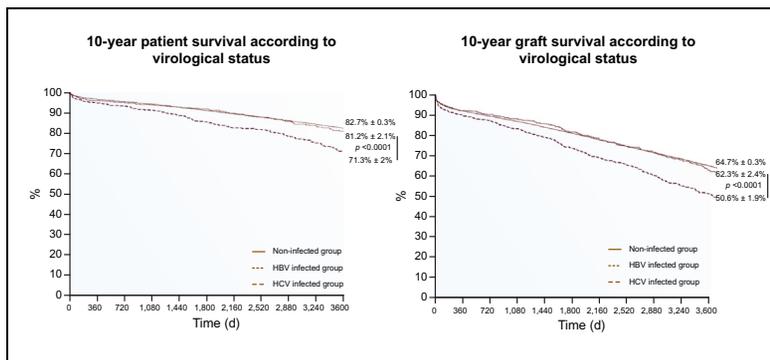


# Control of replication of hepatitis B and C virus improves patient and graft survival in kidney transplantation

## Graphical abstract



## Highlights

- Chronic HBV infection no longer influences 10-year patient or graft survival in kidney transplant recipients.
- Chronic HCV infection still negatively impacts 10-year patient and graft survival.
- The negative effect of chronic HCV infection is removed by sustained viral suppression.
- Antiviral therapy should be systematically proposed for HBV- and/or HCV-infected kidney transplant recipients/candidates.

## Authors

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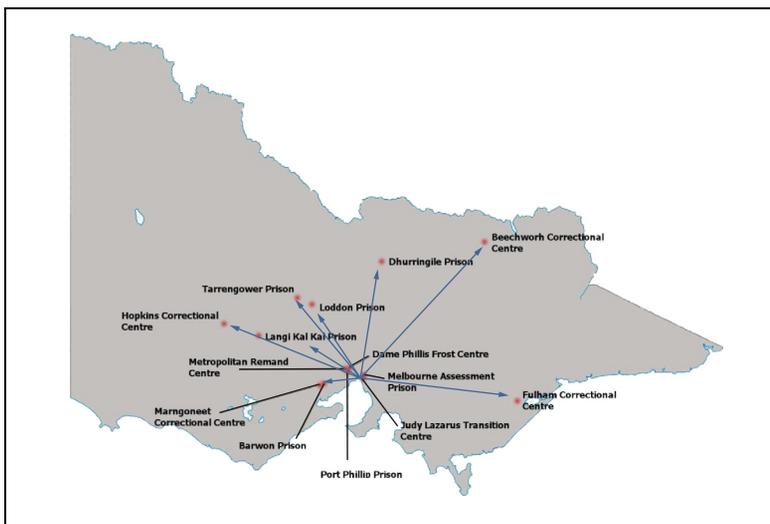
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## Lay summary

Previously, infections with hepatitis B or hepatitis C virus led to poor outcomes in kidney transplant recipients. However, the outcomes of kidney transplants in patients with viral suppression are as good as those for kidney transplants in non-infected patients. Antiviral therapy should be systematically proposed to hepatitis B and/or hepatitis C-infected kidney transplant recipients or candidates to prevent the deleterious hepatic and extrahepatic impact of chronic viral replication. Recent access to direct-acting antivirals in patients with hepatitis C virus and renal dysfunction provides exciting new opportunities.

# Outcomes of treatment for hepatitis C in prisoners using a nurse-led, statewide model of care

## Graphical abstract



## Highlights

- Nurse-led care was associated with SVR12 rates of >95% in large numbers of prisoners.
- <20% of prisoners required specialist input.
- >80% of prisoner had never pursued specialist hepatitis C care in the community.

