

Chapter 2

Natural History and Stages of Cirrhosis

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Introduction

The natural history of cirrhosis is characterized by an asymptomatic phase, referred to as “compensated cirrhosis,” followed by a progressive phase marked by the development of complications of portal hypertension and/or liver dysfunction, designated “decompensated cirrhosis.” In the compensated phase portal pressure may be normal or below the threshold of clinically significant portal hypertension [1] although esophageal varices may appear still in the compensated phase of the disease. Decompensation is defined by the development of ascites, portal hypertensive gastrointestinal (GI) bleeding, encephalopathy, or jaundice [2]. Progression of the decompensated disease may be accelerated by the development of other complications such as (re)bleeding, renal impairment [refractory ascites, hepatorenal syndrome (HRS)], hepatopulmonary syndrome, and sepsis [spontaneous bacterial peritonitis (SBP)]. The development of hepatocellular carcinoma (HCC) may accelerate the course of the disease at any stage.

This chapter summarizes the major steps in the progression of cirrhosis through the compensated and the decompensated phases of the disease, and its prognostic indicators.

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Clinical Course of Compensated Cirrhosis

When cirrhosis is first diagnosed about a half of the patients are still in the compensated phase of the disease [3]. Median survival of patients with compensated cirrhosis has been reported as long as 10–12 years with death occurring mostly after transition into the decompensated disease. The reported median proportion of patients surviving at 1 and 2 years after the diagnosis of compensated cirrhosis is, respectively, 95 % and 90 % [3]. Development of esophageal varices and of decompensation are the major clinical events in this phase of the disease [4], mainly dependent on the progression of fibrosis and portal hypertension.

Progression of Fibrosis and Histological Stages of Cirrhosis

Accumulation of fibrosis occurs slowly along the course of the disease. It is a silent process related to the inflammatory activity of the underlying disease. Based on Laennec's cirrhosis classification, three histological stages of cirrhosis have been described and a modification of the Metavir stage 4 of fibrosis has been proposed as stages 4A, 4B, and 4C [5]. This histological staging system is based on thickness of fibrous bands and nodules size: the more thin the fibrous bands and the larger the nodules, the lower is the histological stage. Histological stages are also significantly related to the severity of portal hypertension and to the clinical severity of cirrhosis [6–8]. Several noninvasive tests to measure the amount of fibrosis are now available; liver stiffness (transient elastography, Fibroscan) is increasingly used in clinical practice particularly to rule out significant fibrosis or to rule in cirrhosis [9]. Liver stiffness significantly increases from stage 4A to 4C [8].

Development and Clinical Impact of Esophageal Varices

The median prevalence of varices in prognostic studies of cirrhosis including patients with compensated cirrhosis is 44 % while in those including decompensated patients it is 73 % [3]. Large cohort studies [10–12] have shown that the incidence of esophageal varices in patients with newly diagnosed cirrhosis is in the range of 5–8 % per year.

Varices do not develop below the threshold HVPG value of 10 mmHg [13, 14]. Above this threshold, the median time to development of varices and/or bleeding or other complications of portal hypertension is about 4 years [10]. Once developed, varices increase in size at a cumulative rate of approximately 5–7 % per year [11, 12]. Increase or reduction of HVPG is associated with corresponding variations of the risk of developing varices or of variceal size [10, 14, 15]. Thus, HVPG plays a key role both in development and progression of varices.

Table 2.1 Five-year survival in patients with compensated cirrhosis, respectively, without or with esophageal varices

Author (ref.)	Year	Patients (n)	5-Year survival %		Risk ratio	p
			No varices	Varices		
Merli [12]	2003	206	8	17	2.1	<0.05
D'Amico [3]	2006	806	6	13	2.1	<0.001
Bruno [4]	2009	327	2	9	4.5	<0.001
D'Amico [16]	2010	739	4	9	2.3	<0.0001
Zipprich [17]	2012	120	10	25	2.5	0.019
Vilar [18]	2013	402	3	8	2.6	<0.0001

Increasing size of esophageal varices is associated with increasing risk of bleeding (fourfold from absent to small varices and two- to threefold from small to large varices), of developing ascites, and of death.

