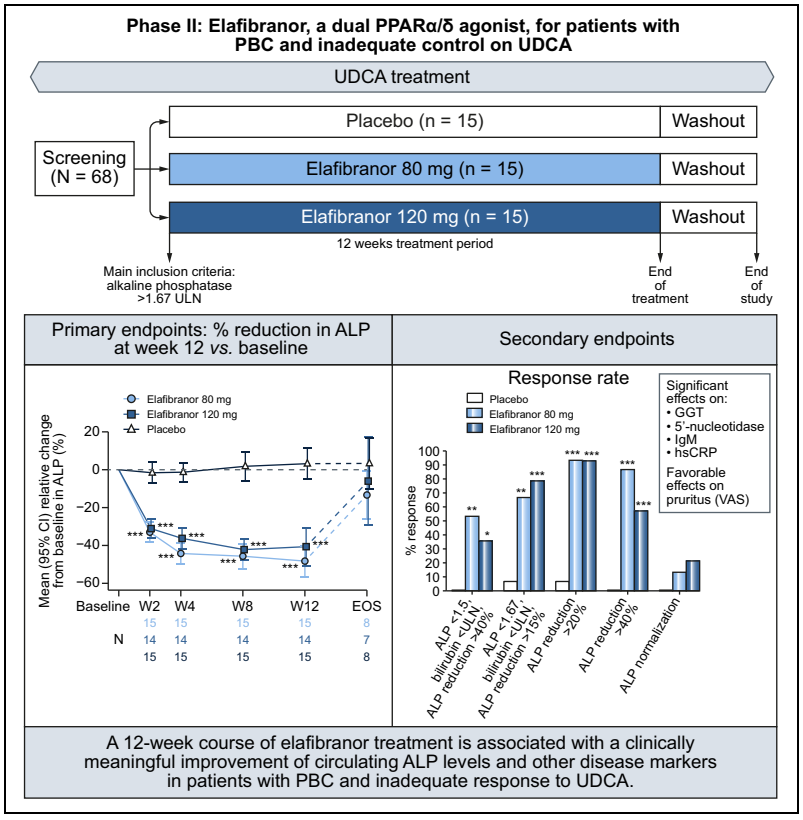
 J. Hepatol. 2021, 74, 1335–1343

Research Article
DILI, Autoimmune, Cholestatic and Genetic Diseases

JOURNAL
OF HEPATOLOGY

A randomized placebo-controlled trial of elafibranor in patients with primary biliary cholangitis and incomplete response to UDCA

Graphical abstract



Highlights

- In a phase II trial in PBC, the dual PPARα and δ agonist elafibranor achieved the primary endpoint of reducing ALP.
- Compared to placebo, the 80 mg and 120 mg dose had positive effects on prognostically important composite endpoints.
- In patients with pruritus at baseline, an improvement was noted in both elafibranor arms.
- Elafibranor was generally well-tolerated over the duration of treatment.

Authors

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Lay summary

Patients with primary biliary cholangitis (a rare chronic liver disease) that do not respond to standard therapy remain at risk of disease progression toward cirrhosis and impaired quality of life. Elafibranor is a nuclear receptor agonist that we tested in a randomized clinical trial over 12 weeks. It successfully decreased levels of disease activity markers, including alkaline phosphatase. Thus, this study is the foundation for a larger prospective study that will determine the efficacy and safety of this drug as a second-line therapy.

