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Review Article

The Baveno VII concept of cirrhosis recompensation

Thomas Reiberger[a,b,c,*], Benedikt Silvester Hofer[a,b,c]

[a] Division of Gastroenterology and Hepatology, Department of Medicine III, Medical University of Vienna, Vienna, Austria
[b] Vienna Hepatic Hemodynamic Lab, Division of Gastroenterology and Hepatology, Department of Medicine III, Medical University of Vienna, Vienna, Austria
[c] Christian Doppler Lab for Portal Hypertension and Liver Fibrosis, Medical University of Vienna, Vienna, Austria

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ABSTRACT

Traditionally, the progression from compensated to decompensated cirrhosis has been regarded as a point of no return in the natural history of the disease. However, this point of view is increasingly being challenged by new evidence on disease regression and hepatic recompensation upon suppression/cure of the underlying aetiology. In order to create a uniform definition of recompensated cirrhosis, standardised criteria have been set out by the Baveno VII consensus, which include the removal of the primary aetiological factor, the resolution of any decompensating events and a sustained improvement in hepatic function. Initial insights into the concept of hepatic recompensation come from previous studies, which have demonstrated that a cure/suppression of the underlying aetiology in patients with prior decompensation leads to significant clinical improvements and favourable outcomes and can even enable the delisting of transplant candidates. Nevertheless, future studies are required to shed light on the natural history of hepatic recompensation, assess modifying factors and potential non-invasive biomarkers of recompensation and explore the molecular mechanisms of disease regression.

1. The natural history of advanced chronic liver disease

Cirrhosis is a leading cause of morbidity and mortality worldwide and can develop on the basis of repetitive and/or chronic liver injury due to toxic, infectious, metabolic and genetic pathogenic factors [1]. Traditionally, the natural history of cirrhosis has often been considered a one-way street, with a definite and irreversible progression from a compensated to a decompensated disease stage [2]. The transition to a decompensated stage is linked to a considerably increased risk of experiencing further decompensating events and death, thus indicating a watershed moment in the clinical course of the disease [2]. However, an increasing body of evidence indicates that an effective treatment or a successful elimination of the underlying liver disease aetiology not only slows down disease progression but may even induce disease regression. These insights have led to a paradigm shift in the perception of the natural history of cirrhosis towards a dynamic liver disease model which accounts for the possibility of disease regression. This change in perception gave rise to the concept of hepatic recompensation [3].

Currently, a limited number of high-quality studies on the definition and clinical implications of hepatic recompensation exist. Some studies have reported data on the effects of a successful aetiological (mostly antiviral) therapy in decompensated patients, or on the outcomes of transplant candidates who were delisted due to clinical improvements. However, until recently, the definitions of “clinical improvement” and “hepatic recompensation” were heterogenous. As an important step towards gaining deeper insights into the bi- (or even multi-) directional clinical course after hepatic decompensation, the Baveno VII consensus has proposed uniform criteria for the definition of hepatic recompensation [3].

In light of the introduction of these novel criteria, we conducted a comprehensive literature review focusing both on studies which explored the importance of aetiological therapy in decompensated patients overall, as well as studies which have provided initial insights into hepatic recompensation. Thus, this review aims to (i) summarise the current evidence on hepatic recompensation and disease regression, (ii) present available data on the clinical implications of achieving recompensation, and (iii) highlight directions for future research. A visual summary is provided in Fig. 1.

2. The Baveno VII concept of hepatic recompensation

Fundamentally, hepatic recompensation following the successful treatment of the underlying aetiology is based on a significant

* Corresponding author at: Division of Gastroenterology and Hepatology, Department of Medicine III, Waehringer Guertel 18-20, A-1090 Vienna, Austria.
E-mail address: Thomas.Reiberger@meduniwien.ac.at (T. Reiberger).

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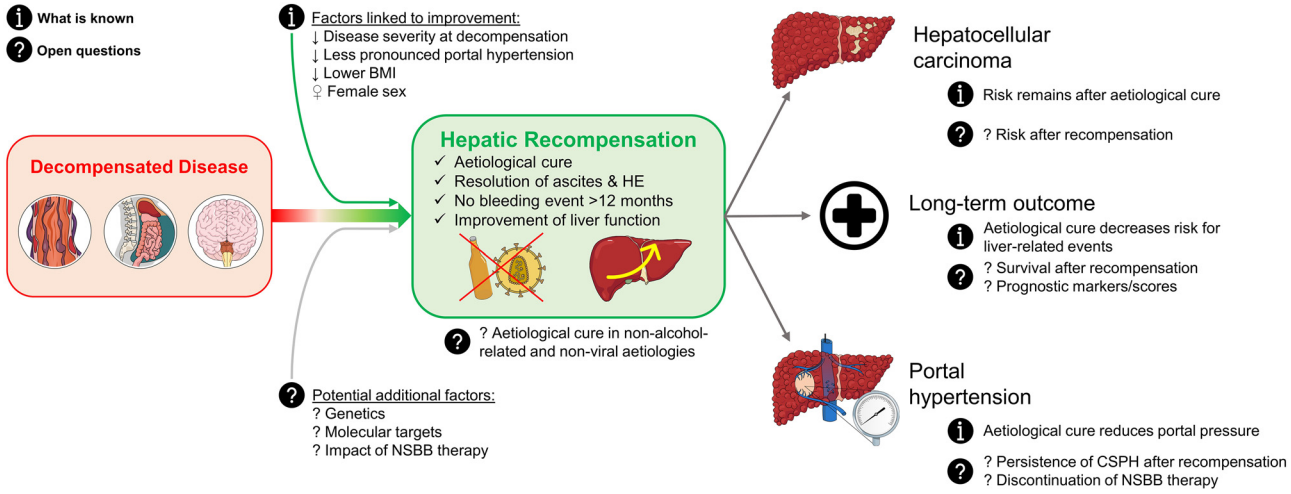

Fig. 1. Baveno VII concept of hepatic recompensation – available insights and open questions. Abbreviations: BMI, body mass index; CSPH, clinically significant portal hypertension; HE, hepatic encephalopathy; NASH, non-alcoholic steatohepatitis; NSBB, non-selective betablocker.

improvement in hepatic function, combined with a reduction of functional and structural drivers of disease progression, including hepatic inflammation, fibrosis and portal hypertension. Clinically, these improvements correlate with a sustained resolution of any previous hepatic decompensation events. Standardised criteria for the definition of hepatic recompensation have been introduced in 2021 at the Baveno VII consensus meeting [3]. In order for a patient to be considered recompensated, all of the following criteria have to be met:

- Sustained cure, suppression or removal of the underlying aetiology of cirrhosis.
- Resolution of ascites and hepatic encephalopathy (HE) after discontinuation of diuretics and prophylactic therapies, as well as the absence of variceal bleeding for 12 months.
- Sustained improvement of biochemical liver function, as assessed by serum albumin, bilirubin and INR (international normalized ratio).

3. Evidence on hepatic recompensation

Owing to the novelty of the Baveno VII criteria, data on hepatic recompensation are still limited and comparisons to previous studies are likely biased by heterogenous definitions of recompensation. Nevertheless, previous reports on the delisting of liver transplant candidates following clinical improvements and the regression to Child-Pugh stage A cirrhosis following aetiological therapy may offer initial insights.

Importantly, curing, removing or suppressing the primary aetiological factor in cirrhosis represents the fundamental prerequisite for achieving hepatic recompensation and has thus far only been defined for alcohol-related liver disease (ALD), hepatitis C virus (HCV)- and hepatitis B virus (HBV)-associated liver disease [3]. Due to the varying natural history and distinct clinical and therapeutic challenges in different aetiologies of liver disease, a detailed and aetiology-specific assessment of existing data on hepatic recompensation is given in this review. A summary of all included studies is provided in Table 1.

3.1. Alcohol-related cirrhosis

The removal of the underlying aetiology in alcohol-related cirrhosis, i.e. sustained abstinence from ethanol-containing beverages and foods, has been linked to a significantly improved prognosis [4–6]. Despite the clear overall benefit of alcohol abstinence, insights into clinical implications of abstinence-induced improvements in decompensated patients remain scarce. In 1996, Vorobioff et al. [7] published a landmark study which prospectively assessed the clinical course of patients with ALD cirrhosis and linked abstinence to significant improvements in Child-Pugh score and portal pressure. Nevertheless, the interpretation of these findings is limited by the small size of the study cohort and the low proportion of decompensated patients.

