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# Mechanisms and implications of recompensation in cirrhosis ☆

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## Summary

Decompensated cirrhosis has long been considered the irreversible end stage of liver disease, characterised by further decompensating events until death or liver transplantation. However, the observed clinical improvements after effective antiviral treatments for HBV and HCV and after sustained alcohol abstinence have changed this paradigm, leading to the concept of "recompensation" of cirrhosis. Recompensation of cirrhosis was recently defined by Baveno VII as (i) cure of the primary liver disease aetiology; (ii) disappearance of signs of decompensation (ascites, encephalopathy and portal hypertensive bleeding) off therapy; and (iii) stable improvement of liver function tests (bilirubin, international normalised ratio and albumin). Achieving these recompensation criteria is linked to a significant survival benefit. However, apart from aetiological therapies, no interventions/treatments that facilitate recompensation are available, the molecular mechanisms underlying recompensation remain incompletely understood, and early predictors of recompensation are lacking. Moreover, current recompensation criteria are based on expert opinion and may be refined in the future. Herein, we review the available evidence on cirrhosis recompensation, provide guidance on the clinical management of recompensated patients and discuss future challenges related to cirrhosis recompensation.



## Introduction

Decompensation marks a watershed in the progression of cirrhosis, having a profound impact on prognosis.[1] The initial, compensated state represents a prolonged and mostly asymptomatic condition with favourable prognosis, while clinically significant portal hypertension (CSPH) and varices may develop but remain unidentified. The subsequent decompensated stage is characterised by the development of complications, such as ascites, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis and other severe bacterial infections, with potential detrimental impact on extrahepatic organs.[2] Decompensated cirrhosis is associated with considerable mortality of up to 60% at 1 year and has been traditionally regarded as end-stage liver disease, with liver transplantation (LT) as the only rescue option to avoid liver-related death[3]

However, recent evidence has demonstrated that this sequence of events is not inevitable, since impressive improvements have been documented in terms of clinical symptoms, liver function, and CSPH severity upon control of the primary aetiological factor driving liver disease. Aetiologic treatment, with effective antivirals against HBV and HCV being the prototypic examples, has even resulted in regression of cirrhosis in a substantial percentage of patients after 3-5 years.[4–6] This has led to a change of paradigm, with cirrhosis no longer considered irreversible. An inherent consequence is that if cirrhosis is cured or markedly ameliorated, its complications will spontaneously subside, and long-term survival will dramatically improve without the need for transplantation.[7]

Cirrhosis "recompensation" is intended to denote a clinical state with a substantially improved prognosis when complications have disappeared and liver function has significantly improved to a level usually observed in compensated cirrhosis after removing or controlling the primary underlying cause of the liver disease.[7]

However, many aspects regarding recompensation remain poorly understood, including factors facilitating its occurrence, the early prediction of recompensation after initiating aetiologic treatment, the non-invasive assessment of structural improvements, and the understanding of underlying molecular mechanisms.

## Definition and incidence of recompensation

Recompensation of cirrhosis requires the disappearance of complications of cirrhosis and improvement of liver function after achieving cure from or control of the primary liver disease aetiology. By definition, patients must no longer require specific treatment for decompensation-related conditions. Therefore, true "recompensation" should not be confused with the control of cirrhosis complications by medical therapy, as exemplified by control of ascites by means of diuretics or transjugular intrahepatic portosystemic shunt (TIPS) placement or

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**Keypoints**

- Recompensation of cirrhosis refers to a clinical state where liver function significantly improves, and complications of cirrhosis disappear, after controlling or eliminating the primary cause of liver disease.
- Recompensation likely involves partial regression of histologic features like fibrotic septa, allowing for an improvement of liver function, reduction of portal pressure, systemic inflammation and hyperdynamic circulation.
- Recompensation may occur if cirrhosis has not reached a structural "point of no return" where architectural changes become irreversible. Identifying this point is critical for predicting whether recompensation is achievable.
- Clinically significant portal hypertension and related features (*e.g.* thrombocytopenia) may persist after recompensation.
- More research is needed to validate recompensation criteria, understand its pathophysiology, identify early biomarkers for predicting recompensation, and explore its impact on long-term outcomes, including HCC risk.

prevention of hepatic encephalopathy by lactulose or rifaximin.[2] Recompensation and control of decompensation may have different prognostic implications, since recompensation is associated with considerably prolonged life expectancy and improved quality of life without depending on specific therapies,[8,9] whereas the medical control of the complications of cirrhosis often has a much more limited effect on prognosis. Whether patients with resolution of complications under minimal therapy (low dose of diuretics and lactulose/rifaximin) may have a life expectancy similar to fully recompensated patients is still to be determined. The first formal definition of recompensation was put forward by the Baveno VII consensus[7] as a combination of: a) removal/suppression/cure of the primary aetiology of cirrhosis (viral elimination for HCV, sustained viral suppression for HBV, sustained alcohol abstinence for alcohol-induced cirrhosis); b) resolution of ascites (off diuretics), encephalopathy (off lactulose/rifaximin) and absence of recurrent variceal haemorrhage (for at least 12 months); and c) stable improvement in liver function tests (albumin, international normalised ratio [INR], bilirubin) (Fig. 1).

By definition, recompensation requires effective control of the aetiology of liver disease. However, in some aetiologies of cirrhosis or cholestatic liver disease, specific curative treatments are either missing or only partly effective.

The current definition of recompensation cannot be applied to patients with TIPS, while the use of non-selective beta-blockers (NSBBs) is allowed, since they are used even in the compensated phase for prevention of decompensation.

