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Compensated liver cirrhosis: Natural course and disease modifying strategies

Kumar R *et al*. Compensated liver cirrhosis

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Abstract

Compensated liver cirrhosis (CLC) is defined as cirrhosis with one or more decompensating events, such as ascites, variceal hemorrhage, or hepatic encephalopathy. Patients with CLC are largely asymptomatic with preserved hepatic function. The transition from CLC to decompensated cirrhosis occurs as a result of a complex interaction between multiple predisposing and precipitating factors. The first decompensation event in CLC patients is considered a significant turning point in the progression of cirrhosis, as it signals a drastic decline in median survival rates from 10 to 12 years to only 1 to 2 years. Furthermore, early cirrhosis has the potential to regress as liver fibrosis is a dynamic condition. With the advent of effective non-invasive tools for detecting hepatic fibrosis, more and more patients with CLC are currently being recognised. This offers clinicians with a unique opportunity to properly manage such

patients in order to achieve cirrhosis regression or, at the very least, prevent its progression. There are numerous emerging approaches for preventing or delaying decompensation in CLC patients. A growing body of evidence indicates that treating the underlying cause can lead to cirrhosis regression, and the use of non-selective beta-blockers can prevent decompensation by lowering portal hypertension. Additionally, addressing various co-factors (such as obesity, diabetes, dyslipidemia, and alcoholism) and precipitating factors (such as infection, viral hepatitis, and hepatotoxic drugs) that have a detrimental impact on the natural course of cirrhosis may benefit patients with CLC. However, high-quality data must be generated through well-designed and adequately powered randomised clinical trials to validate these disease-modifying techniques for CLC patients. This article discusses the natural history of CLC, risk factors for its progression, and therapeutic approaches that could alter the trajectory of CLC evolution and improve outcomes.

Key Words: Compensated cirrhosis; Compensated advanced chronic liver disease; Clinical decompensation; Cirrhosis reversal; Disease modifying agents; Acute-on-chronic liver failure

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Core Tip: Compensated liver cirrhosis (CLC) might be reversible if the underlying cause is treated before the disease progresses. The median survival for these individuals is typically 10 to 12 years; however, after the first decompensation, it drastically drops to 1 to 2 years. As a result, the outcomes of such patients can be significantly improved by integrating a number of disease-modifying therapy strategies that address complex pathophysiology, risk factors, and triggering events linked with disease progression. This article discusses the natural course of CLC, risk factors for its progression, and

potential therapeutic strategies to favourably influence its natural evolution and enhance outcomes.

INTRODUCTION

The prevalence and mortality associated with liver cirrhosis (LC) continue to increase despite improvements in knowledge and medical care. According to data from the United States, the annual number of LC-related deaths has risen by 65%, while the number of hospitalisations for LC has nearly doubled in a decade[1,2]. LC has traditionally been regarded as a singular entity with a continuum of increasing degrees of severity until death or liver transplantation. Recently, these paradigms have shifted, leading to the recognition of LC as a heterogenous condition with varying prognosis across the different stages[3,4]. The term "compensated liver cirrhosis" (CLC) is used to describe LC without one or more decompensating events, such as ascites, hepatic encephalopathy (HE), variceal haemorrhage (VH), and jaundice[5]. After experiencing a decompensation event, LC patients are always classified as decompensated LC (DLC) because the pathogenic mechanisms that caused the decompensation persist. When LC patients were separated into two groups based on decompensating events, the median 1-year survival in CLC patients was 95%, compared to 61% in DLC patients[6]. Therefore, the first decompensation in CLC patients is regarded as a prognostic watershed due to a substantial reduction in median survival from 10 to 12 years in CLC to only 1 to 2 years in DLC[6].

LC has long been viewed as the end stage of chronic liver disease (CLD). However, this perception has started to shift in the past two decades. Wanless *et al*[7] were the first to describe the reversal of LC, and since then, numerous series of LC patients with diverse aetiologies have demonstrated the same[7,8]. Patients with CLC remain asymptomatic and undiagnosed for the first few years[9]. Despite being asymptomatic, between one-third and half of CLC patients have varices and clinically significant portal hypertension (CSPH) at the time of diagnosis[10-12]. Over time, CLC patients develop several risk factors that increase their susceptibility to clinical decompensation, such as

rising portal pressure, systemic inflammation, and hemodynamic changes. Moreover, certain triggers including bacterial infection, medications, or alcohol, can acutely precipitate decompensation. When the underlying cause of CLC is eliminated early on, a significant proportion of patients experience cirrhosis regression[7,8]. Even when regression of LC is not possible, there are variety of evolving strategies for preventing or delaying decompensation in such patients. Therefore, the prognosis of such patients can be greatly enhanced by early diagnosis of CLC. However, the medical community has predominantly focused its efforts on managing and improving the outcomes for patients with DLC, with little attention given to the medical management of CLC. In order to enhance ease of diagnosis of advanced CLD noninvasively using transient elastography, the Baveno VI consensus introduced the new term "compensated advanced CLD" which encompass CLC and CLD with advanced fibrosis[13]. Due to efficient non-invasive testing tools, more and more LC patients are now being recognised at an early compensated stage[14]. This offers the gastroenterologists and hepatologists greater opportunities to intervene and alter the trajectory of natural evolution of CLC. This article discusses the natural history of CLC, risk factors for its progression and decompensation, and potential therapeutic strategies to change the course of the illness and improve the outcomes.