First insights directly addressing recompensation in ALD were published by Aravinthan et al. [8], who investigated the delisting of liver transplant candidates following recompensation. Overall, 16.5% of ALD patients (47/284) achieved recompensation, as defined by the absence of ascites and HE despite treatment discontinuation, and a decrease in MELD (model for end-stage liver disease) to <15. Independent factors linked to a higher likelihood of delisting following recompensation within the multivariable model included a low MELD and high serum albumin at the time of listing.

Similar findings were reported by Pose et al. [9], who demonstrated 8.6% of all patients (36/420) with decompensated alcohol-related cirrhosis listed for transplantation achieved significant clinical improvements and could subsequently be delisted. At the time of delisting, the majority of patients demonstrated signs of hepatic recompensation, highlighted by the resolution of ascites and HE. Nevertheless, more than 20% of delisted patients still required low-dose diuretic therapy and 3% had presented an episode of overt HE within 3 months of delisting, thus not fulfilling the Baveno VII criteria for recompensation. Female sex, a lower height, lower MELD, as well as a higher platelet count were modifying factors independently associated with a higher probability of delisting. Importantly, Pose et al. demonstrated that two thirds of all delisted patients were alive after a median follow-up period of more than 3 years. Of those patients, close to 90% remained compensated. Nevertheless, the authors observed that 25% of delisted patients showed liver disease progression, which primarily occurred following alcohol relapse.

Further evidence regarding delisting was provided by Giard et al. [10], who assessed the outcomes of over 64,000 transplant candidates with non-alcohol-related aetiologies of cirrhosis and compared them to over 19,000 ALD patients listed for transplantation. Overall, 1.6% of patients with non-alcoholic aetiologies and 2.0% of ALD patients were delisted due to improvements within 2 years after listing. This difference is reflected by a 2.91-fold higher likelihood of delisting in ALD patients compared to non-ALD pa-

Table 1
Summary of studies assessing hepatic improvement following aetiologic therapy.

Study/Year/ Country/Design	Patients and aetiologies	Criteria for delisting/ clinical improvement	Incidence of recompensation/delisting	Factors linked to recompensation/delisting	Outcome of delisted/ recompensated patients	Key limitations/Risk of bias
Aravinthan et al. [8] 2017 Canada Retrospective Single-centre	$n = 935$ patients listed for LT 30% ALD 26% HCV 12% NAFLD 8% PSC 6% HBV 18% other Analyses mainly limited to ALD.	Delisting due to improvement. Criteria: - No ascites / hepatic hydrothorax / peripheral oedema and HE (despite treatment discontinuation) - Decrease in MELD to <15	Overall delisting: 77/935 (8.2%) ALD: 16.5% HCV: 5.0% NAFLD: 2.6% PSC: 1.4% HBV: 5.5%	In ALD: Multivariable logistic regression model: -Low MELD -High albumin Female sex, high platelet count and individual MELD components (low bilirubin, low INR, low creatinine, high serum sodium) significant in univariable model.	Fourrecompensated patients were re-referred for LT (5.2%; n = 2 ALD, n = 1 HCV, n = 1 AIH).	Analysis of factors linked to delisting only in ALD. No detailed outcome analysis after delisting. Statistical analysis of factors based on logistic regression, thus not accounting for time to delisting or competing events.
Pose et al. [9] 2021 Spain Retrospective Multicentre Registry-based	$n = 1001$ patients listed for LT 42.0% ALD 40.3% HCV 10.8% Cholestatic 7.0% NASH Of HCV patients: 73.2% only HCV 26.8% HCV+ALD Analyses mainly limited to ALD.	Delisting due to improvement. At delisting: - Improvement in MELD - No or medically controlled ascites - Only 3% with HE episode within last 3 months	Overall delisting: 70/1001 (7.0%) ALD: 8.6% HCV: 7.7% Cholestatic: 1.9% NASH: 1.4% In HCV: HCV only: 7.0% HCV+ALD: 9.2%	In ALD: multivariable competing risk model: - Female sex - Lower height - Lower MELD - Higher platelet count Lower BMI and higher albumin significant in univariable model.	67% of ALD/71% of HCV patients alive after median of 39/32 months after delisting. In patients alive at end of study: 87% of ALD and 91% of HCV still compensated. In ALD: Alcohol relapse in 67% of patients with disease progression after delisting.	May not fully reflect recompensation: >20% of delisted ALD patients required low-dose diuretics and 3% had presented and episode of overt HE within 3 months of delisting. Analysis of factors only for ALD patients.
Giard et al. [10] 2019 USA Retrospective Registry-based	$n = 83,348$ patients listed for LT 22.9% ALD 77.1% non-ALD	Delisting due to improvement.	Overall delisting: 1408/83,348 (1.7%) ALD: 2.0% Non-ALD: 1.6%	Multivariable competing risk model: - ALD as aetiology - Younger age - Female sex - Lower BMI - No diabetes - No ascites/HE - Lower MELD - Blood group O/A/B - Regions with shorter waiting time - Listing between 2007 and 2011 or 2012–2016 vs 2002–2006	No data presented.	May not fully reflect recompensation: Clinical improvements required for delisting not stated. Based on registry data. No outcome data or data on alcohol-consumption prior to and during listing.
El-Sherif et al. [20] 2018 Retrospective analysis of 4 clinical trials	$n = 622$ decompensated patients (80.7% CP-B 19.3% CP-C) receiving sofosbuvir-based therapies 100% HCV	Post-DAA-treatment reduction in CP stage to A.	Reduction to CP-A including only patients achieving SVR12 ($n = 528$): CP-B: 31.6% CP-C: 12.3%	Competing risk model: - SVR12 - No ascites/HE - High albumin - Low bilirubin - High ALT - Low BMI - African American ethnicity	No data presented.	May not fully reflect recompensation: CP-A patients might still demonstrate low-grade ascites or HE. No outcome data.
Macken et al. [21] 2019 UK Prospective Multicentre	$n = 39$ decompensated patients receiving DAA therapy 100% HCV	No standardised criteria. Improvement based on assessment of treating clinician.	Recompensation: 20/39 (51.3%) 18/20 achieved SVR12.	No in-depth analysis provided. Lower baseline creatinine levels in patients who recompensate post treatment.	No data presented.	No standardised assessment of recompensation. No outcome data. Small cohort size.
Gentile et al. [22] 2019 Italy Prospective Multicentre	$n = 89$ decompensated patients (all CP-B) receiving DAA therapy 100% HCV	Post-DAA-treatment reduction in CP stage to A (return to a compensated stage).	Overall reduction to CP-A: 55/89 (61.8%) At 12 weeks post therapy: 50.6% Amongst patients achieving SVR12: 55/85 (64.7%)	Multivariable logistic regression model: - No previous HCV treatment - Recompensation at 1 month of treatment	No data presented.	May not fully reflect recompensation: CP-A patients might still demonstrate low-grade ascites or HE and recompensation criteria not stated. No outcome data.

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Table 1 (*continued*)

