Cirrhosis is considered the end stage of chronic liver disease of any etiology with a broad spectrum of clinical manifestations that are due to portal hypertension and/or liver insufficiency. The gold standard in the diagnosis of cirrhosis is considered histological and is characterized by a disrupted liver architecture secondary to regenerative nodules surrounded by fibrous septa. Once cirrhosis is established, it has been considered that the process is progressive and irreversible with an inevitable progression to death unless liver transplantation (LT) is performed. Cirrhosis had also been considered a single entity with a continuum of increasing degrees of severity and common predictors of death. These paradigms have shifted in recent years [1] as described in the following paragraphs.

Is Cirrhosis the Same Irrespective of Etiology?

The pathophysiological process that leads to cirrhosis is complex but, at its core, consists of progressive fibrogenesis. However, as recently pointed out, different types of chronic liver disease lead to different patterns of fibrosis and may therefore lead to different clinical manifestations [2]. For example, in primary biliary cirrhosis, where the process is predominantly portal and therefore fibrosis is mainly portal to portal, the initial clinical complications may be secondary to presinusoidal portal hypertension (varices and variceal hemorrhage without liver insufficiency or ascites) while in alcoholic cirrhosis, where fibrosis is sinusoidal, initial complications will be secondary to sinusoidal portal hypertension and liver insufficiency (ascites, in addition to varices and variceal hemorrhage). Therefore, although cirrhosis is the end stage of any chronic liver disease, its natural history may vary depending on its etiology.

Is Liver Biopsy the Gold Standard in the Diagnosis of Cirrhosis?

Even though liver biopsy remains the gold standard in the diagnosis of cirrhosis, it is an imperfect test. It is an invasive procedure with potential complications, including death, along with sampling errors that can lead to a missed diagnosis of cirrhosis. It has been shown that measurement of hepatic venous pressure gradient (HVPG), an indirect measure of sinusoidal pressure obtained through catheterization of the hepatic vein, has a greater diagnostic accuracy than liver biopsy in the diagnosis of cirrhosis. In a study of 116 patients with recurrent hepatitis C post-LT, HVPG was very accurate in predicting the development of disease progression (with an area under the curve [AUC] of 0.96), more so than the presence of significant fibrosis on liver biopsy (AUC...
An HVPG measurement of 6 mmHg or greater indicates the presence of cirrhosis. HVPG addresses a larger area of hepatic parenchyma than liver biopsy, since the pressure obtained is the average pressure of many sinusoids, thus reducing the possibility of sampling error due to the presence of fibrosis heterogeneity within the diseased liver. More recently, noninvasive tests including serum markers, ultrasound, and liver and/or spleen stiffness measurements have become important tools in ruling in or excluding cirrhosis with a high diagnostic accuracy and may substitute for liver biopsy in the diagnosis of cirrhosis.

Nevertheless, the extent of liver fibrosis (by semiquantitative or quantitative assessment of liver biopsy) correlates with different prognostic strata in the cirrhotic liver and histological features (thickness of fibrous septae or fibrosis area) in a liver biopsy may have a prognostic stratifying role [4–7].

**Is Cirrhosis Irreversible?**

The advent of effective therapies, specifically antivirals, has shown that cirrhosis is a dynamic and potentially reversible process. Several recent studies performed in patients with chronic hepatitis B infection have shown that histological regression (by at least one stage) of advanced fibrosis/cirrhosis occurs in at least 50% of patients receiving antiviral therapy [8]. Likewise, in studies performed in patients with hepatitis C infection, sustained virological response (i.e., viral elimination) to specific antiviral therapy has led to histological regression of cirrhosis in about 62% of patients [8].

The assessment of regression of fibrosis by liver biopsy is also subject to sampling variability and therefore the rate of regression may be overestimated. A better way to assess such reversibility would be by the application of HVPG measurements (or noninvasive surrogates) because of its higher diagnostic accuracy. It is probable that the likelihood of reversibility will depend on the amount of fibrosis deposited in an already cirrhotic liver [1].

**Is Cirrhosis a Single Entity?**

Numerous prognostic studies over the years have demonstrated that cirrhosis is not a single entity. In a systematic review evaluating 116 of such studies, the median survival of patients with cirrhosis ranged widely, from 1 to 186 months [9], indicating that cirrhosis is a heterogeneous disease.

When patients were divided in two stages depending on the presence or absence of clinically evident decompensating events (specifically ascites, variceal hemorrhage, hepatic encephalopathy [HE] and jaundice), 1-year survival in those who were compensated, that is, those who had no clinical decompensating events was 95% (interquartile range 91–98%) while in decompensated patients, it was 61% (interquartile range 56–70%) [9]. Analysis of individual patient data from two prospective Italian cohort studies that included over 1600 patients demonstrated a median survival of greater than 12 years in patients with compensated cirrhosis, while patients with decompensated cirrhosis had a median survival of 1.8 years [9]. Compensated patients have a very low probability of death (10% in 20 years) before becoming decompensated [10]. Importantly, the systematic review revealed that predictors of death were different in patients with compensated versus those with decompensated cirrhosis [9].

