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Perspective

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Recompensation in cirrhosis: unravelling the evolving natural history of nonalcoholic fatty liver disease

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Abstract

Recompensation has gained increasing attention in the field of cirrhosis, particularly in chronic liver disease with a definite aetiology. The current global prevalence of obesity and nonalcoholic fatty liver disease (NAFLD) is increasing, but there is currently a lack of a clear definition for recompensation in NAFLD-related cirrhosis. Here, we provide an up-to-date perspective on the natural history of NAFLD, emphasizing the reversible nature of the disease, summarizing possible mechanisms underlying recompensation in NAFLD, discussing challenges that need to be addressed and outlining future research directions in the field. Recompensation is a promising goal in patients with NAFLD-related cirrhosis, and further studies are needed to explore its underlying mechanisms and uncover its clinical features.

Sections

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Introduction

Cirrhosis is an anatomopathological term describing a diffuse hepatic process characterized by inflammation, necrosis, advanced fibrosis and regenerative nodule formation caused by long-term and repeated insults to the hepatic parenchyma[1]. Along with the disruption of hepatic architecture and vascular remodelling, liver function is impaired, the vascular tone is increased and portal hypertension develops[2]. In general, cirrhosis can be divided according to its clinical features into two stages: compensated (that is, without clinical symptoms) and decompensated (accompanied by ascites, hepatic encephalopathy and variceal bleeding). However, mounting evidence indicates that control of the aetiological agent, such as alcohol abstinence and antiviral therapy, even in the decompensated stage, might lead to improved liver function, together with clinical resolution and absence of decompensation[3–5]. There is evidence pointing to a gradual disappearance of complications, and histologically confirmed lesions show signs of regression[5,6]. This phenomenon has attracted increasing attention in the medical community and has developed into a concept known as 'cirrhosis recompensation'.

As the prevalence of obesity and metabolic syndrome increases, nonalcoholic fatty liver disease (NAFLD) (also known as metabolic dysfunction-associated fatty liver disease (MAFLD) and metabolic dysfunction-associated steatotic liver disease, the new names currently proposed by international liver disease associations) affects approximately 30% of the global population and has become the leading cause of chronic liver disease[7–11]. NAFLD is a spectrum of liver disease that includes nonalcoholic fatty liver, nonalcoholic steatohepatitis (NASH), cirrhosis and hepatocellular carcinoma (HCC)[12,13]. The prevalence of NASH in the general population is estimated to be between 1.5% and 6%[14]. The prevalence of NASH in the USA will increase by 63% by 2030, whereas the incidence of decompensated cirrhosis will increase by 168%, and the incidence of HCC will increase by 137%[15]. Notably, the incidence of NASH-related cirrhosis is rapidly growing, and NASH is the first indication (together with alcohol-associated liver disease (ALD)) for a non-HCC aetiology in the liver transplant list[16]. Moreover, NASH is the first indication for liver transplantation in older adults and women[17,18]. Although evidence suggests that NASH-related cirrhosis is a major cause of liver decompensation and HCC, monitoring disease progression for early detection of cirrhosis in patients with NAFLD remains problematic and not sufficiently standardized.

Current evidence on the natural history of NAFLD before the development of hepatic decompensation indicates that the disease is bidirectional and reversible and that, under certain circumstances, all of the histological features of the disease (steatosis, inflammation and fibrosis) can improve over time[19]. In a study in 1,001 patients with decompensated cirrhosis, including NAFLD and cirrhosis from other causes, clinical improvements were found even in patients with NAFLD who had progressed to the decompensated cirrhosis stage, which led to the hypothesis of a cirrhosis recompensation[20]. Unfortunately, the definition of recompensation for this phenomenon is inconsistent in the published literature. For example, a Canadian study published in 2017 defined recompensation as (1) no prophylactic treatment being required for complications; (2) regression of signs of decompensated cirrhosis, including ascites, hepatic hydrothorax, hepatic encephalopathy and gastrointestinal bleeding; and (3) reduction of the model for end-stage liver disease (MELD) score to 15 or less for at least 6 months[21]. In 2022, the Baveno VII consensus proposed a new conceptualization of hepatic recompensation, which considered the removal of the drivers of liver disease as a key prerequisite; however, a clear definition for NAFLD-related liver cirrhosis recompensation was not formulated[22]. This lack of a definition for NAFLD-related liver cirrhosis can be attributed to several factors, including the multifactorial nature of NAFLD and the complex pathophysiological mechanisms[22–24]. A better understanding of NAFLD-related cirrhosis recompensation might help to identify patient groups more likely to achieve favourable outcomes, thereby improving prognostic stratification and current strategies for clinical management. Here, we review the natural history of NAFLD, discuss the occurrence of recompensation in NAFLD-related cirrhosis and other aetiologies of liver disease, and suggest future directions.

Conceptualization and evidence of recompensation in cirrhosis

The recompensation concept

Current evidence indicates that some patients with decompensated cirrhosis can clinically improve to a state that resembles compensated cirrhosis (recompensation) through correction of the underlying causes and supportive measures[25]. The definition and clinical characteristics of recompensated cirrhosis are currently the subjects of intense debate. According to the 2022 Baveno VII consensus criteria, three conditions must be met to document the occurrence of recompensated cirrhosis, that is: (1) correction of the underlying cause; (2) disappearance of complications that define a decompensated state; and (3) improvements in liver function tests[22]. Notably, the disappearance of complications should be sustained for at least 12 months and accompanied by improvement in the liver lobular architecture[22]. Consequently, patients who continue to require diuretics for the management of ascites or drugs to prevent hepatic encephalopathy cannot be considered recompensated even if there is evidence of improved liver function tests, including reduced serum levels of albumin and bilirubin, as well as the international normalized ratio (INR) blood test. INR reflects the status of blood coagulation function. In end-stage liver disease, the liver fails to synthesize clotting factors normally, leading to increased INR and decreased coagulation function, Thus, the INR can be an important indicator of liver function. Hepatic encephalopathy is a neurological impairment caused by liver disease and is closely related to coagulopathy. Hepatic encephalopathy results from impaired liver function, leading to the accumulation of toxic substances, such as ammonia, in the blood, which exerts neurotoxic effects on the brain. Consequently, an elevated INR might correlate with an increased risk of hepatic encephalopathy[26].

