CZU: 616.36-004-085.281.8

RECOMPENSATION FACTORS IN PATIENTS WITH DECOMPENSATED CIRRHOSIS

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https://doi.org/ 10.52556/2587-3873.2024.5(102).27

Summary

Decompensated cirrhosis marks an irreversible stage in chronic liver disease. Effective etiological treatment may induce hepatic recompensation. We have evaluated the factors which contribute to the improvement of patients with decompensated liver cirrhosis. This review followed a comprehensive literature search using PubMed, Clinical Review, and Google Scholar, focusing on articles, meta-analyses, and references from relevant articles and textbooks published between 2021 and 2024. Our analysis of current literature demonstrates that antiviral therapy and alcohol cessation significantly enhance prognosis and facilitate hepatic recompensation in patients with decompensated cirrhosis. The pathophysiology of recompensation in cirrhosis involves several mechanisms: reduction of liver injury, hepatocyte regeneration, resolution of fibrosis, reduction of portal hypertension, improvement in hemodynamics (decreased cardiac output, splanchnic vasodilation, and improved vascular responsiveness). The patients who achieve HBV DNA levels <20 IU/ml during antiviral therapy experience resolution of ascites, encephalopathy, and absence of recurrent variceal bleeding for at least 12 months. Patients with HCV decompensated liver cirrhosis in case of attaining the sustained virologic response have a great chance for post-treatment recompensation. Further, patients with decompensated alcohol-related cirrhosis achieved recompensation through sustained abstinence. Recompensation has become a significant focus in the study of cirrhosis, especially in cases of chronic liver disease with known causes like viral hepatitis and alcohol consumption. Achieving recompensation in patients with virus- and alcohol-related cirrhosis is promising, but more studies are needed to understand its underlying mechanisms and clinical characteristics.

Keywords: *liver cirrhosis, decompensation, anti-viral therapy, alcohol abstinence*

Rezumat

Factori de recompensație la pacienții cu ciroză decompensată

Ciroza decompensată marchează o etapă ireversibilă în boala hepatică cronică. Tratamentul etiologic eficient poate induce recompensarea hepatică. Noi am evaluat factorii care contribuie la îmbunătățirea stării pacienților cu ciroză hepatică decompensată. La baza aceastui riviu o fost evaluarea literaturii din bazele de date PubMed, Clinical Review și Google Scholar, concentrându-se pe articole, meta-analize și referințe din articole și manuale relevante publicate între 2021 și 2024. Analiza literaturii actuale demonstrează că terapia antivirală și renunțarea la consumul de alcool îmbunătățesc semnificativ prognosticul și facilitează recompensarea hepatică la pacienții cu ciroză decompensată. Fiziopatologia recompensării în ciroză implică mai multe mecanisme: reducerea leziunilor hepatice, regenerarea hepatocitelor, rezolvarea fibrozei, reducerea hipertensiunii portale, îmbunătățirea hemodinamicii (scăderea debitului cardiac, vasodilatația splahnică și îmbunătățirea răspunsului vascular). Pacienții care ating nivelurile ADN HBV <20 IU/ml în timpul terapiei antivirale atestă rezolvarea ascitei, encefalopatiei și absența sângerărilor variceale recurente timp de cel puțin 12 luni. Pacienții cu ciroză hepatică decompensată de etiologie virală HCV, în cazul obținerii răspunsului virologic susținut, au o mare șansă de a obține recompensarea post tratament. De asemenea, pacienții cu ciroză decompensată asociată consumului de alcool au atins recompensarea prin abstinență susținută. Recompensarea a devenit un focus semnificativ în studiul cirozei, în special în cazurile de boală hepatică cronică cu cauze cunoscute, cum ar fi hepatita virală și consumul de alcool. Obținerea recompensării la pacienții cu ciroză legată de virus și alcool este promițătoare, dar sunt necesare mai multe studii pentru a înțelege mecanismele sale subiacente și caracteristicile clinice.

Cuvinte-cheie: *ciroză hepatică, decompensare, terapie antivirală, abstinența de la alcool*

Резюме

Факторы рекомпенсации у больных декомпенсированным циррозом печени

Декомпенсированный цирроз обозначает необратимую стадию хронического заболевания печени. Эффективное этиологическое лечение может вызвать рекомпенсацию цирроза. Мы изучали факторы, способствующие улучшению состояния пациентов с декомпенсированным циррозом печени. В этом обзоре проведен всесторонний поиск литературы с использованием PubMed, Clinical Review и Google Scholar, с акцентом на статьи, мета-анализы и ссылки из релевантных статей и учебников, опубликованных в период с 2021 по 2024 годы. Наш анализ современной литературы показывает, что противовирусная терапия и отказ от алкоголя значительно улучшают прогноз и способствуют рекомпенсации у пациентов с декомпенсированным циррозом. Патофизиология рекомпенсации при циррозе включает несколько механизмов: снижение повреждения печени, регенерацию гепатоцитов, разрешение фиброза, снижение портальной гипертензии, улучшение гемодинамики (уменьшение сердечного выброса, спланхническую вазодилатация и улучшение сосудистой реакции). Пациенты, достигшие уровней ДНК HBV <20 МЕ/мл в ходе противовирусной терапии, отмечали разрешение асцита, энцефалопатии и отсутствие рецидивов варикозных кровотече-

ний в течение как минимум 12 месяцев. Пациенты с декомпенсированным циррозом печени, вызванным HCV, в случае достижения устойчивого вирусологического ответа имеют высокие шансы на рекомпенсацию после лечения. Кроме того, пациенты с декомпенсированным алкогольным циррозом достигли рекомпенсации благодаря стойкому воздержанию. Рекомпенсация стала важным направлением в изучении цирроза, особенно в случаях хронического заболевания печени вызванного вирусами или употреблением алкоголя. Достижение рекомпенсации у пациентов с циррозом, связанным с вирусами и алкоголем, является многообещающим, но необходимы дальнейшие исследования для понимания его основных механизмов и клинических характеристик.