https://doi.org/10.1016/j.jhep.2021.01.013

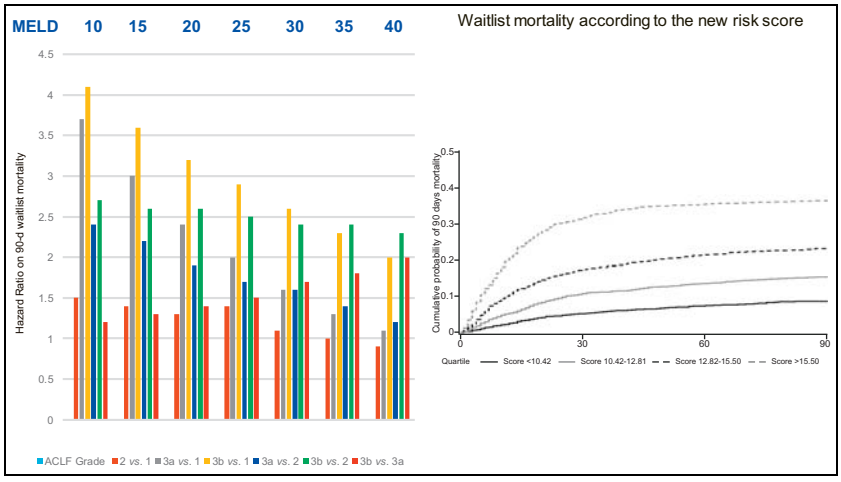
 J. Hepatol. 2021, 74, 1344–1354

Research Article
Cirrhosis and Liver Failure

JOURNAL
OF HEPATOLOGY

Validating a novel score based on interaction between ACLF grade and MELD score to predict waitlist mortality

Graphical abstract



Highlights

- Among candidates with ACLF who are listed for liver transplantation, MELD score and ACLF interact in predicting cumulative risk of 90-day waitlist mortality.
- The impact of ACLF grade on 90-day waitlist mortality is much higher at lower listing MELD score, especially below 25.
- A validated novel score using MELD score and ACLF grade at listing provides an estimate of 90-day waitlist mortality.

Authors

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Lay summary

In patients with cirrhosis listed for liver transplantation, the presence of multi-organ failure, a condition referred to as acute-on-chronic liver failure, is associated with high waiting list mortality rates. Current organ allocation policy disadvantages patients with this condition. This study describes and validates a new scoring method that performs better than the currently available scoring systems. Further validation of this approach may reduce the deaths of patients with cirrhosis and acute-on-chronic liver failure on the transplant waiting list.

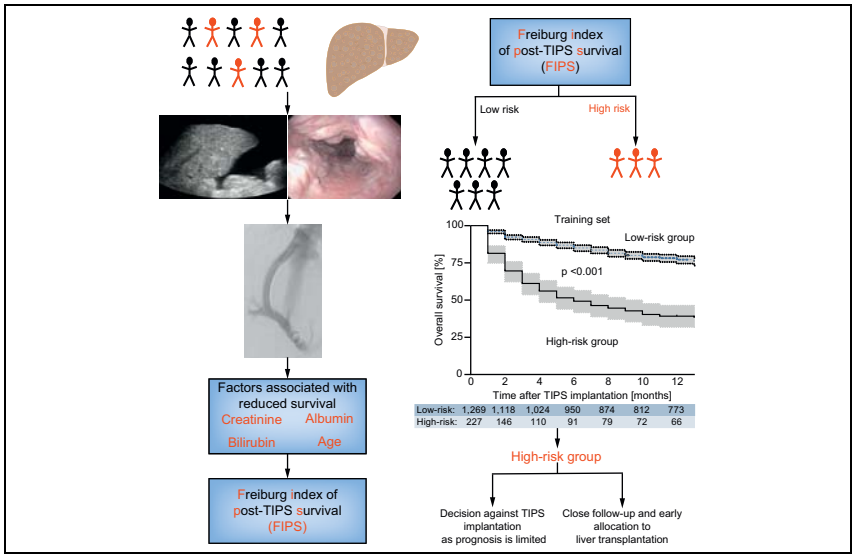
https://doi.org/10.1016/j.jhep.2020.12.003

Research Article
Cirrhosis and Liver Failure

JOURNAL
OF HEPATOLOGY

Refining prediction of survival after TIPS with the novel Freiburg index of post-TIPS survival

Graphical abstract



Highlights

- Risk stratification is a major challenge in patients undergoing TIPS implantation.
- Age, bilirubin, albumin and creatinine emerged as the most significant predictors of 6-months survival after TIPS implantation.
- These measures were summarized in a new score named the Freiburg index of post-TIPS survival (FIPS).
- The FIPS score clearly identifies a high-risk group of patients with a markedly reduced survival after TIPS implantation.
- Importantly, prognostic discrimination was superior to the MELD, MELD-Na, Child-Pugh score and the bilirubin-platelet model.