Evidence of recompensation in chronic liver disease other than NAFLD

Given that the concept of liver recompensation is fairly new, published data in the field of NAFLD remain limited. On the one hand, evidence of liver recompensation in patients with decompensated cirrhosis has been mainly gained from studies in which the aetiologies of chronic liver diseases were well-defined, including ALD, hepatitis B virus (HBV) infection-related cirrhosis and hepatitis C virus (HCV) infection-related cirrhosis; on the other hand, there have been limited studies investigating recompensation in NAFLD. This section, therefore, focuses on the evidence related to cirrhosis recompensation in aetiologies other than NAFLD.

Hepatitis B-related cirrhosis. A 10-year observational study in 295 Korean patients with HBV infection-related decompensated liver cirrhosis found that a maintained virological response (MVR) to either entecavir or lamivudine was a significant ($P < 0.001$) predictor of both

short-term and long-term transplant-free survival[27]. The benefits of MVR were maintained for 10 years even after decompensation, and patients who achieved MVR showed a significant ($P < 0.05$) improvement in liver function over time[27]. In a study involving 311 patients with HBV infection-related decompensated cirrhosis, a prognostic model, BC2AID, was developed to accurately predict the likelihood of recompensation[28]. This model was based on six clinical parameters, including bilirubin ≤5 mg/dl, no severe complications, α-fetoprotein ≥50 ng/ml, alanine aminotransferase ≥200 IU/l, INR ≤1.5, and time from initial decompensation to start of nucleos(t)ide analogue treatment ≤6 months[28]. In a study investigating the effects of antiviral therapy in 130 patients with HBV infection-related decompensated cirrhosis, approximately 40% of patients in the immediate-treatment group maintained stable recompensation over 6 years[29]. The research further suggested that a 2-year period free of complications could be a predictor of stable recompensation[29]. Wang and colleagues conducted a multicentre prospective study that validated the Baveno VII definition of recompensation in HBV infection-related cirrhosis and explored the criteria for stable improvement of liver function; 490 patients with HBV infection-related decompensated cirrhosis were screened for eligibility at ten participating hospitals[30] and, of these patients, 56.2% achieved recompensation after 120 weeks of antiviral therapy[30]. Collectively, these data indicate that long-term antiviral treatment might successfully suppress HBV replication and promote liver recompensation, ultimately resulting in an increased prolongation of transplant-free survival even in patients with decompensated cirrhosis.

Hepatitis C virus infection-related cirrhosis. The introduction of highly effective interferon-free direct-acting antiviral (DAA) therapies represents a major step forward in treating chronic HCV infection. Growing evidence indicates that liver function tests and clinical symptoms of HCV infection-related decompensated cirrhosis might improve following HCV clearance[4,31–33]. A study by Cheung and colleagues investigated 406 patients for up to 15 months after starting DAA therapy and found a decrease in cirrhosis-related decompensating events among those who achieved a sustained virological response (SVR)[4]. Similar evidence of liver recompensation following DAA therapy was reported by El-Sherif and colleagues[31]. The researchers retrospectively examined four clinical trials of sofosbuvir-based regimens in patients with HCV infection-related decompensated cirrhosis. Of 528 patients who achieved SVR of 12 weeks with follow-up data available to week 36, 31.6% and 12.3% of patients with cirrhosis of Child–Pugh class B and class C (decompensated), respectively, showed regression of cirrhosis to Child–Pugh class A (compensated) after achieving SVR following DAA therapy[31,33]. The main predictors of the return to Child–Pugh class A included the absence of ascites or hepatic encephalopathy, high serum levels of albumin, low serum levels of bilirubin, high serum levels of alanine transaminase and low BMI.

Alcohol-related cirrhosis. The risk of adverse clinical outcomes is markedly lower in patients with alcohol-related cirrhosis who manage to abstain from alcoholic beverages. Aravinthan and colleagues investigated the effects of recompensation of alcohol-related cirrhosis on the removal from a liver transplant waiting list[21] and used the following criteria to define recompensation: (1) absence of ascites and hepatic encephalopathy in the absence of treatment, and (2) a decrease in MELD score to <15. In their study, 47 of 284 patients with ALD (16.5%) achieved recompensation[21]. In a study by Pose and colleagues, of 420 patients with alcohol-related decompensated cirrhosis who were candidates for liver transplantation, 36 (8.6%) were delisted because of substantial clinical improvements[20]. Most patients showed signs of regression of ascites and hepatic encephalopathy[20]. In a study by Hofer and colleagues exploring the effect of alcohol abstinence in 204 patients with decompensated alcohol-related cirrhosis[34], 18.1% of the cohort achieved hepatic recompensation, which was associated with a reduction of >90% in liver-related mortality. The study also suggested a potential decrease in the risk of HCC upon recompensation[34].