Study/Year/ Country/Design	Patients and aetiologies	Criteria for delisting/ clinical improvement	Incidence of recompensation/delisting	Factors linked to recompensation/delisting	Outcome of delisted/ recompensated patients	Key limitations/Risk of bias
Belli et al. [23] 2016 Europe Retrospective Multicentre	$n = 103$ patients listed for LT and receiving sofosbuvir-based therapies 100% HCV	Inactivation following clinical improvement. Subsequent delisting if improvements persist. At delisting: 76.2% resolved decompensation	Inactivation: 34/103 (33.0%) 21 of those eventually delisted (61.8%).	Multivariable competing risk model for inactivation: - Low MELD at baseline - Delta MELD at 12 weeks of DAA therapy - Delta albumin at 12 weeks of DAA therapy	No patient required relisting due to liver decompensation. HCC led to relisting in one inactivated patient.	Does not fully reflect recompensation: 23.8% of delisted patients required low-dose diuretics.
Pascasio et al. [24] 2017 Spain Retrospective Multicentre	$n = 122$ patients listed for LT without HCC receiving DAA therapy 100% HCV	Delisting due to improvement. At delisting: - Complete resolution of ascites and HE in 93.1%. Low-dose diuretics in 6.9% - Decrease to MELD <15 in all patients	Delisting: 29/122 (23.8%)	Univariable competing risk model: - Delta MELD between baseline and end of DAA therapy No multivariable model provided.	*Re*-decompensation occurred in 4 patients and HCC developed in 3 patients over a median follow-up time of 88 weeks.	Does not fully reflect recompensation: 6.9% of delisted patients required low-dose diuretics.
Perricone et al. [25] 2018 Europe Prospective Multicentre	$n = 142$ patients listed for LT receiving DAA therapy 100% HCV	Delisting due to improvement. Criteria: - SVR - No ascites / HE (low-dose diuretics in 20.5% of patients) - Decrease in MELD to <15 90.9% of delisted patients CP stage A (40/44)	Delisting: 44/142 (31.0%)	No competing risk models provided. At baseline, delisted patients showed: - Lower MELD - Lower CP score - Less severe HE - Lower INR - Higher creatinine	Relisting required in 4 patients (1 due to HCC, 3 due to recurrent ascites, all with low-dose diuretics at delisting). One death due to HCC without relisting. Overall 2 cases of HCC in delisted patients (4.5%), both with CP-B at delisting.	Does not fully reflect recompensation: 20.5% of delisted patients required low-dose diuretics. No analysis of factors linked to delisting.
Bittermann et al. [26] 2021 US Retrospective Registry-based	$n = 32,313$ patients with advanced or decompensated cirrhosis listed for LT 100% HCV	Delisting due to improvement. At delisting: - 44.5% had ascites - 27.7% had HE	HCV patients: Post-DAA era: 2013–2017: 6.1% Pre-DAA era: 2009–2012: 5.2% 2005–2008: 4.0% Non-HCV patients during post-DAA era: 5.5%	Delisting of HCV patients due to improvement more frequent in post-DAA era: adjusted SHR 1.78 vs pre-DAA	No data presented.	Does not fully reflect recompensation: 44.5% of delisted patients had ascites and 27.7% HE. No details regarding treatment or SVR. Registry-based study without outcome data.
Martini et al. [27] 2018 Italy Prospective Multicentre	$n = 86$ patients with decompensated cirrhosis and CP score ≥8 and/or MELD ≥15 listed for LT 100% HCV	Assessment of potential candidates for delisting defined by a regression to CP stage A and MELD <15.	Reduction to CP-A and MELD <15: 15/86 (17.4%)	Baseline variables: - Lower CP score - Absence of HE Dynamic variables at 4 weeks of therapy: - High delta MELD - High delta albumin - High delta bilirubin - High delta INR	No data presented.	May not fully reflect recompensation. Analysis of factors does not account for time to improvement. No outcome data.
Nabatchikova et al. [28] 2021 Russia Prospective Single-centre	$n = 45$ patients listed for LT receiving DAA therapy and achieving SVR 100% HCV	Delisting due to improvement. Criteria: - MELD <15 and CP score <7 At delisting: - 15/18 fully resolved ascites - 10/12 fully resolved HE	Delisting: 26/45 (57.8%)	Multivariable competing risk model: - Female sex - Low CP score - High delta prothrombin index from baseline to SVR (≥2%) Lower bilirubin and higher albumin significant in univariable model.	No re-decompensation events in delisted patients. HCC occurred in 7.7% of delisted patients vs. 31.6% in non-delisted patients.	Does not fully reflect recompensation: 11.5% of delisted patients required low-dose diuretics and 7.7% demonstrated latent HE. Small cohort size.
Jang et al. [33] 2015 Korea Prospective Multicentre	$n = 707$ decompensated patients ($n = 606$ CP ≥7 [85.7%]) of whom 423 (59.8%) received antiviral therapy 100% HBV	For patients with CP score ≥7 at baseline: Regression to CP stage A. For patients listed for LT: Delisting due to improvement.	Reduction to CP-A at 60 months in patients with baseline CP score ≥7: Treated: 12.0% Untreated: 1.7% 33.9% of treated LT candidates delisted within 12 months.	No data presented.	No data presented.	LT candidates were not the focus of this study. Thus no criteria for delisting, no associated factors and no specific outcome data were presented.

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Table 1 (*continued*)

Study/Year/ Country/Design	Patients and aetiologies	Criteria for delisting/ clinical improvement	Incidence of recompensation/delisting	Factors linked to recompensation/delisting	Outcome of delisted/ recompensated patients	Key limitations/Risk of bias
Yao et al. [35] 2001 USA Prospective Single-centre	$n = 23$ patients with CP score ≥10 considered for LT and treated with lamivudine 100% HBV	Reduction in CP stage to A under treatment.	Reduction to CP-A: 8/23 (34.8%) All patients who regressed to CP-A were either inactivated or put on lower priority listing.	No data presented.	No data presented.	Regression to CP-A was not the focus of this study. Thus no associated factors and no specific outcome data were presented. Small cohort size.
Nikolaidis et al. [36] 2005 Greece Prospective Single-centre	$n = 20$ patients listed for LT and treated with lamivudine 100% HBV	Reduction in CP stage to A under treatment.	Reduction to CP-A: 9/20 (45.0%)	No data presented.	No data presented.	Regression to CP-A was not the focus of this study. Thus no associated factors and no specific outcome data were presented. Small cohort size.
Shim et al. [31] 2010 Korea Prospective Single-centre	$n = 70$ decompensated patients treated with entecavir of whom 55 (78.6%) were treated for ≥ 12 months 100% HBV	Reduction in CP stage to A under treatment.	Reduction to CP-A in patients treated for ≥ 12 months: 36/55 (65.5%)	No data presented.	No data presented.	Regression to CP-A was not the focus of this study. Thus no associated factors and no specific outcome data were presented.
Xu et al. [37] 2021 China Retrospective Multicentre	Case-control study $n = 553$ with recompensation $n = 3400$ with acute decompensation In recompensated: 41.2% HBV 5.8% HCV 1.1% ALD 4.3% AIH 47.6% other or unknown	Recompensation criteria in accordance with Chinese guidelines: - Clinically stable state lasting at least 1 year - No recurrence of decompensating events under therapy (controlled ascites included)	Case-control study, thus no incidence data provided.	Key factors based on decision tree model: - Albumin - Total protein - Haemoglobin - ALT - Basophil percentage - Neutrophile/lymphocyte ratio - Diabetes Most relevant factor: albumin (cut-off of 40 g/L)	No data presented.	Case-control design.Thus no data regarding overall incidence and statistical analysis of factors based on logistic regression. Lack of established scores (MELD, CP score). Large proportion of other or unknown aetiologies.
Wang et al. [38] 2022 China Prospective Multicentre	$n = 320$ decompensated patients treated with entecavir of whom 283 (88.4%) completed the 120 week study period 100% HBV	Baveno VII criteria. New suggestion for the definition of sufficient improvement in liver function: - MELD <10 and/or - Hepatic function within CP stage A (albumin >35 g/L & INR <1.5 & bilirubin <34 µmol/L)	Resolution of ascites and HE: 171/283 (60.4%) Additional decrease to MELD <10 or hepatic function within CP stage A: 159/283 (56.2%)	Multivariable logistic regression model: - High AST at baseline - High sodium at baseline - High platelets at 48 weeks of therapy - High albumin at 48 weeks of therapy	34 recompensated patients were followed-up beyond 120 weeks: 91.2% remained compensated and 3 patients were diagnosed with HCC.	Analysis of factors does not include established scores (MELD, CP score) and does not account for time to recompensation. Prognostic implications of proposed criteria for sufficient improvement of liver function unclear.

Abbreviations: LT, liver transplantation; ALD, alcohol-related liver disease; HCV, hepatitis C virus; NAFLD, non-alcoholic fatty liver disease; PSC, primary sclerosing cholangitis; HBV, hepatitis B virus; HE, hepatic encephalopathy; MELD, model for end-stage liver disease; INR, international normalized ratio; AIH, autoimmune hepatitis; CP, Child-Pugh; DAA, direct acting antiviral; SVR, sustained virologic response; HCC, hepatocellular carcinoma.

tients. In addition to ALD as the underlying aetiology, independent factors linked to a higher probability of delisting in the overall cohort included a younger age, female sex, lower body mass index (BMI), lack of diabetes, absence of ascites or HE and lower MELD, as well as blood groups O/A/B (vs. blood group AB) and regions with shorter waiting time. With the exception of female sex, diabetes and blood group, the same set of factors was shown to be significant in ALD patients alone. Nevertheless, when interpreting aetiology-specific differences, it has to be kept in mind that ALD patients may still face discrimination with regard to organ allocation and additionally must abstain from alcohol for at least 6 months prior to listing [11]. Thus, this study [10], as well as all of the abovementioned studies [8,9], did not include patients who had already achieved significant clinical improvements within the first 6 months of abstinence and had thus avoided listing entirely.