## Authors

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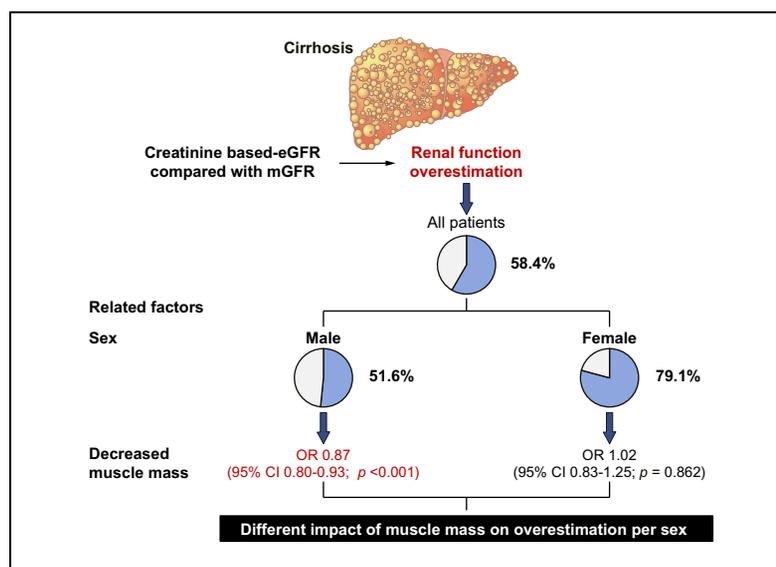
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## Lay summary

There is a high burden of hepatitis C infection among prisoners worldwide. Prisoners who continue to inject drugs are also at risk of developing new infections. For this reason, the prison setting provides an opportunity to treat those people at greatest risk of infection and to stop transmission to others. We developed a new method of providing hepatitis C treatment to prisoners, in which nurses rather than doctors assessed prisoners locally at each prison site. Treatment was safe and most prisoners were cured. Such programs will contribute greatly to achieving the World Health Organization's hepatitis C elimination goals.

# Estimation of renal function in patients with liver cirrhosis: Impact of muscle mass and sex

## Graphical abstract



## Authors

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## Lay summary

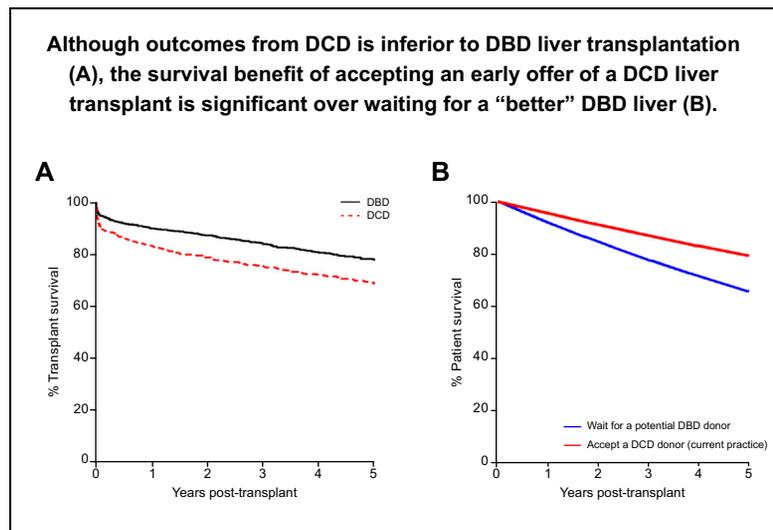
Overestimation of renal function frequently occurs in patients with liver cirrhosis when using serum creatinine. Decreased muscle mass has a great impact on overestimation of kidney function especially in male patients with cirrhosis. Compared with creatinine, cystatin C was more closely correlated with measured glomerular filtration rate and had a higher predictive ability for renal complications and survival than creatinine.

## Highlights

- Renal function overestimation occurs frequently in patients with liver cirrhosis when using serum creatinine.
- Decreased muscle mass impacts on overestimation of kidney function especially in male patients with cirrhosis.
- Compared to creatinine, cystatin C correlated better with mGFR and had a higher predictive ability for clinical outcomes.
- Cystatin C might be a promising marker to accurately assess renal function in cirrhotic patients.

# Survival advantage for patients accepting the offer of a circulatory death liver transplant

## Graphical abstract



## Highlights

- Outcomes for DCD are inferior to DBD liver transplantation in the UK experience.
- There is a survival advantage in accepting a DCD offer rather than waiting for a “better DBD liver.
- This survival advantage is most pronounced in patients with more advanced disease.
- This study provides strong support for the use of DCD livers in all patients.
- This should facilitate discussions with individuals about accepting or declining a DCD liver offer.