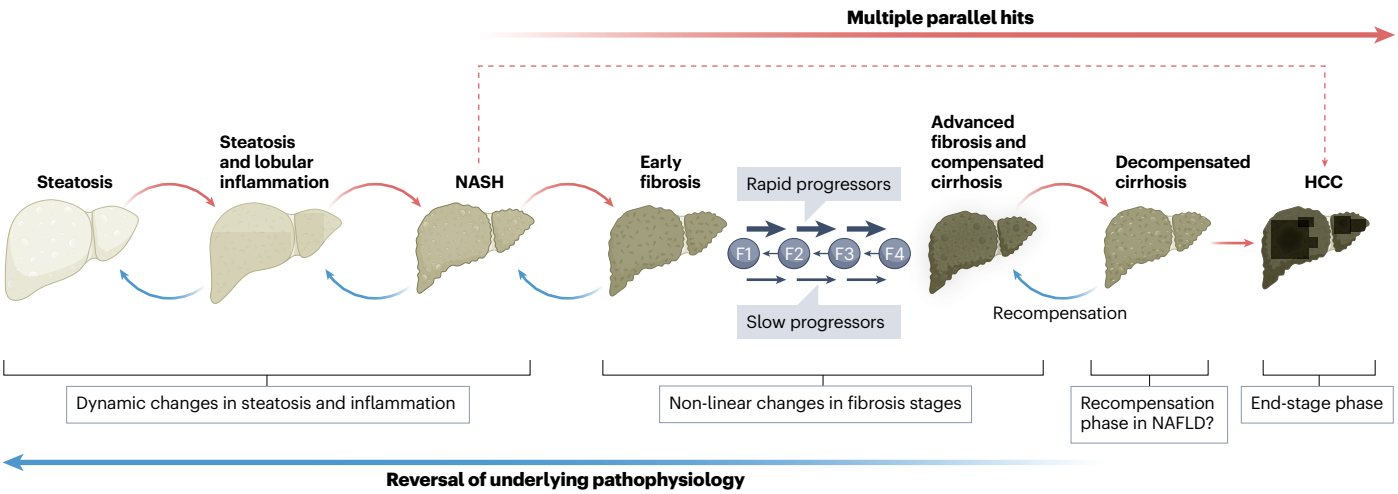

Fig. 1 | The up-to-date natural history of NAFLD. Nonalcoholic fatty liver disease (NAFLD) can progress from the initial nonalcoholic fatty liver to nonalcoholic steatohepatitis (NASH) and to the end-stage hepatocellular carcinoma (HCC), during which both steatosis and inflammation are characterized by bidirectional dynamic changes. Changes in fibrosis, which is categorized into stages F1 to F4, progress nonlinearly and can also be reversed, and some patients are rapid progressors and some are slow progressors. Even if NAFLD-associated cirrhosis progresses to the decompensated stage, recompensation might still occur. The multiple strikes hypothesis can explain the progression of NAFLD disease, and the improvement in NAFLD severity is often caused by reversing the underlying pathophysiological mechanisms.

Natural history characteristics of NAFLD: from a reversible perspective

NAFLD is characterized by a highly heterogeneous disease course (Fig. 1), with both NASH and fibrosis having the potential to progress, regress or remain stable[35]. Disease heterogeneity can be linked to different lifestyle habits and practices, including regular physical activity, weight management, proper nutrition and avoiding or limiting alcohol consumption[36,37]. In the future, risk factor-based trajectory modelling will be useful to identify a favourable cluster of clinical evaluations in the longitudinal course of NAFLD, which would be ultimately reflected in variable degrees of histological progression and improvements in liver function tests and patient-reported outcomes. However, it is important to note that these modifications in disease activity (steatosis, inflammation and ballooning) versus stage (severity of liver fibrosis and portal hypertension) do not always go in the same direction in patients with NAFLD[38]. Indeed, it is well known that patients with advanced fibrosis with disease progression, reduction in liver function and development of portal hypertension, frequently show a reduction in hepatic fat content and inflammation, which can lead to so-called burnt-out NASH, which might be diagnosed as 'cryptogenic cirrhosis'[39].

Dynamic changes in steatosis and inflammation

The transition from NAFLD to NASH is complex and fluid, with the potential for both progression and regression being possible. Diet-based and exercise-based weight loss is an effective intervention for reducing hepatic fat deposition in children, adolescents and adults with obesity and NAFLD[40]. However, the complicated pathophysiology of NASH is influenced not only by genetic determinants, but also by comorbidities, behavioural variables and environmental factors[41,42]. On the other hand, worsening of metabolic triggers such as insulin resistance, dyslipidaemia and abdominal obesity has been associated with episodes of fast disease progression[43]. Despite being a widely studied phenomenon, there remains a lack of comprehensive understanding of the frequency and intensity of these fluctuations. The extent and nature of liver injury that results from these transitions have yet to be fully explored, highlighting the need for further research in this field.

Although no drug for NASH has yet gained FDA approval, several compounds, including semaglutide (glucagon-like peptide 1 receptor agonist), have been shown to improve hepatic inflammation[44]. In this regard, in a phase II trial, significantly ($P < 0.001$) more patients in the semaglutide group (82 patients) than in the placebo group (80 patients) achieved NASH resolution[45]. An improvement in fibrosis stage occurred in 43% of patients in the semaglutide group and in 33% of the patients in the placebo group, but this difference did not reach the significance threshold[45]. The question as to whether glucagon-like peptide 1 receptor agonists or other metabolic drugs might promote liver recompensation remains unanswered. In a randomized controlled trial in 71 patients with NASH cirrhosis and overweight, semaglutide 2.4 mg per week was associated with improvement in metabolic control, liver enzymes and hepatic fat, but this did not translate into an increased rate of fibrosis reversal[46]. As NAFLD is multifaceted, patients are heterogeneous, and the drivers of progression and regression are still unclear, extensive efforts will be needed to identify the most informative outcome measures for recompensation trials[47]. We must remember that the characteristics that these drugs should have to promote recompensation in NAFLD cirrhosis, such as being initially non-toxic, are critical.