NATURAL HISTORY OF CLC

The natural progression of LC is characterised by a continuum from a long silent compensated phase to a more progressive symptomatic decompensation phase (Figure 1). As LC progresses over time, patients develop a variety of risk factors, including altered liver architecture, portal hypertension (PHT), systemic inflammation, and hemodynamic alterations that increase the risk for clinical decompensation. Decompensation may occur insidiously due to slowly increasing portal pressure and deteriorating hepatic function, often referred to as non-acute decompensation (AD)[5]. However, different triggering events, such as bacterial infection, alcohol, bleeding, medications, or a flare-up of liver disease, can lead to AD within days, which may

progress to acute-on-chronic liver failure (ACLF). In patients with CLC, decompensation represents a turning point in terms of mortality risk, patient quality of life, and propensity for hospitalisation. In a systematic review, pooling of data from relevant studies, revealed that the survival of patients with LC varied from 1 mo to 186 mo, with a median survival > 12 years for CLC and 1.8 years for DLC[6]. The rate of transition from a compensated to a decompensated stage is approximately 5%-7% each year[15]. Ascites is typically the first sign of decompensation in the most studies. Overall, the 5-year mortality rate in CLC patients is only 1.5% for those without CSPH, 5% for those with CSPH but no varices, and 10.0% for those with CSPH and varices, highlighting the significance of PHT in mortality risk[3]. Therefore, CLC patients without varices and without CSPH constitute a highly compensated group with a very low mortality risk[6]. The first decompensation of CLC does not always indicate a point of no return in the natural course of LC. Emerging data suggests that although it is an uncommon occurrence, recompensation of DLC is possible if the underlying cause of LC is suppressed[16]. Recompensated cirrhosis is indeed a real condition, and the Baveno VII consensus has provided a standard definition for it[17]. Similarly, it is now more widely acknowledged that CLC can regress to a non-cirrhotic stage when etiological factors are promptly controlled[7,18]. Liver fibrosis is a dynamic condition, and early LC, which lacks extracellular matrix crosslinking and marked angiogenesis, can even revert into normal architecture[19].

FACTORS ASSOCIATED WITH DECOMPENSATION OF CLC

The transition from the CLC to the DLC occurs as a result of a complex interaction between predisposing factor and precipitating factors (Table 1). The development of PHT is the key factor causing switch from CLC to DLC[10,20-22]. In a study, patients with a hepatic venous pressure gradient (HVPG) < 10 mmHg had a 90% probability of not developing clinical decompensation over 4 years. As the HVPG rises above 10 mmHg, which signify CSPH, the risk of decompensation begins to rise[10]. VH typically occurs when HVPG is higher than 12 mmHg[15]. Another study found that CLC with a baseline

HVPG > 20 mmHg had a 47% risk of decompensation in mean duration of just 1.6 years[21]. There is also growing evidence that long-term use of non-selective beta-blockers (NSBBs) significantly reduces the risk of decompensation[22]. Thick fibrous septa and small nodules observed in liver biopsy specimens of CLC patients are associated with CSPH and an increased risk of decompensation[23-25]. Ongoing liver damage caused by etiological factors also increases the risk of decompensation. This is supported by the finding that attaining a sustained virological response (SVR) in hepatitis C virus (HCV)-cirrhosis and maintaining viral suppression HBV-cirrhosis significantly lowers the incidence of decompensation[26-29]. The neurohormonal and inflammatory alterations in LC contribute to decompensation in the form of ascites by causing splanchnic vasodilatation and lymphatic dysfunction[30-32].

Several metabolic factors have also been found to influence the risk of decompensation[33-36]. CLC patients with diabetes have a higher risk for developing any decompensating event than those without diabetes[33]. Obesity has a negative impact on the natural course of CLC, regardless of aetiology, and increases the risk of decompensation[34]. Sarcopenia and myosteatosis, which are common in CLD with various aetiologies, appear to promote the progression of CLD to advanced stages[35]. Another study found that the PNPLA3 G/G genotype, involved in the triacylglycerol hydrolysis, was associated with a 2-fold increase in the probability of decompensation[36]. Gut dysbiosis, characterised by a loss of beneficial commensals and an increase in pathogenic organisms, significantly influences the natural course LC patients[36-40]. Furthermore, cirrhosis-associated immune dysfunction, involving both immune deficiency and proinflammatory immune cell activation, contributes to haemodynamic disturbances and PHT, accelerating the development of decompensation[41-43].