3.2. HCV-associated cirrhosis

In the era of highly effective interferon-free direct-acting antiviral (DAA) treatment regimens, successfully curing chronic HCV infections has become the norm [12]. Even though the efficiency of DAA therapy is highest in patients without prior liver disease or with compensated liver disease, patients with prior hepatic decompensation are able to achieve a sustained virological response (SVR) following sofosbuvir-based DAA treatment in 80–90% of cases [12–16]. Nevertheless, insights into the clinical benefits and long-term outcomes in patients who achieve SVR in advanced stages of liver disease remain scarce.

With regard to clinical improvements, the ASTRAL-4 trial, which assessed sofosbuvir-based regimens in decompensated patients, detected improvements in MELD and Child-Pugh score at 12 weeks

post-treatment in the majority of patients [13]. More specifically, 81% of patients with a baseline MELD ≥15 and 51% with MELD <15 showed a post-treatment reduction in MELD score. Similar improvements in hepatic function were also observed in other studies on sofosbuvir-based DAA therapies in decompensated patients [14–16]. Despite the short-term improvements found in these studies, there is conflicting data regarding long-term outcomes.

A study by Cheung et al. [17] followed patients for up to 15 months after the initiation of DAA therapy and demonstrated a reduced incidence of cirrhosis-related complications in SVR patients. Nevertheless, neither DAA treatment overall nor achieving viral eradication were linked to an improved survival when compared to untreated patients or patients with virological failure, respectively. Furthermore, while the authors observed improvements in MELD at 6 months, it deteriorated significantly after 15 months. Similarly, Verna et al. [18] observed that MELD decreased in 56% of patients with advanced cirrhosis following DAA therapy during the short-term follow-up yet did not improve significantly after a median of 4 years, with a mean decrease of only 0.3 points. Nevertheless, 29% of patients achieved a long-term decrease in MELD of ≥3. Accordingly, Krassenburg et al. [19]. demonstrated that DAA therapy led to a decrease in MELD by at least 2 points in 19% of patients with Child-Pugh B/C cirrhosis at 12 weeks post-therapy, which persisted until week 36 in 82% of patients. However, improvements in MELD did not translate into an improved event-free survival over a median follow-up of 27 months when compared to patients with stable MELD levels. Furthermore, achieving viral cure neither increased the reduction in MELD nor improved clinical outcomes.

First insights into recompensation in HCV-associated cirrhosis were published by El-Sherif et al. [20], who performed a retrospective assessment of 4 clinical trials of sofosbuvir-based therapies in decompensated patients. Overall, 31.6% of Child-Pugh B patients and 12.3% of Child-Pugh C patients who achieved SVR following DAA therapy regressed to Child-Pugh stage A. However, it should be kept in mind that Child-Pugh A patients may still demonstrate low-grade ascites or HE. Key pre-treatment factors associated with a regression to Child-Pugh A included the absence of ascites or HE, high albumin, low bilirubin, high alanine transaminase (ALT) levels and low BMI. Importantly, achieving SVR12 was not only linked to a significantly reduced risk of transplantation or death, but also to a significantly higher likelihood of clinical improvements after accounting for death and transplantation as competing risks. Further findings were published by Macken et al. [21] based on the National HCV Research UK Cohort Study. While this study did not rely on standardised criteria for defining recompensation, the authors demonstrated that 51.3% of decompensated patients (20/39) achieved a reversal of hepatic decompensation under therapy. Similarly, Gentile et al. [22] prospectively assessed 89 patients with Child-Pugh stage B cirrhosis receiving DAA therapy and showed that 61.8% of patients regressed to a compensated disease stage over a median observation period of 11 months. Importantly, early recompensation at one month of treatment, as well as the absence of prior HCV therapy were linked to a significantly higher likelihood of sustained clinical improvements.

Additional insights pertaining to recompensation in HCV-associated cirrhosis have come from studies conducted in transplant settings. In a publication by Belli et al. [23], 33.0% of transplant candidates (34/103) were inactivated, i.e. put on hold, after a median of 25.6 months due to clinical improvements following DAA therapy. Of those, 62% eventually got delisted. Importantly, a low baseline MELD, as well as improvements in MELD and albumin at 12 weeks of DAA therapy were independent predictors of inactivation. In a similar study including data from 18 hospitals in Spain, 23.8% of patients (29/122) with decompensated HCV-associated cirrhosis were delisted due to clinical improvements after a median of 50 weeks [24]. All but two patients had fully resolved ascites and HE and all patients demonstrated a MELD <15 at the time of delisting. Interestingly, the delta MELD from baseline to the end of DAA therapy was the only predictive factor for delisting. With regard to clinical implications, 3 delisted patients developed hepatocellular carcinoma (HCC) and only 4 patients suffered re-decompensation over a median follow up of 88 weeks after delisting. A similarly beneficial prognosis was observed in a study by Perricone et al. [25], who found that 31.0% of transplant candidates (44/142) with HCV-associated cirrhosis were delisted due to clinical improvements after DAA-induced SVR and 91% of them regressed to Child-Pugh stage A. Importantly, only 4 delisted patients required relisting due to recurrent ascites in 3 patients and HCC in 1 patient. Of note, one delisted patient died from HCC prior to a potential relisting.

Further analyses addressing the delisting of advanced or decompensated HCV patients were published by Bittermann et al. [26] based on a US nationwide database. During the post-DAA era (2013–2017), 6.1% of patients could be delisted following clinical improvements. Interestingly, the rate of delisting during the post-DAA era for non-HCV patients (5.5%) was similar to that of HCV patients. Additional real-life data stems from liver transplant candidates treated within the Italian compassionate use program [27]. Within this study, 17.4% of patients (15/86) with a baseline MELD ≥15 or a Child-Pugh score ≥8 regressed to Child-Pugh class A combined with a MELD score below 15. Importantly, in addition to a lower Child-Pugh score and the absence of HE at baseline, patients who were eventually suitable for delisting demonstrated a significantly more pronounced improvement in MELD, INR, albumin and bilirubin at 4 weeks of therapy. Lastly, a recent study by Nabatchikova et al. [28], prospectively assessed 45 liver transplant candidates with decompensated HCV-associated cirrhosis and reported eventual delisting in 57.8% of patients following a decrease in MELD and Child-Pugh score to values below 15 and 7, respectively. Factors linked to non-delisting within this study included male sex, Child-Pugh stage C and a delta prothrombin index <2%.

3.3. HBV-associated cirrhosis

While novel DAA-based antiviral treatment regimens accomplish viral clearance in most HCV patients, therapies for patients with chronic HBV infections have been unable to induce complete viral elimination thus far. Nevertheless, with current HBV therapies, long-term viral suppression is achieved in the vast majority of patients and virtually all patients with drug compliance [29]. In case of prior decompensation, the currently recommended treatment is based on nucleoside/nucleotide analogues (NUCs) that can reduce HBV-DNA to undetectable levels in up to 80% of patients within 1 year of therapy initiation [30–32]. The potential for clinical improvement in patients with prior decompensation receiving long-term NUC therapy has been assessed by multiple studies, all of which demonstrated beneficial effects on hepatic function, highlighted by a significant decrease in MELD and Child-Pugh score, as well as a normalisation of ALT levels [31,33,34].

The impact of NUC therapy on the natural history of decompensated HBV-related cirrhosis was explored in a prospective multicentre study by Jang et al. [33]. In this study, which included 707 patients with a first onset of decompensation, antiviral therapy significantly improved hepatic function and transplant-free survival, particularly in patients who had achieved a response to therapy. Importantly, this study also revealed that at 60 months, 12.0% of treated patients (45/375) with Child-Pugh score ≥7 at baseline achieved a reduction to Child-Pugh stage A. Furthermore, of the 375 patients listed for liver transplantation, 33.9% could be delisted

due to clinical improvements within 12 months of initiating treatment.

Further evidence for recompensation in HBV was made available by Yao et al. [35] with data from 23 patients with severely decompensated HBV cirrhosis (Child-Pugh score ≥10). In this study, lamivudine therapy led to a reduction in Child-Pugh score of ≥3 points in 60.9% of patients, and 34.8% regressed to Child-Pugh stage A. Similarly, Nikolaidis et al. [36] found that 55.0% of patients (11/20) with decompensated HBV-associated cirrhosis achieved a decrease in Child-Pugh score by ≥2 points and 45.0% (9/20) improved to Child-Pugh A under lamivudine therapy.