So far, a few retrospective studies have evaluated the incidence of recompensation and its impact on survival in patients with HBV, HCV and alcohol-related liver disease (ALD) cirrhosis (Table 1). In patients with HBV-related decompensated cirrhosis, viral suppression led to recompensation in 19% to 56% of patients.[8,10,11] In patients with ALD cirrhosis achieving abstinence, recompensation occurred in 18% of cases.[12] Tonon *et al.* evaluated the incidence of recompensation in patients with cirrhosis and ascites due to HCV, HBV or ALD achieving aetiological cure. Among them 12% achieved recompensation.[13] In all the aforementioned studies, recompensation was associated with a lower risk of new decompensating events and mortality. More recently, Hofer *et al.* evaluated the incidence of recompensation in 42 patients with primary biliary cholangitis (PBC). Interestingly, 17% achieved recompensation, however, four out of seven recompensated patients experienced liver-related events after achieving recompensation, questioning the definition in a setting where a definitive aetiologic cure is lacking.[14] Studies in patients with cirrhosis related to HCV or HBV infection have shown that rates of histological regression increase with time, which indicates that the same will occur with the likelihood of recompensation in longer follow-up studies.

## Pathophysiology/mechanisms of recompensation

When evaluating mechanisms that may lead to recompensation, clinical experience has taught us that cirrhosis must not have reached a structural "point of no-return".[15] This is because recompensation requires at least a partial regression of histologic features of cirrhosis (*e.g.* of the fibrotic septa thickness) to an extent allowing for liver function to improve and for portal pressure to decrease below critical threshold values (that remain to be defined). A second concept is that understanding the molecular mechanisms of recompensation may allow for the identification of therapies that could facilitate fibrosis regression and cirrhosis recompensation; however, more information is needed on how we could monitor cirrhosis regression, ideally using non-invasive methods.

### Conversion of cirrhosis progression to cirrhosis regression

Regression of cirrhosis is not merely arresting its progression but requires the activation of biological mechanisms facilitating collagen degradation.[16,17] Because of the uncertainty on the extent to which we can extrapolate results from animal models to the clinical scenario, whenever possible this discussion is based on human data, that mainly emerged in recent years after the introduction of highly effective antiviral therapies for HBV and HCV.

The different mechanisms involved in cirrhosis progression/regression seem to occur sequentially as reviewed elsewhere[18] and include: the starting event, which is the aetiological cause driving liver injury through toxic, inflammatory, circulatory or metabolic abnormalities (Fig. 2). These give rise to hepatocyte dysfunction and necrosis, leading to release of pro-inflammatory cytokines and other injury-related signals (damage-associated molecular patterns) that magnify the disease process by acting on liver macrophages and Kupffer cells that in turn release further inflammatory mediators and chemoattractants. Subsequently, hepatic stellate cells (HSCs) become activated and transdifferentiate into myofibroblasts, acquiring a proliferative and contractile phenotype, expressing

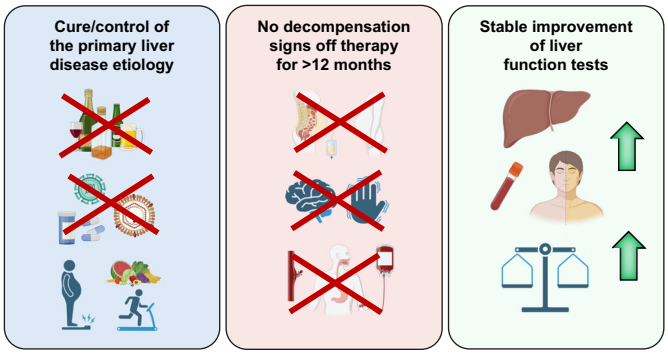


**Fig. 1. Definition of recompensation.** Recompensation requires the combination of aetiological cure, disappearance of signs of decompensation off therapy and improvement of liver function tests. The aetiological cure of liver disease includes alcohol abstinence, sustained virologic response for HCV and suppression of viral replication for HBV. Treatment and control of metabolic comorbidities such as obesity can favour recompensation. Lack of decompensation off therapy means no ascites without diuretics, no bouts of hepatic encephalopathy without lactulose/rifaximin, no episodes of portal hypertension-related bleeding for more than 12 months. Improvement of liver function tests include an increase in serum albumin and reductions in international normalised ratio and bilirubin.

smooth muscle actin fibrils, and increasing collagen synthesis, ultimately resulting in liver fibrosis.[19] Simultaneously, the liver sinusoidal endothelial cells (LSECs) lose their normal phenotype and become dysfunctional, proliferative, pro-angiogenic, prothrombotic and pro-inflammatory, which is accompanied by loss of porosity through the decrease in fenestrations.[20] The loss of fenestrations together with deposition of collagen and extracellular matrix cause capillarisation of the sinusoids with ensuing decreased metabolic exchange between circulating blood and hepatocytes, contributing to liver failure. As the disease advances, collagen deposition forms fibrous septa between the portal tracts and hepatic veins and leads to architectural changes that distort the liver microcirculation, mainly by segmentation of the parenchyma, which tends to regenerate forming regenerating nodules.[18] LSEC dysfunction occurs early and is characterised by decreased production of nitric oxide (NO) and increased production and sensitivity to endogenous vasoconstrictors, such as endothelin, angiotensin and adrenergic stimuli.[16] Decreased NO levels lead to an inability of the liver microcirculation to relax appropriately to adapt to changes in blood flow, causing an increased liver vascular tone that contributes to the increase in portal pressure.[20] The acquired prothrombotic phenotype of LSECs enables platelet aggregation and attachment that facilitates venous thrombosis, which has been recognised as the main cause of parenchymal extinction (loss of non-perfused parenchyma), with collapse of liver tissue and aggravation of liver architectural distortion.[21] The combination of endothelial dysfunction, collagen deposition, formation of regenerating nodules and parenchymal extinction are the main factors leading to progression of chronic disease to cirrhosis.[22] Increased vascular endothelial growth factor (VEGF)-driven angiogenesis contributes to further remodelling of the liver microcirculation.[22–25] Crosstalk between LSECs and adjacent transdifferentiated HSCs modulates fibrosis regression, as illustrated by the fact that counteracting LSEC dysfunction results in deactivation of HSCs and reduced fibrosis.[26] An additional mechanism leading to aggravation and self-perpetuation of fibrosis involves biomechanical stimuli related to increased extracellular matrix stiffness and hydrostatic pressure that lead to the deformation of liver cell nuclei and enlargement of nuclear pores, enabling increased cytoplasmic/nuclear traffic of proteins and transcription factors.[15,27,28] These biomechanical forces *per se* enhance liver fibrosis and in advanced stages may lead to a situation in which liver fibrosis continues despite the cause of the liver disease being removed. There is also experimental evidence that abolishing the nuclei deformation due to biomechanical forces by means of cytoplasmic disruptors or by plating cirrhotic cells in a soft substrate also reverses the activation of HSCs and dedifferentiation of LSECs due to increases in matrix stiffness[27] or increased hydrostatic pressure.[28,29]