Bacterial infection can cause AD by escalating the intensity of systemic inflammation and PHT. In a large prospective study of 1672 patients with compensated HCV- or HBV-related cirrhosis, bacterial infections preceded and precipitated decompensation in 13% patients over 5-year period[44]. Overall, bacterial infection is considered to be the

most frequent precipitant of AD (22% to 29%) and ACLF (33% to 50%)[45]. Alcoholic hepatitis can cause decompensation in patients with CLC through various mechanisms[46,47]. AD and ACLF frequently develop in patients with LC undergoing surgery[48]. In a study using an animal model of CLC, it was discovered that extrahepatic surgery raises the portal pressure during the post-operative period, leading to decompensation[49]. Other situations where decompensation can develop in patients with CLC include superimposed viral hepatitis, consumption of hepatotoxic medications, and vascular thromboses[50].

DISEASE MODIFYING TREATMENT STRATEGIES

The present strategy for managing patients with LC is centred on strategies intended to avoid or treat complications, without giving much thought to their effects on the natural history of LC. There is a need to pay more attention to agents that target key points in the complex pathophysiology of LC. The ideal goal of a disease-modifying medication should be the regression or reversal of cirrhosis, and if this is not possible, the next goal should be to prevent or at least delay the progression of the disease. Growing evidence suggests that addressing the underlying cause of LC and reducing PHT by NSBB have positive impacts on natural history of patients with CLC[7,8,22,26,29]. Moreover, such patients may potentially benefit from addressing a number of co-factors and precipitating factors that have a negative influence on the natural course of LC[51]. Thus, effective disease-modifying treatment strategies might include: (1) Removal of etiological factors; (2) pathophysiology-oriented therapy; (3) management of adverse co-factors like obesity, DM, dyslipidemia, and alcoholism; (4) anti-fibrotic and regenerative therapies; and (5) elimination of precipitating factors that lead to AD/ACLF.

Removal of etiological factors

The main prerequisite for fibrosis regression is the cessation of liver injury, which is accomplished through therapeutic control of causal factor. Regression of LC has been

extensively described in patients with HBV- and HCV-related cirrhosis after aetiological treatment (Table 2). Nevertheless, robust data supporting the regression of non-viral causes of LC are generally lacking.

Viral cirrhosis: Dienstag *et al*[26] reported regression of LC in 73% (08/11) of patients following three years of lamivudine therapy. In another prospective study, treatment with adefovir dipivoxil for up to 240 wk resulted in regression of bridging fibrosis or cirrhosis in 58% (07/12) of patients[27]. Pegylated interferon and ribavirin combination therapy has been shown to reduce liver fibrosis following SVR. Combination therapy led to the reversal of LC in 49% of patients in a pooled data analysis from 4 randomised controlled trials (RCTs) that included 153 patients with HCV-cirrhosis at baseline[52]. Though data are still evolving, a recent study found that direct-acting antivirals were effective in reducing fibrosis based on fibroscan[53]. In a systematic review of 463 patients with HBV-cirrhosis, regression of LC was observed in 33% to 80% of patients following sustained viral suppression. Meanwhile, LC regressed in 33% to 100% of 58 patients with HCV-cirrhosis following SVR[28]. This suggests that once the causal element is removed early in the course of CLC, progression is not only halted, but cirrhosis regression occurs in a significant number of patients.

Non-viral cirrhosis: Weight loss through lifestyle changes improves fibrosis in patients with non-alcoholic steatohepatitis (NASH), but its effects on NASH-cirrhosis per se are still poorly understood. In a recently published study involving 709 patients with compensated NASH-cirrhosis from two RCTs on simtuzumab and selonsertib *vs* placebo, regression of LC was observed in 135 patients during a median follow-up of 16.6 mo. Notably, impact of drug was not better than placebo, indicating influence of lifestyle modification[54]. Another study that assessed the long-term effects of bariatric surgery in 180 patients with obese NASH found significant regression of fibrosis at 5 years after surgery. The fibrosis decreased in 70.2% of patients, disappeared in 42% of patients, and one from three patients with baseline LC turned non-cirrhotic[55].

However, the outcomes of RCTs on a variety of compounds that target the metabolic/inflammatory pathways of NASH-cirrhosis have been dismal[56-59]. In a recent RCT with Emricasan, an oral pan-caspase inhibitor, there was a small treatment effect on HVPG reduction in compensated NASH cirrhosis; however, the drug was overall ineffective in improving clinical outcomes[56]. Belapectin, an inhibitor of galectin-3 that was earlier found to reduce liver fibrosis and PHT in rats, was proven to be ineffective in human NASH-cirrhosis[57].