In a Korean study by Shim et al. [31], treatment with entecavir in decompensated patients resulted in significant improvements in MELD and Child-Pugh score after 12 months and led to a regression to Child-Pugh stage A in 65.5% of patients (36/55). Accordingly, Liaw et al. [34] observed that one third of decompensated patients treated with entecavir or adefovir either showed a reduction in Child-Pugh score by more than 2 points, or an improvement in Child-Pugh class. Furthermore, 41.3% and 37.7% of patients with baseline ascites and 77.3% and 43.5% of patients with baseline HE achieved an improvement or reversal of these decompensating events under entecavir or adefovir, respectively.

Factors that might be linked to a higher probability of achieving recompensation were assessed by Xu et al. [37] in a retrospective case-control study of 553 recompensated patients. The included recompensated cohort consisted primarily of patients with cirrhosis due to HBV (41.2%), but also included HCV (5.8%), ALD (1.1%), autoimmune hepatitis (4.3%) and other causes (47.6%). The criteria used to determine recompensation in this study were in accordance with Chinese guidelines, which define recompensation as a clinically stable state lasting at least 1 year without the recurrence of decompensating events under therapy. Thus, patients with controlled ascites were included in this study. Overall, the primary factors used to predict recompensation in the decision tree model proposed by the authors were albumin, total protein, haemoglobin, ALT, basophil percentage, neutrophile-to-lymphocyte ratio and diabetes. Of note, the clinical applicability of these findings is limited due to the case-control design and the lack of established scores (MELD, Child-Pugh score).

The first authors to apply the Baveno VII criteria were Wang et al. [38] in 2022. In this multicentre study, the authors prospectively administered entecavir therapy to 320 patients with decompensated HBV-associated cirrhosis. Of the 283 patients who completed the 120-week study course, 171 (60.4%) achieved a sustained resolution of ascites and HE. Factors associated with the resolution of hepatic decompensation on multivariable analysis included a high AST and sodium at baseline, as well as a high platelet count and albumin at 48 weeks of treatment. Importantly, of the 34 patients who were followed-up beyond 120 weeks, 91.2% remained compensated over a median follow-up duration of 144 weeks.

4. Current limitations of the Baveno VII criteria

As highlighted by the abovementioned studies, a successful therapy of the underlying aetiology has been linked to significant clinical improvements and represents the primary criterion that has to be met in order to achieve recompensation. The Baveno VII consensus statement provides a clear definition regarding aetiological treatment for cirrhosis due to ALD with abstinence, for HCV-associated cirrhosis with SVR, and for HBV-associated cirrhosis with a suppression of viral replication. However, criteria defining a successful aetiological treatment for other liver disease aetiologies are lacking. The current clinical applicability of hepatic recompensation criteria is thus limited by the fact that patients with non-ALD and non-viral aetiologies might be able to achieve all criteria defining recompensation except for a successful cure/suppression of the underlying aetiology. Furthermore, the definition of a successful aetiological cure in patients with multiple overlapping aetiologies of liver disease remains unclear and requires further investigation.

In patients with rare aetiologies, including autoimmune hepatitis, primary biliary cholangitis and primary sclerosing cholangitis, a successful aetiological therapy may potentially be defined by biochemical and/or histological surrogate markers. The definition of an aetiological cure in patients with non-alcoholic steatohepatitis (NASH) is particularly challenging as the definition of the disease itself is still a topic of ongoing debate and the pathophysiology of NASH is influenced by a complex interplay of multiple factors [39–41]. Nevertheless, in light of the increasing prevalence of obesity and NASH worldwide, a clear definition is urgently needed [1]. As of now, data on recompensation in NASH and rare or genetic aetiologies is almost non-existent. In two previous studies by Pose et al. [9] and Aravinthan et al. [8], the authors observed that 1.4%/2.6% of patients with NASH cirrhosis and 1.9%/0.8% of patients with cholestatic cirrhosis listed for liver transplantation could be delisted following clinical improvements. However, as these aetiologies did not represent the primary focus of the studies, detailed information regarding the therapy of these patients was not provided and further subanalyses were not performed.

In addition to a successful aetiological cure, a complete and sustained resolution of all symptoms of hepatic decompensation (i.e. ascites and HE) and the absence of any portal hypertensive bleeding events for 12 months is required in order to allow a patient to receive the “label” of recompensated cirrhosis. This criterion is of particular ethical relevance in a transplant setting where patients may be delisted on the basis of hepatic recompensation. By including the requirement for a sustained resolution of decompensation into the definition, the proposed criteria counteract a phenomenon termed MELD purgatory. This phenomenon is defined by adverse effects of an early decrease in MELD following a successful treatment of the underlying aetiology on the listing process, despite the absence of any considerable clinical improvement [42]. Future studies on the outcome and correct management of patients who recompensate while on the waiting list are required.

The third requirement for hepatic recompensation according to Baveno VII is a sustained improvement in liver function. While the resolution of previous hepatic decompensation following a successful aetiological therapy may inevitably be linked to an improvement in hepatic function in the vast majority of patients, the Baveno VII criteria do not define an exact functional parameter cut-off that is required for a patient to be considered recompensated. In previous studies on transplant candidates with alcohol-related and HCV-associated cirrhosis, the most commonly used threshold required for delisting was a decrease in MELD to values below 15 [8,24,25,27,28], as this value is a commonly accepted cut-off for the benefit of liver transplantation. Patients who fulfilled this criterion and were eventually delisted had a favourable long-term prognosis, with low rates of relisting or re-decompensation [8,24,25,28]. More stringent criteria were proposed by Wang et al. [38], who prospectively assessed hepatic recompensation according to Baveno VII criteria in HBV-associated cirrhosis and proposed a MELD decrease to values below 10 and/or an improvement in liver function parameters to values within Child-Pugh stage A (albumin >35 g/L & INR <1.5 & bilirubin <34 μmol/L) as an appropriate threshold. In this study, 159 of the 171 patients who achieved a sustained resolution of ascites and HE also fulfilled these criteria at 120 weeks of follow-up. Nevertheless, this study was not designed to address the prognostic implications of applying the proposed cut-off. Overall, while these thresholds might be a first point

of reference, future studies will be necessary to more precisely define the extent of hepatic improvement that is required for recompensation.

Another aspect which should be clarified by future studies concerns the prognosis of decompensated patients who have achieved a cure/suppression of the underlying aetiology and are currently on the road to recovery but do not yet fulfil all recompensation criteria. In this patient collective, i.e. patients with a significant improvement of liver function following aetiological therapy, it is crucial to establish criteria for assisting clinicians with the identification of patients for whom a safe discontinuation of diuretics or anti-HE therapy may be attempted.

5. Factors linked to hepatic recompensation

Overall, the currently available literature demonstrates that clinical improvements and a resolution of hepatic decompensation following a cure or suppression of the underlying aetiology are linked to significant clinical benefits. However, even though the aforementioned studies have granted us initial insights into parameters that might be linked to a higher probability of achieving recompensation, further research is necessary to determine which factors aid or hinder recompensation and to explore whether these factors can be targeted by therapeutic approaches.

One such factor identified as a key predictor of improvements and recompensation following aetiological treatment in the majority of the abovementioned studies is the severity of liver disease [8–10,20,23–25,27,28,37,38]. This finding has two key clinical implications: Firstly, disease severity should be regularly and continuously assessed in order to identify patients who are on the road to recovery. Secondly, the role of disease severity at baseline highlights the need for adequate screening programs and early treatment initiation in order to reduce the proportion of patients who first present with decompensated cirrhosis.

The second factor linked to a higher likelihood of achieving recompensation in previous studies was female sex [8–10,28]. Future studies should assess whether the impact of this factor is mainly a consequence of the transplant setting in which the majority of the studies were conducted, or whether some drivers of disease regression, including pathways related to endocrine and hormonal signals, may indeed play a larger role in female patients.

A third factor which seems to influence recompensation is the severity of portal hypertension, which was primarily assessed by platelet count in previous studies [8,9,38]. Overall, portal hypertension is a known driver of disease progression and develops on the basis of hepatic structural and functional changes [43]. There are currently no approved therapies for liver fibrosis and functional or vascular/endothelial abnormalities. Nevertheless, it is known that a reduction of portal hypertension via non-selective betablocker (NSBB) therapy translates into a decreased likelihood of first hepatic decompensation [44,45]. However, it is unknown whether NSBB therapy may also facilitate hepatic recompensation in patients who (continue to) suffer from clinically significant portal hypertension (CSPH).

