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Recompensation in Cirrhosis: Current Evidence and Future Directions

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The natural history of cirrhosis has usually been conceptualized in the context of progression from compensated cirrhosis to subsequent stages of decompensation. While this unidirectional concept is the most common pathophysiological trajectory, there has been an emerging understanding of a subgroup of patients which undergo recompensation. While literature mostly based on transplant waitlist registries have indicated towards such a population who experience disease regression, the overall literature about this entity remains inexplicit. An effort to generate consensus on defining recompensation has been attempted which comes with its own nuances and limitations. We summarize the available literature on this emerging yet controversial concept of recompensation in cirrhosis and delve into future implications and impact on real-life practice. (J Clin Exp Hepatol xxxx;xxx:xxx)

Chronic liver disease (CLD) is one of the leading causes of mortality around the world. The paradigm of CLD involves a transition from a compensated stage in which a patient may be asymptomatic to a stage of decompensated cirrhosis which may progress and result in poor survival.[1] Decompensated cirrhosis is defined as the appearance of any of the following manifestations: ascites, variceal bleeding, and/or hepatic encephalopathy (HE).[2] Once decompensated, these patients are prone to develop additional decompensations such as refractory ascites and other complications such as acute on chronic liver failure. This transition of one stage to another in decompensated cirrhosis is classically unidirectional in the pioneer natural history studies.[3–5] However, it has begun to realize that this may not always be a one-way traffic. With the concept of potential reversibility at each stage of portal hypertension, hepatologists around the world have started observing a distinct sub-group of patients with decompensated cirrhosis who revert to the original compensated stage. Although the data is preliminary, observational, and largely retrospective based on transplant wait list registries, this has led to a new concept of recompensated cirrhosis. With the advent of aetiology-specific treatment, the term recompensated cirrhosis will become more relevant in the future.

Understanding that this is a new term which may have varied meanings and relevance to treating hepatologists/gastroenterologists around the world, we in this review focus on different aspects of recompensated cirrhosis. However, we acknowledge that this data is preliminary. This will continue to evolve in the future as we become more familiar with this entity.

DEFINITION OF RECOMPENSATED CIRRHOSIS

Decompensated cirrhosis is defined as the appearance of one or more of the above-mentioned clinical decompensations.[2] The fundamental concept underlying recompensation is in having at least a partial regression of the structural and functional changes of cirrhosis after removal of the aetiology of cirrhosis. Translating to clinical practice, for a patient to be considered recompensated, this would involve the disappearance of existing and no new onset of further decompensation for a prolonged period of time (Figure 1). To avoid ambiguity, Baveno-VII consensus has defined recompensated cirrhosis when all the following criteria are met:[6]

a) Resolution of clinical manifestations such as ascites (without the concurrent use of diuretics), HE (without the use of prophylactic medications), and absence of recurrent variceal bleeding for at least a duration of 12 months.

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Abbreviations: ALD: Alcoholic liver disease; ALF: Acute liver failure; APASL: Asia Pacific Association for the Study of Liver; cACLD: Compensated advanced chronic liver disease; CAID: Cirrhosis associated immune dysfunction; CSPH: Clinically significant portal hypertension; CTP: Child-Turcotte-Pugh; DC: Decompensated cirrhosis; FAP: Familial amyloid polyneuropathy; HBV: Hepatitis B Virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C Virus; HE: Hepatic encephalopathy; HVPG: Hepatic venous portal gradient; INR: International normalized ratio; LT: Liver transplantation; MELD: Model for end-stage liver disease; TIPSS: Transjugular intrahepatic porto-systemic shunt
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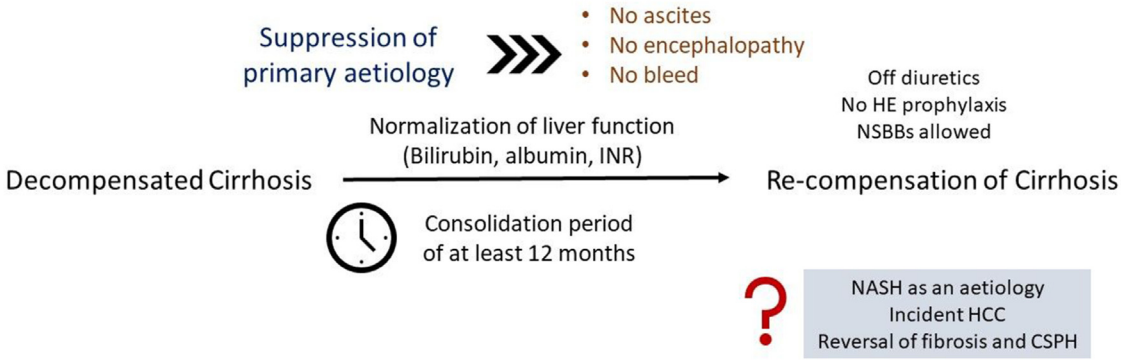

Figure 1 Schematic representation of the concept of recompensation in cirrhosis.

b) Removal or suppression of primary aetiological cause of liver disease such as alcohol abstinence or effective viral suppression.
c) Improvement in synthetic liver function such as serum albumin, International Normalized Ratio (INR), and bilirubin.

