



Recompensation in decompensated cirrhosis

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Recompensation of decompensated cirrhosis has been defined by the Baveno consensus as control or cure of the main underlying cause; resolution of clinical manifestations, including ascites and hepatic encephalopathy, without the use of prophylactic medications, and without variceal bleeding for 12 months; and restoration of hepatic function. Cure and recompensation are usually associated with regression of liver fibrosis. Recompensation can occur when hepatitis C virus is eradicated, if hepatitis B virus infection (without hepatitis D co-infection) is suppressed, and following persistent alcohol abstinence in patients with alcohol-associated cirrhosis. Although cirrhosis related to metabolic dysfunction-associated steatotic liver disease can improve following lifestyle or pharmacotherapy-assisted weight loss, and autoimmune liver disease can respond to immunosuppression, it is unclear if true recompensation can be achieved in such patients. Recompensation of cirrhosis could be an achievable clinical target, offsetting costs of management of advanced liver disease, and decreasing the need for liver transplantation. Consequently, public health policies should pursue programmes that promote alcohol cessation, eliminate viral hepatitis, and address obesity.

Introduction

Compensated cirrhosis represents the initial, asymptomatic phase of liver cirrhosis, during which hepatic function remains sufficient despite significant fibrosis. Patients with compensated cirrhosis do not generally exhibit overt symptoms. Decompensated cirrhosis is defined by the appearance of either ascites, acute variceal bleeding, or hepatic encephalopathy.^{1,2} Patients who develop hepatic decompensation are at risk of further decompensating events, such as refractory ascites, hepatorenal syndrome, spontaneous bacterial peritonitis, and acute-on-chronic liver failure.³ The transition of stages from early to advanced fibrosis, cirrhosis, and decompensation has generally been unidirectional in earlier natural history studies.⁴ However, interventions to manage the underlying cause of cirrhosis, such as alcohol cessation,^{5,6} achieving sustained virological response (SVR) in hepatitis C,⁷⁻⁹ reducing viral load in hepatitis B, treatment of obesity and metabolic dysfunction-associated liver disease (MASLD),^{10,11} immunosuppression in autoimmune liver diseases,^{12,13} and chelation in Wilson disease¹⁴ have evolved over time (figure 1). As such, cause-specific treatments might result in functional and histological improvement in stages of chronic liver disease and reduction in incidence of hepatocellular carcinoma.¹⁵ Improvement in liver function as assessed by MELD score,¹⁶ Child-Turcotte-Pugh (CTP) class¹⁷ and reduction in hepatic venous pressure gradient (HVPG) following hepatitis C virus (HCV) cure¹⁸ has obviated the need for liver transplantation in many patients.

The Baveno VII consensus statement has defined more concretely the concept of recompensation.¹⁵ The course of a patient with decompensated cirrhosis towards recompensation involves three steps: first, cure or control; second, clinical improvement (ie, control of decompensation symptoms [without medication]); and, finally, restoration of synthetic hepatic function (ie, a CTP-A equivalent, that should also include absence of diuretics or medications for secondary prophylaxis of hepatic encephalopathy). As per the Baveno VII consensus statement, for patients who decompensated

due to variceal bleeding, a bleeding-free interval of 12 months is required (during which β blockers can be continued), accompanied by an improvement in liver function. As currently defined, recompensation might be achieved sooner for those with ascites or hepatic encephalopathy.¹⁹ Patients who continue to require diuretics for the management of ascites or prophylactic agents to prevent recurrence of hepatic encephalopathy do not fulfil criteria for recompensation, despite evidence of improvement in liver function, limiting the scope of Baveno definition. However, the definition provides uniformity for comparison across clinical trials globally, and a means to define functional hepatic improvement.

The global burden of cirrhosis is increasing due to an increase in age-standardised prevalence of MASLD-related cirrhosis, and it is anticipated that there will be an increase in alcohol-associated disease, with a likelihood of reduction in hepatitis B virus (HBV)-related and HCV-related disease over the coming decades, as viral hepatitis campaigns seek and treat infected populations.²⁰ Thus, recompensation could mitigate the enormous health-care costs of managing advanced liver disease,²¹ hospitalisation for complications of cirrhosis, and the need for liver transplantation.²² A new paradigm for the management and reversal of complications of cirrhosis with the goal of recompensation is particularly relevant in resource-constrained areas where patients have limited access to liver transplantation.^{7,23}

In this Review, we critically analyse the functional restoration and regression of fibrosis in cirrhosis following effective management of the cause of cirrhosis, and consider the likelihood, predictors, and clinical significance of recompensation, with residual risk of hepatocellular carcinoma, while highlighting some of the unmet needs to be addressed.

Mechanisms of recompensation in advanced liver disease

Liver cirrhosis is characterised by diffuse fibrosis with regenerative nodule formation in the liver parenchyma due to persistent hepatic insults by one or more causal

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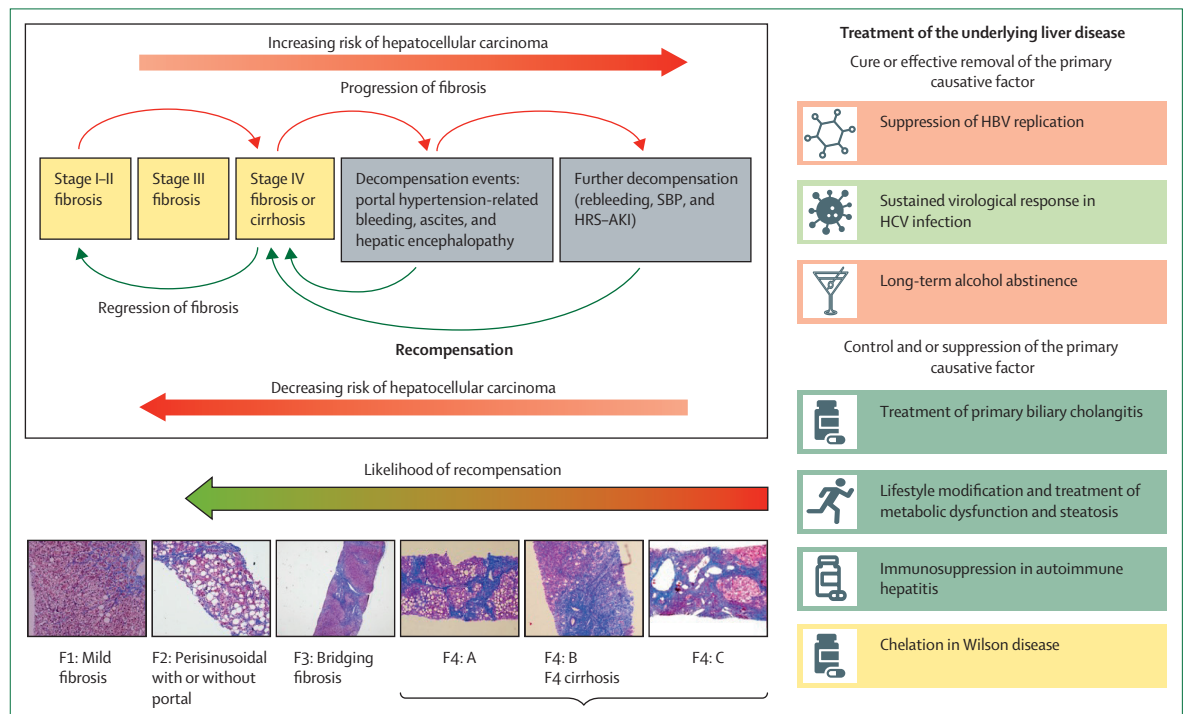