Finally, *fibrosis regression* is facilitated by cells and enzymes capable of degrading collagen with activation of metalloproteinases and deactivation of lysyl oxidase-like 2 (LOXL-2).[26,30]

## Portal hypertension

Portal hypertension is a critical factor modulating the risk of decompensation and the likelihood of recompensation. The risk of decompensation starts when the hepatic venous pressure gradient (HVPG) increases to values ≥10 mmHg (which defines CSPH)[2,31,32] and is associated with the formation of portal-

**Table 1. Summary of studies addressing cirrhosis recompensation (Baveno VII criteria) after cure/control of underlying aetiological factor.**

| Study year | Patients, n | Aetiology | Median follow-up | Rate of recompensation | Outcomes associated with recompensation |
|---|---|---|---|---|---|
| Wang Q *et al.* 2022[8] | 320* | HBV | 120 weeks | 56.2%# | Numerically lower incidence of further decompensation in recompensated patients *vs.* recompensated patients |
| He Z *et al.* 2023[10] | 383 | HBV | 63.1 months | 53% | Recompensation associated with lower risk of death *vs.* decompensated patients |
| Hui VW *et al.* 2023[11] | 1,374 | HBV | 5 years | 19.3% | Recompensation associated with lower risk of death *vs.* decompensated patients |
| Hofer BS *et al.* 2023[12] | 204 | ALD | 24.4 months | 18.1% | Recompensation associated with lower risk of liver-related mortality |
| Tonon M *et al.* 2023[13] | 146 | ALD, HBV, HCV | 48.5 | 12.3% | — |
| Hofer BS *et al.* 2024[14] | 12 | PBC° | 41.9 months | 41.7% | Numerically higher transplant free survival in recompensated *vs.* decompensated patients |

ALD, alcohol-related liver disease; PBC, primary biliary cholangitis.
*Among patients with ascites (n = 320), 178 had grade 1 ascites and 88 received diuretics.
#Among the 283 patients completing follow-up.
°Control of aetiology defined by normalisation of bilirubin and a decrease of alkaline phosphatase to ≤1.5 × the upper limit of normal under ursodeoxycholic acid therapy.

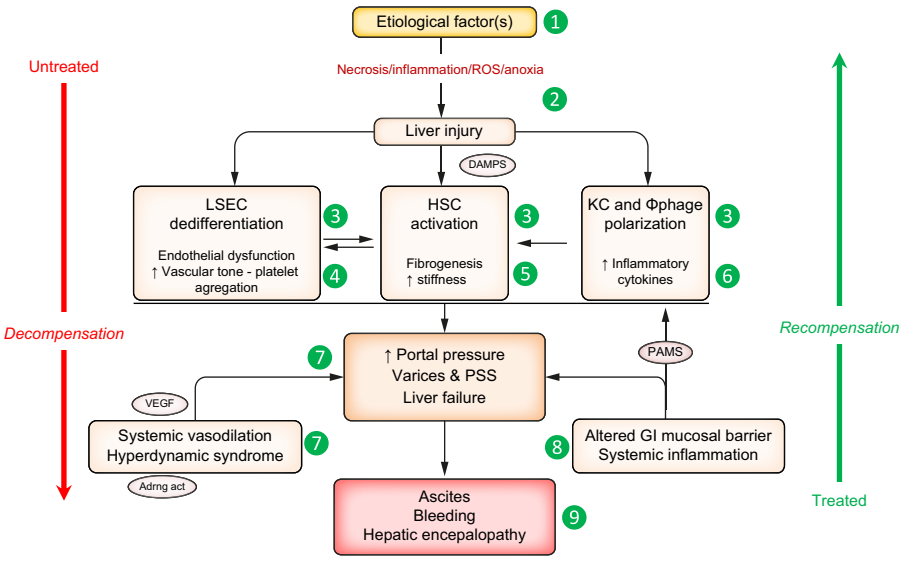


**Fig. 2. Schematic representation of mechanisms of cirrhosis progression and regression.** The numbers refer to specific sites for action in order to promote/accelerate cirrhosis regression, and are listed according to their hierarchical relevance (acting on 1 and 2 is much more likely to achieve regression than acting on 9). 1) Aetiological therapy, safe lifestyle, no alcohol, management of co-factors; 2) decrease injury (decrease oxidative stress, necro-apoptosis); 3) restorative cellular mechanisms; 4) statins, enoxaparin, ASA?; 5) resmetirom, GLP-1 receptor agonists, PPARα agonists, FGF inhibitors; 6) restorative macrophages; 7) NSBBs/carvedilol; 8) NSBBs/rifaximin?/norfloxacin?; 9) treatment of specific complications: diuretics, SMTa/terlipressin, band ligation, lactulose, rifaximin. DAMPs, damage-associated molecular patterns; HSCs, hepatic stellate cells; KC, Kupffer cells; LSECs, liver sinusoidal endothelial cells; Mϕ, macrophages; NSBBs, non-selective beta blockers; PAMPs, pathogen-associated molecular patterns; PPAR, peroxisome proliferator-activated receptor-α; PSS, portal-systemic shunting; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor.

