Title

Further decompensation in cirrhosis. Results of a large multicenter cohort study supporting Baveno VII statements

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Abstract

Background. Further decompensation in cirrhosis is assumed to be associated with worse survival. However, this has been based on clinical observations rather than scientific evidence. We investigated the incidence of further decompensation and its effect on mortality in patients with cirrhosis. *Methods*. Multicenter prospective cohort study. The cumulative incidence of further decompensation (development of a second event or complication of a decompensating event) was assessed using competing riskss analysis in 2028 patients and a 4-state model has been built-up: first decompensation, further decompensation, liver transplant, death. Cause-specific Cox model was used to assess the adjusted effect of further decompensation on mortality. Sensitivity analyses were performed for patients included before or after 1999. *Results*. In a mean follow-up of 43 months, 1192 patients developed further decompensation and 649 died. Corresponding 5-year cumulative incidences were 52% and 35%, respectively. The cumulative incidences of death and liver transplant after further decompensation were 55% and 9.7%, respectively. The most common further decompensating event was ascites/complications of ascites. Five-year probability of state occupation were: alive with first decompensation 24%, alive with further decompensation 21%, alive with liver transplant 7%, dead after first decompensation without further decompensation 16%, dead after liver transplant <1%, dead after further decompensation 31%. The hazard ratio for death after further decompensation adjusted for known prognostic indicators, was 1.53 (95% CI 1.31-1-81) (p<0.001). The significant impact of further decompensation on survival was confirmed in patients included before or after 1999. *Conclusion*. In cirrhosis, further decompensation occurs in approximately 60% of patients after the first decompensating event, and significantly increases mortality. Further decompensation should be considered a more advanced prognostic stage of cirrhosis beyond the first decompensation.

Introduction

Compensated and decompensated cirrhosis have been recognized as the two major stages of the clinical course of cirrhosis. Compensated cirrhosis is the initial stage, is clinically silent for many years, and is often underdiagnosed because it is mostly asymptomatic. The median survival in this disease stage is ≥ 12 years, and the transition rate to the decompensated stage is 5-8% per year, with a small proportion of patients dying at their first decompensation (1). The small proportion of deaths at the time of the first decompensating event is usually due to acute-on-chronic liver failure (ACLF), while a small proportion of compensated patients die because of non-liver-related causes. After the first decompensating event, the expected median survival is much shorter, on the order of 2-4 years and the disease course is characterized by further decompensating events, that is, the development of a complication of the decompensating event or the development of a second decompensating event, with rapid and progressive clinical deterioration until liver transplant or death.

The main predictor of progression from the compensated to the decompensated stage is the development of clinically significant portal hypertension (CSPH), defined as a hepatic vein portal gradient (HVPG) ≥10 mmHg (2). Pathogenic mechanisms in this stage include not only the severity of portal hypertension but also worsening of liver function (3) and the hyperdynamic circulatory state of cirrhosis, characterized by an increase in cardiac index and a reduction in systemic vascular resistance, which are also driven by inflammation, likely due to bacterial translocation and cell injury (4,5). In response to vasodilatation, cardiac output increases to a point where this circulatory compensating mechanism fails, and further decompensating events may occur (5). This stage of "further decompensation" represents a more advanced stage with rapid and progressive clinical deterioration to death (6). Clinical deterioration involves either the development of clinical complications that result from worsening hemodynamics/liver dysfunction, such as refractory ascites, acute kidney injury (AKI) including hepatorenal syndrome (HRS-AKI), recurrent variceal hemorrhage, jaundice, and spontaneous bacterial peritonitis (SBP), or the development of a second decompensating event. A definition of "further decompensation" has been agreed upon at the Baveno VII consensus conference(6). However, until now, the concept of further decompensation, its

purported higher mortality and whether this associated increase in mortality risk is independent of other known prognostic factors, have not been supported by objective evidence (6). Therefore, we assessed the incidence of further decompensation and its outcome in a large cohort of patients with cirrhosis and first decompensation.

Methods

Study aims. The first aim of this study was to characterize further decompensation in cirrhosis after the first decompensation by investigating its incidence and type of presenting events; the second aim was to assess whether it increases the risk of death independently of other known prognostic factors; the third aim was to put further decompensation in the context of a multistate model for decompensated cirrhosis.