Nonlinear changes in fibrosis stages

Despite past data suggesting that liver fibrosis is challenging to reverse, increasing evidence now indicates that NAFLD-related liver fibrosis can be reversed[48,49]. It should be noted that the following example refers to fibrosis rather than cirrhosis. For example, fibrosis regression was also reported in clinical trials using obeticholic acid and lanifibranor in patients with NASH[50,51]. Resmetirom, a thyroid hormone receptor β-agonist, has emerged as a promising therapeutic agent in the battle against NASH. Resmetirom was shown to reduce liver fat and inflammation, two key aspects in the progression of NASH, leading to NASH resolution more frequently than placebo[52,53]. Moreover, the compound was shown to have the potential to improve hepatic fibrosis, the key prognostic factor in NASH. This improvement in hepatic fibrosis is thought to be achieved through its modulatory effect on the expression of genes involved in lipid metabolism, and consequently inflammation and fibrogenesis within the liver[52,53]. Data presented at the European Association for the Study of the Liver Congress in Vienna provided more insights into this potential[54]. This presentation reported the primary results from the MAESTRO-NASH trial, a pivotal phase III trial that evaluated the efficacy and safety of resmetirom in 966 patients with biopsy-confirmed NASH and fibrosis. Resmetirom significantly improved the rate of both NASH resolution ($P < 0.001$) and fibrosis improvement ($P < 0.001$) compared with placebo at week 52 (ref. 54). Resmetirom might, therefore, be considered as a therapeutic approach to achieve recompensation in patients with NAFLD cirrhosis.

Additional studies are required to test the safety of pharmacological approaches acting on NAFLD-related fibrosis in patients with decompensated cirrhosis. Meanwhile, current evidence suggests that weight loss, bariatric surgery and lifestyle modification in patients with NAFLD reliably decrease the stage of fibrosis[48,55]. Changes in fibrosis stage experienced by patients with NAFLD are nonlinear, with potential progression, regression or stability over time[38]. As the NAFLD patient population is heterogeneous regarding natural history, this aspect might affect trial outcomes, with significant implications for the timing of interventions. Apart from regular surveillance of fibrosis, predicting nonlinear disease progression might be extremely valuable in clinical practice and medical research. Future strategies to achieve this goal include classification and prediction based on expert knowledge, machine learning algorithms and multivariate-based prediction models.

Recompensation of NAFLD-related cirrhosis

Decompensation in NAFLD might differ from that in other viral chronic liver diseases. For example, a multicentre cross-sectional study including 548 patients with advanced NAFLD and 444 with advanced HCV infection suggested that NAFLD might occur at lower hepatic venous pressure gradient levels than in patients with viral disease[56]. Currently, published data on the recompensation of NAFLD-related cirrhosis remain limited. In two clinical trials, Sanyal and colleagues investigated the effectiveness of simtuzumab and selonsertib in a total of 1,135 patients with NASH-related cirrhosis[57]. Regression of cirrhosis was seen in 16% of patients and was associated with reduced liver-related complications[57]. Pose and colleagues found that, of 70 liver transplant candidates with NASH-related cirrhosis, one (1.4%) could be delisted because of clinical improvement[20]. However, these data should be interpreted cautiously because the main focus of the study was alcohol-related decompensated cirrhosis. Other study limitations included the lack of information on treatment modalities and limited subgroup analyses. In another study, Aravinthan and colleagues

examined the clinical characteristics of patients who were delisted following recompensation, and sought to identify the clinical parameters associated with the occurrence of recompensation while the patient was on the waiting list[21]. Of the 935 patients included in the study, 77 were delisted owing to recompensation and, of these, 3 (4%) had NASH[21].

End-stage phase

NASH has become one of the leading causes of HCC in Western countries. A systematic review and meta-analysis of 61 studies, including 94,636 individuals worldwide, found that approximately 15% of all HCC cases were related to NAFLD[58]. The highest rates of NAFLD-associated HCC were observed in Southeast Asia, whereas the lowest occurred in the Americas. In general, NAFLD-associated HCC tends to affect patients without evidence of cirrhosis; additionally, a lower proportion of patients with NAFLD-related HCC were found to undergo surveillance than patients with HCC due to other causes[58]. This observation calls for additional efforts to improve the effectiveness of current HCC surveillance schemes in patients with a high risk of developing NAFLD without evidence of cirrhosis. Clinical and preclinical studies on the pathogenesis of NAFLD-related HCC are still in an exploratory phase. In addition, there is still no consensus on the optimal screening strategies for HCC in this clinical population; this has, in turn, hampered the ability to implement effective prevention and treatment strategies[59]. Along with public awareness programmes, there is, therefore, a need to focus on HCC surveillance to provide periodic information on its burden, patterns and trends in patients with NAFLD. This information would ultimately assist evidence-based public health decision-making and measure the effect of interventions.