Five-year mortality ranges from 2 to 10 % in patients with compensated cirrhosis without esophageal varices, while it ranges from 8 to 25 % year, after the development of varices [3, 4, 12, 16–18] (Table 2.1).

Decompensation

Overall, decompensation occurs at a fairly constant rate of 5 % per year [19, 20]. The risk of decompensation has been reported to be approximately double in patients with esophagogastric varices compared to patients without varices [3, 4, 18]. Other reported prognostic indicators of decompensation, although not yet validated, are the model for end stage liver disease (MELD) [21], albumin, hepatic vein pressure gradient ≥ 10 mmHg [22], and increased body mass index (BMI) [23]. Ascites is the most frequent decompensating event, followed by bleeding, jaundice, and encephalopathy [19, 20]. It is to note that jaundice and encephalopathy are rarely the first decompensating event, occurring mainly after ascites or bleeding [16]. Decompensation is associated with expected 1- and 2-year survival rate of approximately 60 % and 45 %, respectively, compared with 95 % and 90 % in compensated cirrhosis [3].

Mortality

Mortality in patients with compensated cirrhosis is low, in the order of 1–3 % per year and it is significantly higher in patients with than without esophagogastric varices (Table 2.1). It is caused by a decompensating event or by a liver-related event in approximately half of patients dying while compensated: most frequently bleeding, HRS, or liver failure precipitated by sepsis, bleeding, or other acute clinical events.

In the remaining cases, death is usually caused by non-liver-related causes [4, 18]. Although death is the most important event in whichever disease stage, it is clearly a rare event in compensated cirrhosis, particularly when it is not linked to a decompensating event. Competing risks analysis of the clinical course of the disease has shown that death occurs very rarely before the development of esophagogastric varices or of decompensation. Both these events herald disease progression and increased risk of death. It is therefore at the prevention of these events that clinical research should aim to improve survival of compensated cirrhosis.

Clinical Course of Decompensated Cirrhosis

The appearance of ascites, variceal bleeding, encephalopathy, or jaundice, the major clinical manifestations of liver cirrhosis, marks the transition from the *compensated* phase into the *decompensated* phase of cirrhosis [19, 20, 24].

Ascites and Related Complications

Ascites develops when HVPg has increased above 10–12 mmHg. When cirrhosis is first diagnosed, the prevalence of ascites ranges from 20 to 60 % according to the referral pattern [3]. The incidence of ascites in compensated cirrhosis is about 5 % per year [19, 20]. Median survival after the appearance of ascites was reported in the order of approximately 2 years in the 1980s [19, 20, 24] while it approaches 4 years in the 2000s [25]. Therefore, although the outcome of patients with ascites has much improved in the last 2–3 decades, mortality after development of ascites is still high. The clinical course of patients with ascites is characterized by several events which markedly affect the expected survival. Refractory ascites, SBP, and HRS are the most relevant.

Refractory ascites is defined as ascites that cannot be mobilized or which recurs early after paracentesis because of a lack of response to sodium restriction and diuretic treatment, provided that criteria for diuretic treatment have been fulfilled. Refractory ascites occurs in approximately 5–10 % of patients with ascites [25, 26]: the incidence is approximately 2–4 % per year following the first episode of ascites [25]. When refractory ascites is established, the expected 1-year survival is in the order of 36–50 % [25, 27]; transjugular intrahepatic portacaval shunt (TIPS) may increase this figure up to approximately 60 % particularly in patients with bilirubin <3 mg, serum sodium ≥ 130 mEq/L, and age <60 [28]. Prognostic indicators of development of refractory ascites are Child-Pugh [29] score >8 and hepatitis C virus (HCV) infection, while indicators of poorer survival in patients with refractory ascites are low protein level in the ascitic fluid, higher Child-Pugh score, previous SBP, and history of heavy alcohol consumption (>80 g/day in men and >40 g in women) [30].