Abstinence from alcohol improves the prognosis in all stages of alcohol-related LC; nevertheless, there is scant clinical support for fibrosis/cirrhosis regression in alcoholic liver disease[60-62]. In one study, patients who were abstinent *vs* those who were not showed a 3-year decompensation likelihood of 32.4% *vs* 60.0%[60]. Early alcohol abstinence after LC diagnosis was found to be a significant predictor in survival, with abstinent patients having a 72% survival rate at 7 years compared to 44% in drinkers who continued to consume alcohol[61]. Reversibility of hepatic fibrosis has also been documented in autoimmune hepatitis patients[63,64]. A study on corticosteroid-treated autoimmune hepatitis has revealed regression of histological LC from 16% to 11%[63]. Ursodeoxycholic acid treatment may halt disease progression and improve survival of patients with primary biliary cholangitis, but it appears to be less effective in promoting fibrosis regression[65]. In a retrospective analysis of patients with hemochromatosis treated with venesection, LC regression was observed in 15 out of 66 (23%) over a median period of 9.5 years[66].

Pathophysiology-oriented therapy

NSBB: In patients with LC, CSPH appears to be an important pathophysiologic driver of the first decompensating event[10,20-22]. The onset of PHT is primarily caused by elevated portal blood inflow resistance resulting from architectural distortion (fixed component) and increased elevated hepatic microvascular tone (dynamic component). The increased hepatic vascular tone is attributed to decreased intrahepatic vasodilators, primarily nitric oxide (NO), and increased production of vasoconstrictors such as

angiotensin, endothelins, and prostanoids. Portosystemic collaterals appear later, heralding splanchnic vasodilation, increased splanchnic blood flow, and hyperkinetic circulation, all contributing to further raise of portal pressure. The only pharmacological class that is still recommended for long-term treatment of PHT is NSBB. Importantly, NSBBs are only beneficial in patients with CSPH and not in those with subclinical PHT because they reduce portal venous flow, and significant hyperdynamic circulation only develops once CSPH is set[67]. Adequate responses to NSBBs are associated with a lower incidence of decompensating events and improved survival rate, indicating a positive influence on the natural history of LC (Table 3). According to current recommendations, patients with high-risk varices should have NSBBs or endoscopic variceal ligation (EVL) as primary prophylaxis for VH[68]. While choosing between NSBBs and EVL, the patient's preferences, tolerance, side effect profile, and contraindications can all be taken into account[69]. Importantly, NSBB, in addition to being as effective as EVL at preventing VH, have the added benefit of lowering the risk of decompensation and mortality[22,70-73]. Among commonly used NSBBs, Propranolol and nadolol reduce portal pressure by reducing portal venous inflow by blocking β_1 and β_2 adrenergic receptors, whereas carvedilol has additional intrinsic vasodilatory activity because of its anti-α-adrenergic activity and its ability to increase NO release[74]. Moreover, carvedilol has been observed to cause greater reduction in HVPG compared to propranolol or nadolol[75,76]. Carvedilol might be especially useful for patients with CLC, where a higher hepatic vascular resistance is the main cause of PH[76,77].

The emerging evidence strongly indicates that NSBBs can prevent decompensation in patients with CLC. The PREDESCI trial, a multicentre, double-blind, RCT, studied whether the administration of NSBBs over an extended period of time prevents the development of clinical decompensation and increase survival in CLC patients with CSPH[22]. In this study, 201 patients with CLC with CSPH were randomly assigned to receive NSBBs or a placebo. After a median follow-up of 37 mo, the NSBB arm showed considerably lower rates of clinical decompensation compared to the placebo arm (17% *vs* 27%, HR 0.51, 95%CI 0.26-0.97). Among, decompensating events, decreased incidence

of ascites (20% *vs* 9%) was the main effect of NSBB. However, the PREDESCI trial hinged the choice of NSBB on the HVPG response to intravenous propranolol, which is impracticable for a large population of patients. In a recent competing-risk time-to-event meta-analysis that included 352 patients with CLC, 181 carvedilol-treated patients, and 171 controls from 4 RCTs, long-term carvedilol therapy was associated with a decreased risk of decompensating events and improved survival. Carvedilol decreased the risk of decompensation, mainly ascites, with a subdistribution hazard ratio (SHR) of 0.506 (95%CI 0.289-0.887), and the risk of death with an SHR of 0.417 (95%CI 0.194-0.896)[78].

