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Prediction of Decompensation in Patients with Compensated Cirrhosis: Does Etiology Matter?

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Abstract

Purpose of Review Transition from compensated to decompensated cirrhosis, defined by overt clinical signs, represents a turning point in the clinical course of the disease. In fact, while compensated cirrhosis is a silent disease characterized by long survival, decompensated cirrhosis is associated with symptoms markedly reducing the quality of life and with a median survival of 2–4 years. Therefore, identifying predictors of decompensation and investigating potential interventions for its prevention is a major objective. Mechanisms and incidence of decompensation, together with its predictors, are summarized here, with regard to the etiology of the disease.

Recent Findings In a total of 92 studies including 105 cohorts and 152,320 patients, the mean ± SD 5-year decompensation rate was 24.5 ± 13.6%. The 5-year decompensation rate was significantly different across different etiologies, ranging from 12.8% for biliary etiologies to 33.6% in alcoholic liver disease ($p < 0.0001$). The most frequently reported significant predictors of decompensation were liver function, portal hypertension, and inflammation/fibrosis indicators. Etiologic treatment was associated with significant risk reduction.

Summary While the risk of decompensation significantly varies across different etiologies of cirrhosis, etiology per se has not been properly studied as a decompensation predictor. Although decompensation appears to be related more to inflammation/fibrosis and portal hypertension, the causing factors may determine different activation intensity of the decompensating mechanisms.

Keywords Compensated cirrhosis · Decompensated cirrhosis · Predictors · Etiology · Portal hypertension · Systemic inflammatory response

Introduction

The clinical course of cirrhosis is characterized by a usually long asymptomatic phase followed by overt disease manifestations resulting from the progressive deterioration of liver function. In the early stage of the disease, liver function is enough to allow a satisfactory quality of life and the disease may progress even undetected for many years. This phase is referred to as "compensated cirrhosis" [1–2]. The appearance of any overt clinical sign marks the transition to a more advanced phase of the disease characterized by a rapid progression towards death or liver transplantation. This more rapid phase of the disease is referred to as "decompensated cirrhosis" and is defined by the presence of any of ascites, variceal bleeding, hepatic encephalopathy, or jaundice [1–2]. Median survival in compensated cirrhosis is 12 years, while in decompensated cirrhosis, it is 2 years [3]. These marked clinical and survival differences have brought about the concept that compensated and decompensated cirrhosis should be considered two different clinical states of the disease [4].

Decompensation ensues to the progressive increase of portal hypertension (PH) caused by a continuing exposition of the

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liver to the etiological factors which activate inflammation, fibrogenesis, and angiogenesis. In fact, eliminating or controlling the underlying cause of cirrhosis may result in fibrosis reduction and improvement of PH as shown with eradication of hepatitis C virus, suppression of hepatitis B virus, withdrawal of alcohol, reducing weight in obese patients with non-alcoholic steatohepatitis, resolving biliary obstruction, or phlebotomy in hemochromatosis [5–7, 8••, 9••].

However, etiologic treatments are not widely available in several countries and even when successfully applied do not halt the disease progression in all treated patients, leaving a proportion of them still at risk of decompensation and of hepatocellular carcinoma.

It would be therefore important to know who the patients at higher risk of decompensation are in order to plan adequate follow-up and preventive treatments when available, as well as to know whether this risk is similar or differs across the various etiologies of liver disease.

In this review, we summarize the present-day knowledge on the incidence rate of decompensation across different disease etiologies and relevant risk predictors.

Clinical Course of Cirrhosis

Cirrhosis results from chronic liver inflammation from a wide range of insulting factors, which cause profound structural and vascular changes, a gradual increase in hepatic resistance to the blood flow and PH. The consequent adaptive splanchnic vasodilation increases portal venous inflow, thus aggravating PH, and progressively results in hyperdynamic circulation [10–12].