Figure 1: Natural history of cirrhosis

The progression of fibrosis from F1 to F4 can be halted and reversed by cure or sustained control of the primary disease cause, as indicated in the right panel. Recompensation is a functional improvement in liver disease severity after addressing the underlying disease driver, and has clinical and histological correlates pertaining to reversal of fibrosis. The risk of hepatocellular carcinoma and further decompensation remains even after attainment of recompensation. HBV=hepatitis B virus. HCV=hepatitis C virus. HRS-AKI=hepatorenal syndrome-acute kidney injury. SBP=systolic blood pressure.

factors. In patients with compensated cirrhosis, regression in fibrosis stage and inflammation have been observed following effective suppression of HBV, and by curing HCV infection.^{24,25} Decompensated disease is associated with further disruption of hepatic architecture, and vascular remodelling resulting in portal hypertension and impaired hepatic function, culminating in formation of ascites, hepatic encephalopathy, and acute variceal bleeding. In addition, patients with portal hypertension have endothelial dysfunction, gut dysbiosis,²⁶ increased vascular permeability,²⁷ endotoxaemia, and cirrhosis-associated immune dysfunction, which lead to decompensation events, including ascites, hepatic encephalopathy, acute variceal bleeding, spontaneous bacterial peritonitis, and hepatorenal syndrome.²⁸ The factors that lead to decompensation, if adequately reversed, might lead to hepatic recompensation. Thus, it is speculated that one or more mechanisms are likely to be involved in recompensation: remodelling of the liver parenchyma with collagen degradation and fibrosis regression, vascular remodelling, and amelioration of hepatic inflammation (figure 2).^{29,30}

Current evidence of recompensation in decompensated cirrhosis

Evidence of recompensation can be found indirectly in transplant registries indicating delisting due to clinical

improvement and large cohort studies showing attainment of CTP class A following cure of different causes of liver cirrhosis.^{6,31-34} Most of the data pertaining to recompensation comes from studies showing clinical improvement following SVR in HCV after direct-acting antiviral therapy^{7,9,35-43} through suppression of chronic HBV infection,⁴⁴⁻⁵⁰ or alcohol cessation in alcohol-associated liver disease.^{5,51} There is scarce data on improvement in primary biliary cholangitis following therapy.⁵² The table presents those studies where all Baveno criteria for recompensation have been met; further studies showing clinical improvement of patients with decompensated cirrhosis are shown in the appendix (pp 1-12), irrespective of whether or not the Baveno criteria for recompensation were met.^{5-7,9,31-33,35-37,39-52} Currently only a few studies fulfil the long-term assessment criteria for attainment of recompensation.^{5,7,48,52}

HBV-related cirrhosis

Long-term use of nucleoside and nucleotide analogue therapy has been shown to result in regression of fibrosis in patients with HBV infection²⁵ and compensated liver disease. Among 295 individuals with HBV-related decompensated cirrhosis treated with entecavir or lamivudine, 116 (39.3%) had a maintained virological response of persistent undetectable HBV DNA during therapy; maintained virological

See Online for appendix

response was associated with longer transplant-free survival over a period of 10 years compared with not having a maintained response.³³ Another long-term study of 400 patients with HBV-related cirrhosis, in which 210 (52.5%) patients had decompensated cirrhosis at the outset, showed that maintained virological response was attained in 202 (91.8%) of 220 of participants who initiated tenofovir and 160 (88.8%) of 180 of those who initiated entecavir. CTP scores improved in 65 (29.5%) of 202 patients on tenofovir, and 45 (25%) of 160 those on entecavir. The 5-year cumulative rate of a decompensation event was 3.1% (12 of 400) and 1.9% (eight of 400) for hepatocellular carcinoma.⁵⁴

In a multicentre prospective study of patients with decompensated HBV-related cirrhosis treated with entecavir for over 120 weeks, 159 (56.2%) of 283 participants fulfilled the Baveno VII definition of recompensation.⁴⁸ In a retrospective extension of this study, 175 patients were followed up for beyond 120 weeks (median 240), of whom 106 had achieved recompensated by week 120.⁴⁹ 92 (86.8%) of these patients remained recompensated until 120 weeks (range 72–168) of extended follow up. Among the 69 patients without recompensation by week 120, 28 (40.6%) attained late recompensation during the subsequent 30 months. The incidence of de novo hepatocellular carcinoma was lower in the recompensated group (5.0% vs 16.13%; $p=0.002$).

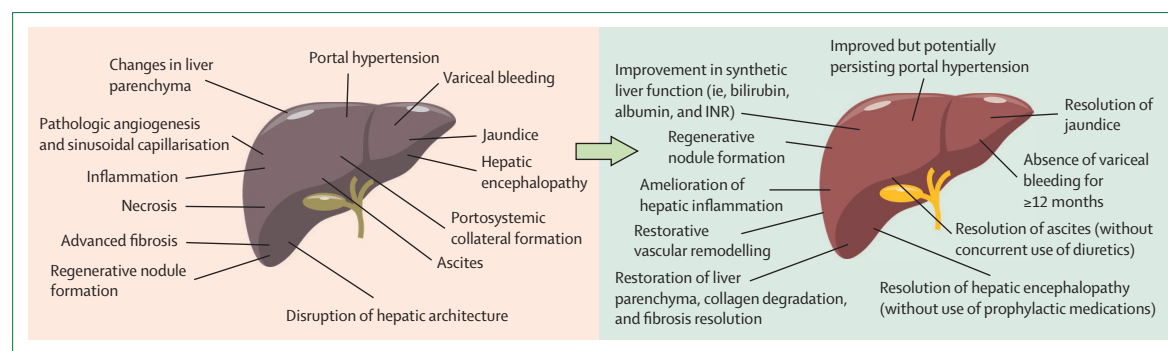


Figure 2: Transition from decompensated cirrhosis to recompensated cirrhosis following cure or control of the causative factor for chronic liver disease
INR=international normalised ratio.