SBP is among the most frequent infections in patients with cirrhosis, representing 25 % of all infections in these patients. The incidence may be as high as 65 % in 1 year in high risk patients with borderline renal function, ascitic fluid protein level ≤ 1.5 g/dL, and Child-Pugh score ≥ 9 with bilirubin ≥ 3 mg/dL [31]. Median 1- and 12-month mortality following an episode of SBP is 32 % and 66 %, respectively [32]. Early diagnosis and prompt antibiotic treatment allow 30-day survival of 80 % [33], compared with the 0 % reported in the 1960s when SBP was first described [34]. However, failure of initial treatment occurs in 10 % of patients and is associated with 30-day survival of 30–50 %. Following a first episode of SBP the 1-year probability of a recurrent episode is 70 % [33] and corresponding survival is 50–80 % [35, 36]. Daily quinolone prophylaxis reduces the recurrence rate to approximately 20–25 % [37].

HRS is a functional renal failure defined by creatinine >1.5 mg/dL, no beneficial effect of plasma expansion, the absence of shock, exclusion of recent use of nephrotoxic drugs, and exclusion of parenchymal kidney disease [36]. Type-1 HRS consists of a severe and rapidly progressive renal failure with doubling of serum creatinine reaching a level greater than 2.5 mg/dL in less than 2 weeks. Bacterial infections, gastrointestinal hemorrhage, major surgical procedures, or acute-on-chronic liver failure (ACLF) are the most frequent precipitating events. Type-2 HRS is a moderate renal failure with serum creatinine ranging from 1.2 to 2.5 mg/dL with a steady, slowly progressive course. The overall incidence of HRS (type-1 and type-2) was reported 39 % over 5 years in the 1990s [36] while in a recent study it was approximately 15 % over a similar time period [25]. In patients with refractory ascites it may be as high as 53 % in 1 year [38]. In type-1 HRS, hospital survival is less than 10 % and the expected median survival time only 2 weeks while patients with type-2 have a much longer median survival time in the order of 6 months [39].

Variceal Bleeding

The overall incidence of variceal bleeding is approximately 5 % per year in patients unselected for the presence of varices. The corresponding figure is 1–2 % in patients without varices at a previous endoscopy, 5 % with small varices, and 15 % with medium or large varices [40, 41].

Besides variceal size, major indicators of the bleeding risk are the Child-Pugh class, ascites, and red weal marks (newly formed vessels on the variceal wall) on endoscopy. The NIEC index [42] combines these risk indicators in a score which enable to identify patients with predicted 1-year bleeding risk from 6 to 76 %.

Variceal bleeding does not occur if HVPG is lower than 12 mmHg [13, 14] and the bleeding risk is virtually abolished if HVPG is reduced to levels below this threshold and it is significantly reduced if HVPG is reduced of ≥ 20 % from baseline [43].

The cause of upper gastrointestinal bleeding is ruptured esophageal varices in 60–70 % of all episodes in cirrhosis [44]. A rebleeding episode is separated from the index bleeding by at least a 24-h bleeding-free period [45, 46].

Variceal bleeding ceases spontaneously in 40–50 % of patients and treatment achieves control of bleeding within 24 h from admission in nearly 85 %. Immediate mortality from uncontrolled bleeding is approximately 5 % [44]. Prognostic indicators of failure to control bleeding are active bleeding on endoscopy, bacterial infection, and HVPG >20 mmHg. Six-week rebleeding is 20 % [44] and its risk indicators are active bleeding at emergency endoscopy, gastric varices, low albumin, high blood urea nitrogen, and HVPG >20. A simple prognostic score based on Child-Pugh score, systolic blood pressure, and nonalcoholic etiology has been recently shown to have similar predictive accuracy for 5-day treatment failure as HVPG in patients treated with pharmacologic and endoscopic therapy [47], suggesting that measurement of HVPG is not needed for early prognostic stratification in patients bleeding from esophageal varices.