Ключевые слова: *цирроз печени, декомпенсация, противовирусная терапия, воздержание от алкоголя*

Introduction

Chronic liver disease (CLD) stands as a prominent contributor to global mortality rates. The progression of CLD typically involves a shift from an asymptomatic compensated stage to decompensated cirrhosis, posing a significant risk to survival as it advances. The major factors associated with decompensated cirrhosis are portal hypertension associated with ascites, varices, hepatic encephalopathy (HE), jaundice, hepato-renal syndrome, and coagulopathy [4]. The progression to cirrhosis is a major cause of morbidity and death worldwide, as a result of recurrent or chronic liver injury caused due to toxic, infectious, metabolic, or genetic causes [19]. Efficient antiviral treatment can prevent the hepatitis viruses from replicating, enhance liver function in individuals with decompensated cirrhosis, and restore liver function in certain sub-group of patients [22]. Hepatologists globally have noticed a specific subset of patients with decompensated cirrhosis who show signs of reverting to the initial compensated stage, reflecting the potential for reversibility at different stages of portal hypertension. While the available data is preliminary, observational, and largely retrospective, often derived from transplant wait list registries, this observation has introduced the concept of "recompensated cirrhosis" [5].

The *Baveno VII consensus* has established standardized criteria for defining recompensated cirrhosis, including the elimination of the primary cause, resolution of decompensating events, and sustained improvement in hepatic function [26]. Certain research indicates that individuals with decompensated cirrhosis experience enhanced survival rates without needing a transplant, as well as improvements in their Child-Turcotte-Pugh and MELD scores following antiviral treatment. In patients with alcoholic decompensated cirrhosis awaiting liver transplantation, having a MELD score below 20 and a serum albumin level equal to or greater than 32g/L upon enrolment were identified as independent factors predicting recompensation or removal from the transplant list. [3]

Give of introducing these new criteria, we underwent an extensive review of existing literature. This review encompasses studies examining the significance of etiological therapy in decompensated patients, along with those offering initial insights into hepatic recompensation.

This review aims to comprehensively analyze the current evidence on hepatic recompensation in patients with decompensated cirrhosis to enhance understanding of its mechanisms and predictors.

Material and methods

This review was conducted following a comprehensive and structured methodology to ensure the inclusion of relevant and high-quality studies. The literature search was performed across electronic databases, including PubMed, Clinical Review, and Google Scholar, targeting articles published in English from 2021 to 2023. The search strategy was designed to identify cohort studies, randomized controlled trials, and systematic reviews focusing on the recompensation of liver cirrhosis following hepatitis B, hepatitis C, and alcohol-related liver diseases. The inclusion criteria encompassed studies that specifically investigated the factors associated with hepatic recompensation and disease regression in patients with decompensated cirrhosis. Articles were included if they provided detailed data on clinical, biochemical, and therapeutic predictors of recompensation. Studies that did not meet these criteria, such as case reports, editorials, and studies not focused on recompensation mechanisms, were excluded from the review. Data extraction was performed independently by two reviewers to ensure accuracy and consistency, and any discrepancies were resolved through discussion or consultation with a third reviewer. After applying the inclusion and exclusion criteria, 27 articles were deemed suitable for detailed analysis.

Results

Hepatic compensation, decompensation, recompensation, and the Baveno VII concept

Hepatic compensation refers to the ability of the liver to maintain its essential functions despite the presence of underlying liver disease. Compensated cirrhosis is defined by the absence of bleeding (including any instance of hematemesis or melena), ascites observed during physical examination (confirmed by fluid removal), jaundice (defined as serum bilirubin levels of 3 mg/dL or higher), or symptomatic