Statins: Several studies have been published in recent years on the beneficial effects of statins in patients with LC. The benefits include a decrease in portal pressure, favourable effects on sinusoidal endothelial function, hepatic microcirculation, and liver fibrosis[79]. In the first such study of statins in LC, simvastatin was found to increase NO generation in liver sinusoids and reduced intrahepatic vascular resistance[80]. Furthermore, it was found that simvastatin was had an additive effect with NSBB on HVPG reduction[81]. Several moderate-qualitystudies have suggested that the use of statins in CLC lowers the risk of hepatic decompensation and mortality[82-84]. In a large study form Taiwan, including 1350 patients with LC, statin use decreased the risk of decompensation, mortality, and hepatocellular carcinoma in a dose-dependent manner. With statins, the incidence of decompensation was 61% lower in HBV-cirrhosis and 49% lower in HCV-cirrhosis[85]. In a recent systematic review and meta-analysis, statin was associated with a 46% reduced risk of hepatic decompensation and a 46% lower risk of mortality in patients with LC[86]. Notably, LC patients who benefit from statins are mainly those with Child-Pugh classes A or B, but not those with Child class C. In DLC, simvastatin at higher doses may even cause rhabdomyolysis and hepatotoxicity[87,88]. Therefore, despite a strong case for statins being helpful for patients with LC, more evidence from high-quality RCTs is required before they can be regularly recommended

for patients with CLC. Until then, it is safe to presume that patients with CLC with dyslipidemia should not be denied statin therapy.

Anticoagulant: As LC progresses, endothelial damage and occlusion of small hepatic veins causes parenchymal extinction, which contributes to tissue collapse and architectural distortion[8]. Furthermore, studies have shown that the oral anticoagulant rivaroxaban and the low molecular weight heparin enoxaparin lower intrahepatic vascular resistance in cirrhotic rat models[89,90]. These beneficial effects of anticoagulants were attributed to a decreased intrahepatic microthrombosis, hepatic stellate cells deactivation, and increased NO bioavailability. In a small RCT, a 12-mo regimen of enoxaparin in patients with LC with a Child-Pugh score of 7 to 10 appeared to prolong survival and delay the emergence of hepatic decompensation[91]. In a recent meta-analysis, use of antiplatelets agents was associated with a 32% decreased odds of hepatic fibrosis[92]. Still, more data are required before a conclusive statement can be made about the usage of anticoagulants and antiplatelet agents in CLC patients.

Management of co-factors

Weight loss and glycemic control: Obesity is a condition characterised by systemic inflammation and immunological dysregulation that is linked to poor clinical outcomes in LC patients, including decompensation[34,93]. Obese patients with LC have higher levels of inflammatory cytokines, increasing the risk of decompensation through a systemic inflammatory response[94]. Obesity has a negative impact on the course of CLC across all aetiologies, regardless of portal pressure or liver function. In a study including 161 patients with CLC, clinical decompensation occurred in 15% of lean, 31% of overweight, and 43% of obese patients during a median follow-up of 59 mo[34]. Class III obesity was found to be an independent risk factor for the development of ACLF in a recent study using data registries[95]. Hence, weight loss may be an effective therapeutic strategy for obese patients with cirrhosis[96,97]. Following bariatric surgery, the advantages of weight loss have been established in obese patients with LC[96].

Nonetheless, bariatric surgery is not generally recommended for people with CLC and is contraindicated in DLC. Patients with LC may be safely recommended to change their lifestyles under the care of a dietician with an aim to reduce body weight.

In LC patients, the prevalence of abnormal glucose regulation, including type-2 DM and hepatogenous diabetes, is quite high (20% to 70%)[98,99]. This high incidence appears to be due to poor insulin clearance and dysfunctional pancreatic beta-cells[98]. Hyperinsulinemia is also implicated in vasodilatory and antinatriuretic effects in patients with CLC[100]. Impaired glycemic indices in LC are associated with disease progression, decompensation, complications, and poor outcomes[101,102]. Hence, maintaining appropriate glycemic control can benefit the course of LC. However, standardised diabetes management for LC patients has not been established yet. In addition to lifestyle modification, oral hypoglycemic agents can be used in LC patients up to Child-Pugh class B, while insulin is recommended for LC at all stages.

Alcohol abstinence: Abstinence from alcohol reduces the risk of decompensation and improves outcomes in all stages of alcohol-related LC[60-62]. Early alcohol abstinence after diagnosis of LC is important for a better outcome[61]. According to a meta-analysis of seven cohort studies involving 1235 patients with alcoholic cirrhosis, at least 1.5 years of abstinence is required before a statistically significant difference in survival between the abstinent and continuing drinking groups can be observed[103].

Diet, salt, and physical activity: Dietary interventions should include a target protein intake of 1.2-1.5 g/kg/d and regular aerobic exercise to prevent or ameliorate sarcopenia, which is associated with poor outcomes in LC patients[104-106]. In a recent prospective study, 16 wk of personalised hypocaloric normoproteic diet and 60 min per week of supervised physical activity were found to reduce body weight and portal pressure in overweight/obese patients with CLC[107].