The most important aspect in this concept of reversibility is the presence of stringent criteria for calling a patient as recompensated. As mentioned in definition, subgroups of patients such as diuretic controlled ascites or those on treatment for prevention of HE cannot be considered recompensated. An exception to this rule is patients with variceal bleeding prophylaxis with either nonselective beta blockers (NSBB) and transjugular intrahepatic portosystemic shunt (TIPS) placement. From the definition, it can be implied that the term recompensated cirrhosis cannot be used presently for aetiologically nonmodifiable causes of cirrhosis such non-alcoholic fatty liver disease (NAFLD). The emphasis on improvement in synthetic functions of liver is because, after hepatic venous pressure gradient (HVPG) estimation, serum albumin has emerged as the most important predictor of survival in natural history studies of advanced compensated cirrhosis.[7] Unlike HVPG, the changes in serum albumin are easy to measure and demonstrate improvement. What this also implies is that for studies evaluating recompensation, demonstrating improvement in prognostic scores incorporating albumin (Child Turcotte Pugh, Albumin-Bilirubin Score) may be more relevant than demonstrating changes in model for end-stage liver disease (MELD) score.

PATHOPHYSIOLOGY OF RECOMPENSATED CIRRHOSIS: A POTENTIAL STEP BEYOND CLINICAL IMPROVEMENT

For a patient with decompensated cirrhosis to be restratified as recompensated cirrhosis, not only should there be a disappearance of clinical manifestations, but also reversal of pathways which trigger, sustain, and predispose to further clinical decompensations. Isolated clinical decompensation without reversal of underlying pathophysiology can put patients at risk of future decompensations. The drivers of decompensation are.

1) Presence of clinically significant portal hypertension (CSPH) with its consequent changes such as hyperdynamic circulation, increased cardiac output, and splanchnic vasodilatation.[8]
2) Hepatic fibrosis and increased intrahepatic vascular resistance.
3) Increased gut permeability, endotoxemia, bacterial translocation, and subsequent activation of systemic inflammation.[9]
4) Cirrhosis-associated immune dysfunction (CAID) and risk of infections.[10]

For a patient to be considered recompensated, there should be an improvement seen in one or the other pathways. For example, NSBB and TIPS placement can promote recompensation by not only targeting portal pressure-dependent pathway but also the systemic inflammatory and the gut permeability pathway.[11,12] The relative contribution of these pathways to sustain decompensation and the potential of these modalities to completely reverse them is the reason why only subset of patients on these therapeutic modalities revert to recompensated state. Hepatic fibrosis contributes to increased vascular resistance and can revert with aetiology-specific treatment. While hepatic fibrosis is relatively an early player in the pathophysiology of portal hypertension and subsequent decompensations, reversal of clinical manifestations after targeting aetiology suggests this is a relevant therapeutic target. However, not all patients may recompensate and there is data to suggest that even though clinical improvement occurs, complete reversal of CSPH does not occur with treatment.[13] The persistently increased HVPG over time puts the patient at risk of decompensation. Systemic inflammation and CAID are important triggers of future decompensation and ACLF and it is not

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Table-1 Available Evidence Based on Literature Review Highlighting the Data on Recompensation.