## Authors

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## Correspondence

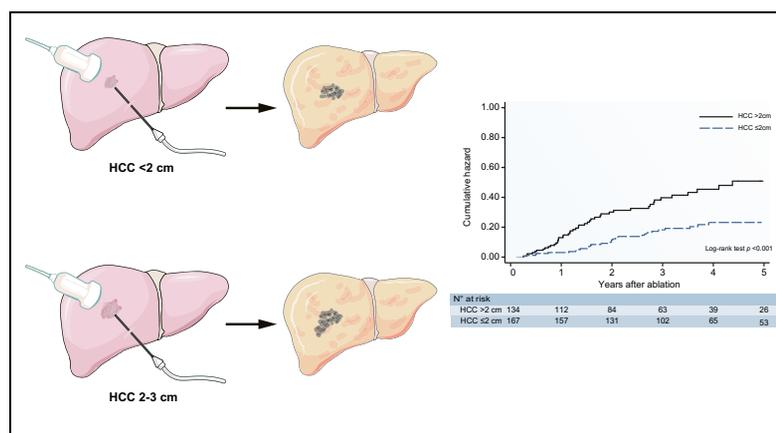
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## Lay summary

This study looks at patients who require a liver transplant to save their lives; this liver can be donated by a person who has died either after their heart has stopped (donation after cardiac death [DCD]) or after the brain has been injured and can no longer support life (donation after brainstem death [DBD]). We know that livers donated after brainstem death function better than those after cardiac death, but there are not enough of these livers for everyone, so we wished to help patients decide whether it was better for them to accept an early offer of a DCD liver than waiting longer to receive a “better liver from a DBD donor. We found that patients were more likely to survive if they accepted the offer of a liver transplant as soon as possible (DCD or DBD), especially if their liver disease was very severe.

# Outcomes of radiofrequency ablation as first-line therapy for hepatocellular carcinoma less than 3 cm in potentially transplantable patients

## Graphical abstract



## Highlights

- Most patients with single HCC  $\leq 3$  cm treated by RFA will eventually develop recurrent HCC distant to the ablation site.
- Many patients treated with HCC will recur beyond the Milan criteria despite close post-RFA surveillance.
- Patients with tumors  $>2$  cm and higher serum alpha-fetoprotein are at greater risk of recurrence beyond Milan criteria.

## Authors

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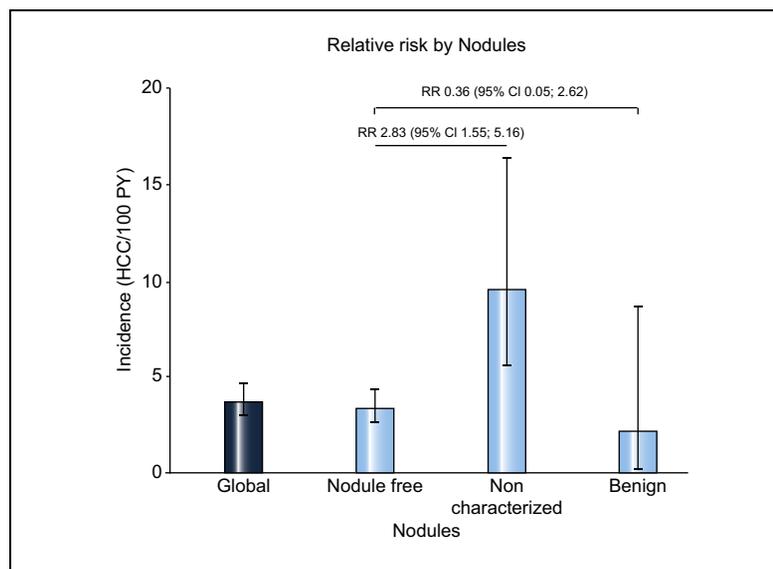
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## Lay summary

Radiofrequency ablation and liver transplantation are treatment options for early stages of hepatocellular carcinoma (HCC). After ablation some patients will experience recurrence or metastatic spread of the initial tumor or may develop new tumors within the liver. Despite close follow-up, these recurrences can progress rapidly and exceed transplant criteria, preventing the patient from receiving a transplant. We identified that patients with HCC  $>2$  cm and higher serum alpha-fetoprotein are at greater risk of recurrence beyond the transplant criteria. These data suggest that liver transplantation should be considered immediately after the first HCC recurrence for these patients.

# Time association between hepatitis C therapy and hepatocellular carcinoma emergence in cirrhosis: Relevance of non-characterized nodules

## Graphical abstract



## Highlights

- The risk of HCC in patients with HCV cirrhosis treated with DAAs persists despite viral cure.
- The presence of indeterminate nodules before starting DAA is associated with a 3 times greater risk of HCC.
- A time association between DAA therapy and developing HCC reflects increased short-term HCC risk.
- DAA therapy elicits a mechanism that primes the emergence of HCC early during follow-up.