Another modifying factor identified in previous studies is BMI [9,10,20]. In light of the available evidence linking obesity, diabetes and other components of the metabolic syndrome to a worse prognosis, regardless of liver disease aetiology, this finding may not be surprising [46]. The role of BMI might also point towards the presence of a dual aetiology, i.e. the additional presence of NASH, which is associated with metabolic cofactors that may interfere with molecular pathways of liver regeneration and fibrosis regression. The potential impact of weight loss and a targeted therapy of other components of the metabolic syndrome on the probability of clinical improvements and recompensation needs to be assessed in future studies.

In addition to the abovementioned factors, it is important to better understand the molecular mechanisms underlying cirrhosis regression and liver regeneration, as it may be possible to specifically target these factors in order to facilitate hepatic recompensation. While these may not be the same pathways that drive liver disease progression, it may still be worth assessing therapies that show a beneficial impact on fibrogenesis, angiogenesis and hepatic function. These therapies may help patients achieve stable recompensation and reduce the risk of further clinical complications. Potential areas of interest in this regard include systemic inflammation, gut permeability and bacterial translocation, which have been shown to influence liver disease progression [47]. Importantly, antibiotics that target bacterial translocation are already in use for the prophylaxis of spontaneous bacterial peritonitis and the treatment of HE [48]. The potential role of systemic inflammation was further highlighted in a study by Monteiro et al. [49], who demonstrated that recompensated patients (note: medically controlled ascites was allowed) with detectable levels of the inflammasome-driving interleukins IL-1α and IL-1β showed a higher (persisting) risk of fatal acute-on-chronic liver failure (ACLF) when compared to patients with undetectable levels. This was not observed in compensated patients. Furthermore, while IL-1β levels were identified as an independent predictor of fatal ACLF in recompensated patients with detectable levels, IL-1α was a significant predictor in compensated patients. Thus, inflammation and abnormal intestinal permeability may represent potential targets for future therapies which aim to facilitate and maintain recompensation.

Another potential therapeutic target is angiogenesis, which is known to drive liver disease progression, and specifically liver fibrosis and portal hypertension [50–52]. Importantly, there is already experimental evidence indicating that vascular endothelial growth factor is required for hepatic tissue repair and fibrosis resolution [53]. Further evidence on the potential involvement of angiogenesis in recompensation was published by Salehi et al. [54], who demonstrated a distinct serum microRNA (miRNA) expression signature in HCV patients who went on to show improvements in Child-Pugh score following DAA-induced SVR when compared to those who did not improve. Specifically, the most differentially expressed miRNAs are linked to angiogenesis, fibrogenesis and cell proliferation. Interestingly, HCV patients who achieved clinical improvements showed a miRNA expression signature similar to that of patients spontaneously recovering after acetaminophen-induced acute liver failure, thus pointing towards a distinct miRNA signature reflecting liver regeneration.

6. Reversibility of portal hypertension

Portal hypertension represents a major pathophysiological driver of disease progression and decompensation in cirrhosis [55]. Consequently, hepatic recompensation and disease stabilisation are presumably accompanied by an amelioration of portal hypertension. Indeed, platelet count, a surrogate for portal hypertension severity, was identified as a modifying factor of clinical improvements in previous studies [8,9]. Furthermore, studies have demonstrated that curing the underlying aetiology consistently leads to a reduction in portal pressure [7,56–60]. However, these studies, which assessed portal pressure prior to and after aetiological therapy, were primarily limited to compensated patients receiving antiviral therapy for HBV or HCV. Thus, it has yet to be clarified whether CSPH can resolve in decompensated patients who achieve recompensation. By extension, future studies should also assess whether NSBB treatment can be safely discontinued in recompensated patients following the resolution of CSPH, or whether NSBB treatment should be continued, not least due to advantageous non-haemodynamic effects [61,62].

7. The distinction between compensated and recompensated cirrhosis

While the clinical phenotype of recompensated patients cannot be distinguished from that of compensated patients, it has yet to be assessed whether the long-term prognosis is comparable between these groups. As the risk of hepatic re-decompensation and mortality in recompensated patients has a direct effect on patient management, these insights would be of high clinical relevance. In order to facilitate risk stratification in recompensated patients, it has to be clarified whether the validity of specific prognostic cut-offs for non-invasive tests which are currently used for compensated patients [3] might also be applied following recompensation.

8. Screening for hepatocellular carcinoma in recompensated patients

The question of whether hepatic recompensation is linked to a reduced risk of HCC development is of particular relevance for daily clinical practice. While specific data on the rate of HCC development following recompensation are not yet available, studies assessing HCC incidence following a cure/suppression of the underlying aetiology in patients with cirrhosis might offer preliminary insights.

With regard to the effects of alcohol abstinence in alcohol-related cirrhosis, Rodríguez et al. [63] performed a large prospective observational study comparing HCC incidence in 354 abstinent patients and 373 patients with continued alcohol intake. Over a median follow-up of 54 months, alcohol abstinence did not decrease the risk of HCC development in patients with prior decompensation but did result in a significant risk reduction in compensated patients. As for recompensated patients, Pose et al. [9] observed that HCC-related complications were accountable for 50% of all liver-related deaths in delisted ALD patients over a median follow-up of 39 months.

Concerning decompensated HCV-associated cirrhosis, previous studies have failed to demonstrate a significantly reduced risk of developing HCC following DAA therapy [14,17]. Nevertheless, Cheung et al. [17] observed a significant reduction in the incidence of HCC in patients who achieved SVR at 24 weeks compared to non-responders. However, as this study also included patients with a history of HCC and nearly 65% of all HCC cases developed within only 6 months of therapy initiation, the observed results may underestimate the impact of SVR. Despite the slight reduction in HCC risk following SVR observed by Cheung et al. [17], D'Ambrosio et al. [64] demonstrated that HCC remained the most common liver-related complication in decompensated patients who had achieved SVR, with a 5-year cumulative incidence of 19.7%. When assessing the risk of HCC in HCV transplant candidates who were delisted due to clinical improvements, Pascasio et al. [24] observed 3 cases of de novo HCC (10% of delisted patients) over a median time of 88 weeks following delisting. In accordance with these findings, 4.5% of delisted patients (2/44) developed HCC over a median follow-up of 22 months in a study by Perricone et al. [25] Furthermore, Nabatchikova et al. [28] observed that HCC was diagnosed in 7.7% of delisted transplant candidates (2/26), as compared to 31.6% of non-delisted patients (6/19) over a median follow-up of 21 months after delisting.

Similar to SVR in HCV-associated cirrhosis, antiviral therapy with subsequent viral suppression has yet to be linked to a significant decrease in the risk of HCC in patients suffering from decompensated HBV-associated cirrhosis. The overall impact of NUC therapy on HCC incidence was assessed in a prospective multicentre study by Jang et al. [33], who failed to observe a significant benefit in propensity score-matched decompensated patients with and without NUC treatment. Similarly, Eun et al. [65] as well as Papatheodoridis et al. [66] demonstrated that a sustained viral suppression was not linked to a significant decrease in HCC incidence in their decompensated patient collectives. In contrast, Kim et al. [30] reported that the absence of a response to entecavir after 12 months was a significant risk factor for HCC development in decompensated HBV patients. As for recompensated patients, Wang et al. observed that 3 out of 34 patients who had achieved recompensation according to the Baveno VII criteria and underwent long-term follow-up presented with de novo HCC [38]. Overall, longer follow-up data regarding HCC development in patients with decompensated HBV-associated cirrhosis receiving highly effective NUC therapy, i.e. tenofovir and entecavir, are required.

9. Conclusion

The traditional unidirectional model of disease progression in cirrhosis is increasingly being challenged by new insights into the potential for disease regression and recompensation following a successful suppression/cure of the underlying aetiology. In order to standardise the definition of recompensated cirrhosis, uniform criteria have been introduced by the Baveno VII consensus which are based on (i) the removal of the aetiological factor in patients with ALD, HBV and HCV cirrhosis, (ii) the absence of decompensating events and (iii) a sustained improvement in hepatic synthetic function. While these criteria are a crucial step in the right direction, further research is necessary to define recompensation in other liver disease aetiologies and to determine a clear and prognostically-relevant definition for improvement in liver function reflected by laboratory values.

With regard to the clinical implications of recompensation, first insights from previous studies indicate a considerable reduction in the risk of developing further liver-related events, including further decompensation and liver-related mortality. However, these previous insights are either based on the delisting of transplant candidates or on a reduction to Child-Pugh A disease stage. Since low-grade ascites or HE may still be present in both of these settings, prior studies may have also included not fully recompensated patients. Thus, future studies applying the Baveno VII criteria are required to fully elucidate the natural history of recompensated patients and to explore non-invasive biomarkers and modifying factors of recompensation. Consequently, future insights will help identify patients with a high likelihood of recompensation and those who are at a high risk of disease progression and may ultimately require liver transplantation.