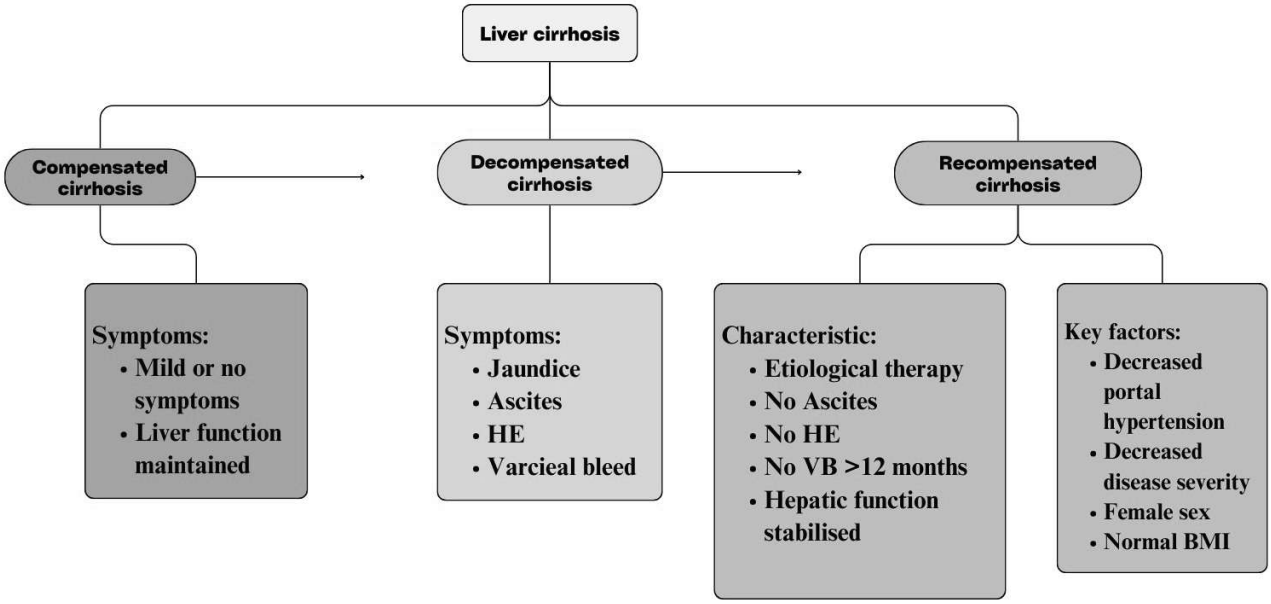

Figure 1. *Representation of recompensation factors following decompensated cirrhosis. Abbreviations: HE - Hepatic encephalopathy, VB - Variceal bleeding, BMI - Body Mass Index [26]*

encephalopathy [6]. Patients with compensated liver disease may be asymptomatic, and laboratory tests may show relatively mild abnormalities. Compensated cirrhosis can be categorized into two stages depending on the presence or absence of clinically significant portal hypertension (CSPH). Patients with CSPH are at a higher risk of decompensation. The primary aim of treating compensated cirrhosis is to prevent the complications that signify decompensation [4].

Using the *Baveno VII consensus* statement as a model, first hepatic decompensation was defined with the appearance of one or more of the following clinical manifestations: (i) bleeding from varicose veins; (ii) ascites, which was determined by the need for large volume paracentesis or diuretic treatment; or (iii) overt hepatic encephalopathy (HE), which was determined by the presence of a West-Haven grade III/IV HE event or the need for HE therapy. Once decompensated, these patients are more likely to develop subsequent decompensations such as refractory ascites and other complications like acute or chronic liver failure [4].

Hepatic recompensation has been defined as attaining all of the requirements outlined in national standards and *Baveno VII* consensus: (i) absence of ascites and hepatic encephalopathy(HE) after stopping HE therapy and diuretics; (ii) absence of variceal bleeding in the preceding year(>12 months); and (iii) a steady improvement in liver function as measured by the model for end-stage liver disease natrium (MELD-Na) score, serum albumin, bilirubin, and International normalized ratio (INR); (iv) Elimination or suppression of the main cause of liver disease, such as effective virus suppression or abstinence from alcohol [20, 24].

The critical element in understanding reversibility lies in establishing strict criteria to identify patients as recompensated. As outlined in the definition, certain patient subgroups, such as those with diuretic-controlled ascites or those undergoing treatment to prevent hepatic encephalopathy, cannot be classified as recompensated. However, patients receiving variceal bleeding prophylaxis with non-selective beta-blockers (NSBB) or transjugular intrahepatic portosystemic shunt (TIPS) placement are exceptions to this rule [20].

It's important to note that, according to the definition, the term "recompensated cirrhosis" cannot presently be applied to cirrhosis caused by non-modifiable factors such as non-alcoholic fatty liver disease. The focus on enhancing the synthetic functions of the liver is from research indicating that, following hepatic venous pressure gradient (HVPG) estimation, serum albumin has emerged as a crucial predictor of survival in studies tracking the natural progression of advanced compensated cirrhosis [21]. Unlike HVPG, measuring changes in serum albumin is straightforward and reflects improvement. This suggests that, in studies assessing recompensation by *Ripoll C. et al. (2015)*, showcasing enhancements in prognostic scores incorporating albumin (such as Child Turcotte Pugh and Albumin-Bilirubin Score) may hold greater relevance than demonstrating changes in the model for end-stage liver disease (MELD) score [20].

Pathophysiological Mechanisms behind Recompensated Cirrhosis: A Possible Advancement Beyond Clinical Improvement

Recompensation in cirrhosis describes the improvement of symptoms and the restoration of liver function following a period of decompensation, during which the liver function has decreased significantly. Decompensation in cirrhosis can lead to complications including jaundice, variceal bleeding, hepatic encephalopathy, and ascites [1]. The pathophysiology of recompensation in cirrhosis involves several complex mechanisms:

1. *Reduction of Liver Injury*: Recompensation usually occurs when additional liver damage is reduced or stopped and the underlying source of the injury—such as alcoholism, viral hepatitis, or fatty liver disease—is treated. This could involve lifestyle changes, treatment adherence, or receiving target therapies meant to slow down the underlying cause of the illness [22].