Six-week mortality after variceal bleeding is 10–15 % with nearly a half of deaths caused by bleeding or early rebleeding and a quarter occurring in the first 5 days. Albumin, bilirubin, creatinine, encephalopathy, HCC, the number of transfused blood units, bacterial infection, and HVPG >20 mmHg are indicators of the risk of mortality within 6 weeks.

Following a first episode of variceal bleeding 1-year mortality is in the range of 30–60 % [48, 49], although early TIPS in selected patients at high risk of death may reduce this figure to 16 % [50]. Rebleeding occurs within 1–2 years in approximately 60 % of untreated patients and 30 % of those given treatments for the prevention of rebleeding [48, 49]. Reduction of HVPG to below 12 mmHg totally prevents recurrent bleeding [43].

Encephalopathy and Jaundice

The incidence of encephalopathy is approximately 2–3 % per year [19]; however, in the absence of ascites or previous bleeding it is even lower. Jaundice behaves similarly to encephalopathy with a low incidence in the range of 2–3 % per year [19] and almost always it occurs in patients with other severe manifestations of advanced cirrhosis [20]. When encephalopathy occurs in patients without ascites it is often related to a spontaneous portacaval or spleno-renal shunt. Median survival after appearance of jaundice or encephalopathy is 1–2 years (D'Amico, unpublished observations from references [11] and [20]). Therefore, the most important markers of decompensated cirrhosis are bleeding and ascites, while encephalopathy and jaundice are seldom the first decompensating event.

Sepsis

Bacterial infections may occur along the whole course of cirrhosis but they are far more frequent in patients with ascites. Bacterial translocation has been postulated as the main mechanism in the pathogenesis of spontaneous infections in cirrhosis,

as well as the hyperdynamic circulation which is a key factor in portal hypertension, ascites, and HRS. Approximately 30 % of infections are community-acquired, 30 % are health care-associated, and 35–40 % are nosocomial [51]. Clinical risk factors include poor liver function, variceal bleeding, low protein ascites, previous SBP, and hospitalization [51]. Moreover, in patients with variceal bleeding, bacterial infection is significantly associated with increased risk of failure of treatment in controlling the acute bleeding, as well as with increased risk of rebleeding and death. For this reason a specific recommendation to treat any cirrhotic patient with gastrointestinal bleeding for the prevention of bacterial infection has been made [52]. In a systematic review of studies reporting on the outcome of sepsis in cirrhosis, the median prevalence of ascites in patients with infections was 100 % (range 6.3–100 %) [32]. The most frequent infections are SBP (≈ 25 %), urinary tract infections (≈ 20 %), pulmonary infections (≈ 15 %), and bacteremia (12 %) [32]. Mean 1-year mortality following an episode of infection is 58.6 % [32].

Hepatocellular Carcinoma

Patients with cirrhosis are at high risk of developing HCC. In fact 70–90 % of HCC occur in patients with chronic liver disease or cirrhosis. Globally, HCV and hepatitis B virus (HBV) chronic infections are the most frequent risk factors for HCC in cirrhosis. The incidence is different according to the geographical area. In Europe and the USA the 5-year incidence of HCC in patients with HCV-related cirrhosis is about 17 % and it is 15 % in patients with HBV-related cirrhosis [53]. Other factors associated with the occurrence of HCC in cirrhosis are older age (>55 years), male sex, elevated α -fetoprotein (>20 ng/mL), and obesity [54, 55]. More recently esophageal varices have also been reported to be significantly associated with the development of HCC in cirrhotic patients with HCV-related cirrhosis [56].

