Natural Course of Liver Cirrhosis and Potential Disease-Modifying Strategies

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Liver cirrhosis: Overview

Liver cirrhosis is a condition marked by extensive disruption of the normal liver structure due to fibrosis, resulting from chronic progressive liver diseases such as alcohol-related steatotic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD). Cirrhosis is characterized by severe liver scarring, loss of organ function, and complications associated with portal hypertension. The prevalence and mortality rates of liver cirrhosis are on the rise. Traditionally viewed as a singular entity with a continuum of severity, recent paradigms acknowledge liver cirrhosis as a heterogeneous condition with varying prognoses at different stages.[1-3]

Clinical stages of liver cirrhosis

Liver cirrhosis is categorized based on the absence or presence of complications, termed 'compensated' in the absence and 'decompensated' when complications are present or have occurred previously. The compensated phase, often asymptomatic, precedes the decompensated phase, marked by clinical signs such as ascites, hepatic encephalopathy, variceal hemorrhage, and jaundice (Table 1).[1-5] Compensated liver cirrhosis refers to cirrhosis without decompensating events. In compensated liver cirrhosis, clinically significant portal hypertension [hepatic venous pressure gradient (HVPG) ≥ 10 mmHg] indicates a higher risk of complications. The decompensated stage carries a substantial risk of progressing to further decompensation, liver failure, and death.[5]

Natural course of compensated liver cirrhosis

Liver cirrhosis follows a natural progression from an asymptomatic compensated phase to a symptomatic decompensation phase (Figure 1). Patients with compensated liver cirrhosis can remain asymptomatic for several years, despite one-third to one-half having varices and clinically significant portal hypertension at diagnosis. As liver cirrhosis advances, patients develop various risk factors such as altered liver architecture, portal hypertension, systemic inflammation, and hemodynamic changes, heightening the risk of clinical decompensation. Decompensation can occur gradually due to slowly increasing portal pressure and deteriorating hepatic function, often referred to as acute decompensation (AD). However, in certain cases, various triggers can acutely precipitate decompensation, leading to acute-on-chronic liver failure (ACLF). The transition from compensated to decompensated liver cirrhosis happens at a rate of 5% to 7% annually, with decompensation marking a critical point in terms of mortality risk, patient quality-of-life, and likelihood of hospitalization.[2,3]

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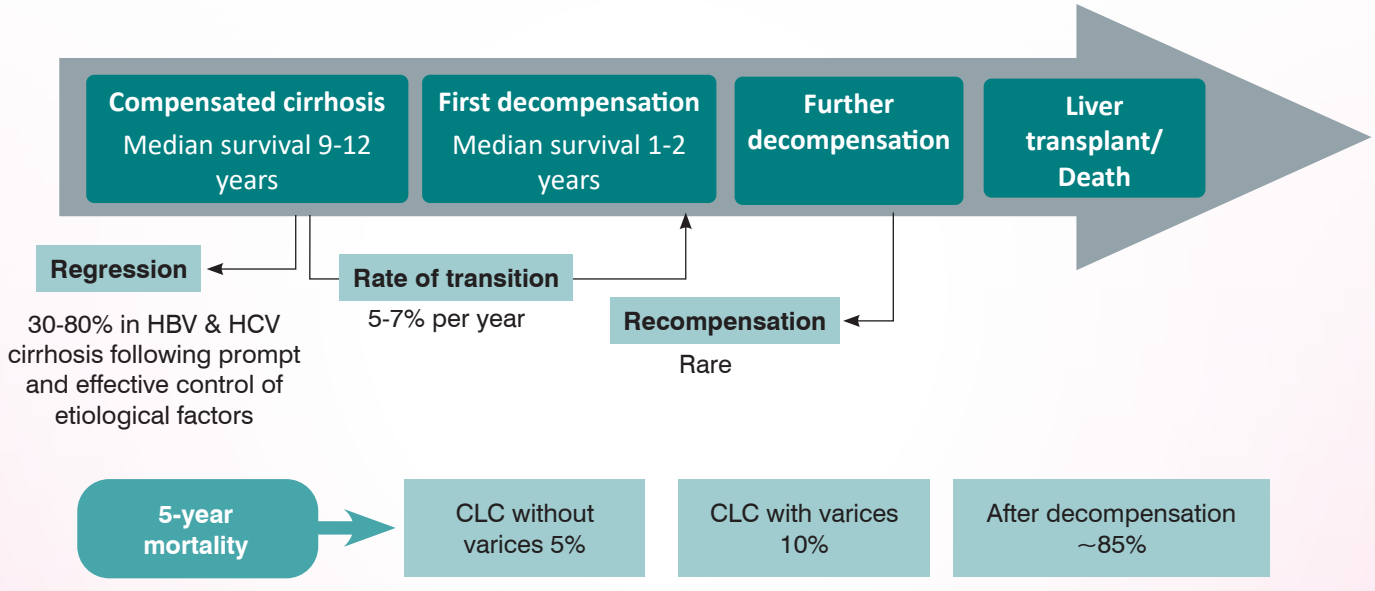
Following a decompensation event in liver cirrhosis, patients are consistently classified as decompensated liver cirrhosis, as the underlying pathogenic mechanisms persist. Decompensated liver cirrhosis transforms into a systemic disease with involvement of multiple organs and a dysregulated inflammatory state. The initial decompensation in compensated liver cirrhosis marks a pivotal prognostic point in the natural course of chronic liver disease, as median survival sharply decreases from 10-12 years for compensated liver cirrhosis to approximately 1-2 years for decompensated liver cirrhosis.[2,3]