Potential mechanisms of recompensation in NAFLD-related cirrhosis

Owing to the limited number of clinical and preclinical studies on the recompensation of NAFLD-related cirrhosis, we can only deduce the possible underlying mechanisms from research focused on other chronic liver diseases. In the presence of recompensation, reversal of the physiological pathways that lead to decompensated cirrhosis must have occurred, along with improved clinical symptoms. However, decompensation of recompensated cirrhosis might still occur following further injury to the liver. Potential driving factors for decompensation include clinically substantial portal hypertension, worsening liver fibrosis accompanied by increased vascular thrombosis, alterations in intestinal permeability, endotoxaemia, bacterial translocation from the gastrointestinal tract, activation of systemic inflammation, cirrhosis-related immune dysfunction and infectious episodes[60–63]. In turn, the mechanisms of cirrhosis recompensation are closely related to the reversal of factors that precipitate decompensation. On examining the potential underpinnings of recompensation, we specifically focus on (1) collagen degradation and hepatocyte regeneration; (2) vascular remodelling; and (3) improvement in systemic inflammation (Fig. 2). There have already been numerous clinical studies on hepatic recompensation after removal of the aetiological factors[20,28,29,31]. However, for NAFLD, the aetiological factors cannot be completely reversed in most patients[64]. For example, weight loss through lifestyle interventions can improve steatosis, inflammation and fibrosis in patients with NAFLD, but sustained weight loss is challenging and weight regain is common[65]. Whether recompensation is possible for diseases that can only be partially controlled will be an important topic to discuss. We look forward to further scholarly investigations elucidating the mechanisms underlying recompensation in cirrhosis, especially those focusing on data pertaining to decompensated disease or NAFLD as aetiological factors.

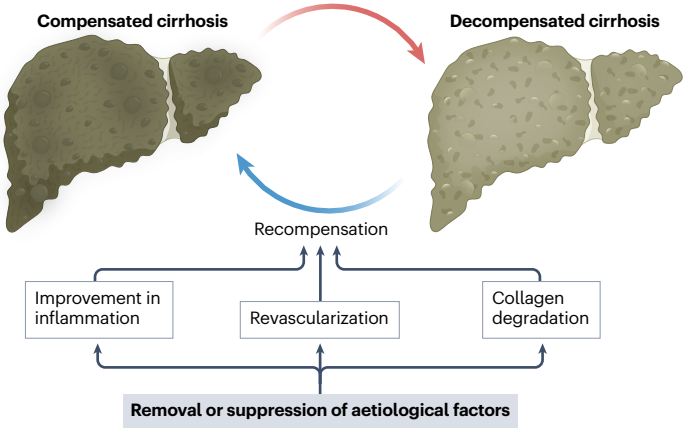

Fig. 2 | Possible main mechanisms of recompensation in nonalcoholic fatty liver disease-related cirrhosis. Compensated cirrhosis can progress to decompensated cirrhosis, whereas decompensated cirrhosis can achieve recompensation. The possible main mechanisms of recompensation include collagen degradation and hepatocyte regeneration, vascular reconstruction and improvement in systemic inflammation.

Collagen degradation and hepatocyte regeneration

Chronic liver injury in NAFLD involves hepatocyte necrosis, chronic fibrogenic pathway activation, fibrous septa formation and an altered lobular architecture[66]. Conversely, fibrotic extracellular matrix degradation and hepatocyte regeneration are the molecular and cellular substrates of recovery from liver fibrosis and improvements in lobular architecture, which might ultimately lead to cirrhosis recompensation. This phenomenon has been observed in animal models and patients with cirrhosis as a result of reductions in portal hypertension and improvements in liver function test abnormalities[19,67].

Vascular reconstitution and functional recovery of liver sinusoidal endothelial cells

Under persistent damage, the hepatic sinusoidal endothelium, which represents the microcirculatory bed of the liver, becomes dysfunctional. Alterations in hepatic microcirculation associated with cirrhosis include vascular occlusion and sinusoidal endothelium de-differentiation (capillarization), mainly owing to architectural changes together with impairment of vascular dilatation leading to a pathological increased intrahepatic resistance and development of portal hypertension[68]. Several molecular players, including angiopoietin 2 and platelet-derived growth factor, together with a vasoregulatory imbalance (hyperresponse to vasoconstrictors such as endothelin 1) and hyporesponse to vasodilators (such as nitric oxide) have been implicated in the pathogenesis of this condition[69]. However, if the injurious chronic aetiological agent is removed or targeted by drugs, portal vein pressure can decrease, therefore contributing to recompensation by modifying the natural history of the disease. A phase II trial of belapectin (that targets galectin 3), to evaluate its effects on hepatic fibrosis versus placebo, was conducted in 162 patients with NAFLD cirrhosis and portal hypertension. Despite the overall negative results (belapectin was not associated with significant

changes in hepatic venous pressure gradient or fibrosis compared with placebo), in a subgroup analysis in patients without oesophageal varices, 2 mg per kg body weight belapectin reduced hepatic venous pressure gradient and the development of varices[70].

Statins might promote regression of portal hypertension by ameliorating hepatic endothelial dysfunction, and they can also reduce intrahepatic vascular resistance through increasing nitric oxide synthase activity, but their safety in decompensated cirrhosis remains to be addressed[71,72]. In addition, faecal microbiota transplantation was shown to reduce portal vein pressure by improving vascular responsiveness, decreasing mesenteric angiogenesis and reducing blood flow in portosystemic collaterals in a rat model of cirrhosis[73]. In a multicentre prospective study including 226 patients with HCV infection-related cirrhosis and clinically significant portal hypertension achieving SVR, HCV infection eradication progressively reduced portal pressure during follow-up[6]. In 50 patients with HCV infection and with or without cirrhosis (25 with cirrhosis and 25 without cirrhosis), achievement of SVR reduced markers of endothelial dysfunction, including von Willebrand factor[74]. However, if and to what extent these markers correlate with hepatic vascular reconstitution deserves further scrutiny.