	Causative factor	Patient numbers	Predictors of recompensation	Baveno VII criteria met?	Comments
Hofer et al (2023) ⁵	204 patients with alcohol-associated cirrhosis	37 of (18.1%) 204 patients had abstinence-induced recompensation	Lower baseline HVPG, lower CTP score, lower BMI, higher albumin, and higher mean arterial pressure were linked to a higher probability of recompensation	Alcohol abstinence	Only 18% recompensation per Baveno VII, although a clinically significant number improved hepatic function, with reduction in bilirubin, INR, and MELD-Na, and an improvement in serum albumin concentration.
Hofer et al (2023) ⁵¹	42 patients with PBC-related decompensated cirrhosis, treated with UDCA	Seven (16.7%) of 42 patients had recompensation	Lower MELD-Na, bilirubin, and alkaline phosphatase at decompensation, as well as variceal bleeding as a decompensating event were linked to a higher probability of recompensation	Causal cures unclear	Recompensation occurred in five (41.7%) of 12 patients with UDCA response and in two (9.5%) of 21 patients without UDCA response at 1 year
Wang et al (2022) ⁴⁸	320 patients with decompensated HBV-related cirrhosis treated with entecavir, of whom 283 (88.4%) completed the 120-week study period	171 (60.4%) of 283 patients had resolution of ascites and hepatic encephalopathy; 159 (56.2%) of 283 patients had additional decrease to MELD <10 or hepatic function within CTP-A	Multivariable logistic regression model: MELD <10 or liver function tests within CTP-A (albumin >35 g/L, INR <1.50, and total bilirubin <34 μmol/L) as the criteria for stable improvement of liver function tests	Baveno VII criteria partially met; unclear if patients were off prophylaxis for hepatic encephalopathy or diuretics	34 patients who recompensated were followed-up beyond 120 weeks; 31 (91.2%) remained compensated and three patients were diagnosed with hepatocellular carcinoma
Premkumar et al (2024) ⁷	1152 patients with HCV-related decompensated cirrhosis	Recompensation in 284 (24.7%) of 1152 patients over a follow-up of 4 years	Low bilirubin (aHR 0.6, 95% CI 0.5–0.8; $p<0.001$), international normalised ratio (aHR 0.2; 95% CI 0.1–0.3, $p<0.001$), absence of large oesophageal varices (aHR 0.4; 95% CI 0.2–0.9; $p=0.048$), or gastric varices (aHR 0.5; 95% CI 0.3–0.7; $p=0.022$) predicted recompensation	Previous decompensation with variceal bleeding (aHR 1.6; 95% CI 1.2–2.8; $p=0.042$), and presence of large varices (aHR 2.9; 95% CI 1.3–6.5; $p<0.001$) were associated with portal hypertension progression	Further decompensation was seen in 221 (19%) of 1152 patients, 145 died, and six underwent liver transplantation

aHR=adjusted hazard ratio. CTP=Child–Turcotte–Pugh. HCV=hepatitis C virus. HBV=hepatitis B virus. HVPH=hepatic venous pressure gradient. INR=international normalised ratio. PBC=primary biliary cholangitis. UDCA=ursodeoxycholic acid.

Table: Recompensation in studies based on fulfilment of Baveno VII criteria

An analysis of a registry-based cohort of 4701 patients with HBV-related cirrhosis on nucleos(t)ide analogue therapy retrospectively classed patients as having compensated (3327 [70.8%]), decompensated (1347 [29.2%]), or recompensated cirrhosis (265 [5.6%]) over a median follow-up of 5 years. The patients who recompensated had similar transplant-free survival as compared with those with compensated cirrhosis in a time-dependent competing risk analysis. The 5-year transplant-free survival rates were 76% (95% CI 51.5–89.3) for recompensated cirrhosis and 89.3% (95% CI 88.2–90.4) for compensated cirrhosis.⁵⁰ However, published studies have used variable entry criteria and the retrospective designs also limit the evaluation of decompensating events and their resolution, and thus a thorough assessment of the Baveno criteria.

HCV-related cirrhosis

Recompensation in HCV-related decompensated cirrhosis is attributable to highly effective direct-acting antiviral therapy. Although the efficacy of direct-acting antivirals is highest in patients without cirrhosis,⁵⁵ around 80–90% of individuals with hepatic decompensation can achieve SVR at 12 weeks (SVR12) using non-protease inhibitor-based anti-HCV regimens.^{56–58} Reduced incidence of cirrhosis-related complications (death, hepatocellular carcinoma, and acute decompensation) has been seen in patients up to 15 months from treatment initiation.⁵⁹ In a UK-based cohort study, 20 (51%) of 39 participants with hepatic decompensation had a reversal of decompensation after direct-acting antiviral therapy.³⁵ In an Italian cohort of 89 patients with decompensated HCV-related CTP class B cirrhosis treated with direct-acting antivirals,³⁶ 55 (61.8%) patients transitioned to CTP class A cirrhosis, 30 (33.7%) remained in CTP-class B, and 4 (4.5%) worsened to CTP class C.³⁶ Data from the HCV-TARGET cohort⁸ indicate that 56% of patients treated with direct-acting antivirals had an improvement in MELD score following SVR12; however, clinically meaningful reductions of 3 or more MELD points were seen in only 24% of patients in the short term (9–26 weeks after the end of treatment), with no meaningful change in MELD in patients followed up long term (median 4 years after treatment). Short-term MELD score improvement was more likely in women, individuals younger than 60 years, and patients with baseline MELD of 16 or more. In a large prospective study of 1152 patients with HCV-related decompensated cirrhosis,⁷ followed for nearly 4 years, baseline CTP stage was CTP class B in 624 (54.2%) and CTP class C in 528 (45.8%). At 12 months following SVR12, regression to CTP class A was noted in 419 (36.4%) patients while 451 (39.1%) were in CTP class B, and 282 (24.5%) remained in or progressed to CTP class C. Of the cohort, 284 (24.7%) met the Baveno VII criteria for recompensation (figure 3).⁷ A retrospective analysis of 622 patients with HCV-related decompensated cirrhosis (502 [80.7%]