2. *Hepatocyte Regeneration:* The liver has a remarkable ability to regenerate. Recompensation involves the regeneration of hepatocytes to replace the damaged or dead cells. This regeneration is mediated by various growth factors and cytokines, such as hepatocyte growth factor and transforming growth factor-beta [3].

3. *Resolution of Fibrosis:* In cirrhosis, there is excessive deposition of collagen and other extracellular matrix proteins, leading to fibrosis and distortion of the liver architecture. Recompensation involves a reduction in fibrosis through the action of matrix metalloproteinases and tissue inhibitors of metalloproteinases, which regulate the turnover of extracellular matrix components [26].

4. *Reduction of Portal Hypertension:* Portal hypertension is a hallmark manifestation of cirrhosis and contributes to complications such as ascites and variceal bleeding. Recompensation involves the reduction of portal pressure through various mechanisms, including the regression of liver fibrosis, decompression of portal circulation through shunting procedures (ex. TIPS), and pharmacological interventions targeting splanchnic vasodilation (ex. NSBB) [26].

5. *Improvement in Hemodynamics:* Cirrhosis is associated with alterations in systemic and splanchnic hemodynamics, including increased cardiac output, splanchnic vasodilation, and impaired vascular responsiveness. Recompensation involves normalization of these hemodynamic abnormalities, which can improve symptoms such as ascites and hepatic encephalopathy [3].

To classify a patient as recompensated, there must be observed improvement in one or more pathways. For instance, NSBB and TIPS placement can facilitate recompensation by targeting not only the portal pressure-dependent pathway but also the systemic inflammatory and gut permeability pathways. The varying contributions of these pathways to sustaining decompensation, as well as the potential for these interventions to completely reverse them, explain why only a subset of patients undergoing these therapies revert to a recompensated state [22].

Portal hypertension plays a significant role in driving disease progression and decompensation in cirrhosis. Therefore, it's assumed that hepatic recompensation and disease stabilization coincide with an improvement in portal hypertension. For instance, previous studies have indicated that platelet count, which serves as a proxy for the severity of portal hypertension, influences clinical improvements. Additionally, research has consistently shown that resolving the underlying cause of cirrhosis results in a decrease in portal pressure [24].

For a patient with decompensated cirrhosis to be reclassified as recompensated cirrhosis, it's essential not only for the clinical manifestations to disappear but also for the reversal of the underlying pathways that trigger, sustain, and predispose to further clinical decompensations. Simply resolving the clinical manifestations without addressing the underlying pathophysiological causes can leave patients vulnerable to future decompensations. The major factors of decompensation include: 1) Clinically significant portal hypertension (CSPH), leading to changes such as hyperdynamic circulation, increased cardiac output, and splanchnic vasodilatation. 2) Hepatic fibrosis and heightened intrahepatic vascular resistance. 3) Increased gut permeability, resulting in endotoxemia, bacterial translocation, and subsequent systemic inflammation. 4) Cirrhosis-associated immune dysfunction (CAID), increasing the risk of infections [23].

Hepatic fibrosis contributes to elevated vascular resistance and can potentially regress with treatment tailored to the underlying cause. While hepatic fibrosis plays an early role in the development of portal hypertension and subsequent decompensations, the reversal of clinical manifestations following targeted treatment of the underlying cause indicates that addressing fibrosis is a pertinent therapeutic goal. However, not all patients may experience recompensation, and suggesting that even though clinical improvement occurs, complete resolution of CSPH may not be achieved with treatment [22, 23].

The persistent elevation of HVPG over time increases the patient's risk of decompensation. Systemic inflammation and CAID are significant triggers of future decompensation and acute-on-chronic liver failure (ACLF). It's clear that to achieve a true

reversal of the pathophysiology of decompensation, there must be evident improvement in these pathways as well [23].

The pathophysiology of decompensation provides guidance on which pathways to achieve recompensation. Currently, we have treatments that target individual pathways of decompensation, but not all of them. This concept has two potential implications. Firstly, as per the definition, the term "recompensated cirrhosis" can only be applied to those etiologies for which there are treatments available that target hepatic fibrosis. Secondly, in the absence of a reversal of the pathophysiology of decompensation, patients with clinically recompensated cirrhosis remain susceptible to future decompensation [18].

The evidence of hepatic recompensation

As the *Baveno VII* criteria are relatively new, limited data is available on hepatic recompensation, and comparisons with previous studies may be biased due to varying definitions of recompensation. However, earlier reports on liver transplant candidates being removed from the waiting list after showing clinical improvement and the regression to Child-Pugh stage A cirrhosis following treatment of the underlying cause may provide initial insights [1].

It's important to note that curing, removing, or suppressing the primary etiologic of cirrhosis is essential for achieving hepatic recompensation. So far, this has only been clearly defined for alcohol-related liver disease (ALD), hepatitis C virus (HCV), and hepatitis B virus (HBV) associated liver disease. Because different etiologies of liver disease have unique natural histories and present distinct clinical and therapeutic challenges, this review provides a comprehensive and etiology-specific assessment of existing data on hepatic recompensation.