These results have been confirmed in a recent prospective study that analyzed a concurrent cohort of patients with cirrhosis (both compensated and decompensated) and showed that decompensation was the strongest predictor of death [11]. Furthermore, both stages had different prognostic indicators (age for compensated; model for end-stage liver disease (MELD) score for decompensated), and that those predictors that were common to both stages (albumin, platelet count) had different strengths of association [11].

All these findings support considering the natural history of cirrhosis not as a continuum of a single entity but as a progression across different prognostic stages, with the compensated and decompensated stages being the most important. Sub-stages within these two main stages
are being increasingly described and are summarized below. An additional terminal stage in cirrhosis characterized by multi-organ failure has been designated “acute-on-chronic liver failure” (ACLF) and is also discussed. Hepatocellular carcinoma (HCC), although strictly a complication of cirrhosis, is not considered a separate stage of cirrhosis as it may occur in both compensated and decompensated cirrhosis and, when it develops in the compensated patient it can lead to decompensation. Therefore, HCC will not be considered further in this chapter.

1 Compensated Stage of Cirrhosis

Compensated cirrhosis is defined as cirrhosis in the absence of ascites, variceal hemorrhage, HE or jaundice. It is asymptomatic. Importantly, patients in whom ascites is controlled through the use of diuretics or in those with HE that is controlled with specific medications are not compensated patients. Even though therapy may initially resolve some of the clinical complications, the pathogenic mechanisms that led to their development are still in place and, in general, prognosis is not improved by therapy.

In patients with compensated cirrhosis, liver insufficiency is minimal or absent and portal hypertension is the predominant pathogenic mechanism (Fig. 2.1).

Portal hypertension is the initial consequence of cirrhosis. An HVPG ≥ 6 mmHg defines portal hypertension, and therefore, as discussed previously, the presence of cirrhosis. This is true in diseases in which the resistance to portal flow is located at the sinusoids, such as alcoholic and/or viral-related cirrhosis [12], as well as cirrhosis secondary to nonalcoholic steatohepatitis. In portal-based diseases (cholestatic liver diseases), there will be an important presinusoidal component of portal hypertension that is not reflected by the HVPG which, at least initially, will underestimate the actual portal pressure. Therefore, patients with cholestatic liver disease have been routinely excluded from therapeutic or prognostic studies using HVPG. Once a threshold HVPG of 10 mmHg has been reached/surpassed, patients are at a higher risk of developing gastroesophageal varices [13]. Patients in whom varices are present have an HVPG of 12 mmHg or greater [14].

Different prognostic sub-stages have been identified in patients with compensated cirrhosis based on the following stratifying factors:

a. Gastroesophageal varices

The initial mechanism leading to portal hypertension is an increase in intrahepatic vascular resistance to portal flow. One of the early consequences of portal hypertension is the formation of porto-systemic collaterals, the most important being those that form via the coronary or the short gastric veins and constitute gastroesophageal varices. Although varices are a complication of cirrhosis, they are asymptomatic (unless they rupture) and are only diagnosed by endoscopy. About a third to half of patients with compensated cirrhosis have varices when first diagnosed [10, 13]. Patients with varices (without ascites, HE or jaundice) that have not bled are still in the low-mortality compensated stage, although studies have shown that rates of mortality and evolution to decompensation are higher in these patients than in those without varices [10, 15, 16]. This has led to the classification of compensated cirrhosis into two sub-stages: stage 1 are patients with compensated cirrhosis who do not have varices (the very compensated patient) while patients with varices are designated as being at stage 2 [9, 10].

One may assume that visualization of porto-systemic collaterals on imaging studies may have the same prognostic significance as the presence of endoscopically-proven gastroesophageal varices, but this remains to be determined.

b. Clinically significant portal hypertension

As mentioned above, in patients with compensated cirrhosis without varices, the main predictor of the development of varices is the HVPG. The cutoff that best predicts variceal development is 10 mmHg. While the probability of developing varices at 2 and 5 years in patients with an HVPG ≥ 10 mmHg was 18 and 45%, respectively, these probabilities were 7 and 30% in those with an HVPG < 10 mmHg.
In fact, an HVPG ≥ 10 mmHg is also the best predictor of the development of clinical decompensation [17] and HCC [18]. The probability of developing decompensation at 2 and 5 years in patients with an HVPG ≥ 10 mmHg was 13 and 29%, respectively, while in patients with an HVPG < 10 mmHg, it was 6 and 15%, respectively [17]. An HVPG ≥ 10 mmHg has been termed “clinically significant portal hypertension” (CSPH).