Initially, PH is mild with hepatic vein portal gradient (HVPG) < 10 mmHg and cirrhosis remain compensated usually for a long time. Depending on the curability of the underlying cause, disease progression may be halted or even reverted in this phase [5–7, 8••, 9••]. By contrast, the persistence of liver damage results in increasing fibrosis and portal hypertension [13–15].

Further increase of portal pressure may be associated to the occurrence of esophageal varices or decompensation, defined by the occurrence of any of variceal bleeding, ascites, hepatic encephalopathy, or jaundice [1–2]. Either varices or decompensation may occur when HVPG reaches values equal or greater than 10 mmHg, which is therefore considered the threshold value of HVPG for clinically significant portal hypertension (CSPH) [16••, 17]. The incidence rates of esophageal varices and decompensation are 7–8% and 5% per year, respectively [18–21]; decompensation is significantly more frequent in patients with esophageal varices [21–23]. After their development, varices increase in caliber at a rate of approximately 5–7% per year [20–24] and may rupture in 5 to 15% patients per year, with risk increasing with variceal size, red signs, or Child B-C class [25]. When varices rupture, bleeding is associated with a mortality of 10–20% [26–27].

Following the first episode of variceal bleeding, rebleeding and death risks are approximately 60% and 30%, respectively, within 1–2 years [28–29], and are significantly reduced by non-selective beta-blockers plus endoscopic variceal ligation, or early TIPS in selected patients [30–32].

Ascites is the most frequent sign of decompensation and is associated with a 5-year mortality of about 50% [33–34]. Due to the profound hemodynamic changes, bacterial translocation and inflammatory activation in this disease stage [35••], ascites may become refractory or resistant to treatment at a rate of approximately 20% in 5 years [36]. When this occurs, the expected survival is in the order of 35% at 2 years, although it may be significantly improved by a transjugular intrahepatic portosystemic shunt (TIPS) in selected patients [36–37].

Hepatic encephalopathy and jaundice rarely occur as a first decompensating event and are associated with a 5-year survival of about 20% [21, 23], underlying their weight as of late disease markers, while the predictive role of covert encephalopathy [38] remains still unclear [38–41].

In the more advanced stages of cirrhosis, due to the progressive hemodynamic changes, renal function may deteriorate and hepatorenal syndrome (HRS) may occur either spontaneously or following some precipitating factor [42–44]. Progressive cardiac impairment may also occur in this late phase of the disease [45]. The expected survival after the appearance of renal insufficiency is approximately 60% at 1 year [46–47].

Bacterial translocation occurs with increasing PH and liver dysfunction [48–49] and increases the risk of infections. The important inflammatory response associated with infections may precipitate organ failures [48, 50] and the associated mortality may be as high as 38% [51]. Following infections, 1-year readmission and mortality rate may be as high as 35% [52] and 60% [53], respectively.

Hepatocellular carcinoma (HCC) occurs in 2–8% patients per year [54–56] and is associated with a median survival of approximately 9 months in untreated patients [57] and 2 years in treated patients [58].

Systemic inflammatory response accompanying a triggering event (bleeding, bacterial infection, viral or toxic acute liver damage, other) may precipitate acute-on-chronic liver failure (ACLF) [59–61, 62••, 63–65]. ACLF is more frequent in decompensated patients but may rarely present also in compensated patients [66•] and is associated with a very high short-term mortality [59–60].

Liver failure, bleeding, HCC, infections, HRS, and ACLF are the most frequent causes of death.

Mechanisms of Decompensation

The peripheral arterial vasodilatation hypothesis (PAVH) has been previously accredited as the most plausible explanation for the occurrence of decompensation in cirrhosis. According

to this hypothesis, splanchnic vasodilatation, which occurs as a response to the increase of intrahepatic resistance [10–12], results in aggravation of PH while reducing the effective blood volume and hence causing systemic hypotension despite marked activation of endogenous vasoconstrictor systems. Increased plasma volume and cardiac output (CO) tend to mitigate the effects of initial hyperdynamic circulation but are ineffective in the more advanced disease when the cardiac reserve is insufficient to further increase CO, which may even decrease, and the ensuing hypotension causes further sodium and water retention leading to ascites formation.