Alcohol-related cirrhosis. The cessation of the underlying cause in alcohol-related cirrhosis, such as sustained abstinence from alcohol-containing beverages and foods, has been associated with a notably improved prognosis [13]. Despite the evident benefits of alcohol abstinence overall, there is limited understanding of the clinical implications of abstinence-induced improvements in patients with decompensated cirrhosis. A significant study was conducted in 1996 by *Vorobioff et al.* that prospectively evaluated the clinical course of patients with alcohol-related cirrhosis and correlated abstinence with notable improvements in Child-Pugh score and portal pressure. However, these findings are constrained by the small size of the study cohort and the low proportion of decompensated patients [25].

The initial insights focused on recompensation in ALD were presented by *Aravinthan et al. (2017).* They examined the removal of liver transplant candidates from the waiting list after achieving recompensation. Out of 284 ALD patients studied, 16.5% (47 patients) reached recompensation, defined by the absence of ascites and hepatic encephalopathy despite treatment discontinuation, along with a decrease in the MELD score to less than 15. The major factors which were associated with higher probability of delisting after recompensation in the multivariable model were a low MELD score and high serum albumin levels at the time of listing for transplantation. This highlights how serum albumin can be used as a better prognostic indicator [1].

Pose et al. (2021) similarly found that a subset of patients with decompensated alcohol-related cirrhosis listed for transplantation experienced significant clinical improvements, with 8.6% of all patients (36 out of 420) achieving such improvements and subsequently being removed from the transplant list. Upon delisting, most of these patients exhibited signs of hepatic recompensation, including the resolution of ascites and hepatic encephalopathy. However, more than 20% of delisted patients still required low-dose diuretic therapy, and 3% experienced an episode of overt hepatic encephalopathy within 3 months of delisting, not meeting the criteria for recompensation according to the *Baveno VII* guidelines. Factors such as female sex, lower height, lower MELD score, and higher platelet count were independently associated with a higher likelihood of delisting. Two-thirds of all delisted patients were alive after a median follow-up period of more than 3 years, with nearly 90% of them remaining compensated. However, the authors observed that 25% of delisted patients experienced liver disease progression, primarily following alcohol relapse [17] .

Hepatitis-C associated liver cirrhosis. Highly effective interferon-free direct-acting antiviral (DAA) treatments have revolutionized the management of chronic HCV infections, making successful cure the norm. While DAA therapy shows the highest efficacy in patients without liver disease or with compensated liver disease, even those with prior hepatic decompensation can achieve a sustained virological response (SVR) in 80–90% of cases with sofosbuvir-based regimens [8].

Studies, including the ASTRAL-4 trial, indicate that DAA therapy can lead to short-term improvements in liver function, evidenced by reductions in MELD and Child-Pugh scores. For instance, 81% of patients with a baseline MELD ≥15 and 51% with MELD <15 showed reduced MELD scores post-treatment. However, the long-term benefits are less clear, with some studies showing no significant improvement in survival or sustained liver function over extended follow-up periods [15].

El-Sherif et al. (2018) demonstrated that 31.6% of Child-Pugh B and 12.3% of Child-Pugh C patients regressed to Child-Pugh A following DAA therapy, with key factors for regression including absence of ascites or HE, high albumin, low bilirubin and ALT levels, and low BMI. Achieving SVR12 was linked to a reduced risk of transplantation or death and higher likelihood of clinical improvements [5].

Further studies have shown varied outcomes in delisting patients from transplant lists. For example, *Perricone et al.* reported that 31% of transplant candidates with HCV-associated cirrhosis were delisted due to clinical improvements, with 91% regressing to Child-Pugh A [16]. However, a significant minority of delisted patients experienced recurrent complications such as ascites and hepatocellular carcinoma (HCC). Overall, while DAA therapy offers substantial short-term benefits for patients with advanced liver disease, the long-term outcomes, particularly regarding survival and sustained liver function, require further investigation (Table 1).

undetectable levels in up to 80% of patients within one year [7].

Multiple studies have shown that long-term NUC therapy improves hepatic function in patients with prior decompensation, with significant decreases in MELD and Child-Pugh scores and normalization of ALT levels. A prospective multicenter study by *Jang et al.* involving 707 patients with initial decompensation demonstrated that antiviral therapy significantly improved hepatic function and transplant-free survival, at 60 months, 12% of treated patients with a baseline Child-Pugh score ≥7 reduced to Child-Pugh stage A, and 33.9% of those listed for liver transplantation were delisted within 12 months due to clinical improvements [12].

Xu et al. (2021) identified factors linked to recompensation in a retrospective case-control study of 553 recompensated patients, primarily with HBV cirrhosis. One-third of decompensated patients treated with entecavir or adefovir had a reduction in Child-Pugh score by more than 2 points or an

Table 1

Benefits of antiviral therapy (DAA for HCV and NUC for HBV) associated with recompensation of liver cirrhosis. [1, 5, 8, 15, 16, 17]

Aspect	HCV-Associated Cirrhosis	HBV-Associated Cirrhosis
Therapy Type	Direct-acting antivirals (DAAs)	Nucleoside/nucleotide analogues (NUCs)
Viral Clearance	High clearance rate, 80-90% with sofosbuvir-based regimens	Long-term viral suppression, but no complete viral elimination
Short-Term Benefits	Significant improvement in MELD and Child-Pugh scores post-treatment	Significant improvement in MELD and Child-Pugh scores, normalization of ALT levels
Long-Term Benefits	Mixed results, some studies show no significant long-term improvement	Significant improvement in hepatic function and transplant-free survival
Predictive factors for recompensation	Absence of ascites or HE, high level of albumin, low level of bilirubin, high level of ALT, normal BMI. Early recompensation linked to sustained clinical improvements	Albumin, total protein, hemoglobin, ALT, basophil percentage, neutrophil-to-lymphocyte ratio, absence of diabetes
Benefits of antiviral therapy	DAAs are effective but long-term benefits need further study. Short-term improvement does not always translate to long-term survival	Treatment with NUCs achieve significant improvements in hepatic function by long-term viral suppression, that induce recompensation and delisting from transplant list