Therefore, it can be proposed that patients without varices could be stratified into those with an HVPG < 10 mmHg (without CSPH), that would be the extremely compensated patients (a redefined stage 1), and those with an HVPG ≥ 10 mmHg (with CSPH). The staging system in cirrhosis is clearly in evolution and at this point, simply describing the populations at risk (e.g., patients with compensated cirrhosis with varices or patients with compensated cirrhosis without varices and an HVPG < 10 mmHg) is recommended. Of note, patients with varices have, by definition, CSPH because all patients with gastroesophageal varices have an HVPG of at least 11–12 mmHg [14, 19].
c. Ascites detectable only by ultrasound
Patients who have ascites detectable only by ultrasound have no symptoms or signs referable to ascites and therefore are still compensated. However, a recent study evaluated the prognostic significance of subclinical ascites \( n=38 \) in a population of patients with predominantly alcoholic cirrhosis and compared them to patients without ascites \( n=153 \) and to patients with clinically-evident ascites \( n=252 \) [20]. Patients with subclinical ascites had a survival that was intermediate between patients with overt ascites and those without ascites. This situation would be akin that of the patient with cirrhosis (without ascites or HE) and varices that have never bled who is considered compensated because the presence of varices cannot be established by physical examination. Therefore, as for nonbleeding varices, patients with subclinical ascites should be considered compensated, albeit at a higher risk of death and clinical decompensation than those without any ascites.

d. Portosystemic encephalopathy without liver insufficiency
Perhaps one exception to the definition of decompensation is the case of HE that presents in patients with compensated cirrhosis (no variceal hemorrhage, no ascites) and essentially normal liver synthetic function, in whom HE is the result of a large spontaneous portosystemic shunt [21]. It has been shown that patients with a MELD score less than 11 (i.e., compensated) are more likely to respond to occlusion of the spontaneous shunt, without changes in MELD score in the short-term [22]. The long-term course of patients with HE due to these shunts (and the effect of their occlusion) needs to be further evaluated to determine their prognostic significance. Until then, these (rare) patients could be considered compensated.

2. Decompensated Stage of Cirrhosis
This is the symptomatic stage of cirrhosis and is defined by the presence of ascites, variceal hemorrhage, HE or liver insufficiency (jaundice). The main pathogenic mechanisms are portal hypertension and the hyperdynamic circulatory state [23]. This hemodynamic abnormality is the result of splanchnic and systemic vasodilation that increases as HVPG surpasses 10 mmHg and portosystemic collaterals develop. The vasodilatation (manifested clinically as arterial hypotension) leads to activation of the neurohumoral systems, sodium and water retention, increased blood volume and increased cardiac output, that is, a hyperdynamic circulatory state.

Of the decompensating events, overt ascites is clearly the most common, accounting for 60–80% of initial clinical events, followed by gastrointestinal hemorrhage, while HE and jaundice occur as the first clinical event in only a minority of patients [10, 24].

Sub-staging of patients with decompensated cirrhosis is not as well-defined as compensated cirrhosis and requires further investigation. The following are different proposed prognostic sub-stages based on the following stratifying factors:

a. Type and number of decompensating clinical events
Even though each of the individual complications of cirrhosis has an impact on survival in patients with cirrhosis, the magnitude of the impact is different. The Baveno IV consensus conference, based on results from a large Italian cohort, had stratified patients with decompensated cirrhosis into two sub-stages based on the type of initial decompensating event: (1) patients with ascites with or without varices (stage 3) and (2) patients with gastrointestinal bleeding with or without ascites (stage 4) [25]. However, it was shown in another cohort that decompensated patients with ascites have a significantly poorer outcome than those presenting with variceal hemorrhage as the only decompensating event [16]. This led to a re-staging of cirrhosis, based on an Italian prospective inception cohort study of 464 patients in which patient flow across stages was assessed by competing risk analysis [10]. In this re-staging, decompensated patients would be placed in three strata: (1) bleeding without other complications; (2) first nonbleeding decompensation (mainly ascites); and
(3) patients with any second decompensating event [10]. Five-year mortality rates for each of these three stages was 20, 30, and 88%, respectively. The mortality rate difference between patients who present with variceal hemorrhage (no other complication) and those that presented with one nonbleeding complication was not large, similar to findings in another cohort followed for a median of 33 months in which a poor outcome (death or LT) was 20% in patients with variceal hemorrhage and 36% in those with ascites [24]. It is not unexpected that patients that develop more than one complication have the highest mortality. The higher mortality in the different sub-stages was confirmed in a retrospective study of patients on a transplant list with a MELD score < 20 that combined patients with compensated and decompensated cirrhosis [26].