Improvement in systemic inflammation

Although the treatment-induced reversal of systemic inflammation is another key path to recompensation, the dynamics of inflammatory reactions occurring in decompensated cirrhosis remain only partially elucidated. In general, the systemic inflammatory response accompanying cirrhosis is multifactorial and might involve intestinal bacterial overgrowth and dysbiosis accompanied by the entering of bacterial toxins into the portal and/or systemic circulation[75]. As expected, patients with decompensated cirrhosis have higher circulating levels of inflammatory markers (for example, leukocyte count, C-reactive protein and serum levels of pro-inflammatory interleukins) than those with compensated cirrhosis[61,76]. Interestingly, biomarkers of inflammation have been associated with the severity of portal hypertension and clinical outcomes[61,77]. Monteiro and colleagues reported that different inflammasome activation is involved in acute-on-chronic liver failure development in patients with compensated cirrhosis and in those with recompensated cirrhosis[78]. Specifically, IL-1α was identified as an independent predictor of acute-on-chronic liver failure in patients with compensated cirrhosis, whereas IL-1β was an independent risk factor for acute-on-chronic liver failure in patients with recompensated cirrhosis[78]. More studies are required to shed further light on inflammatory response mechanisms, resolution of inflammation, and liver-specific inflammatory responses concerning cirrhosis recompensation.

Challenges in the field of recompensation for NAFLD-related cirrhosis

Limitations of the definition

According to the strict criteria recommended by the Baveno VII consensus statement, the term cirrhosis recompensation should be used only when (1) a clear underlying cause has been identified, and (2) targeted therapy is available[33]. Removal of the injurious chronic aetiological agent in patients with cirrhosis is an important criterion that needs to be met to achieve recompensation. The Baveno VII consensus statement provides clear definitions for aetiological management due to the following causes: (1) ALD (abstinence from alcohol); (2) HCV infection (SVR); and (3) HBV infection (suppression of viral replication)[33]. However, a consensus on cirrhosis due to NAFLD or other causes, including mixed aetiologies, was not reached. Defining an aetiological treatment for NAFLD-related cirrhosis is particularly challenging because of its complex and multifactorial pathophysiology and a lower likelihood of normalizing insulin resistance, especially in patients with more advanced disease[23,79]. Nevertheless, the current global prevalence of obesity, type 2 diabetes and NAFLD is increasing, so clear definitions of recompensation for NAFLD-related cirrhosis are urgently needed and are a key prerequisite for investigating the prevalence and predictors of recompensation in NAFLD-related cirrhosis[80].

Optimal cut-off values for sustained improvement in liver function tests

Apart from the two previously mentioned criteria, the definition of recompensation recommended by the Baveno VII consensus statement requires a sustained improvement in liver function tests[33]. However, defining the optimal cut-off values to describe the transition from decompensation to recompensation remains an open issue. In a multicentre study, Wang and colleagues prospectively evaluated the occurrence of liver recompensation, defined according to the Baveno VII criteria, in HBV infection-related cirrhosis. As criteria to define recompensation, they proposed a reduction in MELD score to <10 and/or improvement in liver function parameters to Child–Pugh grade A (serum albumin >35 g/l, INR <1.5 and bilirubin <34 μmol/l) as appropriate thresholds for improved liver function[30]. Of the 283 patients in the study who completed 120 weeks of follow-up, 159 achieved sustained disappearance of ascites and hepatic encephalopathy at 120 weeks of follow-up and met the above criteria for improved liver function. Thus, 56.2% of patients (159 of 283) in the study met the recompensation definition according to the Baveno VII criteria[30]. However, the prognostic importance of the proposed cut-off values was not specifically investigated. Translating continuous variables (for example, laboratory markers) to clinically meaningful information, such as 'recompensation (yes or no)' would be helpful in future studies. The question of what constitutes an essential improvement in liver function tests (identifying clinically relevant cut-off values) to define recompensation is already an issue of increasing interest.

Long-term prognostic characteristics

The long-term prognosis in patients with recompensated cirrhosis is still not fully elucidated. There might be some patients in whom the underlying cause has been cured or suppressed and who are on the road to recovery with marked improvements in liver function but have not yet met all the recompensation criteria. Clear criteria need to be established for these patients to help clinicians identify when to attempt to discontinue diuretic or anti-hepatic encephalopathy therapies safely[33]. In addition to clinical outcomes, recompensation can lead to improvement in health-related quality of life and other patient-reported outcomes, which is also a direction to focus on in the future[81].

Ethical issues

Owing to the increase in risk factors such as obesity and metabolic syndrome, the incidence of NAFLD is expected to increase by 168% and 137% in decompensated cirrhosis and liver cancer, respectively, and the number of deaths is expected to increase by 178% by 2030 in the USA[82]. Thus, the number of patients with NAFLD and related end-stage liver diseases requiring liver transplantation is gradually increasing in the USA[83]. Liver transplantation is the only available treatment for NAFLD-related end-stage liver disease[84]. Owing to the influence of obesity, metabolic

syndrome and other adverse factors, the recurrence rate of NAFLD after liver transplantation is high[85]. A growing adoption of the recompensation concept in NAFLD-related cirrhosis might raise ethical concerns with respect to the waiting list priority for organ allocation; this issue is expected to markedly affect counties in which disease-specific criteria are applied to guide the timing of transplantation[86]. Importantly, patients showing signs of recompensation might also be removed from the transplantation list. Hence, long-term longitudinal studies are required to assess the effects of recompensation in patients with NAFLD and establish their long-term outcomes.