## Authors

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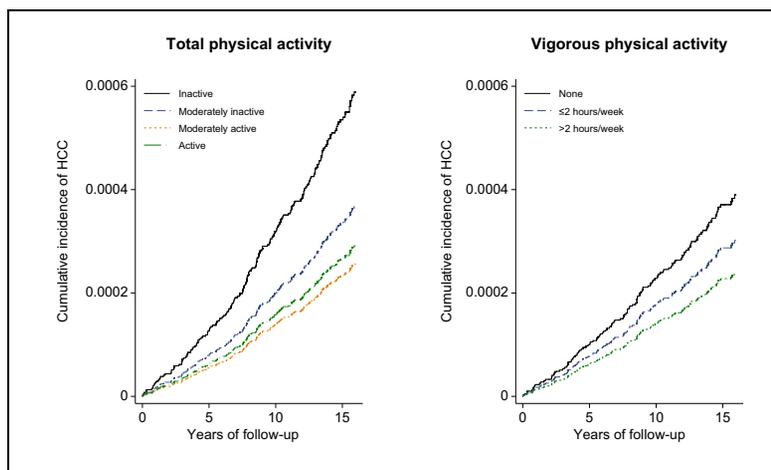
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## Lay summary

In this cohort of cirrhotic patients, interferon-free therapies achieved a high rate of sustained virologic response (>95%); however, we reported a risk of *de novo* hepatocellular carcinoma of 3.73 per 100 person-years and a clear-cut time association with antiviral therapy. The time association between starting direct-acting antivirals and developing hepatocellular carcinoma, together with the association with the presence of non-characterized nodules at baseline ultrasound, suggests that antiviral therapy elicits a mechanism (probably immune-related) that primes the growth and clinical recognition of hepatocellular carcinoma early during follow-up. As a result, short-term liver cancer risk is significantly increased.

# Association between physical activity and risk of hepatobiliary cancers: A multinational cohort study

## Graphical abstract



## Highlights

- Liver cancer rates are increasing in Western countries, possibly due to increases in obesity, diabetes, and physical inactivity.
- Previous evidence was not convincing to support an effect of physical activity on liver cancer.
- We found that physical activity reduced the risk of hepatocellular carcinoma by about 45%.

## Authors

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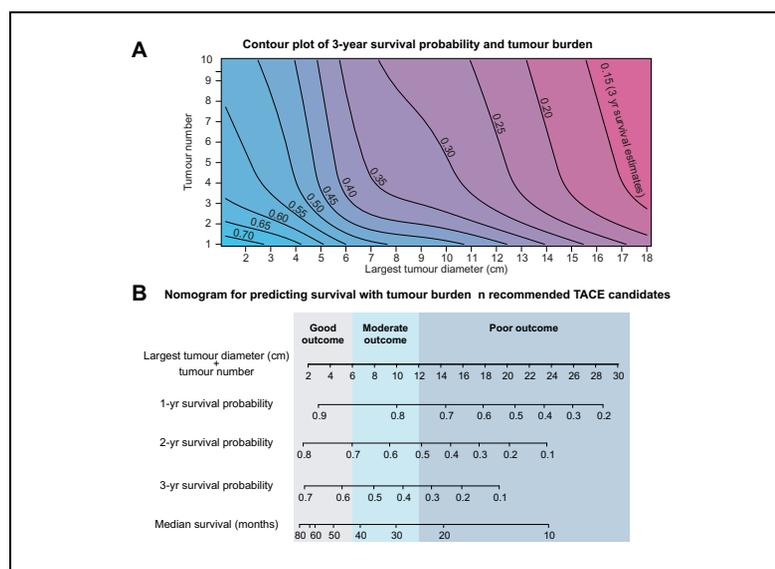
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## Lay summary

In a pan-European study of 467,336 men and women, we found that physical activity is associated with a reduced risk of developing liver cancers over the next decade. This risk was independent of other liver cancer risk factors, and did not vary by age, gender, smoking status, body weight, and alcohol consumption.