Survival in patients with HCC and cirrhosis depends on the severity of the underlying disease and on the degree of portal hypertension [57–59]. In fact, median survival in patients with HCC and esophageal varices is in the order of 24 months and in those without varices is about 36 months [60]. Overall, these considerations indicate that HCC is a major clinical event in the course of cirrhosis, which may occur in any disease stage and, whenever occurs, it invariably determines a significant reduction of survival.

Disease Stages

The typical representation of cumulative survival by Kaplan–Meier curves does not account for the real clinical course of patients with a definite clinical characteristic or disease stage. For example, a survival curve of patients with compensated cirrhosis at diagnosis does not account for the progressive development of decompensation

Table 2.2 Causes of death in compensated and decompensated cirrhosis

Cause of death	Compensated (n=377)		Decompensated (n=333)	
	No.	%	No.	%
Total number of deaths	65	17	295	86
Bleeding	12	3	52	16
Liver failure	9	2	99	30
HCC	4	1	91	27
Sepsis	3	0.1	13	4
Malignant tumors	8	2	8	2.4
Heart ischemic disease	4	1	—	—
Stroke	7	2	5	1.5
Other	11	3	8	2.4
Undefined	7	2	16	5

Data from D'Amico G, Pasta L, Madonia S, Tarantino G, Mancuso A, Malizia G, et al. The incidence of esophageal varices in cirrhosis. *Gastroenterology* 2001;120:A2

and for the increased risk of death after decompensation. As a consequence, the increased risk of death after decompensation is unduly associated with a presentation of compensated cirrhosis.

In recent years, the use of competing risks analysis has shown that mortality of compensated patients while they are still compensated is very low, because most of them die only after developing decompensation. The competing risks approach allowed to measure the intensity of transition from compensated to decompensated cirrhosis before death, therefore introducing the concept of clinical stages and transition across them [3]. Compensated and decompensated cirrhosis have been therefore considered as two distinct entities characterized by different clinical course, different survival, different prognostic indicators, and different causes of death [2, 3] (Table 2.2). This concept posed the study of the clinical course of cirrhosis in a very different perspective compared to the traditional approach of previous studies. A four-stage system was initially proposed [3] which was subsequently modified into a five-stage one [16]: two stages in compensated and three in decompensated cirrhosis. The following summary of the outcome of cirrhosis is drawn from unpublished data from a multicenter retrospective study of clinical stages of cirrhosis [16]:

- *Stage 1* is characterized by the absence of esophageal varices in compensated patients. While patients remain in this stage, the 1-year mortality rate is 1.5 % (Fig. 2.1). Patients exit this stage at a cumulative rate of 11.9 % per year: 6.2 % because of the development of varices and 4.2 % because of decompensation, mostly marked by development of ascites.
- *Stage 2* is characterized by the presence of esophageal varices with compensated cirrhosis. While patients remain in this stage, the 1-year mortality rate is 2 %. Patients leave this stage also by developing decompensation (12.2 % per year) (Fig. 2.1), mostly characterized by bleeding or ascites.
- *Stage 3* is characterized by upper digestive bleeding without other decompensating events. While patients remain in this stage, the 1-year mortality rate is

Fig. 2.1 One-year outcome of patients with compensated cirrhosis according to the absence (stage 1) or presence (stage 2) of esophageal varices