systemic collaterals and oesophageal and gastric varices (by the combined effect of increased portal pressure and active angiogenesis driven by VEGF[18,33]), variceal bleeding (which usually requires a HVPG ≥12 mmHg),[34] and is also crucial for the development of ascites. The role of an increased portal pressure in these complications is illustrated by the fact that they are markedly decreased or disappear if portal pressure is reduced below 12 mmHg. Another consequence of portal-systemic collaterals and varices is the portal-systemic shunting of substances normally metabolised by the liver to the systemic circulation, which together with liver failure is a driver of hepatic encephalopathy.[35]

Development of ascites and of other complications of cirrhosis (spontaneous bacterial peritonitis, and AKI/HRS [acute kidney injury/hepatorenal syndrome]) is further influenced by the existence of systemic inflammation, which is thought to be mainly determined by impaired gastric mucosal barrier function with resulting translocation of bacterial products or even bacteria into the portal blood and splanchnic lymphatic system. Systemic inflammation is considered the main driver of acute-on-chronic liver failure (ACLF) a syndrome characterised by decompensation of cirrhosis, organ failures (hepatic/extrahepatic) and high short-term mortality.[36] In addition, shunting of portal blood to the systemic circulation through portal-systemic shunts decreases portal blood supply to the liver[18] and leads to the hepatic synthesis of VEGF and other hypoxia-stimulated growth factors that cause splanchnic vasodilatation through the release of NO by the endothelial cells of small splanchnic arteries,[37,38] further supported by an increased production of glucagon and vasodilatory gastrointestinal peptides[39,40] that worsen portal hypertension and increase the risk of variceal bleeding. The intense splanchnic vasodilation leads to a reduction in systemic vascular resistance and arterial blood pressure, which triggers the activation of endogenous vasoactive factors (the renin-angiotensin-aldosterone system, the adrenergic nervous system, and the non-osmotic release of arginine vasopressin) to counteract systemic hypotension, but that consequently lead to renal sodium retention and expansion of the plasma volume resulting in increased heart rate and cardiac index. This constellation is known as the hyperdynamic circulatory syndrome of cirrhosis. In the initial stages, this hyperkinetic syndrome achieves a rebalancing of the systemic circulation.[41] However, if the HVPG increases further, or the sodium retention worsens, or plasma oncotic pressure decreases (due to low albumin concentration), the Starling equilibrium is lost, and expansion of the extracellular volume leads to the formation of ascites and oedema.[42] Deterioration of cardiac function because of concomitant heart disease, systemic inflammation, infections or cirrhotic cardiomyopathy aggravates the circulatory dysfunction and favours further decompensation, ACLF and death.[43]

Bacterial translocation, as mentioned, may exacerbate liver dysfunction by enhancing liver necro-inflammation due to release of pathogen-associated molecular patterns and damage-associated molecular patterns, thereby enhancing fibrogenesis, and causing systemic inflammation, which in turn may aggravate the circulatory dysfunction of cirrhosis and contribute to decompensation.[38,44] The decreased intestinal mucosa barrier function is multifactorial. It is directly related to increased portal pressure,[45] to increased serum bile acid levels,[46] to the presence of associated conditions (obesity, hypovolemic shock), and to increased adrenergic tone.[47]

Bacterial translocation is more intense after decompensation than in earlier stages[44]

### Degree of improvement required for recompensation

Knowledge on the degree of improvement needed to achieve recompensation is only partial, as it is mostly derived from clinical studies regarding prevention of progression of cirrhosis to more advanced stages or control of its complications. Most evidence comes from randomised-controlled trials (RCTs) assessing either the effects of curing HCV or of controlling HBV infection on viral cirrhosis, or assessing interventions for portal hypertension. To what extent this can be extrapolated to other aetiologies and treatments remains unknown. Mechanistically, the first and early phenomena that are observed in patients with a cure/control of the primary aetiologic factor is usually the cessation of liver injury/damage, presenting as a reduction in transaminases early after starting direct-acting antivirals in patients with HCV, or a reduction in gamma-glutamyltransferase after stopping alcohol intake in patients with ALD (Fig. 3). This presumably restores liver sinusoidal endothelial function leading to decreased hepatic vascular resistance and an early decrease in portal pressure, while liver fibrosis and other architectural changes persist for longer. While a reduction in liver fibrosis has been demonstrated in patients with HBV under long-term nucleos(t)ide analogue treatment and in patients with HCV after sustained virological response (SVR) in paired biopsy studies, this usually takes longer periods (*i.e.* years) to occur.[5,48] Control of complications and symptoms related to decompensation may thus occur earlier than true cirrhosis regression, but fibrosis may improve continuously via mechanisms including myofibroblast deactivation and macrophage polarisation towards a restorative/fibrolytic phenotype expressing matrix-degrading enzymes such as matrix metalloproteinases. The improvement of portal hypertension has been documented in patients with viral eradication and suppression and in patients who maintain alcohol abstinence; it translates into a reduced risk of decompensation and is likely key for achieving recompensation. Indeed, in patients with compensated cirrhosis, the reduction of HVPG by ≥10% of the baseline values by administering NSBBs has been shown to be associated with a markedly decreased risk of decompensation.[49,50] In patients with decompensated cirrhosis, a decrease of the HVPG to below 12 mmHg or, at least, by ≥20% of the baseline value with NSBBs is associated with a significant reduction in the risk of further bleeding, new or worsening ascites, hepatorenal syndrome, spontaneous bacterial peritonitis, and increased survival.[51–54] When using TIPS, an optimal response is to reduce the HVPG to below 12 mmHg or, at least, by ≥50% of baseline.[52,53] Importantly, while recompensation is usually associated with structural improvements of the liver parenchyma and portal pressure reductions, cirrhotic septa and CSPH or mild portal hypertension, including associated features like splenomegaly, varices and thrombocytopenia, may persist despite recompensation. Additionally, varices may remain despite normalisation of portal pressure, especially if the cardiac index (and hence, portocollateral blood flow) remain elevated (as after HCV cure or orthotopic LT)[54,55] These low-pressure varices are usually flatter and carry no or negligible bleeding risk.