Table 1: Clinical stages of liver cirrhosis[1-5]

	COMPENSATED LIVER CIRRHOSIS			DECOMPENSATED LIVER CIRRHOSIS		
	Stage 1a	Stage 1b	Stage 2	Stage 3	Stage 4	Stage 5
HVPG (mmHg)	6-10		>10	>10	>12	>16 >20 in acute variceal bleeding
Clinical features	No CSPH No varices	CSPH No varices	CSPH Varices	Variceal bleeding with no other complication	First non-bleeding decompensation (ascites, HE, SBP)	Any second decompensation (recurrent variceal hemorrhage, refractory ascites HRS, hyponatremia, recurrent HE, jaundice)
1-year mortality	1.5%		2%	10%	21%	5-year mortality 87%
Progression/ complications		7% GEV (stage 2) 4% ascites (stage 4)	4% EV bleeding (stage 3) 6.6% ascites (stage 4)	21% ascites (stage 4)	10% further decompensation (stage 5)	
Major known risk modifiers	Alcohol intake, ongoing liver injury, obesity		All previous + HVPG response to NSBB	Liver and renal function, HVPG response to NSBB, alcohol intake, sarcopenia, vitamin D deficiency		

Abbreviations: HVPG, Hepatic venous pressure gradient; CSPH, clinically significant portal hypertension; HE, hepatic encephalopathy; SBP, spontaneous bacterial peritonitis; HRS, hepatorenal syndrome; GEV, gastroesophageal varices; EV, esophageal varices; NSBB, non-selective beta-blockers.

Figure 1: Natural course of compensated liver cirrhosis[3]



Abbreviations: HBV, Hepatitis B virus; HCV, Hepatitis C virus; CLC, compensated liver cirrhosis.

Table 2:Factors leading to decompensation of compensated liver cirrhosis[3]

Factors contributing to acute decompensation	Triggers for acute decompensation
Presence of dense fibrous septa and micronodularity on liver biopsy	Bacterial infection
Persistent liver damage caused by etiological factor	Active alcoholism
Elevated portal pressure	Gastrointestinal hemorrhage
Systemic inflammation and hemodynamic alterations	Consumption of hepatotoxic drug/alternative medicine
Metabolic risk factors, such as diabetes, obesity, and dyslipidemia	Superinfection or viral hepatitis flare-ups
Genetic risk factors, such as *PNPLA3* G/G genotype	Major surgery and general anesthesia

Abbreviations: DM: Diabetes mellitus; PNPLA3: Patatin-like phospholipase domain-containing protein 3.

Factors leading to decompensation of compensated liver cirrhosis

The transition from compensated to decompensated liver cirrhosis results from a complex interplay of predisposing and precipitating factors (Table 2).[3] Portal hypertension emerges as the key driver in this progression, directly or indirectly giving rise to most of the complications with liver cirrhosis. Formation of varices stems directly from increased portal pressure and/or portosystemic shunting triggered by portal hypertension, while complications like ascites and encephalopathy arise from systemic circulatory abnormalities, parenchymal loss or extinction, and/or portosystemic shunting triggered by portal hypertension.[4,5] Liver biopsy findings of thick fibrous septa and small nodules in patients with compensated liver cirrhosis correlate with clinically significant portal hypertension and increased decompensation risk. Ongoing liver damage from etiological factors, such as hepatitis C or B viruses, heightens decompensation risk, while achieving sustained virological response (SVR) in HCV-cirrhosis or maintaining viral suppression in HBV-cirrhosis decreases decompensation incidence. Timely control of etiological factors not only leads to the regression of compensated cirrhosis but also facilitates recompensation in decompensated cirrhosis.[3]