However, growing evidence in the last years suggests that a systemic inflammatory response, primarily consequent to bacterial translocation, may play a key role in decompensation and its progressive course [35••, 62••]. According to this hypothesis, bacterial by-products (pathogen-associated molecular patterns, PAMPs) deriving from an immune reaction against translocated bacteria from the intestine cause the release of pro-inflammatory cytokines, leading to systemic inflammation with altered circulatory homeostasis. Circulatory dysfunction is sustained by the vasodilatory effect of pro-inflammatory molecules on the arteriole walls, with overproduction of nitric oxide, and on cardiomyocytes leading to cardiac dysfunction. PAMPs and cytokines may also play a role in the kidney, brain, and pulmonary dysfunction. The plausibility of this hypothesis is supported by the role played by bacterial infections or other acute stimuli, like a viral breakthrough in chronic virus B hepatitis or variceal bleeding, in precipitating acute decompensation in advanced cirrhosis.

It is therefore nowadays accepted that liver decompensation derives from both a peripheral arterial vasodilatation component with the ensuing hyperdynamic circulation and by a systemic inflammation syndrome mostly triggered by bacterial translocation and resulting in further vasodilatation and cardiac and other organ dysfunction.

Decompensation of Cirrhosis

Pertinent scientific evidences on the incidence and predictors of decompensation were retrieved by searching the MEDLINE database using the following search terms: (cirrhosis [Title/Abstract]) AND decompensation. We included in the present review either prospective or retrospective studies including consecutive patients with cirrhosis and reporting the incidence of decompensation with or without prognostic analysis. Exclusion criteria were the following: inclusion of non-consecutive patients; inclusion of patients with and without cirrhosis without separate analysis of decompensation incidence; analysis of the incidence of decompensation not performed; etiology of cirrhosis not reported; baseline characteristics not clearly described; lack of information on the completeness of follow-up. The search yielded 1559 articles among which 92 were selected for the present review [8••, 22–23, 67–155]. Fourteen studies included patients with mixed etiologies but reported separate analysis according to the different etiologies. Therefore, there were overall 105 cohorts including a total of 152,320 patients, available to assess the incidence and prognostic indicators of decompensation.

Definition of Decompensation

The definition of decompensation was reported in 88 of the 91 studies included. It was based on the development of ascites, bleeding, or encephalopathy (*abe*) in 34 studies; the development of ascites, bleeding, jaundice or encephalopathy (*abje*) in 27 studies; any combination of ascites, bleeding, encephalopathy, or jaundice with hepatocellular carcinoma (+*hcc*) in 12 studies; any combination of ascites, bleeding, encephalopathy, or jaundice with the increase of Child-Pugh score of at least 2 point (+*CPS*) in 6 studies; any combination of ascites, bleeding, encephalopathy, or jaundice with the increase in prothrombin time or development of varices or need of diuretics (+*other*) in 5 studies; and only ascites ± bleeding (*ab*) in 4 studies.

Incidence of Decompensation

Overall, the mean 2-, 3-, and 5-year decompensation risks ± standard deviation (SD) were respectively 11.6 ± 6.1% (53 cohorts, 137,977 patients), 16.4 ± 8.4% (73 cohorts, 147,313 patients), and 24.6 ± 13.6% (95 cohorts, 150,415 patients). The corresponding decompensation risks in studies published before 2010 ($n = 29$) and from 2010 on ($n = 62$) were 12.1 ± 6.8% versus 11.4 ± 5.8% at 2 years, 17.2 ± 9.8% versus 16.1 ± 7.6% at 3 years, and 26.5 ± 16.1% versus 23.5 ± 12.1% at 5 years (difference not significant in any of the 3 comparisons). The mean 5-year incidence of decompensation varied significantly across cohort groups according to the definition of decompensation: *ab* 40.8 ± 10.1%, *abje* 29.5 ± 14.3%, +*hcc* 22.6 ± 8.0%, +*CPS* 22.3 ± 5.9%, *abe* 20.7 ± 13.9%, +*other* 19.4 ± 10.9%, ($p = 0.009$). The 5-year risk of decompensation was also significantly different across different etiologies: biliary etiology, including primary biliary and primary sclerosing cholangitis 12.8 ± 10.9%, hepatitis B virus-related cirrhosis 14.6 ± 7.7%, NAFLD/NASH cirrhosis 23.6 ± 7.8%, hepatitis C virus-related cirrhosis 24.3 ± 10.2%, undefined etiologies 32.6 ± 11.6%, alcoholic cirrhosis 33.6 ± 13.9% ($f = 8.11$, df = 5, $p = 0.00001$). Relevant median and interquartile ranges are shown in Figs. 1 and 2.