Authors/Year/ Country	Design	Key Selection criteria	Aetiology of CLD	Definition of recompensation	Key results	Limitations
Xu *et al.* (2021)/ China[15]	Retrospective	Inclusion: Adults (>18) with decompensated cirrhosis (any aetiology) Exclusion: Malignancies including HCC, ACLF as defined by APASL, cardiac failure, renal failure, elective admissions	HBV (41%) HCV (5.8%) ALD (1.1%) AIH (4.3%) Others (23.1%)	Clinically stable outpatients with either controlled ascites or previously treated decompensation events who were clinically stable for at least 1 year	• 553 patients with recompensation • Decision tree model used to identify predictors of recompensation: • Albumin ≥40 g/L as the most influential indicator of occurrence of recompensation.	• No external validation • Common prognostic scores like CTP, MELD not used
Aravinthan *et al.* (2017)/ Canada[14]	Retrospective	Inclusion: Transplant waitlisted patients with DC but later delisted following recompensation Exclusion: HCC, vascular liver disorders, metabolic liver disorders, ALF, transplantation, patients listed for decompensation and later delisted for reasons other than recompensation,	ALD (30%) NAFLD (12%) HCV (20%) HBV (6%) AIH (4%) Others (28%)	The absence of ascites/hepatic hydrothorax/ peripheral oedema (off diuretics), the absence of HE (off prophylactic treatment), and an improvement in the MELD score to <15 after a hold period of 6 months for confirming durability of recompensation	• Out of 935 listed patients 77 (8.2%) had recompensation • ALD was largest aetiological cohort of recompensation (47/ 77). • MELD <20 and Albumin>3.2 g/dl were only predictors of recompensation. • If both were present there was a 70% chance of recompensation in those abstinent	• Overall cohort was alcohol predominant • Dynamic profile of patients not evident • Even for those with alcohol risk stratification with lifetime alcohol usage not available
Pose *et al.* (2021)[16]	Retrospective	Inclusion: Patients listed for LT for any aetiology Exclusion: HCC, Re-transplantation, FAP, Polycystic liver disease	ALD (42%) HCV (40%) Others (20%)	Focuses on delisting due to clinical improvement	• Out of 1001 waitlisted patients 70 (7%) had clinical improvement leading to delisting • Probability of delisting significantly more in HCV and alcohol as an aetiology • With alcohol as an aetiology, female sex, lower MELD, and high platelets were predictors of delisting.	• Does not define a "recompensation" criteria • Lack of monitored alcohol abstinence
Pascasio *et al.* (2017)[17]	Retrospective	Inclusion: Patients with HCV DC listed for LT Exclusion: Patients with DC with concurrent HCC	HCV	Focuses on delisting due to improvement and does not address recompensation definition	• Out of 122 patients 29 (24%) got delisted. • Delta MELD between listing and end of treatment was the only predictive factor • No patient with MELD >20 got delisted	• Does not define a "recompensation" criteria

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Table-1 (*Continued*)

Authors/Year/ Country	Design	Key Selection criteria	Aetiology of CLD	Definition of recompensation	Key results	Limitations
Perricone *et al*. (2018)[18]	Prospective	Inclusion: HCV DC listed for LT Exclusion: HCC	HCV	Delisting criteria: Sustained Virological Response Regression of HE and of ascites MELD <15. Low doses of diuretics (frusemide 25 mg and aldosterone antagonist 100 mg)	• Out of 142 patients 44 (30.9%) were delisted. • 4 patients required re-listing. • Complete discontinuation of diuretics in those with ascites was an important cause of relisting • None with MELD >20 got delisted	• Does not define a "recompensation" criteria
Nabatchikova *et al*. (2021)[19]	Prospective	Inclusion: HCV DC with MELD >15 listed for LT Exclusion: HCC, ALF, re-transplantation	HCV	Delisting criteria: MELD score <15 and a CTP score <7 at the time of SVR and/or during subsequent follow up they exhibited a durable clinical improvement, with a MELD score <15 and a CTP score of 7	• Out of 45 patients, 26 (57.8%) experienced delisting • Male gender, baseline CTP class C and delta prothrombin index <2% between baseline and at the time of SVR were independent risk factors of non-delisting	• Does not define a "recompensation" criteria • Overall low MELD scores at listing for the cohort

*APASL, Asia Pacific Association for the Study of Liver; ALF, Acute liver failure; ALD, Alcoholic liver disease; AIH, autoimmune hepatitis; CLD, Chronic liver disease; CTP, Child-Turcotte-Pugh; DC, Decompensated cirrhosis; HBV: Hepatitis B Virus; HCV, Hepatitis C Virus; FAP, Familial amyloid polyneuropathy; HE, Hepatic encephalopathy; HCC Hepatocellular carcinoma; LT, Liver transplantation; MELD, Model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; SVR, Sustained Virological Response.

difficult to understand that for a true reversal of pathophysiology of decompensation, there must be a demonstrable improvement in these pathways as well.

The pathophysiology of decompensation also lays down a roadmap for pathways to target to achieve recompensation. Presently, we have agents that target one or the other but not all pathways of decompensation. This concept has two potential implications. First, as outlined in the definition that the term recompensated cirrhosis can only be applied to those aetiologies which have treatment available which targets hepatic fibrosis. Second, in the absence of reversal of pathophysiology of decompensation, patients with clinically recompensated cirrhosis remain at risk of future decompensations.