CTP-B; 120 [19.3%] CTP-C) from four clinical trials who received sofosbuvir-based direct-acting antiviral therapy⁹ reported an SVR12 rate of 85% (528 of 622 patients). Of the 528 patients who had SVR12 with follow-up data available to week 36, 31.6% of patients with baseline CTP-B cirrhosis and 12.3% of patients with CTP-C cirrhosis had a change in class to CTP-A compensated cirrhosis that was sustained until the end of follow up. Achieving SVR12 resulted in clinical improvement, associated with a reduction in mortality or need for liver transplantation.⁹ In a study of 868 patients with HCV-related cirrhosis (719 [83%] with CTP-A cirrhosis and 149 [17%] with CTP-B or CTP-C cirrhosis),⁶⁰ SVR was attained by 647 (90%) patients with CTP-A and by 120 (81%) with CTP-B or CTP-C. The median MELD score at baseline was 13.4 (IQR 10.8–15.2) and the median MELD score 12 weeks after cessation of direct-acting antiviral therapy was 12.8 (IQR 10.3–18.1). A decrease in MELD score by 2 or more points was seen in 28 (19%) patients with CTP-B or CTP-C cirrhosis at the time of SVR12 and persisted until week 36 weeks post-completion of antiviral therapy in 23 (82%) of these individuals. However, improvement in MELD score was not associated with a lower rate of recurrent decompensating events, compared with those with stable or increasing MELD scores. Thus, some patients with more advanced cirrhosis as indicated by higher MELD scores might not necessarily recompensate, despite attainment of SVR12.

Although not based on standardised criteria for defining recompensation, these studies provide evidence to support the notion that direct-acting antivirals allow for the reversal of advanced liver disease. However, the risk of hepatocellular carcinoma and further episodes of decompensation remains in individuals who have cleared HCV, and as such they should continue to undergo surveillance for hepatocellular carcinoma and monitoring or interventions for complications of portal hypertension.^{49,50,61}

Alcohol-associated cirrhosis

Globally, there has been a rising rate of alcohol consumption and an increasing global burden of alcohol-associated liver disease.^{63,63} The age-standardised death rate due to cirrhosis in eastern Europe and central Asia has risen between 1990 and 2019, primarily due to increases in the prevalence of alcohol-associated liver disease.⁶³ However, there is potential for recompensation with cessation of alcohol intake. In an Austrian study, abstinence related recompensation was achieved in 37 (18.1%) of 204 patients with decompensated cirrhosis caused by alcohol-associated liver disease during a median follow-up of 24.4 months.⁵ A large Spanish transplant registry reported that among 420 patients with decompensated cirrhosis from alcohol-associated liver disease,⁶ 36 (8.6%) were delisted from liver transplantation after clinical improvement following alcohol cessation.

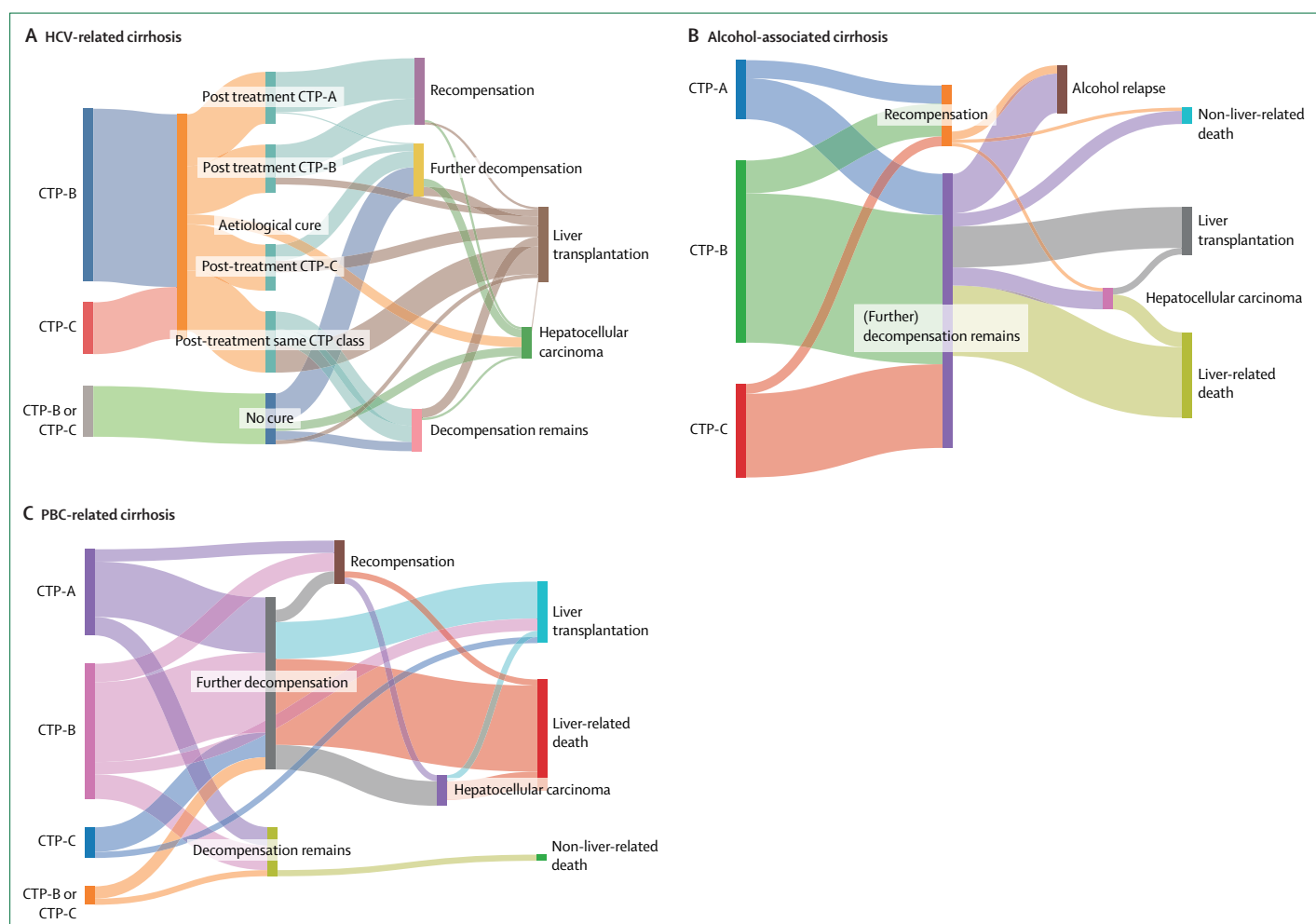


Figure 3: Clinical course of decompensated cirrhosis following cure or control of the causative factor for chronic liver disease

(A) Sankey plot generated from data from the national hepatitis C virus elimination programme in India.⁵² (B) Outcomes of patients with alcohol-associated decompensated cirrhosis.⁵¹ (C) Outcomes of PBC-related decompensated cirrhosis.⁵² CTP=Child-Turcotte-Pugh class. HCV=hepatitis C virus. PBC=primary biliary cholangitis.