Authors

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Lay summary

Implantation of a transjugular intrahepatic portosystemic shunt (TIPS) is a safe and effective treatment for patients with cirrhosis and clinically significant portal hypertension. However, risk stratification is a major challenge in these patients as currently available scoring systems have major drawbacks. Age, bilirubin, albumin and creatinine were included in a new risk score which was named the Freiburg index of post-TIPS survival (FIPS). The FIPS score can identify patients at high risk and may guide clinical decision making.

https://doi.org/10.1016/j.jhep.2021.01.023

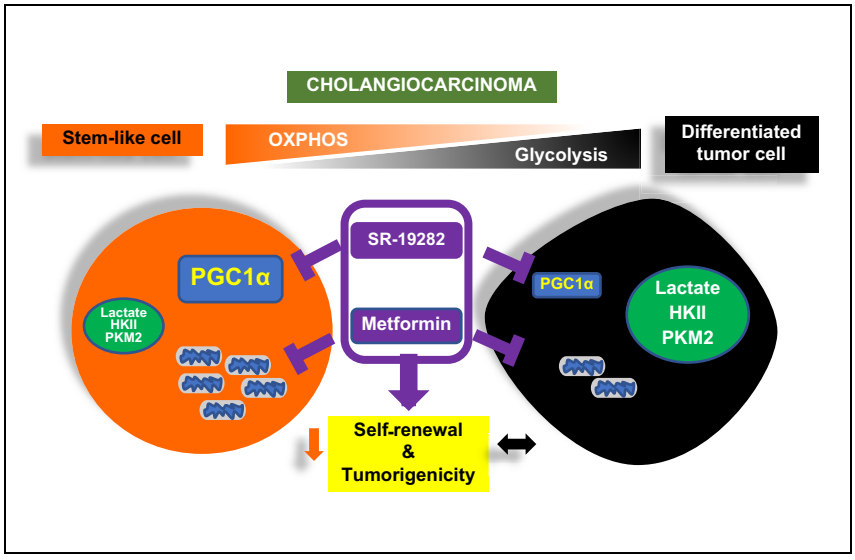
 J. Hepatol. 2021, 74, 1362–1372

Research Article
Hepatic and Biliary Cancer

JOURNAL
OF HEPATOLOGY

Mitochondrial oxidative metabolism contributes to a cancer stem cell phenotype in cholangiocarcinoma

Graphical abstract



Highlights

- The metabolic characteristics of cancer stem cells in cholangiocarcinoma are not known.
- Cholangiocarcinoma stem-like cells preferentially use oxidative phosphorylation as a source of energy.
- PGC-1α is a key molecule regulating the metabolic features of cholangiocarcinoma stem-like cells.
- Interfering with oxidative phosphorylation or PGC-1α limits the development of tumors originating from stem-like cells *in vivo*.
- Expression of PGC-1α or proteins of the mitochondrial respiratory complex correlate with clinical outcomes in patients with cholangiocarcinoma.

Authors

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Lay summary

The growth of many cancers is sustained by a specific type of cells with more embryonic characteristics, termed ‘cancer stem cells’. These cells have been described in cholangiocarcinoma, a type of liver cancer with poor prognosis and limited therapeutic approaches. We demonstrate that cancer stem cells in cholangiocarcinoma have different metabolic features, and use mitochondria, an organelle located within the cells, as the major source of energy. We also identify PGC-1α, a molecule which regulates the biology of mitochondria, as a possible new target to be explored for developing new treatments for cholangiocarcinoma.