Hepatitis-B associated liver cirrhosis. While novel DAA treatments achieve viral clearance in the most HCV patients, therapies for chronic HBV infections have not yet reached the same level of success in eliminating the virus. However, current HBV therapies can achieve long-term viral suppression in most patients, especially with good drug compliance. For patients with prior hepatic decompensation, nucleoside/nucleotide analogues (NUCs) are recommended, reducing HBV-DNA to

improvement in Child-Pugh class, with notable improvements in ascites and HE. Predictive factors linked to recompensation included albumin, total protein, hemoglobin, ALT, basophil percentage, neutrophil-to-lymphocyte ratio, and diabetes [27]. (Table 1).

Wang et al. (2022) applied the *Baveno VII* criteria in a multicenter study, administering entecavir therapy to 320 patients with decompensated HBV cirrhosis. Factors associated with resolution included

high baseline AST and sodium, and high platelet count and albumin at 48 weeks. Of the patients followed beyond 120 weeks, 91.2% remained compensated over a median follow-up of 144 weeks. After 120 weeks, 60.4% achieved sustained resolution of ascites and HE [9]. However, the clinical applicability of these findings is limited by the study design and lack of established scoring systems [12].

Key Factors of Recompensation

Recompensation in decompensated cirrhosis is driven by a combination of antiviral therapy, for hepatitis B and C, and NSBB, which reduce portal hypertension and systemic inflammation. Effective management of complications such as HE, ascites, and bacterial infections, along with lifestyle modifications like alcohol abstinence, are crucial factors for recompensation. The pathophysiological mechanisms underlying recompensation in cirrhosis involve a complex interplay of hepatic cellular regeneration, reduction of hepatic fibrosis, and improved vascular dynamics within the liver. The reversal of fibrogenesis, a process mediated by decreased hepatic stellate cell activation and matrix degradation, is fundamental to recompensation. Gender-specific responses to recompensation have been observed, with female sex generally exhibiting a more favorable outcome compared to males. This disparity may be attributed to differences in hormonal profiles, genetic factors, and the differential impact of alcohol metabolism on liver between genders. Additional factors contributing to recompensation include nutritional support, management of comorbid conditions, and adherence to a tailored therapeutic regimen. Optimal management of diabetes and obesity is essential in reducing metabolic stress on the liver. Patient adherence to prescribed medical treatments, including diuretics, NSBB, and other supportive medications, further effects the recompensation process [2, 11, 14].

Discussion

Our review of current literature demonstrated that antiviral therapy and lifestyle modifications, such as alcohol cessation, significantly enhance prognosis and facilitate hepatic recompensation in patients with decompensated cirrhosis. Multiple studies underscore the efficacy of these interventions in improving clinical outcomes and reducing liver-related mortality. In a study conducted by *Wang Q. et al.* [26], 283 of 320 patients with decompensated cirrhosis completed a 120-week follow-up, with 261 (92.2%) achieving HBV DNA levels < 20 IU/ml, and 171 (60.4%) experiencing resolution of ascites, encephalopathy, and absence of recurrent variceal bleeding for at least 12 months. Of these, 159 (56.2%) met the criteria for stable improvement in liver function tests, defined by a MELD score < 10 and/or Child-Pugh Class A. Also, in a cohort of 89 HCV patients conducted by *Gentile et al.,* 95.5% achieved SVR, with 61.8% improving to Child-Pugh Class A post-treatment, and significant enhancements in liver parameters [8]. *Hofer et al.* among 204 patients with decompensated alcohol-related cirrhosis, 37 (18.1%) achieved recompensation through sustained abstinence over a median follow-up of 24.4 months [10]. Lower baseline HVPG, Child-Pugh score, BMI, higher albumin levels, and mean arterial pressure were significantly linked to higher recompensation rates, leading to a marked reduction in liver-related mortality [10]. These results collectively highlight that antiviral therapies and lifestyle modifications (alcohol cessation) are pivotal in achieving hepatic recompensation, thus improving the long-term prognosis for patients with decompensated cirrhosis (Table 2) [5, 15].

Conclusion

Recompensation in decompensated cirrhosis is achievable through a multifaceted approach encompassing etiological/antiviral therapy, alcohol abstinence, gender-specific considerations, and comprehensive medical management. Evidence of recompensation has been documented extensively in clinical studies, with measurable improvements in liver function tests, decreased incidence of variceal bleeding, reduced ascites, and improved survival rates.

The pathophysiological basis of recompensation highlights the liver's inherent regenerative capacity and underscores the potential for significant clinical improvement with appropriate therapeutic interventions. Imaging studies, including elastography and magnetic resonance imaging, have substantiated these findings by demonstrating reduced liver stiffness and improved hepatic morphology in patients who achieve recompensation.