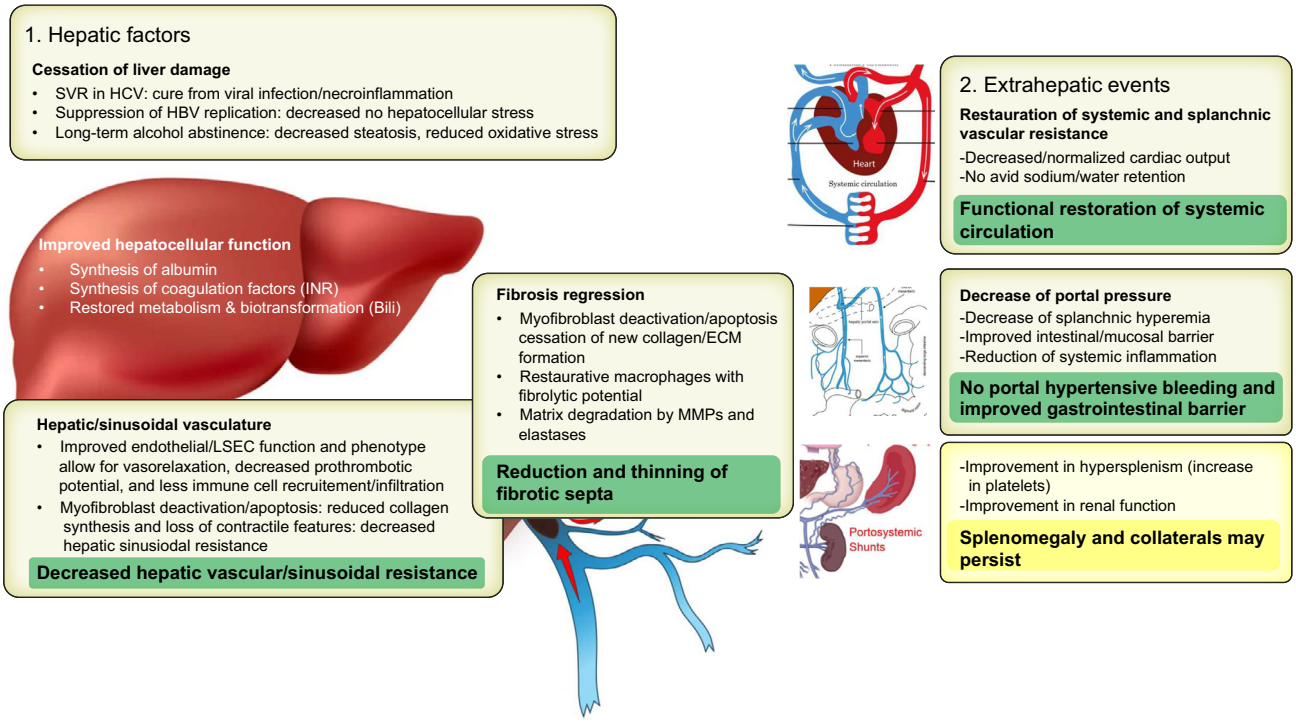


**Fig. 3. Structural and functional changes required for recompensation.** After aetiological cure, hepatic and extrahepatic structural and functional changes are required to achieve recompensation. Improvement in synthetic liver function, a reduction in fibrosis septa thinning and a decrease in hepatic vascular/sinusoidal resistance are key mechanisms leading to a reduction in portal pressure. The reduction in portal pressure is expected to be associated with a restoration of cardiovascular alterations and the gut vascular barrier. Signs of portal hypertension such as splenomegaly/hypersplenism or portosystemic shunts are usually attenuated but may persist after recompensation. CSPH, clinically significant portal hypertension; LSECs, liver sinusoidal endothelial cells; MMPs, matrix metalloproteinases; SVR, sustained virological response.

In patients achieving recompensation, the systemic and splanchnic vascular resistance may be restored, leading to normalisaton of cardiac output, the hyperdynamic circulation, and cessation of sodium/water retention – helping with the control of ascites and leading to further reductions in portal pressure.

While bacterial translocation[56] and immune dysfunction[57] may already occur in compensated cirrhosis, systemic inflammation is most pronounced in patients with further decompensation or ACLF.[58] It remains to be investigated whether a reduction in systemic inflammation favours recompensation and if recompensated patients show a similar pattern of systemic inflammation to always-compensated patients. The anti-inflammatory and immune-modulating effects of albumin have been hypothesised to play a role in preventing further decompensation. However, the results of trials investigating long-term use of albumin are still controversial and further data are needed.[59,60]

As previously mentioned, prevention of further decompensation by NSBBs, albumin or TIPS does not indicate true recompensation according to the Baveno definition.