# Development of a prognostic score for recommended TACE candidates with hepatocellular carcinoma: A multicentre observational study

## Graphical abstract



## Authors

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## Lay summary

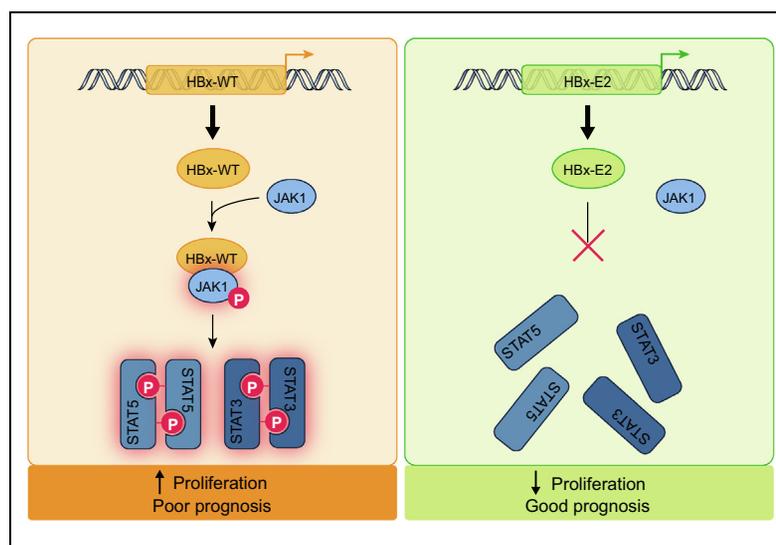
There is currently no prognostic model specifically developed for recommended or ideal transarterial chemoembolization (TACE) candidates with hepatocellular carcinoma, despite these patients being frequently identified as the best target population in pivotal randomized controlled trials. The six-and-twelve score provides patient survival prediction, especially in ideal candidates of TACE, outperforming other currently available models in both training and validation sets, as well as different subgroups. With cut-off values of 6 and 12, the score can stratify ideal TACE candidates into 3 strata with significantly different outcomes and may shed light on risk stratification of these patients in clinical practice as well as in clinical trials.

## Highlights

- First prognostic model specifically developed for ideal TACE candidates.
- The individualized prediction score is presented as the sum of tumour size (cm) and number.
- With cut-offs of 6 and 12, the score can stratify these patients into 3 prognostic strata.
- The score outperformed other available models in performance and discrimination.
- The score is advantageous for easy-to-use and individualized prediction.

# A novel HBx genotype serves as a preoperative predictor and fails to activate the JAK1/STATs pathway in hepatocellular carcinoma

## Graphical abstract



## Authors

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## Lay summary

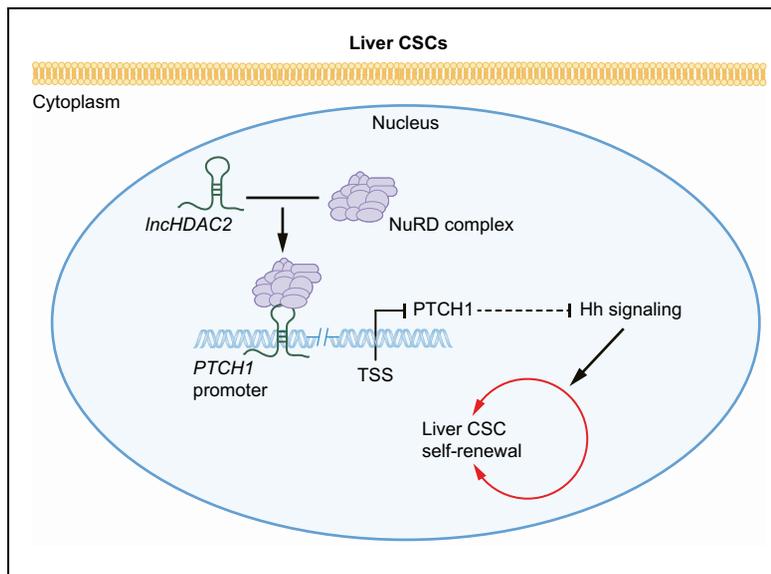
We classified a novel genotype of the full-length hepatitis B virus X gene (HBx), HBx-E2. This genotype was identified in tumor and nontumor tissues from patients with hepatitis B virus-related hepatocellular carcinoma. HBx-E2 could preoperatively predict the prognosis of patients with intermediate stage hepatocellular carcinoma, after resection.