Future research directions

More population-based studies

Owing to the novelty of the Baveno VII criteria for recompensation, data on recompensation for NAFLD-related cirrhosis are still limited. Most of these data are preliminary and based primarily on transplant registries, which might be biased by the heterogeneous definition of recompensation compared to those used in previous studies[33,86]. Therefore, more in-depth clinical and basic research is urgently needed to gain further insights into this condition of recompensation for NAFLD-related cirrhosis.

As for clinical research, given the limited data on NAFLD-related liver cirrhosis recompensation, more prospective population-based studies are needed to increase the evidence-based medical evidence for this concept. In addition to identifying optimal cut-off values for sustained improvement of liver function tests to describe the transition from decompensation to recompensation, further exploration of the factors influencing the recompensation of NAFLD-related cirrhosis is also of interest. In a cohort of 241 patients with decompensated ALD, the MELD score predicted recompensation in those with ALD-related cirrhosis[21]. Xu and colleagues showed that seven parameters, including serum albumin, total protein, haemoglobin, basophil count, alanine aminotransferase, neutrophil-to-lymphocyte ratio and diabetes, might be useful to define the presence of recompensated cirrhosis[3]. Further research is needed to confirm and expand these findings. Although the substaging of decompensated cirrhosis is not yet well defined, it remains possible that additional classification systems will emerge that can further discriminate different stages of recompensation.

Identification of noninvasive methods for evaluating the recompensation of NAFLD cirrhosis

Invasive examination, namely liver histological biopsy, is the gold standard for the diagnosis of cirrhosis and its reversal[87]. Reversal of cirrhosis is characterized by collagen degradation, vascular changes and hepatocyte regeneration[33,57]. The stage of cirrhosis can be assessed based on the results of liver biopsy[88]. However, as most patients with decompensated cirrhosis might need a transjugular approach that is not easily available and might be invasive and costly, noninvasive examination of liver decompensation and recompensation has become a research hotspot in this field[89]. The noninvasive examination of liver cirrhosis recompensation mainly includes imaging examination and biomarker detection. Notably, all those tests proposed have been validated in liver fibrosis progression, but not in fibrosis changing in the other direction, so that their values in fibrosis regression are unknown. The imaging methods include transient elastic imaging and magnetic resonance elastic imaging, but the latter is more valuable for reference[90]. Compared with a single serological index, the comprehensive scoring model integrating multiple serological indexes has an increased availability value[91]. Serological models related to cirrhosis include the MELD score, Child–Pugh grade, the aspartate aminotransferase to platelet ratio index, FibroTest (also known as FibroSure) and the FIB-4 index. Some clinical studies have used relevant models to study the recompensation of cirrhosis[21]. In a study including 241 patients with decompensated alcohol-related liver cirrhosis, a MELD score of <20 together with a serum albumin level of ≥32 g/l was associated with a 70% probability of recompensation of alcohol-related liver cirrhosis[21]. The researchers developed and validated the BC2AID score, a prognostic model using six clinical parameters, to predict early recompensation in patients with HBV infection-related decompensated cirrhosis starting potent nucleos(t)ide analogue therapy, based on data from 311 patients with 152 in the derivation cohort and 159 in the validation cohort[28].

The lack of specific diagnostic techniques for recompensation of NAFLD-related cirrhosis still represents a marked unmet clinical need. Unfortunately, the complex and multifactorial nature of this condition is a major obstacle to achieving this goal. The deployment of advanced machine learning tools in precision diagnostics and prognostication has gained much attention in the clinical community[92] and merits further investigations in the field of NAFLD-related cirrhosis recompensation. A potential strategy might be the use of an ensemble approach that stacks different panels to improve predictive accuracy. Given that NAFLD is inherently heterogeneous, the successful development of a reliable clinical workflow for the diagnosis, prognostic stratification and clinical management of cirrhosis recompensation is likely to require a combination of methods incorporating clinical, imaging, serological and genetic parameters with the aid of high-dimensional data analysis and machine learning. A summary of potential noninvasive methods for evaluating recompensation in NAFLD-related cirrhosis is shown in Box 1.

Actively exploring effective treatment strategies

In the field of chronic liver disease, cell transplantation, antifibrotic therapy and immunoregulatory therapy have become hot spots in the research around treatment strategies for decompensated cirrhosis. Clinical studies have shown that mesenchymal stem cells have the potential to differentiate into hepatocytes[93]. Their therapeutic value lies in the immunomodulatory effect and anti-inflammatory potential of mesenchymal stem cells, which might be an effective potential alternative therapy and needs additional evidence[94,95]. Over the past decade, the number of clinical studies on antifibrotic therapies has also increased substantially[96]. Unfortunately, only a few molecules have reached the clinical trial stage. Multiple αv integrin inhibition strategies to effectively inhibit fibrogenic gene expression have been explored[96].