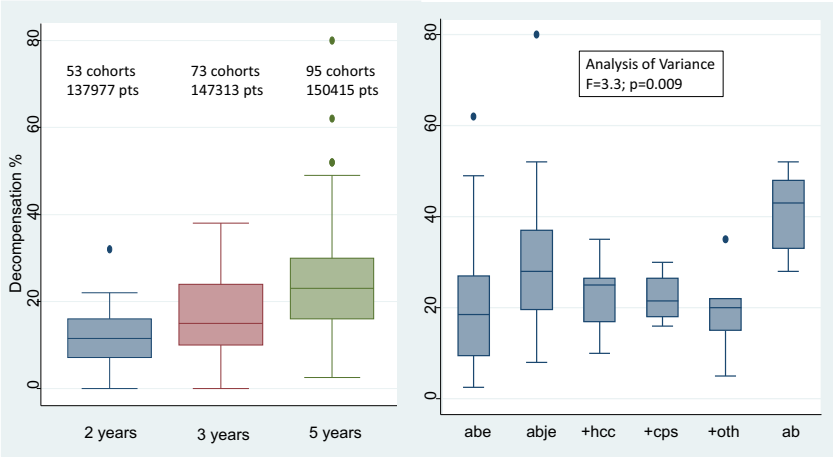

Fig. 1 *Left panel*: boxplots of median and interquartile ranges of decompensation rate at 2, 3, and 5 years as reported in a total of 105 cohorts including a total of 152,320 patients. *Right panel*: boxplots of median and interquartile ranges of 5-year decompensation rate across cohort groups according to the definition of decompensation. *abe*: ascites, bleeding or encephalopathy; *abje*: ascites, bleeding, jaundice or encephalopathy; *+hcc*, any combination of *abje* plus hepatocellular carcinoma; *+cps*, any combination of *abje* plus a Child-Pugh score increase of at least 2 points; *+oth*, any combination of *abje* plus development of varices, or prothrombin time increase, or need of diuretics; *ab*, only ascites ± bleeding

Incidence of Decompensation According to Disease Etiology

Biliary Etiology

The lowest decompensation risk was found for biliary etiology of cirrhosis. There were 8 studies including 11 patient cohorts with cirrhosis from biliary etiology totaling 2068 patients [67, 84, 90, 105, 126, 131, 142, 148], of whom 1639 in 6 studies (9 cohorts) of primary biliary cholangitis (PBC) and 429 in 2 studies (2 cohorts) of primary sclerosing cholangitis (PSC).

Overall, the mean ± SD 5-year decompensation rate was 13.2 ± 12.1% in PBC and 11 ± 2.8% in PSC ($t = 0.25$, $p = 0.81$). In one study of PBC [126], including 936 patients, the decompensation risk was compared in 4 different cohorts according to the year of diagnosis (1970–1979, 1980–1989, 1990–1999, 2000–2010) and a significantly higher risk in the oldest cohort was found (4.8% compared with 3.5%, 3.5%, and 2.5%, respectively for the 1970, 1980, 1990, and 2000 cohorts) ($p < 0.0001$).