Lower MELD scores, higher platelet count, and female sex were predictive of delisting. Duration of alcohol abstinence was not associated with likelihood of delisting. 5 years after delisting, the probability of liver transplant-free survival was 76%. Data from a prospective European registry on advanced chronic liver disease shows that stopping alcohol reduces acute decompensation (aHR 0.391; $p<0.001$), liver-related deaths (0.4278; $p<0.001$), and all-cause mortality (0.453; $p<0.001$), after adjusting for the severity of baseline liver disease.⁵¹

Since abstinence is crucial to attaining recompensation in patients with alcohol-associated cirrhosis, there is a need to improve integrated care for alcohol use disorder and pharmacotherapy to prevent relapse in addition to management to decompensated liver disease.⁶⁴ The use of either acamprosate and (or) naltrexone has been associated with improved survival, as shown in a propensity-score matched retrospective study that included both patients with compensated and

decompensated alcohol-associated cirrhosis, with an HR of 0.80 (95% CI 0.67–0.97; $p=0.024$) when compared with no pharmacotherapy, even after adjustment for confounders of age and liver disease severity.⁶⁵ Thus, structured management of alcohol use disorder, including pharmacotherapy, provides long-term survival benefit in those with alcohol-associated compensated cirrhosis, but more data are needed regarding safety of alcohol use disorder pharmacotherapy in those with decompensated liver disease.

The assessment of (maintained) alcohol abstinence in clinical practice is often done by structured interviews complemented by biomarkers.⁶⁶ In the setting of liver transplantation, when abstinence is commonly required for listing, urinary, or in-hair ethylglucuronide concentrations, or blood phosphatidylethanol (PEth) levels concentration are used as objective tests of alcohol abstinence over the recent weeks. Self-reported abstinence has been shown to be reliable, but PEth is

superior for predicting liver-related complications.⁶⁷ Although structured interviews for alcohol abstinence seem to be of use in the clinic setting, alcohol biomarkers are favoured in trials and studies where the assessment of alcohol abstinence should follow the highest standards.

Cirrhosis from metabolic dysfunction-associated steatotic liver disease

Currently there is no pharmacotherapy for MASLD that is proven to be safe and is recommended for patients with decompensated cirrhosis; thus, the possibility of recompensation in such cases might result from management of metabolic dysfunction and portal hypertension.

Bariatric surgery is contraindicated in patients with decompensated cirrhosis.⁶⁸ However, in a cohort of highly selected patients with obesity (BMI >40 kg/m², median MELD 12, and controlled metabolic parameters) who were candidates for liver transplantation and had a history of hepatic decompensation (but with well controlled complications of liver disease at the time of bariatric surgery),⁶⁹ sleeve gastrectomy was safely performed in 32 patients. Median weight loss at 6 months after sleeve gastrectomy was 22.0 kg (IQR 18.9–26.8) and at 12 months was 31.0 kg (IQR 23.6–50.3), corresponding to a loss of excess bodyweight of 33.4% and 52.4% at each time point. Within 6 months of sleeve gastrectomy, 28 (88%) of 32 candidates were deemed eligible for liver transplant.

Endoscopic bariatric interventions can induce weight loss and improve non-invasive fibrosis scores and HbA_{1c}⁷⁰ with a low risk of decompensation in patients with MASLD, but there are no data on recompensation rates with such interventions.⁷¹ Current guidelines for MASLD and MASH recommend lifestyle modification, including nutritional counselling, alcohol cessation,⁷² regular physical exercise, use of pharmacotherapy for alleviating the metabolic syndrome, surveillance for portal hypertension and hepatocellular carcinoma, and liver transplantation in decompensated cirrhosis.⁷³ It is possible to hypothesise that reversal of metabolic dysfunction and sustained weight loss facilitates recompensation. However, there is a need for more evidence for these considerations in cirrhosis caused by MASLD or MASH.

Cirrhosis caused by autoimmune hepatitis and primary biliary cholangitis

There is little data on management of decompensated cirrhosis caused by autoimmune hepatitis, as most patients are likely to be listed for liver transplantation. A small study⁷⁴ noted that patients with decompensated cirrhosis caused by autoimmune hepatitis (N=82) fared better on corticosteroid therapy (N=64) than those who remained untreated (N=18), but the cohorts were not propensity matched, with patients with more advanced disease remaining steroid ineligible. In patients who received corticosteroids, 40 improved to a compensated

state, 15 had persistent decompensated disease, and nine had either liver-related death or underwent liver transplantation. Patients with autoimmune hepatitis-related cirrhosis who attained a recompensated state had higher aminotransferase, total leucocyte count, and platelet counts at presentation.⁷⁴

In a small cohort of 42 patients with decompensated cirrhosis caused by primary biliary cholangitis with a median age of 64 years and MELD-Na of 13.5, 33 patients were treated with ursodeoxycholic acid (UDCA) for 1 year or more and 12 (36%) achieved Paris-II response criteria. Recompensation occurred in five (41.7%) of 12 with UDCA response at 1 year (but also in two patients without UDCA treatment). Nonetheless, four (57.1%) of the seven recompensated patients presented with liver-related complications after developing hepatic malignancy or portal vein thrombosis, and two eventually died.⁵²

In patients with autoimmune hepatitis and primary biliary cholangitis, the definition of cure or effective control needs to be harmonised based on evidence of clinical, biochemical, and histological resolution of inflammation, remodelling of the liver, and regression of fibrosis.

Recompensation following insertion of transjugular intrahepatic portosystemic shunts

Insertion of a transjugular intrahepatic portosystemic shunt (TIPS)⁷⁵ has the potential to improve hepatic haemodynamics with control of portal pressure-related decompensation events such as acute variceal bleeding and ascites, but at an increased risk for hepatic encephalopathy.⁷⁶ In a series of 116 patients with decompensated cirrhosis who received a TIPS,⁷⁷ 28 (24%) recompensated per Baveno VII criteria, with reduction in incidence of hepatocellular carcinoma, although it is unclear whether recompensation was secondary to TIPS or due to treatment of the underlying disease. The 2-year cumulative survival probability of the whole population was 0.65 (95% CI 0.63–0.68), and was significantly better with TIPS than with standard of care (0.71 vs 0.63; *p*=0.0001) and in the subgroups of p-TIPS (0.75 vs 0.66; *p*<0.0001) and ascites (0.61 vs 0.40; *p*=0.0144), whereas there was no significant difference in the setting of prevention of bleeding.⁷⁸ The reports on TIPS-induced recompensation lack specific data, such as changes in synthetic function and withdrawal of supportive medications, including diuretics, which are required to assess Baveno criteria of recompensation.