Antiviral agents have been shown to significantly reduce viral load, subsequently diminishing liver inflammation and fibrosis. This therapeutic approach halts the progression of hepatic damage and promotes hepatic regeneration, thereby enhancing recompensation rates.

Alcohol abstinence is another paramount factor. Continued alcohol consumption exacerbates liver injury, hepatic inflammation, and accelerates the progression of cirrhosis. On the other hand, strict abstinence has been correlated with a marked improvement in liver function, stabilization of disease, and in many instances, partial reversal of liver damage, facilitating recompensation.

Table 2

Recompensation Factors and Prognosis in Decompensated Cirrhosis Patients Across Different Etiologies.

Etiology	NB	Recompensation Factors	Prognosis
HBV-related decompensated cirrhosis. (*He Z, et.al*) [9].	283	Achieved HBV DNA levels <20 IU/ml, resolution of ascites, encephalopathy, and no recurrent variceal bleeding for at least 12 months	56.2% met stable improvement criteria (MELD <10, Child-Pugh A), significant reduction in mortality
HCV-related decompensated cirrhosis. (*Gentile, I et.al*) [8].	89	Sustained abstinence, lower baseline HVPG, lower Child-Pugh score, lower BMI, higher albumin levels, higher mean arterial pressure	18.1% achieved recompensation, significant reduction in liver-related mortality (adjusted HR: 0.091)
HCV/HIV coinfected patients. (*Quaranta, MG et. al*. Liver function following hepatitis C virus eradication by direct acting antivirals in patients with liver cirrhosis: data from the PITER cohort. In: *BMC Infect Dis.* 2021, nr. 21(1), pp. 413.	108	Sustained virologic response 12 (SVR12), improvement to Child-Pugh Class A	61.8% improved to Child-Pugh A, significant liver parameter improvements
HCV monoinfected patients (*Quaranta, MG et. al*. Liver function following hepatitis C virus eradication by direct acting antivirals in patients with liver cirrhosis: data from the PITER cohort. In: *BMC Infect Dis.* 2021, nr. 21(1), pp. 413.	1242	HIV-associated factors: more advanced liver disease before treatment (OR: 3.73), significant improvement post-eradication	85% improved C-P class, lower rate of decompensation compared to HCV monoinfected
Alcohol-related decompensated cirrhosis. (*Hofer, BS et.al*) [10].	204	Post-eradication improvement, factors associated with worsening: male sex, low platelet count, elevated INR	64.6% improved C-P class, significant improvements in clinical outcomes

Additionally, amelioration of portal hypertension through medical or interventional therapies improves the hemodynamics of liver, promoting a more favorable condition for hepatic recovery.

Overall, our review highlighted the critical role of tailored antiviral therapies and lifestyle changes in achieving hepatic recompensation, thereby improving long-term outcomes and reducing liver-related mortality in patients with decompensated cirrhosis. Further research is necessary to evaluate the long-term effects on survival and quality of life.

Conflict of interest declaration

The authors declare that there is no conflict of interest.

Funding statement

No funding was received for this work.

Bibliography

1. ARAVINTHAN, A.D., BARBAS, A.S., DOYLE, A.C., et al. Characteristics of liver transplant candidates delisted following recompensation and predictors of such delisting in alcohol-related liver disease: a case-control study. In: *Transpl Int.* 2017, nr. 30, pp. 1140-1149. ISBN: 978-973-115-052-9.
2. COSTA, D., SIMBRUNNER, B., JACHS, M., et al. Systemic inflammation increases across distinct stages of advanced chronic liver disease and correlates with decompensation and mortality. In: *J Hepatol.* 2021, nr. 74, pp. 819-828. ISBN: 978-973-115-052-9.
3. D'AMICO, G., PASTA, L., MORABITO Competing risks and prognostic stages of cirrhosis: a 25-year inception cohort study of 494 patients. In: *Aliment Pharmacol Ther.* 2014, nr. 39, pp. 1180-1193. ISBN: 978-973-115-052-9.
4. DE FRANCHIS, R., BOSCH, J., GARCIA-TSAO, G., et al. "Baveno VII–Renewing Consensus in Portal Hypertension." In: *Journal of Hepatology.* 2022, nr. 76.4, pp. 959-974. ISSN 0168-8278.
5. EL-SHERIF, O., JIANG, Z.G. Baseline factors associated with improvements in decompensated cirrhosis after direct-acting antiviral therapy for hepatitis C virus