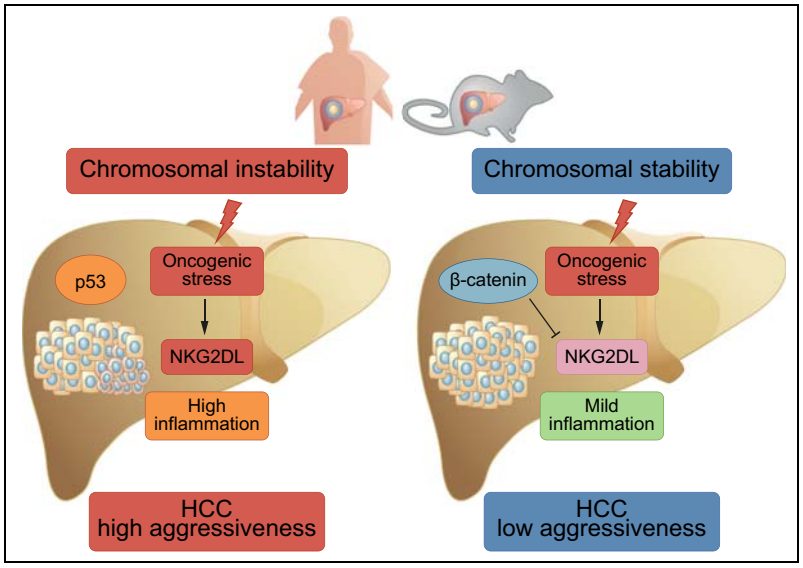
https://doi.org/10.1016/j.jhep.2020.12.031

Research Article
Hepatic and Biliary Cancer

JOURNAL
OF HEPATOLOGY

Expression of NKG2D ligands is downregulated by β-catenin signalling and associates with HCC aggressiveness

Graphical abstract



Highlights

- The expression of *MICA* and *MICB* is associated with HCC tumour aggressiveness and poor patient outcome.
- The expression of *ULBP1* and *ULBP2* is associated with poor patient outcome and is downregulated in *CTNNB1*-mutated HCC.
- Expression of the mouse *Rae-1* NKG2D ligand is regulated by β-catenin signalling via TCF4 in hepatocytes.
- The expression of *KLRK1* (NKG2D) and *ULBP1* is associated with immune cell signatures in HCC.
- Low levels of NKG2D ligand expression in *CTNNB1*-mutated HCC may account for the less inflamed and less aggressive phenotype of these tumours.

Authors

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Lay summary

The NKG2D system is a potent immunosurveillance mechanism in cancer. However, its role in hepatocellular carcinoma development has not been widely investigated. Herein, we should that the expression of NKG2D ligands by tumour cells is associated with a more aggressive tumour subtype.

https://doi.org/10.1016/j.jhep.2021.01.017

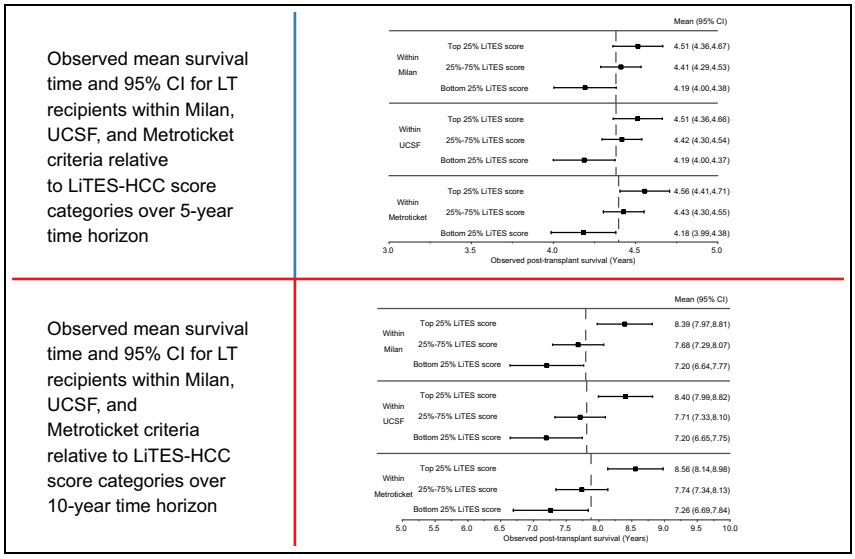
 J. Hepatol. 2021, 74, 1386–1397

Research Article
Liver Transplantation

JOURNAL
OF HEPATOLOGY

Predicting survival after liver transplantation in patients with hepatocellular carcinoma using the LiTES-HCC score

Graphical abstract



Highlights

- Patients with HCC frequently die of non-HCC-related causes after liver transplant.
- Inclusion of non-HCC variables improves the discrimination of a HCC risk score.
- Allocation based on predicted survival could improve population-level outcomes.