Hepatitis B Virus

Twelve studies including a total of 3565 patients reported the incidence of decompensation in hepatitis B virus (HBV)-related cirrhosis [71–72, 82–83, 89, 92, 94–95, 109, 115–116,

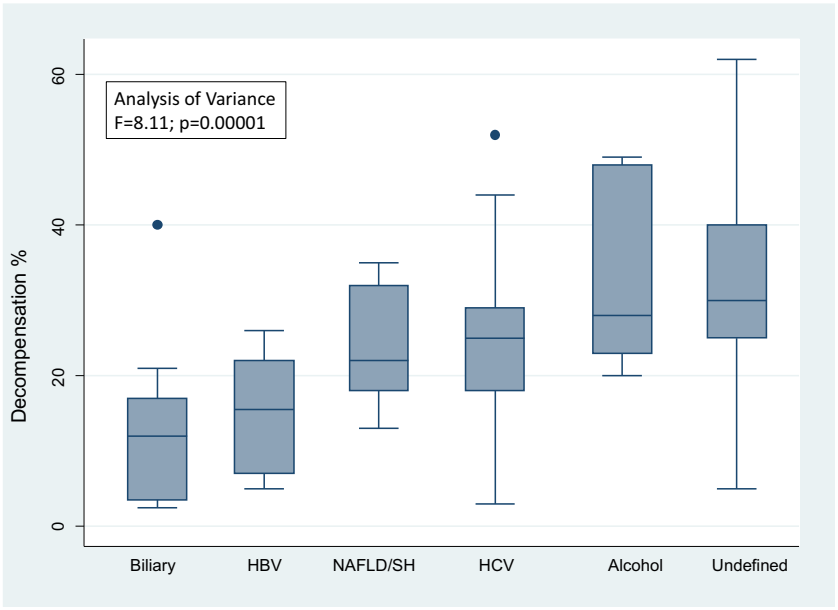

Fig. 2 Boxplots median and of interquartile ranges of decompensation rate at 5 years as reported in a total of 96 cohorts including a total of 150,982 patients grouped according to different etiologies. Biliary: primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC); HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD/NASH, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis; alcohol, alcoholic cirrhosis; undefined, studies including cirrhosis from any etiology without providing a separate analysis of decompensation risk

128]. The 5-year risk was overall 16.5 ± 6.9%. One of the HBV studies [116] was a randomized controlled trial comparing lamivudine (436 patients) with placebo (215 patients). Lamivudine significantly delayed the risk of disease progression, including decompensation and death, from 17.7% in placebo-treated patients to 7.8% with lamivudine after a median follow-up of 32 months (range 0 to 42). Overall, lamivudine or other nucleos(t)ide treatments were used in 3 studies including 677 patients of the 12 studies included. The mean 5-year decompensation rate in these studies was 6.3 ± 2.3% while in the 9 studies of untreated patients, it was 17.3 ± 6.7% ($p < 0.01$).

Hepatitis Delta Virus

Four studies assessed the incidence of decompensation in HBV-delta superinfected cirrhosis including a total of 514 patients [76, 100, 130, 137]. The mean 5-year decompensation rate in the only study including untreated patients [100] was 80%, while in the other three, where a proportion of 100 to 40% of patients was given antiviral treatments, it ranged from 8 to 18%, suggesting that antiviral treatment is a major factor improving the clinical course of HDV-HBV co-infected cirrhosis. However, it is conceivable that in the study including untreated patients other factors than treatment may have been responsible for the high risk of decompensation as suggested by an European multicenter series [92] including 200 HBsAg-positive patients with cirrhosis and untreated for HBV infection, of whom 39 were anti-HDV positive (37 of them HBeAg-negative): in this study the 5-year incidence of decompensation in HDV co-infected patients was 20%. On the other hand, it is well known that antiviral treatment significantly reduces the incidence of clinical events in hepatitis delta-infected patients, independently of the presence of cirrhosis at diagnosis [155].