Furthermore, the specific effects of portal hypertension itself and the effects of treatments that decrease portal hypertension on the probability of and long-term follow-up after hepatic recompensation require further investigation. Similarly, the role of metabolic comorbidities, especially obesity and diabetes that both impact the risk of first decompensation, needs to be explored in the setting of hepatic recompensation. Overall, a better molecular understanding of the underlying mechanisms of cirrhosis regression and recompensation will allow for the development of targeted therapies for the improvement of clinical outcomes in patients with decompensated cirrhosis.

Finally, hepatocarcinogenesis does not seem to be completely attenuated by a successful cure/suppression of the underlying aetiology once decompensation has occurred. Whether the risk of HCC is significantly reduced in patients who achieve recompensation according to Baveno VII criteria requires further investigation. Thus, routine HCC screening programs in patients with recompensated cirrhosis should be continued until further insights become available.

Conflict of interest

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References

[1] Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. J Hepatol 2019;70:151–71.
[2] D'Amico G, Morabito A, D'Amico M, Pasta L, Malizia G, Rebora P, et al. Clinical states of cirrhosis and competing risks. J Hepatol 2018;68:563–76.
[3] de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C, Abraldes JG, et al. Baveno VII - renewing consensus in portal hypertension. J Hepatol 2021: 0.
[4] Lackner C, Spindelboeck W, Haybaeck J, Douschan P, Rainer F, Terracciano L, et al. Histological parameters and alcohol abstinence determine long-term prognosis in patients with alcoholic liver disease. J Hepatol 2017;66:610–18.
[5] Jepsen P, Ott P, Andersen PK, Sørensen HT, Vilstrup H. Clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. Hepatology 2010;51:1675–82.
[6] Pearson MM, Kim NJ, Berry K, Moon AM, Su F, Vutien P, et al. Associations between alcohol use and liver-related outcomes in a large national cohort of patients with cirrhosis. Hepatol Commun 2021;5.
[7] Vorobioff J, Groszmann RJ, Picabea E, Gamen M, Vllavicencio R, Bordato J, et al. Prognostic value of hepatic venous pressure gradient measurements in alcoholic cirrhosis: a 10-year prospective study. Gastroenterology 1996;111:701–9.
[8] Aravinthan AD, Barbas AS, Doyle AC, Tazari M, Sapisochin G, Cattral MS, et al. Characteristics of liver transplant candidates delisted following recompensation and predictors of such delisting in alcohol-related liver disease: a case–control study. Transpl Int 2017;30:1140–9.
[9] Pose E, Torrents A, Reverter E, Perez-Campuzano V, Campos-Varela I, Avitabile E, et al. A notable proportion of liver transplant candidates with alcohol-related cirrhosis can be delisted because of clinical improvement. J Hepatol 2021;75:275–83.
[10] Giard JM, Dodge JL, Terrault NA. Superior wait-list outcomes in patients with alcohol-associated liver disease compared with other indications for liver transplantation. Liver Transpl 2019;25:1310–20.
[11] Marroni CA, de Medeiros Fleck A, Fernandes SA, Galant LH, Mucenic M, de Mattos Meine MH, et al. Liver transplantation and alcoholic liver disease: history, controversies, and considerations. World J Gastroenterol 2018;24:2785–805.
[12] Pawlotsky JM, Negro F, Aghemo A, Berenguer M, Dalgard O, Dusheiko G, et al. EASL recommendations on treatment of hepatitis C: final update of the series☆. J Hepatol 2020;73:1170–218.
[13] Curry MP, O'Leary JG, Bzowej N, Muir AJ, Korenblat KM, Fenkel JM, et al. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. N Engl J Med 2015;373:2618–28.
[14] Foster GR, Irving WL, Cheung MCM, Walker AJ, Hudson BE, Verma S, et al. Impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. J Hepatol 2016;64:1224–31.
[15] Manns M, Samuel D, Gane EJ, Mutimer D, McCaughan G, Buti M, et al. Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicentre, open-label, randomised, phase 2 trial. Lancet Infect Dis 2016;16:685–97.
[16] Charlton M, Everson GT, Flamm SL, Kumar P, Landis C, Brown RS, et al. Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. Gastroenterology 2015;149:649–59.
[17] Cheung MCM, Walker AJ, Hudson BE, Verma S, McLauchlan J, Mutimer DJ, et al. Outcomes after successful direct-acting antiviral therapy for patients with chronic hepatitis C and decompensated cirrhosis. J Hepatol 2016;65:741–747.
[18] Verna EC, Morelli G, Terrault NA, Lok AS, Lim JK, di Bisceglie AM, et al. DAA therapy and long-term hepatic function in advanced/decompensated cirrhosis: real-world experience from HCV-TARGET cohort. J Hepatol 2020;73:540–8.
[19] Krassenburg LAP, Maan R, Ramji A, Manns MP, Cornberg M, Wedemeyer H, et al. Clinical outcomes following DAA therapy in patients with HCV-related cirrhosis depend on disease severity. J Hepatol 2021;74:1053–63.
[20] El-Sherif O, Jiang ZG, Tapper EB, Huang KC, Zhong A, Osinusi A, et al. Baseline factors associated with improvements in decompensated cirrhosis after direct-acting antiviral therapy for hepatitis C virus infection. Gastroenterology 2018;154 2111-2121.e8.
[21] Macken L, Gelson W, Priest M, Abouda G, Barclay S, Fraser A, et al. Efficacy of direct-acting antivirals: UK real-world data from a well-characterised predominantly cirrhotic HCV cohort. J Med Virol 2019;91:1979–88.
[22] Gentile I, Scotto R, Coppola C, Staiano L, Amoruso DC, de Simone T, et al. Treatment with direct-acting antivirals improves the clinical outcome in patients with HCV-related decompensated cirrhosis: results from an Italian real-life cohort (Liver Network Activity—LINA cohort). Hepatol Int 2019;13:66–74.
[23] Belli LS, Berenguer M, Cortesi PA, Strazzabosco M, Rockenschaub SR, Martini S, et al. Delisting of liver transplant candidates with chronic hepatitis C after viral eradication: a European study. J Hepatol 2016;65:524–31.
[24] Pascasio JM, Vinaixa C, Ferrer MT, Colmenero J, Rubin A, Castells L, et al. Clinical outcomes of patients undergoing antiviral therapy while awaiting liver transplantation. J Hepatol 2017;67:1168–76.
[25] Perricone G, Duvoux C, Berenguer M, Cortesi PA, Vinaixa C, Facchetti R, et al. Delisting HCV-infected liver transplant candidates who improved after viral eradication: outcome 2 years after delisting. Liver Int 2018;38:2170–7.
[26] Bittermann T, Reddy KR. In the era of direct-acting antivirals, liver transplant delisting due to clinical improvement for hepatitis C remains infrequent. Clin Gastroenterol Hepatol 2021;19 2389-2397.e2.
[27] Martini S, Donato MF, Mazzarelli C, Rendina M, Visco-Comandini U, Filì D, et al. The Italian compassionate use of sofosbuvir in HCV patients waitlisted for liver transplantation: a national real-life experience. Liver Int 2018;38:733–741.
[28] Nabatchikova EA, Abdurakhmanov DT, Rozina TP, Nikulkina EN, Tanaschuk EL, Moiseev SV. Delisting and clinical outcomes of liver transplant candidates after hepatitis C virus eradication: a long-term single-center experience. Clin Res Hepatol Gastroenterol 2021:45.
[29] Lampertico P, Agarwal K, Berg T, Buti M, Janssen HLA, Papatheodoridis G, et al. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67:370–98.
[30] Kim SS, Hwang JC, Lim SG, Ahn SJ, Cheong JY, Cho SW. Effect of virological response to entecavir on the development of hepatocellular carcinoma in hepatitis B viral cirrhotic patients: comparison between compensated and decompensated cirrhosis. Am J Gastroenterol 2014;109:1223–33.
[31] Shim JH, Lee HC, Kim KM, Lim YS, Chung YH, Lee YS, et al. Efficacy of entecavir in treatment-naïve patients with hepatitis B virus-related decompensated cirrhosis. J Hepatol 2010;52:176–82.
[32] Peng CY, Chien RN, Liaw YF. Hepatitis B virus-related decompensated liver cirrhosis: benefits of antiviral therapy. J Hepatol 2012;57:442–50.
[33] Jang JW, Choi JY, Kim YS, Woo HY, Choi SK, Lee CH, et al. Long-term effect of antiviral therapy on disease course after decompensation in patients with hepatitis B virus-related cirrhosis. Hepatology 2015;61:1809–20.
[34] Liaw Y-F, Raptopoulou-Gigi M, Cheinquer H, Sarin SK, Tanwandee T, Leung N, et al. Efficacy and safety of entecavir versus adefovir in chronic hepatitis B patients with hepatic decompensation: a randomized, open-label study. Hepatology 2011;54:91–100.
[35] Yao FY, Terrault NA, Freise C, Maslow L, Bass NM. Lamivudine treatment is beneficial in patients with severely decompensated cirrhosis and actively replicating hepatitis B infection awaiting liver transplantation: a comparative study using a matched, untreated cohort. Hepatology 2001;34:411–16.
[36] Nikolaidis N, Vassiliadis T, Giouleme O, Tziomalos K, Grammatikos N, Patsiaoura K, et al. Effect of lamivudine treatment in patients with decompensated cirrhosis due to anti-HBe positive/HBeAg-negative chronic hepatitis B. Clin Transplant 2005;19:321–6.
[37] Xu X, Wang H, Zhao W, Wang Y, Wang J, Qin B. Recompensation factors for patients with decompensated cirrhosis: a multicentre retrospective case-control study. BMJ Open 2021;11.
[38] Wang Q, Zhao H, Deng Y, Zheng H, Xiang H, Nan Y, et al. Validation of Baveno VII criteria for recompensation in entecavir-treated individuals with hepatitis B-related decompensated cirrhosis. J Hepatol 2022:0.
[39] Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. J Hepatol 2020;73:202–9.
[40] Méndez-Sánchez N, Pal SC. New terms for fatty liver disease other than MAFLD: time for a reality check. J Hepatol 2022.
[41] Diehl AM, Day C. Cause, pathogenesis, and treatment of nonalcoholic steatohepatitis. N Engl J Med 2017;377:2063–72.
[42] Carrion AF, Khaderi SA, Sussman NL. Model for end-stage liver disease limbo, model for end-stage liver disease purgatory, and the dilemma of treating hepatitis C in patients awaiting liver transplantation. Liver Transpl 2016;22:279–80.
[43] Iwakiri Y, Trebicka J. Portal hypertension in cirrhosis: pathophysiological mechanisms and therapy. JHEP Rep 2021;3.