## Treatments for achieving recompensation

### Aetiological therapy

HVPG is significantly and progressively ameliorated in patients with HCV-related cirrhosis who have achieved an SVR.[61,62] Although data are almost exclusively available for compensated cirrhosis, about 50% of patients with pre-treatment CSPH (*i.e.*, those at risk of decompensation) had HVPG values <10 mmHg, *i.e.* below the CSPH threshold 2 years after SVR.[63] In contrast, persistence of increased HVPG values after SVR[64] identified patients at higher risk of *de novo* or further clinical decompensation. Supporting abstinence from alcohol represents a management priority in all patients with cirrhosis, as well as in patients with primary aetiologies of liver disease other than ALD. Importantly, abstinence from alcohol results in a survival benefit[65] even in advanced stages of cirrhosis with pronounced portal hypertension, *e.g.* those with HVPG ≥20 mmHg.[66] In patients with decompensated cirrhosis due to ALD, sustained alcohol abstinence reduced the risk of further decompensation independently from CSPH severity.[66] Importantly, a significant proportion of patients with decompensated alcohol-related cirrhosis (18%) may achieve full recompensation (according to Baveno VII criteria) after maintained alcohol abstinence, which also translates into a significant survival benefit, *i.e.* a >90% reduced risk of liver-related mortality compared to patients without recompensation.[12] In patients with decompensated HBV-related cirrhosis, antiviral therapy with entecavir resulted in suppression of HBV replication in 92% and in resolution of ascites and other decompensating events in 60% of patients, with 56% also achieving a stable improvement of liver function and thus Baveno VII criteria for cirrhosis recompensation.[8] In this study, the authors suggested model for end-stage liver disease (MELD) <10 and albumin >35 g/L, INR <1.5, and total bilirubin <34 μmol/L as criteria for "stable improvement" of liver function.[8] Long-term follow-up studies have confirmed an exceedingly low risk of decompensation after ≥2 years of successful aetiologic therapy.[67] Recompensation following aetiological therapy (*i.e.* antiviral therapy or continued abstinence) have been shown for patients with decompensated cirrhosis due to HBV,[8] HCV[6] or alcohol abstinence.[12] However, the process is slow and takes over 2-3 years for a significant number of patients to show histological regression, although a diminished risk of decompensation is observed after 1-2 years, associated with decreased HVPG[63] and improved surrogate markers of fibrosis (VCTE [vibration-controlled transient elastography], ELF [enhanced liver fibrosis], von Willebrand factor, VITRO).[68–71] Recompensation and regression of cirrhosis due to MASLD is less well studied; however, regression of MASLD-related cirrhosis has been observed in patients after bariatric surgery. Whether new antiviral treatments for HDV can lead to recompensation remains to be proven, but interestingly, during ongoing bulevirtide treatment about 50% of patients with decompensated HDV-related cirrhosis achieved an improvement of liver function (transition from Child-Pugh B to Child-Pugh A class) and 58% showed an improvement/resolution of ascites.[72] Response to ursodeoxycholic acid (UDCA) in patients with cirrhosis due to PBC is associated with a reduced risk of hepatic decompensation and liver-related death.[73] Recently, UDCA response according to Paris II criteria was proposed for defining aetiologic control within the Baveno VII recompensation criteria for patients with PBC-related decompensated cirrhosis.[14] While 7/42 (16.7%) decompensated patients with PBC achieved recompensation upon UDCA treatment, liver-related complications still occurred in four of these seven patients.

These data highlight the need for further studies in patients with non-viral- and non-alcohol-related aetiologies of decompensated cirrhosis.

### Potential drugs and therapeutic concepts to facilitate recompensation

Several agents have been shown to inhibit fibrogenesis and/or accelerate regression of fibrosis in animal models, however, clinical trials are limited, and many drugs were ineffective when tested in humans, in whom kinetics of fibrosis progression and regression are much slower than in rodents.[18] Herein, we highlight some drugs or concepts that have shown positive effects in translational, clinical and/or epidemiological studies.

#### *Carvedilol or other NSBBs*

Carvedilol is a NSBB with anti-alpha1-adrenergic activity that promotes NO release.[74] Carvedilol is the preferred NSBB since it achieves a greater reduction in HVPG and reduces decompensation and mortality while being better tolerated than traditional NSBBs.[49,50] However, it is uncertain if carvedilol/NSBBs may facilitate recompensation.

#### *Lifestyle intervention and weight loss*

Obesity and overweight are common in patients with cirrhosis and are associated with higher risk of decompensation.[75] In patients with overweight/obesity, regular physical activity and calory-restricted diet are recommended for management and can translate into a clinical benefit. Indeed, a short-term lifestyle intervention (personalised hypocaloric normoproteic diet and 60 min/week of supervised physical activity) has been shown to decrease body weight and HVPG in patients with overweight/obesity.[76] Bariatric surgery can cure MASLD but is associated with significant risk in patients with cirrhosis and is not recommended for them.[77]

*Statins*

Statins reverse LSEC dedifferentiation and dysfunction in cirrhosis, de-activate HSCs, reduce collagen synthesis and LSEC dysfunction, and decrease portal pressure.[78] Simvastatin is the best studied statin in patients with cirrhosis and has been shown to increase AKT-dependent endothelial NO synthase phosphorylation and subsequent NO release.[79,80] Simvastatin decreased portal pressure in patients with cirrhosis,[81,82] inhibited fibrogenesis in experimental liver fibrosis,[83,84] and improved and prevented ischaemia/reperfusion injury,[85,86] and ameliorated ACLF severity in experimental models.[87] This lipophilic statin should be used at reduced doses in decompensated cirrhosis to decrease the risk of muscle toxicity (rhabdomyolysis).[88] The effectiveness of simvastatin in preventing decompensation and mortality is still controversial; however, in an RCT, simvastatin significantly improved survival in patients after a bleeding episode, [89] while a second study in more severe patients with decompensated cirrhosis failed to demonstrate any effect of simvastatin (combined with rifaximin) on prevention of ACLF or reduction of mortality.[90] However, multiple epidemiological studies suggested beneficial effects of statins via a reduced risk of progression to cirrhosis, decompensation and death.[91,92] Statins are also associated with a reduced risk of mortality after LT,[93,94] reduced incidence of liver cancer,[95,96] and protective effects in other liver diseases.[97]

*Increasing NO availability in the intrahepatic circulation*

NO donors, such as isosorbide mononitrate at low doses, potentiate the effects of propranolol but may cause systemic hypotension;[98] antioxidants, such as recombinant human superoxide dismutase[99] and resveratrol,[100] increase NO availability by decreasing NO scavenging by superoxide. Antioxidants assessed in patients with cirrhosis are limited to intravenous vitamin C and oral dark chocolate that blunt the postprandial increase in portal pressure by reversing liver endothelial dysfunction.[101,102] Phosphodiesterase-5 inhibitors have been tested with contrasting results, and their ability to prolong the downstream vasodilating effects of NO may result in systemic hypotension.[103] Administration or supplementation of folic acid promotes NO bioavailability by decreasing asymmetric dimethyl arginine (that antagonises NO synthesis) and increasing tetra-hydro-biopterine (a co-factor for NO synthesis) and has recently been demonstrated to significantly decrease HVPG in patients with cirrhosis.[104] In contrast to statins, folate does not cause muscle toxicity. Stimulators/activators of the soluble guanylyl cyclase can decrease the hepatic vascular tone and thereby ameliorate portal hypertension, potentially without causing systemic hypotension,[105] and are currently being evaluated in clinical trials.[106]