Potential disease-modifying treatment strategies

The management of liver cirrhosis predominantly revolves around strategies aimed at avoiding or treating complications without substantial consideration for their impact on the disease's progression. There is a growing call to shift attention towards agents targeting key points in the complex pathophysiology of liver cirrhosis. The ultimate goal of disease-modifying medications should be the regression or reversal of cirrhosis, or if not achievable, at least preventing or delaying disease progression. Addressing the underlying cause of liver cirrhosis and reducing portal hypertension through non-selective beta-blockers show promise in positively influencing the natural history of patients with compensated cirrhosis. Additionally, managing cofactors and precipitating factors may further benefit the natural course of liver cirrhosis.[3]

> Ultimate goal of disease-modifying strategies should be the regression or reversal of cirrhosis, or at least preventing or delaying disease progression

Several interventions currently utilized for treating or preventing specific complications of cirrhosis are being considered as potential disease-modifying agents. Clinical studies have demonstrated their efficacy in improving survival. Proposed disease-modifying treatment strategies may include:[3]

- Elimination of etiological factors
- Pathophysiology-oriented therapy
- Management of adverse cofactors such as obesity, diabetes, dyslipidemia, and alcoholism
- Anti-fibrotic and regenerative therapies
- Elimination of precipitating factors leading to AD or ACLF.

These multifaceted approaches aim to address the underlying causes, physiological abnormalities, associated risk factors, fibrosis, and triggering elements, collectively enhancing the potential for disease modification in liver cirrhosis (Table 3).[2,3,7,8]

Conclusion

Liver cirrhosis progresses from an asymptomatic compensated phase to symptomatic decompensation, with the latter carrying a significant risk of further complications and death. Decompensation marks a pivotal prognostic point with decreased median survival. Transition from compensated to decompensated liver cirrhosis involves complex interactions, predominantly driven by portal hypertension. Disease-modifying treatment strategies aim to target key pathophysiological aspects, emphasizing regression or prevention of cirrhosis progression. These interventions include eliminating etiological factors, pathophysiology-oriented therapy, managing adverse

Table 3: Potential disease-modifying strategies in compensated liver cirrhosis[2,3,7-9]

Disease-modifying treatment strategies	Interventions	Key points
Elimination of etiological factors	Successful etiological treatment	Antiviral drugs, weight loss, alcohol abstinence Halts or slows cirrhosis progression, preventing decompensation
Pathophysiology-oriented therapy	Non-selective β-blockers	Reduces portal pressure, preventing variceal bleeding Potential role as a disease-modifying agent, improving survival
	Statins	Decrease portal pressure, enhance endothelial function, and mitigate liver fibrosis
	Lactulose	Reduces blood ammonia level through different mechanisms, such as the laxative effect, the ammoniuma ionization, and modification of intestinal microbiota
	Rifaximin	Improves the gut epithelial layer homeostasis, decreases inflammatory pathways, and modulates the gut microbiome Lowers ammonia by inhibiting ammonia producing, urea splitting gut flora
	Transjugular intrahepatic porto-systemic shunt	Targets portal hypertension, especially in managing variceal bleeding and refractory ascites
Management of adverse cofactors	Weight loss	Effective for obese cirrhosis patients Reducing inflammation and systemic inflammatory response
	Glycemic control	Maintains appropriate glycemic indices, benefiting cirrhosis course
	Alcohol abstinence	Crucial for all stages of alcohol-related liver cirrhosis, reducing decompensation risk
	Correction of vitamin D deficiency	Essential for patients with liver cirrhosis, associated with hepatic fibrogenesis and osteopenia risk
Regenerative therapies and investigational drugs	Novel treatment targets	Inflammation, fibrogenesis, and microvascular changes
	Medications, such as PDE5 inhibitors, farnesoid X receptor agonists, ERAs, taurine	May reduce portal hypertension and decompensation
Elimination of precipitating factors	Antibiotic prophylaxis	Prevents ACLF triggered by infection
	Vaccination	Advised for all patients with liver cirrhosis, especially hepatitis B vaccine
	General preventive measures	Improving sanitary conditions and providing clean water to reduce infection-induced ACLF

- **Aspirin:** Prevention of platelet degranulation, modulation of bioactive lipids, inhibition of proinflammatory COX-2 enzyme
- **Vitamin E:** Anti-inflammatory and antioxidant actions

Abbreviations: ACLF, Acute-on-chronic liver failure; COX-2, cyclooxygenase-2; PDE5, Phosphodiesterase 5; ERAs, endothelin-A receptor antagonists.

cofactors, employing anti-fibrotic and regenerative therapies, and eliminating precipitating factors leading to acute decompensation or ACLF. Their collective impact enhances the potential for disease modification in liver cirrhosis.

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