Many observational studies have found an inverse relationship between coffee consumption and LC[108,109]. According to two recent meta-analyses, coffee drinkers had

a lower risk of developing LC than non-drinkers[108,109]. Unfortunately, these meta-analyses may not have adequately controlled the bias and confounding factors due to the low quality of the observational studies. Prospective RCTs are needed to establish the impact of coffee consumption on the fibrosis regression in CLC patients. Most of the scientific societies do not recommend sodium (salt) restriction for patients with CLC. However, preascitic LC patients have been found to retain sodium when faced with a high salt intake[110]. It is believed that a new steady state of sodium balance is eventually achieved in such patients primarily because of increased levels of atrial natriuretic peptide, inhibition of the renin-angiotensin-aldosterone system, and suppression of sympathetic activity, which prevent sodium retention and the formation of ascites. Jalan *et al*[111] have reported that the severity of PHT contributes to the abnormalities of sodium handling in patients with CLC. Therefore, it would be intriguing to determine whether a salt restriction could prevent the development of ascites in CLC patients with CSPH.

Correction of vitamin D deficiency: The liver plays a crucial role in 25-hydroxyvitamin D metabolism [25(OH) D]. Vitamin D deficiency and insufficiency are highly prevalent in patients with CLD (64% to 92%), where they are associated with poor outcomes[112]. Emerging evidence suggests protective effects of vitamin D against hepatic fibrogenesis[113,114]. However, Vitamin D supplementation had no beneficial effects in animal models of LC and pre-existing fibrosis[115]. In a recent RCT, vitamin D treatment did raise the serum levels of 25(OH) D in patients with LC, but indicators of liver fibrosis did not improve[116]. The disappointing results can be attributed to the small sample size and short study period, calling for larger and longer studies in the LC population. Nevertheless, LC patients who are vitamin D deficient should receive treatment because LC itself is associated with an increased risk of osteopenia and fracture.

Regenerative therapies and investigational drugs

The potential of cell treatments to improve liver regeneration and modify the course of liver disease has garnered a lot of attention in recent years. There are many different cell types that can be employed to treat LC or fibrosis; however, mesenchymal stem cells (MSCs) are the most often used cell source (73%). Research using animal models have demonstrated that MSC therapy can reduce liver fibrosis, improve liver function, and lessen liver injury[117]. Clinical studies using MSCs for cirrhosis have demonstrated their efficacy in improving liver function; however, large-scale, stratified studies in various CLD settings are required to draw a robust conclusion[117-120]. Also, patients with advanced LC with liver failure, rather than CLC, have been the focus of the majority of clinical trials on stem cells. There is significant heterogeneity between published studies in terms of the type, dose, and method of stem cell delivery, and data accuracy, making it a difficult interpretation[121]. Granulocyte-colony stimulating factor (G-CSF) serves as an alternative to exogenous stem cell infusions by mobilising hematopoietic stem and immune cells. Some randomised controlled trials on G-CSF have reported improved survival in patients with ACLF[122,123]. However, in a recent multicentre, open-label, RCT, G-CSF with or without haemopoietic stem-cell infusions did not improve liver dysfunction or fibrosis in patients with CLC. Moreover, these medicines were associated with a higher frequency of unfavourable events[124]. Therefore, because to conflicting results, GCSF is not currently advised for use in CLC patients.

Recent developments in important pathophysiologic pathways linked to PHT in LC have revealed a number of novel possible treatment targets. These include intrahepatic abnormalities associated with inflammation, fibrogenesis, and microvascular changes[57-59,81,125-128]. Some medications, including phosphodiesterase-5 inhibitors, farnesoid X receptor agonists, endothelin-A receptor antagonists, and amino sulphonic acid taurine, have been found to lower PHT, which may be useful in reducing decompensation in CLC patients[125-128]. However, more solid and consistent evidence is required regarding the safety and effectiveness of these medicines. Currently, there are no pharmacotherapies for fibrosis that have been licenced, but research on antifibrosis medications has made significant strides in recent years, especially with regard to

medications for NAFLD-related fibrosis[129]. It seems that treatment with a single medication may not be sufficient to treat advanced liver fibrosis due to the complexity of the hepatic fibrosis process, which involves interactions between many cell types including immune cells, hepatic stellate cells , and hepatocytes. Therefore, more study is needed into combination therapies using drugs that have several modes of action.