## Highlights

- Three HBx genotypes were identified in tumor and nontumor tissues from patients with HBV-related HCC.
- HBx-E2 indicated better recurrence-free survival and overall survival for patients with HBV-related HCC.
- HBx-E2 preoperatively predicted the prognosis of patients with BCLC stage B HCC after resection.
- HBx-E2 and HBx-E2-N lost the ability to promote the proliferation of HCC cells and normal hepatocytes.
- HBx-E2 and HBx-E2-N failed to interact with JAK1 and activate the JAK1/STAT3/STAT5 signaling pathway.

# The long non-coding RNA *lncHDAC2* drives the self-renewal of liver cancer stem cells via activation of Hedgehog signaling

## Graphical abstract



## Highlights

- Long non-coding RNA *lncHDAC2* is highly expressed in liver cancer stem cells.
- *lncHDAC2* promotes the self-renewal of liver cancer stem cells.
- *lncHDAC2* associates with HDAC2 in liver cancer stem cells.
- *lncHDAC2*-mediated PTCH1 downregulation promotes Hh signaling, driving self-renewal of liver cancer stem cells.

## Authors

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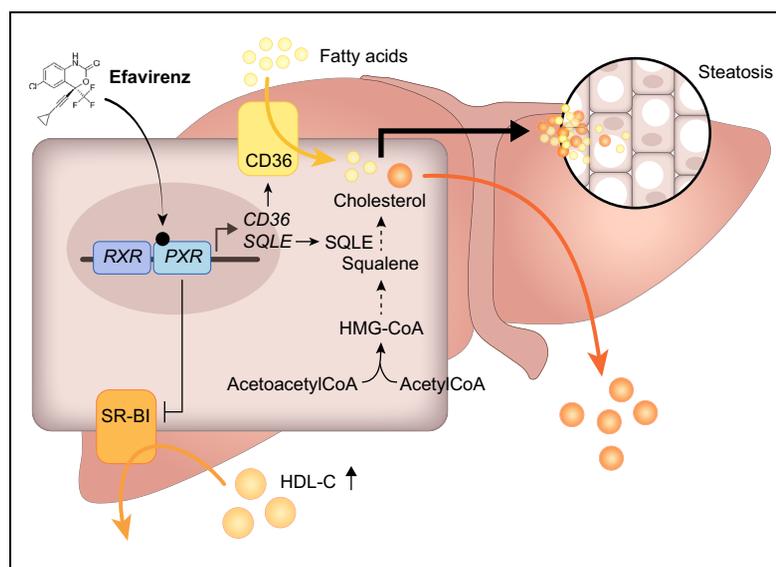
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## Lay summary

Liver cancer stem cells harbor high tumor-initiating potential and confer resistance to typical therapies, but the mechanism underlying their self-renewal remains elusive. *lncHDAC2* augments the self-renewal of these cells, promoting tumor propagation. In liver cancer stem cells, *lncHDAC2* activates Hedgehog signaling to initiate liver tumorigenesis. Therefore, *lncHDAC2* and the Hedgehog signaling pathway may serve as biomarkers and potential drug targets for hepatocellular carcinoma.

# Non-nucleoside reverse transcriptase inhibitor efavirenz activates PXR to induce hypercholesterolemia and hepatic steatosis

## Graphical abstract



## Authors

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## Lay summary

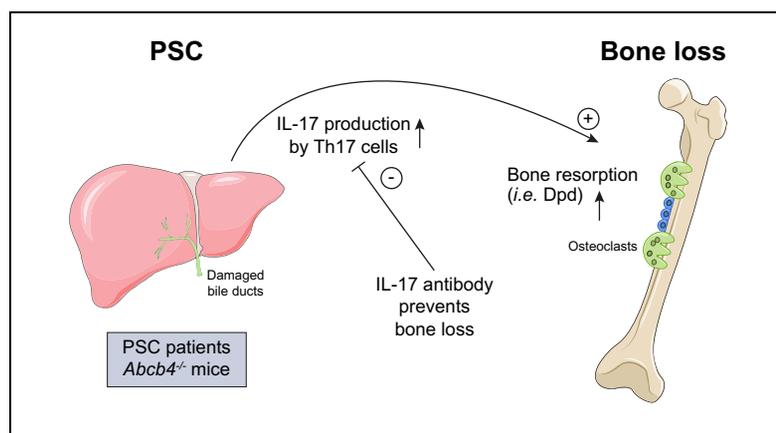
Efavirenz is widely prescribed for HIV-infected patients but has some side effects. It can increase lipid levels in patients' blood and liver. Here we show that efavirenz can activate a unique liver protein called PXR which mediates the adverse effects of efavirenz on lipid levels in mouse models.