Hepatitis C Virus

A total of 35 studies included 24,726 patients with hepatitis C virus (HCV)-related cirrhosis [22, 71, 75, 77, 79–81, 85, 88, 91, 93, 95, 97, 99, 104, 107, 111, 114, 119–125, 127, 132–135, 139, 141, 145, 152–153]. Thirty-one of these studies reported a mean 5-year decompensation rate of 24.3 ± 10.2%, while the remaining 4 studies reported 2- to 3-year decompensation rates ranging from 7 to 32%. In 26 studies, antiviral treatments mostly based on interferon or pegylated interferon were given to 28 to 100% of the included patients. Only a minority of patients received direct antiviral agents (DAAs) but separate analyses of the long-term outcomes are not available. There was a non-significant decrease of the decompensation rate along publication time and with an increasing proportion of patients given antiviral therapy. The 5-year decompensation rate was significantly lower in studies with > 50% of patients treated, respectively 20.1 ± 7.9% versus 27.7 ± 10.8% ($p = 0.02$). The proportion of patients achieving a sustained viral response (SVR) ranged from 0 to 65% (mean ± SD 27.7 ± 14.8) and was associated although non-significantly ($p = 0.067$) to the reduction of the decompensation rate.

Seven of the 35 studies included patients with HIV-HCV coinfection. In the 5 studies reporting the information, the 5-year decompensation rate was 28.8 ± 3.9% (64 ± 26% patients given antiviral therapy for HCV).

Non-Alcoholic Fatty Liver Disease

There were 7 studies assessing the decompensation rate in patients with non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH), overall including 916 patients [69, 103, 139–140, 149, 150, 154]. Five-year risk of decompensation available in 7 studies was 23.6 ± 7.8%. In 4 studies, including NASH patients, the 5-year risk was 20.7 ± 8.0%. Although no specific treatment has yet been proven effective for NAFLD/NASH cirrhosis, it has been proven, in overweight cirrhosis, that weight reduction and physical activity significantly reduce HVPG and the risk of decompensation [8••].

Cryptogenic Cirrhosis

Previously, defined as cirrhosis without an identifiable cause, cryptogenic cirrhosis has been now defined as non-alcohol-related cirrhosis with less than 5% steatosis in liver biopsy. Although it represents a relatively infrequent cause of cirrhosis, a recent study [154] has evidenced that it may have a significantly worse outcome compared to NASH cirrhosis. In this prospective cohort study, the outcome of 147 patients with NASH cirrhosis was compared to that of 103 patients with cryptogenic cirrhosis. The two-patient groups were comparable for gender, age, BMI, PNPLA3 rs738409 genotype, and diabetes. Patients with cryptogenic cirrhosis had a 3-year decompensation rate of 28% compared to 20% for NASH patients. This finding suggests that metabolic changes associated with cryptogenic cirrhosis may prompt a more aggressive disease course with shorter time to decompensation.

Alcoholic Cirrhosis

Decompensation rate in alcoholic cirrhosis was looked for in 5 studies including a total of 5711 patients [23, 50, 81, 98, 145]. Four studies were population-based studies extracting data from large national insurances or health services databases. Time of diagnosis and clinical events was therefore based on times of the first registration of code (e.g., ICD9) corresponding to the events of interest. The fifth study [145] was a retrospective cohort study based on consecutive patients observed in a single

Table 1 Significant prognostic indicators of decompensation reported in the included studies