b. Complications of the initial complication or “further” decompensation
Patients who die of decompensated cirrhosis often do so after development of “further decompensation”—worsening of the pathophysiological mechanisms (portal hypertension, hyperdynamic circulatory state and/or liver insufficiency) lead to a subsequent complication after the initial event. Specifically, patients with ascites would develop diuretic-refractory ascites, hyponatremia or hepatorenal syndrome (HRS) as a result of worsening vasodilatation (and decreasing mean arterial pressure) and activation of neurohumoral systems [27]; patients with variceal hemorrhage would develop recurrent variceal hemorrhage as a result of worsening portal pressure and/or worsening of the hyperdynamic circulatory state [28–30]; and patients would develop recurrent/persistent HE, coagulopathy and jaundice as a result of further impairment in liver function. The development of these added decompensating events may have a trigger that is not clinically evident (e.g., overt bacterial infection versus bacterial translocation). Bacterial infections occur in both compensated and decompensated cirrhosis and are a frequent precipitant for acute decompensation (see below) and therefore do not represent a separate stage.

There is evidence demonstrating that refractory ascites has a higher mortality than diuretic-responsive ascites [31], that the presence of hyponatremia is associated with a significantly poorer survival in patients on the liver transplant waiting list, independent of MELD score [32] and that HRS type 1 (acute renal failure in cirrhosis) has a higher mortality than HRS type 2 (renal failure associated mostly with refractory ascites), which in turn has a higher mortality than refractory ascites [33]. In fact, while the median survival in compensated cirrhosis is greater than 12 years (as long as the patient remains compensated), the median survival in decompensated cirrhosis, refractory ascites and in patients with untreated HRS type 1 is approximately 2 years, 7 months and 1 month, respectively. Therefore, another way to stratify patients with decompensated cirrhosis would be to divide them into those who are decompensated by virtue of the development of ascites, variceal hemorrhage or HE and those that have other complications that denote a more advanced liver disease: refractory ascites, hyponatremia, HRS, recurrent/persistent HE, and jaundice.

c. Organ failures
Most of the complications of the “further” decompensated stage represent an “organ failure” with HRS representing the kidney, hypotension (resulting from extreme vasodilatation) representing the circulatory system, encephalopathy representing the nervous system, coagulopathy and jaundice representing liver failure. The presence of multiorgan failure in cirrhosis has recently been termed ACLF. Many definitions of this entity have been proposed in recent years. Most of them, particularly those developed in the West, have in common the presence of acute deterioration of pre-existing cirrhosis [34]. Results of a large multinational European consortium demonstrate that ACLF is distinct from “mere” decompensated cirrhosis [35]. The consortium built a substaging of ACLF based on a modification of the sequential organ failure assess-
ment (SOFA) score, the SOFA-CLIF score. It divides ACLF into 5 grades with progressively greater 28-day mortality: grade 0 (no organ failure, 2% mortality); grade 1 (one nonrenal failure, 6% mortality); grade 2 (renal failure alone or an extra-renal failure with added criteria, 22% mortality); grade 2 (two organ failures, 32% mortality); and grade 3 (three organ failures, 77% mortality). Similar results relating organ failures with survival were found in hospitalized patients with cirrhosis and bacterial infections in another Western consortium, the North American Consortium for the Study of End-Stage Liver Disease, in which two extra-hepatic organ failures were associated with a significant increase in mortality compared with patients with only one or no organ failures [34].

An entity that requires further study is the ACLF that presents in a patient with compensated cirrhosis. These patients represent a minority of patients presenting with ACLF but, quite interestingly, their mortality (42%) is significantly greater than patients who were decompensated and developed further decompensation (30%) [35].

Summary

Cirrhosis is a dynamic and potentially reversible disease. Large cohort studies looking at predictors of death in cirrhosis have determined that the natural history of cirrhosis is not the continuum of a single entity but is a progression across different prognostic stages, with the compensated and decompensated stages being the most important. Patients in these two stages of cirrhosis should be managed differently both clinically and in research. Within the compensated stage, different prognostic strata have been identified, the main one based on the presence or absence of varices. In patients without varices, the main stratifying marker is an HVPG of 10 mmHg. Within decompensated cirrhosis, the different complications and their coexistence (or not) add to the prognostic granularity of the stage (with ascites having a worse prognosis, more so when associated with variceal hemorrhage). However, a stage of “further” decompensation as defined by the presence of complications of the complications (specifically refractory ascites, HRS, recurrent variceal hemorrhage and recurrent/persistent HE) is likely to provide a larger prognostic differential among patients with decompensated cirrhosis. A final stage characterized by multi-organ failure and that has been termed ACLF has the worst prognosis; however, it can occur in both compensated and decompensated patients and requires further evaluation.

References

Complications of Cirrhosis
Evaluation and Management
Keaveny, A.; Cárdenas, A. (Eds.)
2015, XV, 357 p. 50 illus., 28 illus. in color., Hardcover
ISBN: 978-3-319-13613-4