DATA ON RECOMPENSATED CIRRHOSIS

In view of an evolving concept, we conducted a systematic search of literature using the terms "recompensation", "cirrhosis" and "chronic liver disease" in different Boolean combinations in MEDLINE, EMBASE, and grey literature search of Google Scholar. An analysis of the literature shows only two studies which specifically indicate towards a criteria for recompensation while others focus on the outcome of delisting from transplant waitlist especially in HCV cohorts.[14,15] A summary of selected studies is shown in Table 1. We have elaborated on a few of the studies focusing on delisting as these may serve as important data sources for future definitions of recompensation. While largely retrospective, based on transplant registries database and confined to mostly viral aetiologies and alcoholic liver disease (ALD), the data suggest that patients with decompensated cirrhosis may recompensate and remain asymptomatic over a period of time. However, recompensation is not uniform and may occur in only subgroup of patients. Some aspects such as risk of primary liver cancer may remain despite clinical recompensation. Understanding the risks of selection bias, there is a need to prospectively assess this concept in future studies involving a cohort of decompensated cirrhosis not necessarily restricted to transplant registries.

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RECOMPENSATED CIRRHOSIS- A TERM SPECIFIC TO AETIOLOGY

As highlighted previously, the term recompensated cirrhosis is only limited to aetiologies where a clear cause is identified and can be targeted. This limits the application of this term to aetiologies like viral cirrhosis and ALD. According to the present evidence, patients with NAFLD by definition cannot be categorized as recompensated despite fulfilling other criteria. This may limit the application of this term as NAFLD remains the most common form of liver disease and in the future may become the leading cause of cirrhosis and its complications worldwide. There is an evidence that sustained weight loss decreases hepatic steatosis and can cause reversal of fibrosis. Defining recompensation in the context of NAFLD may need modification of the criteria mentioned above in the future. However, the pertinent question in this aspect is whether or not a patient with NAFLD can ever be considered recompensated as data regarding recompensation in NAFLD does not exist unlike other aetiologies. Conceptualizing a model to define recompensation in NAFLD cirrhosis with the current backdrop of aetiological suppression would be challenging given the dynamics of metabolic risk factors once cirrhosis sets in-patients with NAFLD.

COMPENSATED CIRRHOSIS AND RECOMPENSATED CIRRHOSIS

While both have absence of current clinical decompensation, it is important to understand the difference between recompensated cirrhosis and its compensated counterpart called compensated advanced CLD (cACLD). The term cACLD was coined by Baveno consensus to identify patients who although asymptomatic, are at increased risk of harbouring advanced fibrosis and future risk of complications.[6] There are well-validated cut-off criteria based on transient elastography to not only diagnose but also to prognosticate patients with cACLD with regard to long-term outcomes. Unfortunately, little is known about the long-term outcomes and prognostic stratification about recompensated cirrhosis. Another term which refers to a similar spectrum is compensated cirrhosis which has also been an acceptable term although further granularity is needed before the two terms c ACLD and CC can be used interchangeably.[6]

RECOMPENSATED CIRRHOSIS: ALL-OR-NONE PHENOMENON?

For a patient to be called recompensated, all the above-mentioned criteria (outlined in definition) must be fulfilled. However, it is unclear if recompensated cirrhosis is truly an all-or-none phenomenon. For example, each stage of decompensated cirrhosis has its distinct prognostic implication based on types and numbers of decompensation. In other words, this represents a continuum of a series of events than the final outcome alone. Whether or not the same can be said about recompensated cirrhosis is not known at present. Distinct stage of recompensation may well exist and there is a need to explore this aspect in future studies.

RECOMPENSATED CIRRHOSIS: CAUTIONS USING THIS TERM

For the reasons mentioned above, its clinical course and long-term outcomes need to be assessed in the future and cannot be extrapolated from that of compensated cirrhosis. Adapting a concept of recompensation can have its own ethical issues, especially in countries where disease-specific scores are used to decide the timing of transplantation. Labelling a patient recompensated may lead to delisting from transplant list. This is especially relevant as we don't know the long-term outcomes of this entity presently. Furthermore, the applicability of policies like complete discontinuation of anti-HE measures especially lactulose also needs to be explored in prospective studies prior to making them a core feature of diagnostic recommendation. Other aspects of decompensated cirrhosis such as risk of primary liver cancer may not really change, and it is important to continue surveillance even these patients. Therefore, clinicians should cautiously use this term to identify and manage their patients based on the limited data at present.

The concept of recompensated cirrhosis is important and should be better defined in future studies. However, before using this term in clinical practice it is important to understand its limitations. The term is largely clinical, can only be applied to those aetiologies where treatment is available, and is based on stringent criteria. The data is preliminary and is mostly based on transplant registries. Future studies should focus on aspects such as demonstrating reversal of pathophysiological abnormalities of pathways of decompensation and outlining the natural history of this group of patients.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Sanchit Sharma: Writing - Original Draft, Writing - Review and Editing.

Akash Roy: Conceptualization, Writing-review and editing, Visualization.

CONFLICTS OF INTEREST

The authors have none to declare.

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