Potential predictors of recompensation

Lower bilirubin and international normalised ratio, as a measure of liver synthetic function, and absence of large oesophageal or gastric varices, as a measure of portal hypertension, has been shown to predict recompensation in HCV-related decompensated cirrhosis following SVR12.⁷ Predictive models for recompensation include the BE3A score for HCV-related cirrhosis⁹ and the

BC2AID score for HBV-related cirrhosis.⁷⁹ The BE3A score was derived from a study of 622 individuals with HCV-related decompensated cirrhosis. Pretreatment predictors of improvement to CTP-A included absence of ascites or encephalopathy, higher albumin, lower bilirubin, higher alanine aminotransferase, and lower BMI.⁹ The BE3A score is calculated based on BMI (<25 kg/m²), absence or presence of hepatic encephalopathy and/or ascites, alanine aminotransferase (>60 IU/L) and serum albumin levels (>3.5 g/L), and could be used to predict likelihood of improvement after SVR12 in HCV-related cirrhosis. The BC2AID model has been developed based on six clinical parameters in HBV-related cirrhosis, including bilirubin of 5 mg/dL or less, absence of severe complications or further decompensation, alpha-fetoprotein of 50 ng/mL or less, alanine aminotransferase 200 IU/L or more, and international normalised ratio of 1.5 or less, with time 6 months or less from initial decompensation until initiation of nucleos(t)ide analogues, and was predictive of recompensation.⁷⁹ However this model has a collinear variable—ie, absence of decompensation events—which limits likelihood of external validation. In a cohort of patients with HBV-related cirrhosis on nucleos(t)ide analogues, serum albumin of 34 g/L or more at treatment week 24 was shown to predict recompensation by week 120.⁴⁹ Platelet count, serum albumin, and serum sodium at week 24 as optimal predictors of recompensation, and the resultant score constructed from multivariate model regression coefficients is termed the hepatitis B recompensation prediction (Brec-PAS score). For predicting recompensation by week 120, the AUROC of the Brec-PAS score was 0.749 (0.691–0.808), which was significantly superior to that of the MELD score (0.629; *p*=0.002) but not the FIB-4 score (0.702; *p*=0.097). In 204 patients with decompensated cirrhosis related to alcohol-associated liver disease who remained abstinent, patients with a lower baseline HVPG, lower CTP score, lower BMI, higher albumin, and higher mean arterial pressure had a higher likelihood of recompensation.⁵ None of these scores are currently used in routine clinical practice to inform long-term management or surveillance procedures.

Course of portal hypertension following cure

Following cure, clinically significant portal hypertension and oesophageal varices might persist despite recompensation, as patients might still have residual vascular and haemodynamic changes. Although an improvement in portal hypertension after clearance of the causative agent is possible, this improvement might not occur in all patients, particular in those with pretreatment CTP-B cirrhosis or HVPG of 16 mm Hg or more.⁸⁰ In 1152 patients with HCV-related cirrhosis who received direct-acting antivirals, further decompensation was noted in 221 (19%) following SVR12, with patients having one or more events, including recurrence of

ascites, hepatic encephalopathy, and variceal bleeding.⁷ Even after attainment of SVR in patients with HCV-related cirrhosis, there is often persistent fibrosis in the subendothelial space, features of sinusoidal capillarisation, and persistent portal inflammation.⁸¹ Moreover, data on fibrosis regression and reduction in HVPG are correlative and it is unclear whether matrix changes occur in all patients who recompensate clinically, with complete restoration of vascular physiology and liver architecture, especially in those who have decompensated cirrhosis at baseline.^{82,83}

Role of β blockers after recompensation

Semmler and colleagues⁸⁴ reported on a retrospective analysis of 2335 patients with compensated advanced chronic liver disease related to HCV from 15 European centres, followed up for a median of 6 years, and who had a median baseline liver stiffness measurement (LSM) of 16.6 kPa, with 37.1% having an LSM of over 20 kPa. All patients in this retrospective registry were enrolled only if baseline LSM was greater than 10 kPa. After HCV cure and a median follow-up of 6 years, LSM decreased to a median of 10.9 kPa, with 1002 (42.9%) having an LSM of under 10 kPa and 465 (19.9%) having an LSM of 20 kPa or over. Patients with a follow-up LSM of under 10 kPa had a low risk of hepatic decompensation within 2 years, and those with a follow-up LSM of 20 kPa or over had a higher risk. However, LSM values in the intermediate range of 10–19.9 kPa did not provide clear prognostic information. Although this study pertains to compensated advanced chronic liver disease, it is unlikely that patients with decompensated cirrhosis can reach the stopping threshold for non-selective β blockers—ie, an LSM of less than 12 kPa combined with a normal platelet count following HCV cure. Therefore, patients who recompensate should be continued on non-selective β blockers to prevent further decompensation.⁸⁵

In a small study of 33 patients with HCV-related cirrhosis, ten of 13 patients who attained an HVPG under 12 mm Hg after an SVR stopped receiving non-selective β blockers, and only one had recurrence of acute variceal bleeding.⁸⁶ However, these patients had a median MELD-Na of 9, and only three (9%) of 33 patients had previous ascites. As such, currently there are no data to suggest that non-selective β blockers can be withdrawn after attainment of recompensation in patients with decompensated cirrhosis unless a portal pressure gradient reduction to less than 10 mm Hg is shown by HVPG assessment or is achieved by TIPS insertion.⁸⁷

Surveillance for hepatocellular carcinoma after recompensation

Although there are encouraging data on the reduction of hepatocellular carcinoma risk after cure or suppression of disease cause, there remains a risk of developing

hepatocellular carcinoma.⁸⁸ In patients with HBV-related decompensated cirrhosis on nucleos(t)ide analogue therapy,⁸⁹ there was a higher 5-year cumulative risk of hepatocellular carcinoma compared with patients with compensated cirrhosis (27.6% vs 9.1%; adjusted HR 2.42; 95% CI 1.24–4.71). Patients with non-variceal bleeding decompensation events (ie, ascites or hepatic encephalopathy) had higher risk of hepatocellular carcinoma development than those with variceal bleeding-related decompensation events (27.6% vs 15.8%; aHR 2.69; 95% CI 1.41–4.17). Patients who maintained a virological response had a reduced risk of hepatocellular carcinoma development.⁸⁹ Incidence of hepatocellular carcinoma has been shown to be lower in patients with HBV-related cirrhosis who recompensate versus those who did not despite maintained virological response (5.0% vs 16.13%; $p=0.002$).⁴⁹ Therefore, the incidence of hepatocellular carcinoma was reduced, but not eliminated, after recompensation.