Authors

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Lay summary

We created a risk score to predict how long patients with liver cancer will live if they get a liver transplant. In the future, this could be used to decide which waitlisted patients should get the next transplant.

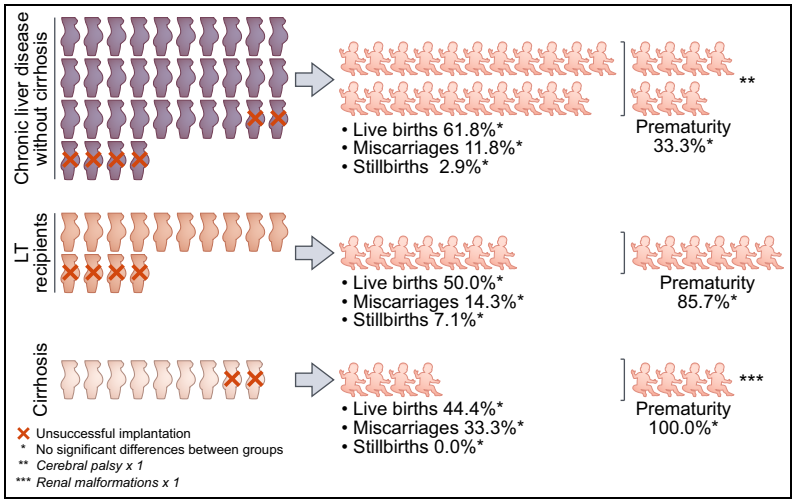
https://doi.org/10.1016/j.jhep.2020.12.021

Research Article
Liver Transplantation

JOURNAL
OF HEPATOLOGY

Safety and efficacy of *in vitro* fertilisation in patients with chronic liver disease and liver transplantation recipients

Graphical abstract



Highlights

- Subfertility is common in women with liver disease and can persist post-LT.
- Although the complications of IVF are well described in the general population, its effects on women with liver disease are unknown.
- Women with LRSF can undergo successful pregnancies with IVF therapy.
- Complications are potentially greater in women with liver disease, so pre-conception counselling is important.

Authors

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Lay summary

Women with liver disease or those who have had a liver transplant can experience difficulties getting pregnant. In this study, we look at whether alternative approaches to achieve pregnancy are harmful in these women. Overall, there were no significant issues with the use of *in vitro* fertilisation in women with liver disease, but they need to be aware of potential risks, such as early delivery of the baby.

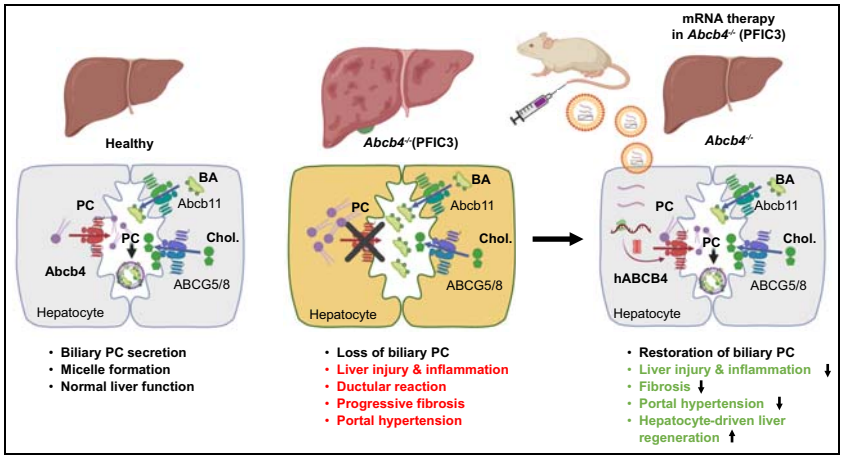
https://doi.org/10.1016/j.jhep.2020.12.022