Elimination of precipitating factors

Several precipitating events can lead to abrupt worsening of clinical condition of LC patients by causing ACLF[130,131]. Furthermore, CLC patients experience a more severe form of ACLF than patients with prior decompensation episodes. Thus, controlling such precipitating variables can thereby significantly reduce cirrhosis-related morbidity and mortality. Antibiotic prophylaxis and prompt, judicious antibiotic treatment can aid in the prevention of ACLF triggered by infection[132]. Prophylactic antibiotics in conjunction with effective gastrointestinal bleeding management can prevent precipitating an ACLF. Another important preventive strategy is vaccination for the viral hepatitis. For all LC patients, hepatitis B vaccine is advised. However, compared to normal subjects, cirrhotic patients achieve lower seroprotection rates following HBV vaccination (mean response rate of 47%)[133,134]. Hepatitis E virus (HEV) and hepatitis A virus (HAV) superinfection is another well-known cause of ACLF in endemic areas[135]. While many nations recommend HAV immunisation for CLD patients, routine vaccination is not advised in some, such as India, where the prevalence of HAV antibodies in CLD is apparently greater than 90%. Recombinant HEV vaccines have also been developed but are not widely available or approved across the world[136]. When vaccination is not an option, general preventive measures like improvement of sanitary conditions and the provision of clean water might decrease the incidence of HEV/HAV-induced ACLF.

CONCLUSION

The life expectancy of patients with CLC is often high, and many of them may be candidates for cirrhosis regression. Therefore, to facilitate the early detection of CLC, medical professionals should employ noninvasive techniques in all CLD patients. Early diagnosis CLC offers the opportunity to treat underlying causes and prevent or halt progression of liver disease. For viral cirrhosis, and to a lesser extent non-viral cirrhosis, fibrosis regression may result in cirrhosis reversal when the underlying cause of CLC is treated before progression. The transition from compensated to decompensated cirrhosis is mainly driven by PHT. This transition is accompanied by a dramatic decline in the median survival rates. NSBBs are currently the cornerstones of treatment for PHT, although a number of emerging therapies may pave the way for tailored multimodal strategies in the future. Some more recent drugs have shown promise in decreasing PHT, but more reliable and consistent data are needed to determine their safety and efficacy in LC patients. Furthermore, there are several known risk factors and triggering events for the decompensation of CLC that need to be taken care of. Regardless of the aetiology of CLC, evolving disease modifying approaches might lead to a paradigm change, a decrease in the burden as well as the morbidity and mortality associated with LC.

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Figure Legends

Figure 1 Natural course of patients with compensated liver cirrhosis. The natural progression of cirrhosis is characterised by a continuum from an asymptomatic compensated phase to a symptomatic decompensation phase. The rate of transition from a compensated to a decompensated stage is about 5%-7% each year. Five-year mortality rate in compensated cirrhosis without or with varices is 5% and 10%, respectively. There are several known factors associated with decompensation such as high portal pressure, persistent etiological injury, systemic inflammation, and hemodynamic alterations. In addition, several types of triggering events, such as bacterial infection, alcohol, viral hepatitis, or medications, may cause AD and ACLF. Prompt and effective control of etiological factors are associated not only with regression of compensated cirrhosis, but also with recompensation of decompensated cirrhosis (data adapted from reference 3, 6, 18, and 31). CLC: Compensated liver cirrhosis; AD: Acute decompensation; ACLF: Acute-on-chronic liver failure; LT: Liver transplantation; HBV: Hepatitis B virus; HCV: Hepatitis C virus; DM: Diabetes mellitus; VH: Variceal haemorrhage; PHT: Portal hypertension.

Table 1 Factors associated with decompensation of compensated liver cirrhosis

Risk factors for non-acute decompensation	Precipitating factors for acute-decompensation
Thick fibrous septa and micronodularity on liver biopsy	Bacterial infection
Persistent liver injury by etiological factor	Active alcoholism
High portal pressure	Gastrointestinal haemorrhage
Systemic inflammation & hemodynamic changes	Consumption of hepatotoxic drug/alternative medicine
Metabolic risk factors: DM, obesity, and dyslipidemia	Superinfection or flare of viral hepatitis
Genetic risk factors: PNPLA3 G/G genotype	Major surgery and general anaesthesia

CLC: Compensated liver cirrhosis; DM: Diabetes mellitus, PNLLA3: Patatin-like phospholipase domain-containing protein 3.

Table 2 Impact of etiological treatment on regression of liver cirrhosis

Ref.	Study design	Drug/duration	Patients (*n*)	Baseline LC	Main results
Dienstag *et al*[26], 2003	Prospective, Partially randomised	Lamivudin/3 yr	63 CHB	11	LC regressed in 8 of 11 patients (73%)
Hadziyannis *et al*[27], 2006	Prospective	Adefovir dipivoxil, up to 240 wk	125 CHB	04	58% has reversal of bridging fibrosis/cirrhosis; 3 of 4 LC patients had reversal
Marcellin *et al*[29], 2013	Randomized trial	TDF/Adefovir for 48 wk then open-label TDF	641 CHB	96	71 of 96 (74%) became non-cirrhotic at 5 yr
Poynard *et al*[52], 2002	Pooled data from RCTs	IFN/PeG IFN + RBV	3010 CHC	153	The reversal of LC was observed in 75 patients (49%)
Mauro *et al*[53], 2018	Retrospective	DAAs/IFN + RBV	112 HCV-infected LT recipients	37	Regression of fibrosis in 43% of LC (16/37)
Lassailly *et al*[55], 2020	Prospective	Bariatric surgery	180 obese NASH	09	At 5 yr, fibrosis regression was seen in 68% of advanced fibrosis and one of three patients had reversal of LC