A retrospective cohort study of all Veterans Affairs patients with HCV who had achieved SVR showed that, among patients with cirrhosis (N=19 678), the incidence of hepatocellular carcinoma decreased as time accrued following attainment of SVR. Among patients who had accrued only 1–2 years since SVR, the incidence of hepatocellular carcinoma was 2.71 per 100 person-years; for those who had accrued 2–4 years, incidence was 2.11 per 100 person-years (aHR 0.80, 95% CI 0.63–1.01); and for those with 4–6 years, it was 1.65 per 100 person-years (aHR 0.61, 95% CI 0.41–0.90). However, hepatocellular carcinoma risk appeared to plateau for those with over 6 years since SVR (incidence 1.68 per 100 person-years; aHR 0.70, 95% CI 0.46–1.07).⁹¹ Among those without cirrhosis, hepatocellular carcinoma risk was 0.23–0.27 per 100 person-years, without a clinically significant association between time since SVR and hepatocellular carcinoma risk. Thus, it is crucial to continue surveillance for hepatocellular carcinoma and for complications of portal hypertension even after achieving cure or clinical recompensation.

Alcohol abstinence is associated with a reduced risk of hepatocellular carcinoma in patients with alcohol-related compensated cirrhosis, but not among those with previous decompensation.⁹² A single study suggests that, in patients with recompensated cirrhosis caused by alcohol-associated liver disease and who are abstinent, risk of hepatocellular carcinoma was not reduced significantly enough to warrant discontinuing hepatocellular carcinoma surveillance.⁹³

Based on current data, the differential risk of hepatocellular carcinoma development in patients who have regression of fibrosis versus those who remain with advanced fibrosis is not well characterised. Thus, long-term follow-up, even in those who regress fibrosis, is needed, and until robust risk and cost-effectiveness prediction models are developed. Kim and colleagues⁹⁴ developed an AI model using a gradient-boosting

algorithm to predict hepatocellular carcinoma in patients with chronic hepatitis B. The model, based on data from 5817 patients from South Korea and 1640 from Europe, used variables of age, sex, platelet count, drug therapy, serum alanine aminotransferase, albumin and bilirubin levels, HBeAg status, HBV viral load, and presence of cirrhosis. It outperformed conventional models in predicting hepatocellular carcinoma risk, suggesting its potential role in refining hepatocellular carcinoma surveillance strategies.

Limitations of the Baveno VII criteria for recompensation of cirrhosis

The Baveno VII definition of cirrhosis recompensation is based on clinical criteria and were established by expert consensus rather than being driven by evidence. Thus, more data are required from adequately powered studies that include well characterised patients with detailed follow-up to gain a better understanding of the underlying mechanisms, key criteria with long-term prognostic implications, and an investigation into a potential point-of-no-return when recompensation is unlikely to occur. The attainment of control or cure of cause is well defined as virological suppression in HBV or as SVR in HCV, as well as for alcohol abstinence (if self-reporting is considered) for alcohol-associated liver disease. However, the time frame is less clear in patients with decompensation due to MASLD, MASH, autoimmune hepatitis, primary biliary cholangitis, and other causes of liver disease.

The underlying cause of liver disease, patient demographics, genetic background, coexisting risk factors and metabolic comorbidities, and liver disease severity at decompensation are all likely to affect the course of liver disease after the primary causative factor has been removed or controlled. Further, recompensation criteria need to be expanded to comment on use of non-selective β blockers in patients who have recompensated, and the safety of statins in such a population. More prospective data are needed on patients who decompensate again after attaining the goal of recompensation, and to develop predictive models for therapeutic intervention. Importantly, the Baveno definition requires that the patient should be completely off diuretics and lactulose as prophylaxis for decompensation (ascites and hepatic encephalopathy) for over a year, but this recommendation seems arbitrary as diuretics such as spironolactone might be used for control of heart failure symptoms, and lactulose for chronic constipation. In addition, drugs such as rifaximin, could be prescribed, albeit transiently, for diverticulosis and irritable bowel syndrome.

The time frame of 1 year for absence of recurrence of variceal bleeding has been empirically chosen and, although supporting evidence is being generated, hepatic recompensation could likely be achieved earlier and with benefits in clinical outcomes.⁷⁷ There is scarce data on the course of oesophageal varices following cure. Patients

might have a reduction of HVPG, but it is unclear whether regression of varices is achieved. In a small study,⁹⁵ ten patients (seven with HCV-related cirrhosis and three with alcohol-related cirrhosis) showed persistent varices despite an HVPG under 10 mm Hg after 5 or more years of SVR or abstinence. In five patients, oesophageal varices remained the same size (two large and three small), and in five patients, varices regressed to small in size.⁹⁵

More mechanistic data are needed on liver stiffness and histological fibrosis changes in patients who recompensate versus those who do not recompensate, as the functional changes of portal hypertension—especially vascular remodelling—might trail clinical and biochemical improvement.

Implications for liver transplantation

It is unclear if patients with recompensation should be delisted from liver transplantation registries, and, importantly, if the outcome of such individuals needs to be recorded. Currently, there are no established criteria for delisting patients with recompensation on the transplant waitlist.^{6,37,40,41,96} Nevertheless, crucial insights for recompensation have come from studies conducted in the setting of liver transplantation. Interesting trends for delisting and recompensation among candidates listed for liver transplantation between 2002 and 2022 in the United Network for Organ Sharing database have been noted across distinct causes. Of 120 451 listings in adults, a total of 7196 (6.2%) were delisted for improvement in liver disease. 567 (9.9%) of 5750 individuals who had decompensated liver disease at listing had recompensation, and recompensation was more common in patients with HBV-related cirrhosis and alcohol-associated cirrhosis than for patients with MASLD-related cirrhosis.³⁴

In an analysis of the effect of direct-acting antivirals on HCV-related cirrhosis using US national data,⁴¹ delisting following clinical improvement remained rare (6.1% for 2013–17 vs 5.2% for 2009–12 vs 4.0% for 2005–08; $p < 0.001$) and, for many, ascites (46.5%) and hepatic encephalopathy (30.5%) persisted at delisting. Thus, although listing rates for HCV-related decompensated cirrhosis have decreased, patients once listed might continue to have complications such as refractory ascites and severe encephalopathy.