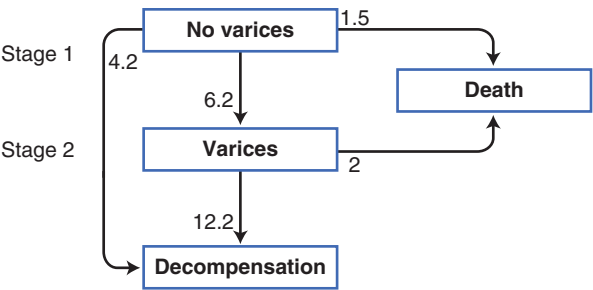
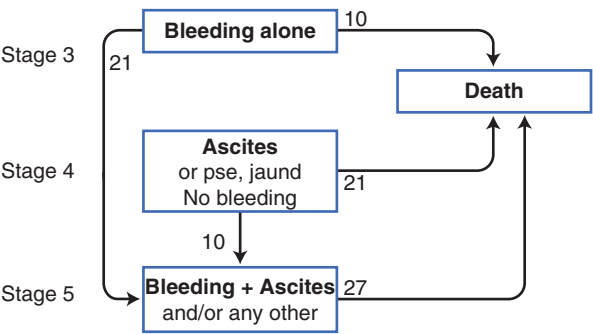


Fig. 2.2 One-year outcome of patients with decompensated cirrhosis according to development of bleeding alone (stage 3), ascites, or other decompensating events (stage 4) and to the presence of two or more decompensating events (stage 5)



- 10 % per year, significantly higher than in the two former stages (Fig. 2.2). Twenty-one percent of patients also exit this stage by developing other decompensating events (mostly ascites).
- *Stage 4* is characterized by ascites, jaundice, or encephalopathy. In this stage the 1-year mortality rate is 21 %, while 10 % of patients develop further decompensating events thus transitioning in stage 5.
 - *Stage 5* is characterized by more than one decompensating event thus indicating a more advanced liver dysfunction. One-year mortality in this stage is 27 %. To note, a total of 87 % of these patients die within 5 years, mostly after developing further decompensating events.

HCC develops at a fairly constant rate of 3 % per year and is associated with a worse outcome at whatever stage it develops.

Although several studies [4, 17, 18, 61] have confirmed the rationale for a staging system in cirrhosis, a full independent and prospective validation of the proposed system is still awaited. Potential advantages of this staging system are the easy applicability and reproducibility. It may also contribute to identify more accurate predictors of the outcome within each single stage. It is in fact conceivable that prognostic scores such as the MELD [21] or the Child-Pugh [29] or other predictors may have a different impact in different stages. In fact, an exploratory unpublished prognostic analysis in a prospective cohort study [11] showed that the most important prognostic indicators yielded markedly different hazard ratios according to whether they were adjusted or not for the clinical stage.

Acute-on-Chronic Liver Failure

Decompensation of cirrhosis may present acutely with ascites, hepatic encephalopathy, gastrointestinal hemorrhage, and bacterial infections that lead to hospitalization. On admission, some of these patients have only decompensated cirrhosis, whereas others may exhibit decompensated cirrhosis associated with newly developed liver and/or extrahepatic organ failure. Patients with cirrhosis and acute organ failure are at high risk for short-term death and this condition has been termed ACLF in the recent years [62]. It is associated with very high mortality and its prevention should be considered a major aim in cirrhosis management strategies.

A universally accepted definition of ACLF is still lacking. In Western countries, it has been suggested that ACLF be defined as an acute deterioration of liver function in patients with cirrhosis that is usually associated with a precipitating event and results in the failure of one or more organs and high short-term mortality. Based on the association of liver dysfunction with liver or other organ failure, ACLF has been classified in four grades from 0 (merely decompensated cirrhosis) to grade 3, depending on the number and severity of associated organ failure [62]. Twenty-eight day mortality has been reported 5 % for grade 0, 22 % grade 1, 32 % grade 2, and 76 % grade 3.