In general, given the intricate pathophysiological nature of NAFLD, potential future strategies for promoting cirrhosis regression might lie in combination therapies. However, although numerous compounds that target different molecular aspects involved in the pathogenesis of NAFLD have been tested in clinical trials, no regulatory approval was achieved. This unmet need highlights the requirement for robust preclinical data before moving to late-stage clinical trial programmes. Lifestyle changes are fundamental to NAFLD and NASH treatment, and are equally important for achieving recompensation in NAFLD-related cirrhosis[37]. Numerous studies have underscored lifestyle modifications, that chiefly involve the augmentation of physical exercise and regulation of calorie intake, as crucial strategies in NAFLD treatment[97–99]. Lifestyle interventions such as exercise and diet therapy are the first line of treatment for NAFLD, and in most interventions, the main goal is between 7% and 10% weight loss as this improves steatosis, inflammation, hepatocyte ballooning and fibrosis[98]. These lifestyle interventions

Box 1

Summary of potential noninvasive methods for evaluating recompensation in NAFLD-related cirrhosis[a]

- Recommend the potential of noninvasive imaging techniques, such as transient elastic imaging and magnetic resonance elastic imaging. These techniques, which assess liver tissue stiffness, a crucial indicator of fibrosis, could be instrumental in evaluating recompensation in nonalcoholic fatty liver disease (NAFLD)-related cirrhosis.
- Suggest the relevance of conventional panels such as the model for end-stage liver disease (MELD) score, Child–Pugh grade, the enhanced liver fibrosis (ELF) score, FibroTest (also known as FibroSure) and the FIB-4 index. These methods, which employ a variety of blood tests, could be particularly useful in assessing recompensation in NAFLD-related cirrhosis.
- Encourage the use of advanced data analysis tools, including machine learning, high-dimensional data analysis and artificial intelligence. These tools, that are capable of integrating diverse parameters (clinical, imaging, serological, genetic), could provide novel insights for the prediction and assessment of cirrhosis recompensation, making them potentially beneficial for evaluating recompensation in NAFLD-related cirrhosis.

[a]Although these techniques are promising, their specific efficacy in evaluating recompensation in NAFLD-related cirrhosis remains to be investigated.

can not only ameliorate NAFLD but can even prompt regression of NAFLD-related cirrhosis[98]. It is recommended that healthy diet principles, such as those of the Mediterranean diet, are followed in people with cirrhosis[97]. In 50 patients with compensated cirrhosis and portal hypertension, independently of aetiology, moderate exercise in combination with nutritional advice and a weight loss of at least 10% was associated with a significant reduction in portal pressure[37]. Therefore, in decompensated liver cirrhosis, we believe that lifestyle interventions, especially dietary modifications, hold substantial potential value. However, the current lack of systematic methods for evaluating how lifestyle affects the outcomes and end points of clinical trials in NASH might hinder clinical trial design, and attention needs to be paid to the standardization of diet and exercise in clinical trials in NAFLD and NASH.

Furthermore, bariatric surgery should be considered as a method to offset the effects of recompensation in NAFLD-related cirrhosis, provided that it can be safely performed in specialist centres in patients with decompensated cirrhosis and severe portal hypertension. Some studies have shown that bariatric surgery can lead to long-term resolution of NASH and regression of fibrosis[100,101]. In addition, bariatric surgery can also substantially improve NAFLD and NASH[85]. In a study in 160 patients, bariatric surgery led to improvement in liver histology regardless of the type of surgery, and improved fibrosis in up to 60% of patients[102]. We hypothesize that bariatric surgery carries the potential to bring about effective recompensation in cirrhosis associated with NAFLD. By enabling substantial weight reduction, this surgical intervention could contribute to reversing or halting cirrhosis, and therefore lead to a beneficial recompensation of liver health and function. Bariatric surgery could be a valuable therapeutic strategy in the management of recompensated NAFLD-related cirrhosis. However, we need to be aware that decompensated cirrhosis should be considered an absolute contraindication for bariatric surgery owing to increased risk and unproven liver-related benefits, unless performed in conjunction with liver transplantation at specialist centres[103].

The application of digital pathology with artificial intelligence analyses

In the study of NAFLD, the application of artificial intelligence and digital pathology is increasingly becoming crucial. These tools can aid in accurately detecting and quantifying hepatic fibrosis, assessing pathological architecture and providing quantitative measures of treatment response[104]. Artificial intelligence can markedly improve diagnostic performance in NAFLD, NASH and liver fibrosis[105]. Digital pathology combined with artificial intelligence analysis can provide deeper insights, assisting in evaluating regression of liver fibrosis induced by treatments, especially in NASH[91]. Through the use of second harmonic generation–two-photon excited fluorescence microscopy in conjunction with artificial intelligence analysis, standardized assessments of NASH characteristics can be carried out, especially the continuous quantification of liver fibrosis and collagen fibres[106]. These research findings illustrate the substantial role of artificial intelligence and digital pathology in the assessment and treatment of NAFLD, and future innovations and breakthroughs in this area are anticipated. Digital pathology with artificial intelligence analyses are also a promising tool for evaluating the morphological alterations of liver tissue leading to recompensation in NAFLD-related cirrhosis in clinical studies. The use of digital pathology can help pathologists analyse large amounts of histological data more efficiently and accurately, whereas artificial intelligence can provide more objective and quantitative measurements of histological features.

Conclusions

Based on the concept and evidence presented, it is clear that recompensation is possible and is an attractive therapeutic outcome in patients affected by NAFLD-related cirrhosis. The updated reversible perspective on the natural history of NAFLD provides a more comprehensive and in-depth understanding of recompensation in NAFLD-related cirrhosis. From this new perspective, we can see that the definition of recompensation in NAFLD-related cirrhosis is a topic that is both challenging and full of opportunities. Possible mechanisms of recompensation have been proposed, but challenges in the field persist (including the cut-off values for stable improvement of liver function tests, long-term prognostic characteristics, and ethical issues related to transplant eligibility). Future research directions in the field should focus on conducting more clinical research (for example, on the natural history and predictors), establishing noninvasive methods, exploring effective treatment strategies, investigating the natural history of recompensation (what happens next in the long term?) and uncovering the molecular mechanisms.

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G.F. researched data for the article. All authors contributed substantially to discussion of the content. M.-H.Z. and G.F. wrote the article. All authors reviewed and/or edited the manuscript before submission.

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