Belli and colleagues reported a retrospective analysis of 103 consecutive patients with decompensated liver cirrhosis (without hepatocellular carcinoma) who were listed for transplantation and treated with direct acting antivirals at 11 European centres between February, 2014, and February, 2015.³⁷ 34 patients were inactivated from the list due to clinical improvement, of whom 21 were subsequently delisted. Baseline MELD score, and the degree of improvement in MELD score and in albumin between baseline and after 12 weeks of direct acting antivirals were predictive of inactivation. In a similar

study from Spain,³⁹ 29 (24%) of 122 patients with HCV-related decompensated cirrhosis without hepatocellular carcinoma were delisted provided baseline MELD was under 20. The change in MELD at the end of therapy was predictive of delisting. Of these patients, three developed hepatocellular carcinoma, three had further decompensation, and 23 remained stable after 88 weeks of delisting.³⁹ Perricone and colleagues⁴⁰ conducted an updated analysis using the ELITA database between February, 2014, and June, 2015, focusing on 142 patients with HCV-related decompensated cirrhosis who did not have hepatocellular carcinoma. Among these patients, 44 (30.9%) were delisted due to clinical improvement. Subsequently, one patient was relisted after developing de novo hepatocellular carcinoma, while three additional patients were relisted following the development of ascites. Analysis of a large liver transplant database from the European Liver Transplant Registry³⁸ showed that the percentage of transplants for HCV-related cirrhosis significantly declined ($p < 0.0001$) from 21.1% (first half of 2014) to 10.6% (first half of 2017). The reduction in need for transplantation was more marked and statistically significant in patients with HCV-related decompensated cirrhosis (–60.5%) than in those with HCV-related hepatocellular carcinoma (–41.2%).³⁸

Implications for resource-constrained settings

The economic effect of outpatient care and hospitalisations for liver disease itself or as a comorbid condition in patients admitted for general surgery or critical care for non-hepatic indications (cardiopulmonary or cerebrovascular emergencies) has increased.⁹⁷ This financial burden also includes the cost of management of acute decompensation,⁹⁸ hepatocellular carcinoma, and palliative care in decompensated cirrhosis.^{99,100} Therefore, early management of the cause of the disease by targeted campaigns for healthy lifestyle and nutrition, amelioration of metabolic risk by screening for obesity and diabetes in populations at risk, formulation of health policies for alcohol cessation, and augmenting the effect of viral hepatitis elimination programmes, is likely to reduce the burden of liver disease.¹⁰¹ Observations of improvements in CTP and MELD scores, and in decompensation events,⁷ are encouraging, particularly for resource-constrained regions where access to liver transplantation is limited. Patient education and hepatocellular carcinoma surveillance can improve disease outcomes, especially by detecting disease at an early stage, enabling curative therapy at a lower cost. Thus, changes in health policy and allocation of resources to prevention of liver disease and improving likelihood of recompensation or functional cure might reduce health-care-related costs attributable to the spectrum of compensated and decompensated liver disease.

Unmet needs and future research directions

Recompensation represents a new functional endpoint in clinical trial design and a new stage in the natural

Panel: Unmet clinical and research needs in those with recompensation

The following priorities should be addressed to ensure appropriate treatment for patients who recompensate

- Identify robust clinical and routine laboratory predictors of clinically significant recompensation
- Stratify the clinical features of recompensation—not all features recompensate equally
- Identify the point of no return for recompensation: decide when are treatments unlikely to have a further effect
- Determine the natural history, clinical course, and regression of portal hypertension (presence of varices) of those who recompensate relative to patients who never had decompensation and remained in a stable state of compensated cirrhosis
- Determine the state of immune dysfunction in patients with decompensated cirrhosis who attain recompensation following cure relative to those who never decompensated
- Identify novel biomarker predictors of recompensation
- Establish dedicated and comprehensive alcohol use disorder care services to prevent recidivism during phase of recompensation and subsequent long-term recovery
- Determine short-term and long-term outcomes following recompensation
- Determine the role of β blockers, statins, and anticoagulants in achieving recompensation
- Harmonise the role of baseline histology assessment, non-invasive tests, and hepatic venous pressure gradient assessment to measure recompensation
- Develop consistent criteria to assess improvement and delisting from liver transplantation

history of advanced chronic liver disease. More data are needed on pharmacotherapy for portal hypertension and gut dysbiosis, and with interventions such as TIPS insertion or bariatric surgery, to increase the likelihood of recompensation.^{30,77} Further, more objective data are needed for using non-invasive fibrosis testing, machine learning in large health-care registries, and radiomic models as predictors of recompensation (panel).^{102–104} Future research should also be directed at the pathophysiological basis of recompensation, which will help in developing interventions that promote liver regeneration and regression of fibrosis or in clinically significant portal hypertension, following causal cure or control. Prospective studies are also required to assess the time-dependent course of recompensation in comparison with those who remain in a decompensated state, and with trajectories for different diseases aetiologies and role of comorbid factors, such as alcohol use or metabolic diseases.⁴

In conclusion, recompensation is a much desired endpoint in the management of decompensated cirrhosis.

Search strategy and selection criteria

References for this Review were identified through searches of PubMed with the search terms “recompensation of cirrhosis”, “liver transplant delisting criteria”, “fibrosis regression”, “Improvement in hepatitis B and hepatitis C related cirrhosis”, or “Improvement in alcohol associated cirrhosis”, from Jan 1, 2000, until Dec 31, 2024. Articles were also identified through searches of the authors’ own work. Only papers published in English were reviewed. The final reference list was generated based on originality and relevance to the broad scope of this Review.

In the era of effective causal therapy, focus has shifted from managing complications of end-stage liver disease and transplantation to the possibility of hepatic fibrosis regression and reversing portal hypertension-related complications. The clinical improvement following recompensation results from downstaging of liver disease severity, such as achieving a status of CTP-A or MELD under 10. Effective cure or control of underlying liver disease cause often prevents recurring or further decompensation events and offset the costs of liver-related hospitalisations and advanced care. Importantly, recompensated patients seem to remain at risk of hepatocellular carcinoma and should continue surveillance for hepatocellular carcinoma and for portal hypertension. From a policy perspective, future efforts should focus on global eradication of viral hepatitis and harm reduction involving reduction of alcohol consumption, addressing obesity, and adequate prevention and treatment of metabolic risk factors.

Contributors

Original draft preparation: MP. Reviewing and editing: PSK. Reviewing and editing: TR. Conceptualisation, writing the primary draft, reviewing, and editing: KRR. All the authors approved the final manuscript.

Declaration of interests

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