Variable*#	Number of studies‡	Etiology					
		Biliary (5)¶	HBV/HDV (2)¶	HCV (30)¶	Alcohol (3)¶	NAFLD/NASH (4)¶	Mixed (20)¶
Demographics							
Age	13	1	5	2		1	4
Gender	3		2			1	
Liver function							
Albumin	16		3	8		1	4
MELD	7		1	3	1		2
Bilirubin	7	1		4		1	1
CPs	6			3			3
INR	2			1		1	
Cholesterol	1						1
ALBI	1						1
Indocyanine	1						1
Portal hypertension							
Platelets	16	1		11		1	3
HVPG	9			2		1	6
Varices	8			5		1	2
γ-globulins	4		2	1			1
Splenomegaly	2		1				1
Arterial pressure	2			2			
Spleen stiffness	1			1			
US portal vein velocity	1						1
^{204}Tl liver/Lung	1						1
Cardiac hemodynamic	1						1
Na	1			1			
Liver inflammation/Fibrosis							
AST/ALT	6		1	3		1	1
LSM	5		1	3			1
CPA	2			1			1
Fib4	2					1	1
APRI	2	1				1	
Alt	1		1				
γ-GT	1			1			
Histologic stage	1	1					
NAFLD score	1					1	
LSN score	1						1
Septa/nodules	1						1
CRP	1						1
Fk7/EpCAM	1			1			
(Co) Etiologic factors							
Alcohol	3	1			1		1
Etiology	1						1
Obesity	1						1
HCV genotype 1	1			1			
HDV	1		1				
HBV	1			1			
CD4 (HIV)	1			1			
Treatment							
SVR	7			7			
Statins	6		1	2	2		1
Antiviral	4		1	3			
UDCAnr	2	2					
Comorbidities and other factors							
Diabetes	4			1		2	1
VWF	1						1
Gene-signature	1			1			
HCC	1			1			

*Abbreviations – MELD: model for end stage liver disease; CPs: Child-Pugh score; INR: international normalized ratio; ALBI: albumin bilirubin score; HVPG: hepatic venous portal gradient; US: ultrasound; ^{204}Tl liver/lung: ^{204}Tl liver/lung uptake ratio; LSM: liver stiffness measurement; CPA: collagen proportionate area; APRI: AST to platelet ratio index; NAFLD: non-alcoholic fatty liver disease; LSN: liver surface nodularity; CRP: c-reactive protein; FK7: cytokeratin 7; EPCAM: epithelial cell adhesion molecule; UDCAnr: ursodeoxycholic acid non responder; VWF: von Willebrand factor

#Shadowed areas indicate the variables which were found significant predictors in > 5 studies

‡ N studies: denotes the number of studies in which the variable was found to be significantly associated with the risk of decompensation

¶ In parenthesis the number of studies in which a multivariable analysis of predictors of decompensation was performed

hospital center. The overall mean 5-year decompensation risk was 33.6 ± 13.9%. The effect of abstinence on the risk of decompensation was assessed in only one study [145] showing that abstinence decreased the risk of decompensation from 30.4% in non-abstainers to 10.5% in abstainers over a median follow-up of 4.9 years.

Undefined Etiologies

In 25 studies, a total of 114,930 patients were included independently of etiology of cirrhosis and no separate analysis of the decompensation risk was reported according to etiology [21, 68, 72–74, 78, 86, 96, 98, 101–102, 106, 108, 110, 112–113, 117–118, 129, 136, 138, 143–144, 146, 151]. These studies were therefore grouped as undefined etiology. As expected, this group of studies had the largest range of reported decompensation rate (median 30%, range 5 to 62%; mean ± SD 31.9 ± 11.7%), although the interquartile range (25% to 40%) was mostly overlapping with that of HCV, NAFLD, and alcoholic cirrhosis, probably reflecting the most frequent etiologies for the patients included in these studies.

Predictors of Decompensation

Multivariable analyses of predictors of decompensation were performed in 62 studies including a total of 138,930 patients with a median 5-year decompensation rate of 25% (range 3 to 52%). A total of 55 variables were found to be significant predictors of decompensation. These variables are grouped according to their potential clinical and pathophysiological role in Table 1. The most frequently reported significant predictors are indicators of liver function, portal hypertension, inflammation and/or fibrosis, and antiviral or pathophysiology-targeting treatments. Predictors significant in at least five studies are highlighted in the shadowed areas in Table 1. Overall, the most frequently significant reported predictors were age, liver function, and portal hypertension indicators. While etiologic factors were not per se frequently reported as significant predictors, it is to note that etiologic treatments as indicated by antiviral therapy or achievement of SVR were reported as significantly modifying the decompensation rate in 17 studies, as well as alcohol habit in 3 studies. Moreover, the 6 studies reporting statin use as a significant predictor of lower decompensation rate are to be regarded as proof of concept that pathophysiological-targeted therapies may impact on the risk of disease progression and decompensation in cirrhosis.