Research Article
Experimental and Translational Hepatology

JOURNAL
OF HEPATOLOGY

Synthetic human *ABCB4* mRNA therapy rescues severe liver disease phenotype in a BALB/c.*Abcb4*$^{-/-}$ mouse model of PFIC3

Graphical abstract



Highlights

- Synthetic liver-targeted h*ABCB4* mRNA therapy was designed for PFIC3, a devastating rare paediatric liver disease.
- Single injection restores hepatocyte ABCB4 expression and biliary phosphatidylcholine secretion in a genetic model of PFIC3.
- Repeated administration rapidly and completely rescues PFIC3 disease in young *Abcb4*$^{-/-}$ mice.
- Treatment ameliorated liver injury, inflammation, ductular reaction, fibrosis, portal hypertension and 'failure to thrive'.

Authors

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Lay summary

This report describes the development of an innovative mRNA therapy as a potential treatment for PFIC3, a devastating rare paediatric liver disease with no treatment options except liver transplantation. We show that administration of our mRNA construct completely rescues severe liver disease in a genetic model of PFIC3 in mice.

https://doi.org/10.1016/j.jhep.2020.12.010

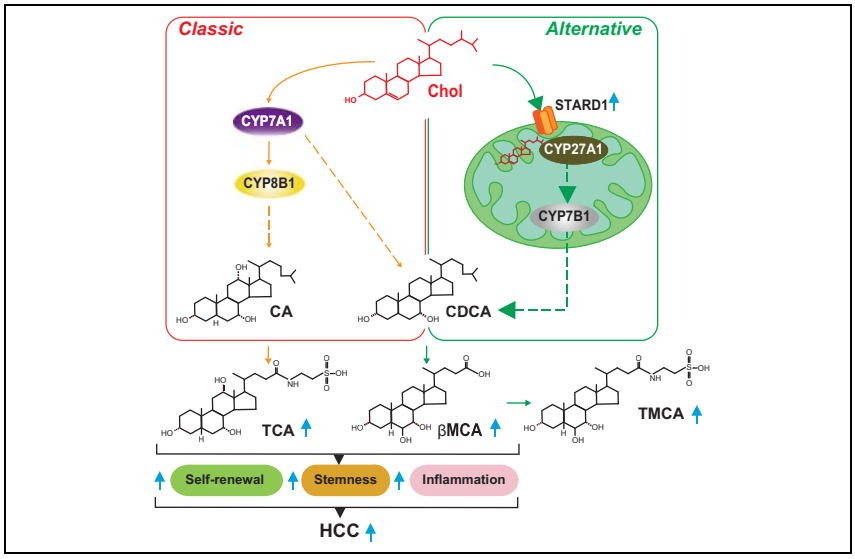
 J. Hepatol. 2021, 74, 1416–1428

Research Article
Experimental and Translational Hepatology

JOURNAL
OF HEPATOLOGY

STARD1 promotes NASH-driven HCC by sustaining the generation of bile acids through the alternative mitochondrial pathway

Graphical abstract



Highlights

- Human non-alcoholic fatty liver disease and steatohepatitis-driven HCC tissue specimens exhibit increased STARD1 expression.
- STARD1 overexpression promotes, whereas STARD1 ablation curtails, NASH-driven HCC.
- STARD1 stimulates bile acid synthesis through activation of the alternative mitochondrial pathway.
- Bile acids stimulate pluripotency, stemness and inflammation-related genes in tumour-initiating stem-like cells.

Authors

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Lay summary

Effective therapy for hepatocellular carcinoma (HCC) is limited because of our incomplete understanding of its pathogenesis. The contribution of the alternative pathway of bile acid (BA) synthesis to HCC development is unknown. We uncover a key role for steroidogenic acute regulatory protein 1 (STARD1) in non-alcoholic steatohepatitis-driven HCC, wherein it stimulates the generation of BAs in the mitochondrial acidic pathway, the products of which stimulate hepatocyte pluripotency and self-renewal, as well as inflammation.

https://doi.org/10.1016/j.jhep.2021.01.028

 J. Hepatol. 2021, 74, 1429–1441