Prognostic Indicators

In a systematic review of 118 prognostic studies of cirrhosis [3] a total of 174 different variables were evaluated. The variable that was found to be the most common independent predictor of death was the Child(-Pugh) score, having been introduced in a multivariable analysis in 67 studies and having been among the first five significant predictors in 42 (63 %) of them. This was followed by all components of the Child-Pugh score (albumin, bilirubin, ascites, encephalopathy, prothrombin time). Age was the only variable that is not part of the Child-Pugh score, which was found to be predictive of survival in more than ten studies. Among variables found to be independently predictive of survival in at least one study, HVPG, MELD, and the presence of HCC were remarkable because they were found to be predictive of death in over two-thirds of studies in which they were evaluated. Almost half of the variables evaluated were not significant in any study and, remarkably, ALT had been non-predictive of death in 31 studies in which it was evaluated. When restricting the analysis to 31 studies that met criteria for “good” quality [3], the same most common prognostic variables were confirmed: Child-Pugh score or its components and age.

When the analysis was performed separately for studies that included only compensated or only decompensated cirrhotic patients, the most common prognostic variables in each group were different, with variables related to portal hypertension (platelet count, varices, spleen size), liver function (bilirubin, albumin, prothrombin), gender, and age, appearing in the compensated group, and variables related to Child-Pugh score, bleeding, renal insufficiency, or HCC appearing in the decompensated group.

Concluding Remarks

Compensated cirrhosis is characterized by a very low mortality, while transition to decompensation is the major outcome for this early disease stage. Once decompensation occurs, the mortality rate is very high, with a median survival time of approximately 2–4 years. Esophageal varices, ascites, bleeding, jaundice, and encephalopathy allow identification of five disease stages with significantly different outcome: two stages in compensated and three in decompensated cirrhosis. In most patients the occurrence of sepsis or renal failure, with or without ACLF, will accelerate the final course towards death. A schematic representation of the clinical course of cirrhosis is reported in Fig. 2.3.

Overall, the most robust predictors of survival are the Child-Pugh [29] score or its components, age, portal hypertension, renal function, and MELD [21]. Predictors of survival are different in compensated and decompensated patients with portal hypertension assuming a greater importance in compensated patients, while in patients with decompensated cirrhosis it is the Child-Pugh score as well as renal dysfunction parameters that carry a greater weight. For present day clinical practice, Child-Pugh [29] and MELD [22] scores are appropriate survival predictors. In future studies, prognostic indicators should be assessed separately in patients with compensated and decompensated cirrhosis. In fact, in patients with compensated cirrhosis the transition to a decompensated stage may be a major endpoint for which prognostic indicators should be assessed.

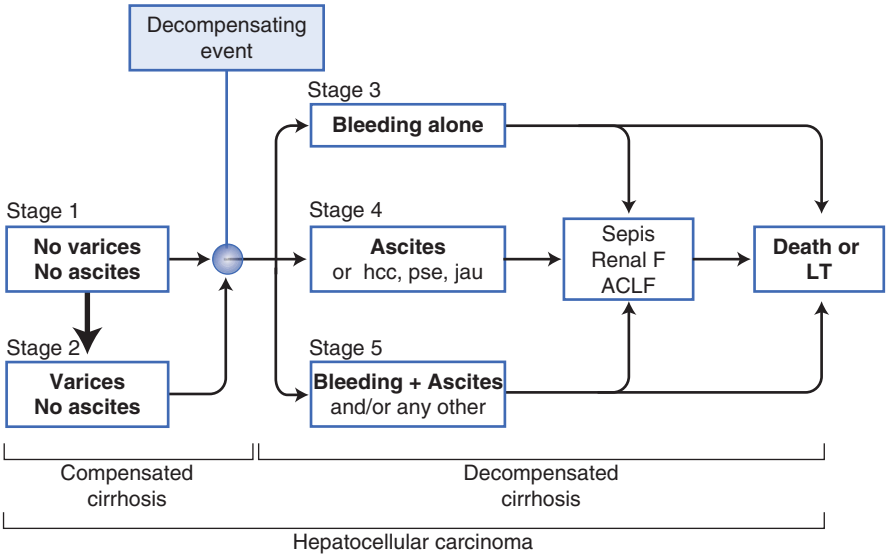


Fig. 2.3 Schematic representation of the clinical course of cirrhosis

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