Interpretation and Conclusions

The body of the evidences here summarized provides more insight in the issue of decompensation of liver cirrhosis and highlights several still unclear areas.

A first issue is that it appears that there is not a consensus on how decompensation should be defined. Most studies have used the development of major disease complications, like ascites, variceal bleeding, and encephalopathy, while many others have added also the appearance of visible jaundice or bilirubin > 3 mg/dL. As expected, increasing the number of possible markers, i.e., the sensitivity of the definition, the decompensation rate was higher. What is the best definition has not yet been investigated. However, it could be conceived that if jaundice depends on liver function than it should be included in the definition of decompensation at least when lasting more than a given time or when other factors acutely causing jaundice may be ruled out. A second consideration regards the appropriateness of some of the definitions used in the included studies. As an example, several studies considered the development of HCC as an indicator of decompensation. However, while it is well known that HCC is associated with increased risk of decompensation and death, it is not at all clear whether it should be considered a decompensation marker in terms of reduced liver function; it is in fact well known that early HCC may precede decompensation even for years. Other definitions used include both any combination of the major clinical signs of decompensation (ascites, bleeding, encephalopathy, jaundice) plus a Child-Pugh score increase of at least 2 points. This kind of definition is probably redundant given that at least ascites, encephalopathy, and bilirubin are already included in the Child-Pugh score, therefore leaving the added value of this definition in the assessment of INR (or prothrombin activity) or albumin and suggesting that it could be simplified. Similarly, the inclusion of spontaneous bacterial peritonitis in the definition used in several studies tends to indicate a more advanced decompensation than ascites alone and could therefore result in underestimation of the decompensation rate.

A second consideration is that while etiology of cirrhosis has been only rarely found as a significant predictor of decompensation, there is a clear and significant difference in the 5-year decompensation risk across the various etiologies encompassed in this review. The lower incidence is reported with biliary etiologies, followed by HBV, HCV, and NAFLD/NASH, and by alcoholic liver disease. However, regarding the biliary etiologies, it should be noted that patients included in the outcome studies of these etiologies may have heterogeneous histologic disease grade, therefore, probably not fully representing the cirrhosis population.

To be added to the importance of etiology in the risk of decompensation is the value of etiological treatments in

reducing the risk of decompensation. In fact, current evidence clearly supports etiological treatments for reducing the risk of disease progression and hence of decompensation.

Finally, as expected, among the most frequently reported significant predictors of decompensation are age and indicators of liver dysfunction. However, the most important predictors are probably those associated with portal hypertension and inflammation/fibrosis, like HVPG, platelet counts, varices, liver stiffness, and other non-invasive markers of fibrosis, because changes in these parameters may precede by long time appearance of dysfunction indicators and therefore may be the true predictors.

Future Research

Evidences provided by this review clearly indicate that there is a need for a consensus on the best definition of cirrhosis decompensation including both clinical and laboratory indicators. Markers of the pathophysiological pathways of decompensation, like mild portal hypertension or early evidence of bacterial translocation, and markers of inflammation/fibrosis progression should be investigated as decompensation predictors. However, a major problem in prognostic research in compensated cirrhosis is the definition of the zero time for risks assessment. In fact, since the disease is asymptomatic in this phase, it is always hard to identify a homogeneous zero time for prognostic studies. To minimize this source of heterogeneity, only patients with newly diagnosed cirrhosis or chronic advanced compensated liver disease (CACLD) should be included, provided that a diagnosis definition based on non-invasive indicators may be agreed upon given that liver biopsy is less and less used for diagnosing cirrhosis.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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