## Highlights

- Efavirenz is widely prescribed for patients with HIV.
- Efavirenz increases the risk of dyslipidemia and hepatic steatosis in patients.
- Efavirenz is a potent agonist of the nuclear receptor PXR.
- Efavirenz activates PXR to elicit the adverse effects on lipid homeostasis in mice.
- PXR regulates the expression of several key lipogenic genes in the liver.

# Th17 cell frequency is associated with low bone mass in primary sclerosing cholangitis

## Graphical abstract



## Highlights

- Decreased bone mass in patients with PSC is associated with increased bone resorption.
- Th17 cell frequency correlates with bone resorption indices in patients with PSC.
- Increased osteoclastogenesis is corrected by IL-17 inactivation in *Abcb4*<sup>-/-</sup> mice.

## Authors

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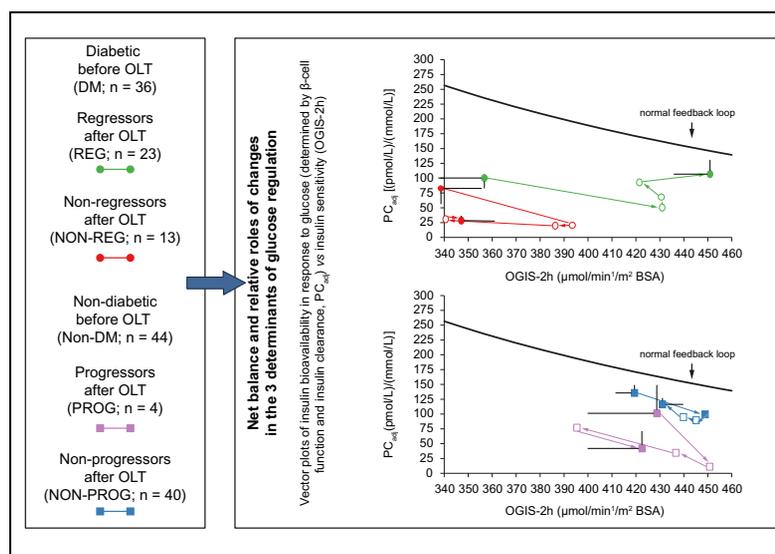
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## Lay summary

Primary sclerosing cholangitis (PSC) is a cholestatic liver disease characterized by progressive bile duct destruction. One serious complication of PSC is reduced bone mass resulting in increased fracture risk. Herein, we demonstrate that Th17 cells mediate bone loss in PSC by inducing bone resorption, which suggests that antibody-based IL-17 blockade might be beneficial for the treatment of bone loss in affected patients.

# Central role of the $\beta$ -cell in driving regression of diabetes after liver transplantation in cirrhotic patients

## Graphical abstract



## Authors

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## Lay summary

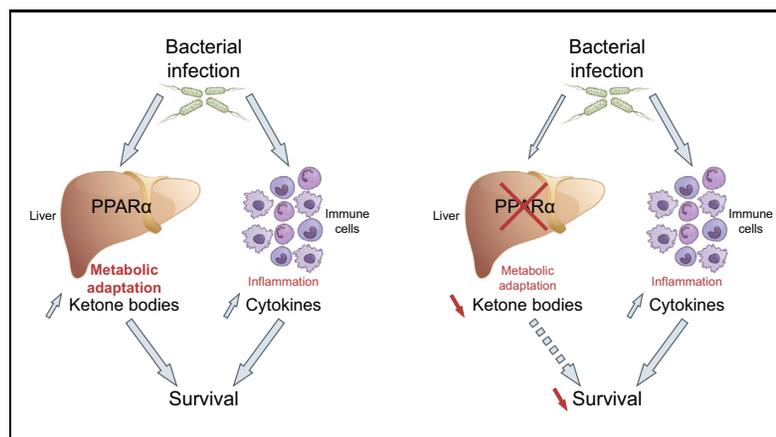
Diabetes occurring in cirrhosis as a direct consequence of loss of liver function should regress after transplantation of a new functioning liver, though the pathophysiological mechanisms are unclear. This is the first study evaluating the contribution of all 3 direct determinants of insulin-dependent glucose regulation using a sophisticated mathematical model. Results show that  $\beta$ -cell function is the key process governing favourable or detrimental changes in glucose regulation in cirrhotic patients undergoing transplantation, pointing to the need to develop therapies to sustain  $\beta$ -cell function in these individuals.