infection. In: *Gastroenterology.* 2018, nr. 154(8), pp. 2111-2121. ISSN 0016-5085.
6. FERENCI, P., LOCKWOOD, A., MULLEN, K Hepatic encephalopathy – definition, nomenclature, diagnosis and quantification: final report of the working party at the 11th world congresses of gastroenterology, Vienna 1998. 2002, pp. 716-721. ISBN: 978-973-115-052-9.
7. FONTANA, R.J., HANN, H.W. Factors influencing early mortality in patients with decompensated chronic hepatitis B undergoing antiviral therapy. In: *Gastroenterology.* 2002, nr. 123(3), pp. 719–727. ISSN 0016-5085.
8. GENTILE, I., SCOTTO, R., COPPOLA, C., 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). In: *Hepatol Int.* 2019, nr. 13(1), pp. 66-74. ISBN: 978-973-115-052-9.
9. HE, Z., WANG, B. Recompensation in treatment-naïve HBV-related decompensated cirrhosis: a 5-year multicenter observational study comparing patients with ascites and bleeding. In: *Hepatol Int.* 2023, nr. 17(6), pp. 1368-1377. ISSN 1936-0533.
10. HOFER, B.S., BURGHART, L., HALILBASIC, E., et al. Editorial: Recompensation in PBC is good. But is it good enough? In: *Alimentary Pharmacology & Therapeutics.* 2024, nr. 59(9), pp. 1146-1147. ISBN: 978-973-115-052-9.
11. JACHS, M., HARTL, L., SCHAUFLER, D., et al. Amelioration of systemic inflammation in advanced chronic liver disease upon beta-blocker therapy translates into improved clinical outcomes. In: *Gut.* 2021, nr. 70, pp. 1758-1767. ISBN: 978-973-115-052-9.
12. JANG, JEONG WON. Long-Term Effect of antiviral therapy on disease course after decompensation in patients with Hepatitis B related cirrhosis. In: *Hepatology*. 2015, nr. 61(6), pp. 1809-1820. ISSN 0016-5085.
13. LACKNER, C., SPINDELBOECK, W., HAYBAECK, J., et al. Histological parameters and alcohol abstinence determine long-term prognosis in patients with alcoholic liver disease. In: J Hepatol. 2017, nr. 66(3), pp. 610-618. ISSN 0168-8278.
14. LENS, S., BAIGES, A., ALVARADO-TAPIAS, E., et al. Clinical outcome and hemodynamic changes following HCV eradication with oral antiviral therapy in patients with clinically significant portal hypertension. In: *J Hepatol.* 2020, nr. 73, pp. 1415-1424. ISSN 0168-8278.
15. PASCASIO, J.M., VINAIXA, C. Clinical outcomes of patients undergoing antiviral therapy while awaiting liver transplantation. In: *Journal of Hepatology.* 2017, nr. 67(6), pp. 1168-1176. ISSN 0168-8278.
16. PERRICONE, G., DUVOUX, C. European Liver and Intestine Transplant Association (ELITA). Delisting HCV-infected liver transplant candidates who improved after viral eradication: Outcome 2 years after delisting. *In: Liver Int.* 2018; nr. 38, pp. 2170–2177. ISSN 1478-3231.
17. POSE, E., TORRENTS, A., REVERTER, E., et al. A notable proportion of liver transplant candidates with alcohol-related cirrhosis can be delisted because of clinical improvement. In: *J Hepatol.* 2021, nr. 75(2), pp. 275-283. ISBN: 978-973-115-052-9.
18. REIBERGER, T., FERLITSCH, A., PAYER, B.A., et al. Non-selective beta-blocker therapy decreases intestinal permeability and serum levels of LBP and IL-6 in patients with cirrhosis. In: *J Hepatol.* 2013, nr. 58, pp. 911-921. ISSN 0168-8278.
19. REIBERGER, T., HOFER, B.S. The Baveno VII concept of cirrhosis recompensation. In: *Digestive and Liver Disease.* 2023, no. 55(4), pp. 431-441. ISSN 1590-8658.
20. RIPOLL, C., BARI, K., GARCIA-TSAO, G. Serum albumin can identify patients with compensated cirrhosis with a good prognosis. In: *J Clin Gastroenterol.* 2015, nr. 49(7), pp. 613-619. ISBN: 978-973-115-052-9.
21. RIPOLL, C., GROSZMANN, R., GARCIA-TSAO, G., et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. In: *Gastroenterology.* 2007, nr. 133, pp. 481-488. ISBN: 978-973-115-052-9.
22. SHARMA, S., ROY, A. Recompensation in cirrhosis: current evidence and future directions. In: *Journal of Clinical and Experimental Hepatology.* 2023, no. 13(2), pp. 329-334. ISSN 0973-6883.
23. VILLANUEVA, C., ALBILLOS, A., GENESCA, J., et al. Bacterial infections adversely influence the risk of decompensation and survival in compensated cirrhosis. In: *J Hepatol.* 2021, nr. 75, pp. 589-599. ISBN: 978-973-115-052-9.
24. VILLANUEVA, C., ALBILLOS, A., GENESCA, J., et al. Development of hyperdynamic circulation and response to beta-blockers in compensated cirrhosis with portal hypertension: liver failure/cirrhosis/portal hypertension. In: *Hepatology.* 2016, nr. 63, pp. 197-206. ISBN: 978-973-115-052-9.
25. VOROBIOFF, J., GROSZMANN, R. J., PICABEA, E., et al. Prognostic value of hepatic venous pressure gradient measurements in alcoholic cirrhosis: A 10-year prospective study. In: Gastroenterology. 1996, nr. 111(3), pp. 701-709. ISSN 0016-5085.
26. WANG, Q., ZHAO, H., DENG, Y., et al. Validation of Baveno VII criteria for recompensation in entecavir-treated patients with hepatitis B-related decompensated cirrhosis. In: *J Hepatol.* 2022, nr. 77(6), pp. 1564-1572. ISSN 0168-8278.
27. XU, X., WANG, H. Recompensation factors for patients with decompensated cirrhosis: a multicentre retrospective case-control study. In: *BMJ.* 2021, nr. 11(6), e043083. ISSN 2044-6055.

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