Sanyal *et al*[54], 2022	Data from two RCTs	Simtuzumab or selonsertib or placebo	1135 NASH patients, 709 (62%) had Ishak stage 6 fibrosis	709	LC regression occurred in 16% (176/1135). Drugs were not better than placebo
Dufour *et al*[64], 1997	Retrospective	Immunosuppressant	08 NASH cirrhosis	08	LC regressed in all
Czaja *et al*[63], 2004	Retrospective	Corticosteroid	87 AIH	14	LC regressed in 04 of 14 patients
Bardou-Jacquet *et al*[66], 2020	Retrospective	Venesection	106 patients with hemochromatosis	66	LC regressed in 15 of 66 (23%) during median follow-up of 9.5 yr

CHB: Chronic hepatitis B; LC: Liver cirrhosis; TDF: Tenofovir disoproxil fumarate; RCT: Randomised controlled trial; IFN: Interferon; RBV: Ribavirin; CHC: Chronic hepatitis C; DAAs: Direct-acting antiviral; HCV: Hepatitis C virus; NASH: Non-alcoholic steatohepatitis; AIH: Autoimmune hepatitis.

Table 3 Impact of non-selective beta-blockers on portal hypertension, variceal haemorrhage, decompensation and survival in patients with liver cirrhosis

Ref.	Study population	Intervention	Study design	Sample size	Study conclusion
Poynard *et al*[70], 1991	LC patients with esophageal varices	Propranolol, nadolol *vs* placebo	Meta analysis of 4 RCTs	589	Both propranolol and nadolol are effective in preventing first VH and reducing the mortality associated with VH
Tripathi *et al*[71], 2009	LC patients with grade II or more varices	Carvedilol *vs* EVL	RCT	152	On intention-to-treat analysis, carvedilol had lower rates of the first VH compared to EVL (10% *vs* 23%)
Gluud *et al*[69], 2012	LC patients with high-risk varices without prior VH	NSBBs *vs* EVL	Meta analysis of 19 RCTs	1504	Both EVL and NSBB reduced VH (RR: 0.69 and 0.67) without difference in mortality rates
Sinagra *et al*[75], 2014	LC patients with PHT	Carvedilol *vs* propranolol	Meta analysis of 5 studies	175	Carvedilol reduces PHT significantly more than propranolol
Bhardwaj *et al*[76], 2017	LC patients with small varices	Carvedilol *vs* placbo	RCT	140	Carvedilol is safe and effective in delaying the progression of small to large oesophageal varices in LC patients
Zacharias *et al*[77],	Adults with LC and varices	NSBBs	Meta analysis	810	Carvedilol was more effective at reducing the HVPG, however, it

2018			of 10 RCTs		was not better than traditional NSBBs with regard to the mortality, VH, or adverse events
Malandris *et al*[72], 2019	LC patients requiring primary or secondary prevention of VH	Carvedilol, NSBBS, EVL	Meta analysis of 13 RCTs	1598	Carvedilol is as efficacious and safe as standard-of-care interventions for the primary and secondary prevention of VH. Also, carvedilol was associated with lower all-cause mortality compared to EVL
Sharma *et al*[73], 2019	LC patients with large esophageal varices and no prior history of VH	NSBB, isosorbide-mononitrate, carvedilol, and EVL alone or in combination	Meta analysis of 32 RCTs	3362	NSBB monotherapy decreased all-cause mortality and the risk of first VH. Additionally, NSBB carries a lower risk of serious complications compared with EVL
Villanueva *et al*[22], 2019	CLC patients and CSPH	Proprano lol, carvedilol *vs* placebo	RCT	201	Long-term treatment with β blockers could increase decompensation-free survival in patients with CLC with CSPH, mainly by reducing the incidence of ascites

Villanueva *et al*[78], 2022	LC patients with CSPH	Carvedilol *vs* EVL/no treatment	Meta analysis of 4 RCTs	352	Long-term carvedilol therapy reduced decompensation and significantly improved survival

LC: Liver cirrhosis; RCT: Randomised controlled trial; VH: Variceal haemorrhage; EVL: Endoscopic variceal ligation; NSBBs: Non-selective beta-blockers; HVPG: Hepatic venous portal gradient; EVL: Endoscopic variceal ligation; PHT: Portal hypertension; RR: Relative risk; CSPH: Clinically significant portal hypertension.

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