[44] Villanueva C, Albillos A, Genescà J, Garcia-Pagan JC, Calleja JL, Aracil C, et al. β blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomised, double-blind, placebo-controlled, multicentre trial. Lancet North Am Ed 2019;393:1597–608.
[45] Villanueva C, Torres F, Sarin SK, Shah HA, Tripathi D, Brujats A, et al. Carvedilol reduces the risk of decompensation and mortality in patients with compensated cirrhosis in a competing-risk meta-analysis. J Hepatol 2022.
[46] Stepanova M, Rafiq N, Younossi ZM. Components of metabolic syndrome are independent predictors of mortality in patients with chronic liver disease: a population-based study. Gut 2010;59:1410–15.
[47] Costa D, Simbrunner B, Jachs M, Hartl L, Bauer D, Paternostro R, et al. Systemic inflammation increases across distinct stages of advanced chronic liver disease and correlates with decompensation and mortality. J Hepatol 2021;74:819–28.
[48] Angeli P, Bernardi M, Villanueva C, Francoz C, Mookerjee RP, Trebicka J, et al. EASL clinical practice guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018;69:406–60.
[49] Monteiro S, Grandt J, Uschner FE, Kimer N, Madsen JL, Schierwagen R, et al. Differential inflammasome activation predisposes to acute-on-chronic liver failure in human and experimental cirrhosis with and without previous decompensation. Gut 2021;70:379–87.
[50] Fernández M, Semela D, Bruix J, Colle I, Pinzani M, Bosch J. Angiogenesis in liver disease. J Hepatol 2009;50:604–20.
[51] Reiberger T, Angermayr B, Schwabl P, Rohr-Udilova N, Mitterhauser M, Gangl A, et al. Sorafenib attenuates the portal hypertensive syndrome in partial portal vein ligated rats. J Hepatol 2009;51:865–73.
[52] Pinter M, Sieghart W, Reiberger T, Rohr-Udilova N, Ferlitsch A, Peck-Radosavljevic M. The effects of sorafenib on the portal hypertensive syndrome in patients with liver cirrhosis and hepatocellular carcinoma - a pilot study. Aliment Pharmacol Ther 2012;35:83–91.
[53] Yang L, Kwon J, Popov Y, Gajdos GB, Ordog T, Brekken RA, et al. Vascular endothelial growth factor promotes fibrosis resolution and repair in mice. Gastroenterology 2014:146.
[54] Salehi S, Tavabie OD, Verma S, McPhail MJW, Farzaneh F, Bernal W, et al. Serum microRNA signatures in recovery from acute and chronic liver injury and selection for liver transplantation. Liver Transpl 2020;26:811–22.
[55] Ripoll C, Groszmann R, Garcia-Tsao G, Grace N, Burroughs A, Planas R, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology 2007;133:481–8.
[56] Klein CP, Kalk JF, Muting D, Klein CG. Influence of alcohol on portal-vein haemodynamics in nutritional-toxic cirrhosis of the liver. Dtsch Med Wochenschr 1993;118:89–93.
[57] Mandorfer M, Kozbial K, Schwabl P, Chromy D, Semmler G, Stättermayer AF, et al. Changes in hepatic venous pressure gradient predict hepatic decompensation in patients who achieved sustained virologic response to interferon-free therapy. Hepatology 2020;71:1023–36.
[58] Mandorfer M, Kozbial K, Schwabl P, Freissmuth C, Schwarzer R, Stern R, et al. Sustained virologic response to interferon-free therapies ameliorates HCV-induced portal hypertension. J Hepatol 2016;65:692–9.
[59] Manolakopoulos S, Triantos C, Theodoropoulos J, Vlachogiannakos J, Kougioumtzan A, Papatheodoridis G, et al. Antiviral therapy reduces portal pressure in patients with cirrhosis due to HBeAg-negative chronic hepatitis B and significant portal hypertension. J Hepatol 2009;51:468–74.
[60] Lens S, Baiges A, Alvarado-Tapias E, LLop E, Martinez J, Fortea JI, et al. Clinical outcome and hemodynamic changes following HCV eradication with oral antiviral therapy in patients with clinically significant portal hypertension. J Hepatol 2020;73:1415–24.
[61] Jachs M, Hartl L, Schaufler D, Desbalmes C, Simbrunner B, Eigenbauer E, et al. Amelioration of systemic inflammation in advanced chronic liver disease upon beta-blocker therapy translates into improved clinical outcomes. Gut 2021;70:1758–67.
[62] Reiberger T, Ferlitsch A, Payer BA, Mandorfer M, Heinisch BB, Hayden H, et al. Non-selective betablocker therapy decreases intestinal permeability and serum levels of LBP and IL-6 in patients with cirrhosis. J Hepatol 2013;58:911–21.
[63] Rodríguez M, González-DIéguez ML, Varela M, Cadahía V, Andrés-Vizán SM, Mesa A, et al. Impact of alcohol abstinence on the risk of hepatocellular carcinoma in patients with alcohol-related liver cirrhosis. Am J Gastroenterol 2021;116:2390–8.
[64] D'Ambrosio R, Degasperi E, Anolli MP, Fanetti I, Borghi M, Soffredini R, et al. Incidence of liver- and non-liver-related outcomes in patients with HCV-cirrhosis after SVR. J Hepatol 2022;76:302–10.
[65] Eun JR, Lee HJ, Kim TN, Lee KS. Risk assessment for the development of hepatocellular carcinoma: according to on-treatment viral response during long-term lamivudine therapy in hepatitis B virus-related liver disease. J Hepatol 2010;53:118–25.
[66] Papatheodoridis GV, Manolakopoulos S, Touloumi G, Vourli G, Raptopoulou-Gigi M, Vafiadis-Zoumbouli I, et al. Virological suppression does not prevent the development of hepatocellular carcinoma in HBeAg-negative chronic hepatitis B patients with cirrhosis receiving oral antiviral(s) starting with lamivudine monotherapy: results of the nationwide HEPNET. Greece cohort study. Gut 2011;60:1109–16.