## Factors influencing recompensation and point of no-return

Elegant studies based on paired liver biopsies have demonstrated histologic regression of cirrhosis after long-term suppression of HBV replication[5] or after SVR for HCV.[107] Intriguingly, however, regression of cirrhosis was not seen in all patients despite HBV suppression or HCV eradication. Factors that hinder the regression of cirrhosis may include obesity and diabetes (both probably causing MASLD), pathologic alcohol use (leading to superimposed ALD) and potentially genetic variants favouring fibrosis (*e.g*. *PNPLAP3, SERPINA1, HFE*). Interestingly, genetic variants in *PNPLA3, TM6SF2, MBOAT7* and *HSD17B13* were not associated with changes in HVPG after SVR in patients with pre-treatment ACLD.[108]

Finally, there is likely a "point of no return" in cirrhosis when architectural changes are irreversible with thick, acellular fibrotic septa lacking effective perfusion and extensive cross-linking of collagen fibres. An exact definition of this "point of no return" is lacking, but morphologically a considerable decrease in liver volume due to parenchymal extinction[4] or pronounced liver surface nodularity, and clinically recurrent episodes of decompensating events (*i.e*. further decompensation[109]) may hint towards irreversible cirrhosis.

Clinically, patients with lower MELD (<15) at index decompensation with ascites have a more favourable prognosis than those with higher MELD (≥15) at index decompensation.[110] Patients with decompensated ALD cirrhosis could more often be delisted from the LT waiting list due to clinical improvement if their listing MELD was lower and their platelet count was higher,[111] suggesting that severity of hepatic dysfunction should not have passed a certain (yet undefined) threshold. In patients with decompensated HCV cirrhosis, male sex and Child-Pugh stage C at listing,[112] pre-SVR MELD >20, and lack of improvement in prothrombin index, albumin and MELD were identified as factors that prevented clinical improvement and thus delisting (a surrogate of recompensation) despite SVR.[112,113]

Decompensation can be associated with extrahepatic organ dysfunction, which may be either acute (*e.g.* in the setting of ACLF) or chronic (*e.g*. chronic kidney disease or sarcopenia); the role of extrahepatic conditions in marking the "point of no return" deserves investigation. Indeed, for patients achieving resolution of ACLF, recompensation is still potentially achievable.

## Management of recompensation

EASL has recently released a position paper on the increasingly common clinical scenario of cured hepatitis C, which provides guidance on how to manage patients with cirrhosis who have achieved virologic cure and thus potentially also recompensation of cirrhosis.[114] Importantly, recompensation may not occur in all decompensated patients achieving HCV cure, and the risk of liver cancer (hepatocellular carcinoma [HCC]) is lower after SVR but remains elevated in patients with pre-SVR cirrhosis.[115] Portal hypertension and varices may also persist despite improvements in portal pressure (HVPG). That said, the guidance is that endoscopic screening can be spared in patients with a liver stiffness measurement (LSM) <20 kPa and normal platelet count (≥150 G/L), while CSPH can be considered resolved and NSBBs potentially discontinued in patients with LSM <12 kPa and normal platelet count.[69,116]

Importantly, in the settings of cured HCV,[115] suppressed HBV and recompensated ALD cirrhosis,[12] the risk of HCC development remains relevant, so patients should remain under HCC surveillance. However, non-invasive tests may help in the future to individualise HCC screening in recompensated patients, as distinct risks for post-SVR HCC development were seen in different patient groups stratified by post-SVR age, albumin, LSM, alpha-fetoprotein levels and alcohol consumption.[115]

In patients with decompensated cirrhosis on the LT waiting list, aetiological cure enables delisting for improvement in a substantial proportion of patients. Among patients with

**Table 2. Unmet needs, implications and areas for future research.**

| The unmet need | The implication | The areas for future research |
|---|---|---|
| Lack of definition of aetiological cure for aetiologies other than HBV, HCV and ALD | Recompensation could be defined for patients with aetiologies other than HBV, HCV or ALD | Assess whether criteria explored in clinical trials (*i.e.* ≥2 log decline in HDV-RNA plus ALT normalisation, reduction in body weight// ≥30% decrease in MRI-PDFF in MASLD, Paris II UDCA criteria in PBC) may define recompensation |
| Lack of evidence-based criteria for withdrawing diuretics, lactulose and rifaximin | The discontinuation of decompensation treatment is subjective and affects the definition of recompensation | Recommendation for discontinuation medical treatments for decompensation should be defined; to ensure objective/reproducible settings in clinical studies<br>Assess criteria for discontinuing decompensation treatment or evaluate expanded criteria in those still on treatment |
| Lack of relative/absolute thresholds for defining improvement of liver function tests | The lack of specific criteria can affect the definition | Evaluate relative changes and/or absolute thresholds of albumin, bilirubin and INR (and of Child-Pugh and/or MELD score) required to define recompensation |
| Pathophysiology of recompensation is poorly known | Limit the development of treatment that may enhance recompensation | Investigate the histophathological, haemodynamic and molecular changes occurring during recompensation.<br>Develop experimental models of recompensation |
| Lack of information about the role of non-aetiologic treatments in favouring recompensation | The addition of non-aetiologic treatments could increase the probability of recompensation after aetiologic treatment | Investigate the role of non-aetiologic treatments like statins, anticoagulants, FXR agonists, GLP-1 receptor agonists, PPAR agonists, rifaximin, long-term albumin in inducing recompensation |
| Lack of predictors of recompensation and point of no return for recompensation | May affect clinical decision about transplant (wait or go) and/or can cause MELD "purgatory" | Investigate predictors of recompensation |
| Lack of knowledge about long-term prognosis of recompensated patients | Affect planning of follow-up visits and clinical monitoring | Evaluate long-term events after decompensation and compare the clinical course *vs*. that in compensated patients |
| Stratification of risk of new decompensation in recompensated patients | Affect the management of patients and the recommendation to use/continue NSBBs | Evaluate the role of non-invasive tests (liver/spleen stiffness, platelets) of portal hypertension in identifying CSPH and predicting new decompensation in recompensated patients |