## Highlights

- The mechanisms underlying diabetes regression after liver transplantation are unclear.
- Diabetes regressed in  $\sim 2/3$  of diabetic patients and developed in  $<10\%$  of non-diabetic individuals.
- Only baseline HbA<sub>1c</sub> and a family history of diabetes independently predicted regression.
- $\beta$ -cell function governed changes in glucose regulation after liver transplantation.
- A sustained improvement of insulin sensitivity accompanied rescue of  $\beta$ -cell function.

# Hepatic PPAR $\alpha$ is critical in the metabolic adaptation to sepsis

## Graphical abstract



## Highlights

- Sepsis activates hepatic PPAR $\alpha$ .
- PPAR $\alpha$  plays a protective role in sepsis.
- *Ppar $\alpha$* -deficiency impairs FA utilization in the liver during sepsis.
- Hepatocyte *Ppar $\alpha$* -deficiency worsens the outcome of bacterial infection.
- PPAR $\alpha$  activity is lower in livers of non-surviving critically ill patients.

## Authors

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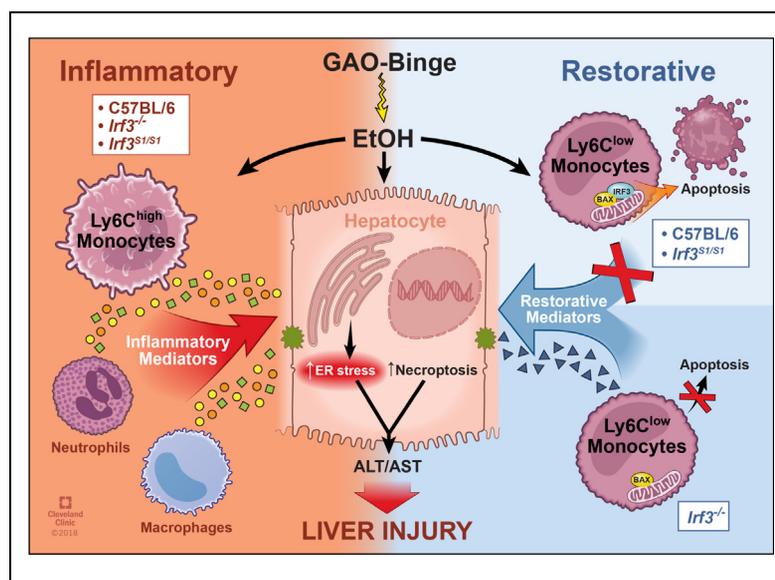
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## Lay summary

As the main cause of death in critically ill patients, sepsis remains a major health issue lacking efficacious therapies. While current clinical literature suggests an important role for inflammation, metabolic aspects of sepsis have mostly been overlooked. Here, we show that mice with an impaired metabolic response, due to deficiency of the nuclear receptor PPAR $\alpha$  in the liver, exhibit enhanced mortality upon bacterial infection despite a similar inflammatory response, suggesting that metabolic interventions may be a viable strategy for improving sepsis outcomes.

# The non-transcriptional activity of IRF3 modulates hepatic immune cell populations in acute-on-chronic ethanol administration in mice

## Graphical abstract



## Authors

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## Lay summary

Activation of the innate immune system contributes to inflammation in the progression of alcohol-related liver disease, as well as to the resolution of injury. Here we show that the protein IRF3 modulates the innate immune environment of the liver in a mouse model of alcoholic hepatitis. It does this by increasing the apoptotic cell death of immune cells that promote the resolution of injury.

## Highlights

- Interferon regulatory factor 3 (IRF3) has both transcriptional and non-transcriptional activity.
- Gao-binge ethanol exposure increases both the phosphorylation and ubiquitination of IRF3.
- *Irf3*<sup>-/-</sup> are protected from ethanol-induced liver injury but mice expressing non-transcriptional IRF3 activity are not.
- The non-transcriptional activity of IRF3 modulates the innate immune environment of the liver.