ALD, alcohol-related liver disease; CSPH, clinically significant portal hypertension; FXR, farnesoid X receptor; GLP-1, glucagon-like peptide-1; MASLD, metabolic dysfunction associated steatotic liver disease; MELD, model for end-stage liver disease; MRI-PDFF, MRI-derived proton density fat fraction; NSBBs, non-selective beta-blockers; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator-activated receptors; UDCA, ursodeoxycholic acid.

decompensated HCV cirrhosis achieving SVR, delisting for improvement has been reported in 6-31%.[117,118] Among patients with ALD decompensated cirrhosis, delisting for improvement has been reported in 9-16%.[111,119] Criteria for delisting varied, but most of them included MELD <15 and absence of complications. Although no data on full recompensation were reported in these studies, it can be argued that many of these patients fully recompensated. Therefore, delisting for improvement can be considered in patients achieving recompensation who have a MELD score <15 points, no history of HCC, and no persistent untreated/uncontrolled liver disease aetiology.[120]

## Unmet needs and areas of future research

The introduction of recompensation as a new stage of cirrhosis represents a significant advancement in the classification of patients with advanced chronic liver disease. However, several unsolved issues persist (Table 2). Baveno VII recompensation criteria are based on expert consensus, warrant further validation and will need to be refined as new data become available. Effective control of the underlying liver disease and/or aetiological cure should be defined for aetiologies other than ALD, HCV and HBV. Additionally, the discontinuation of therapy for decompensation such as diuretics for ascites and rifaximin/lactulose for hepatic encephalopathy is required for the definition, but there is insufficient evidence on the selection of patients in whom it is safe to discontinue these drugs after aetiological cure. Therefore, the decision mostly relies on the treating physician's discretion, representing a relevant bias for epidemiological studies and posing a challenge for the design of clinical trials with the current definition of recompensation as an endpoint. Furthermore, as indications for TIPS are expanding, a method to define recompensation in patients with TIPS who may also fulfil the other criteria in terms of achieving aetiological cure and improved liver function needs to be established.

As for the improvement of liver function tests, there are still no established relative or absolute thresholds for bilirubin, albumin and INR. Although mild to moderate alterations in liver function tests can be observed even in compensated patients, it is crucial to identify at least relative thresholds. The pathophysiology of recompensation remains to be understood, both regarding liver histopathological changes and other key mechanisms of decompensation such as HVPG and systemic inflammation. While one might expect a reduction in HVPG and markers of systemic inflammation in recompensated patients, this hypothesis requires further evidence. A better understanding of the pathophysiology of recompensation will aid in developing non-aetiological interventions (*e.g.* promoting liver

(functional) regeneration and regression of fibrosis/CSPH) to enhance recompensation rates in patients who achieve aetiological cure. Recompensation represents a prolonged process that typically requires more than 1 year following aetiological cure. The time-dependent course and incidence rates of cirrhosis recompensation for different aetiologies and clinical settings remain to be systematically investigated. Moreover, the timeframe for defining recompensation is based on expert consensus and different time points should be explored. Currently, predicting recompensation after aetiological cure and identifying the "point of no return" for recompensation remains challenging. Thus, it is essential to develop biomarkers to monitor these patients and to predict recompensation early, as this information will be crucial to inform clinical decision making regarding the timing of LT.

Additionally, the influence of factors such as age, sex, lifestyle, and comorbidities on facilitating or limiting the rate of recompensation should be evaluated thoroughly. Whether the long-term prognosis of recompensated patients is similar to "always-compensated" patients is still unclear. Nevertheless, recompensated patients remain at risk for new decompensating events due to potential recurrence of the primary aetiology (such as alcohol relapse or HBV flair/HCV reinfection) and/or persistent CSPH. Liver and//or spleen stiffness measurements and platelet count seem promising non-invasive tests to identify (persisting) CSPH and/or predict decompensation after cure, but their true clinical value in recompensated patients needs to be demonstrated in further studies. Finally, it will be important to evaluate if and potentially to what degree the incidence of HCC after recompensation is decreased and whether HCC screening can be individualised in these patients.

Overall, the possibility of recompensation has shifted the treatment approach in patients with decompensated cirrhosis from merely slowing down liver disease progression and preventing liver-related death to actively promoting disease regression ("left shift") towards cirrhosis recompensation.

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## Abbreviations

ACLF, acute-on-chronic liver failure; ALD, alcohol-related liver disease; CSPH, clinically significant portal hypertension; HSCs, hepatic stellate cells; HVPG, hepatic venous pressure gradient; INR, international normalised ratio; LSECs, liver sinusoidal endothelial cells; LSM, liver stiffness measurement; LT, liver transplantation; MELD, model for end-stage liver disease; NSBB, non-selective beta-blockers; PBC, primary biliary cholangitis; RCT, randomised-controlled trials; SVR, sustained virological response; TIPS, transjugular intrahepatic portosystemic shunt; VEGF, vascular endothelial growth factor.

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Please refer to the accompanying ICMJE disclosure forms for further details.

## Authors' contributions

SP, TR, JB reviewed the literature, drafted the manuscript and critically reviewed the manuscript.

## Supplementary data

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