Study design and data source. This was a retrospective study of prospectively collected data of consecutive patients with cirrhosis observed at 21 hepatology units from Italy, Germany, France, Spain, England, and Argentina (details on study centers and number of patients included per each center in supplementary material) aimed at investigating the clinical course of cirrhosis. After obtaining approval from the respective local ethics committees, data from patients who met the inclusion criteria and agreed to participate were obtained and prospectively recorded in specific datasets. Patient accrual (1984-2016) across participating centers and over time are shown in Supplementary Figure 1. For the purpose of the present study, patients with compensated cirrhosis were included in the analysis of further decompensation at the time of their first decompensation (Figure 1, left panel). Because a preliminary survival analysis showed a significantly higher probability of survival in patients included after 1999 (Figure 1, right panel), likely reflecting the progressive introduction of more effective treatments (7)(8–10), a separate analysis was performed on patients included in the study before and after January 1st 1999.

Patients. Inclusion criteria were a new diagnosis of cirrhosis or, in a patient with previously known cirrhosis, the first diagnosis of gastroesophageal varices, or the first decompensating event (variceal bleeding, ascites, hepatic encephalopathy, or jaundice). The exclusion criteria were age < 18 years (n=15),

previous history of decompensated cirrhosis (n=404), and non-hepatic malignancy (n=88). A total of 2506 consecutive patients were included:989 with compensated cirrhosis and 1571 with decompensated cirrhosis. The diagnosis of cirrhosis was biopsy-proven in 756 patients without ascites and based on typical clinical, ultrasonographic, and laboratory findings with ascites (n=916), esophageal varices (n=523), or a firm liver and splenomegaly on physical examination (n=311) in the remaining 1750 (11).

In each cohort, follow-up was based on clinical and laboratory assessment every 6-12 months or sooner (depending on clinical status), ultrasonography (screening for hepatocellular carcinoma, HCC) every 6 months, and upper endoscopy every 2-3 years in patients free of varices. At each participating center, treatment of cirrhosis was based on the standard of care according to the available recommendations at the time of accrual/follow-up.

Disease characterization. Decompensated cirrhosis was defined as the presence of portal hypertensive bleeding, clinically detectable ascites, overt hepatic encephalopathy (HE) or jaundice. The clinical diagnosis of ascites was confirmed by diagnostic paracentesis and portal hypertensive bleeding by endoscopy; overt HE was classified according to the West-Haven classification (12); jaundice was defined as bilirubin>3 mg/dl. Clinical, laboratory, ultrasonographic, and endoscopic findings were recorded for each patient at the time of inclusion. Disease severity was classified according to a clinical staging based on five prognostic stages(13): stage 1, compensated patients without gastroesophageal varices; stage 2, compensated patients with gastroesophageal varices; stage 3, decompensated patients with variceal bleeding alone; stage 4, decompensated patients with any single non-bleeding decompensation; and stage 5, decompensated patients with any combination of ≥2 decompensating events. Although patients in stage 5 presented with more than one decompensating event, these first events occurred simultaneously in a previously compensated patient and were therefore considered to have a first decompensation. The date of any new relevant clinical event during follow-up was recorded, including esophagogastric varices, ascites, HE, jaundice, need for ≥3 large-volume paracenteses (LVP) in one-year, spontaneous bacterial peritonitis (SBP), acute kidney injury (AKI), hepatorenal syndrome (HRS), hepatocellular carcinoma (HCC), liver transplantation (LT), and death. HRS, SBP, and HCC were diagnosed according to guidelines at the time

of identification. The date of the complication "need for LVP" was the date of the first of the three LVPs in one year that defined this complication. AKI was defined as an increase in creatinine to >1.5 mg/dl, which was also recently used (14), rather than the current definition based on an increase in creatinine by ≥0.3 mg/dL (15) which was introduced in clinical practice when this study was already in its final phase.

Outcomes and definitions. The primary outcome was further decompensation defined as: *a)* development of a second portal hypertensive-driven decompensating event (ascites, variceal hemorrhage, or hepatic encephalopathy) and/or jaundice; *b)* recurrent variceal bleeding, worsening ascites (requirement of ≥ 3 large-volume paracenteses within 1 year), recurrent encephalopathy, and development of SBP and/or AKI/HRS-AKI. The last three complications were considered to be *further* decompensating events because they only occurred after the development of ascites. Mortality was defined as all-cause mortality.

As the concepts of acute decompensation and acute-on-chronic liver failure (ACLF) were introduced when data collection for the study was in its final phase (16), data on these outcomes were not collected. In addition, this study focused more on the type and number of presenting events than on the rapidity of presentation. Nevertheless, we considered *post hoc* that patients who died within 28 days of decompensating or a further decompensating event had ACLF (17).

Analysis. Patient characteristics were presented as proportions or means with standard deviations. Where appropriate, the chi-squared test was used to compare proportions and the t-test to compare means. For all survival analyses, data were censored at death or at the end of follow-up according to the study protocol per each cohort.

Cumulative survival estimates were based on the Kaplan-Meier model (18). The cumulative incidence function (CIF) of further decompensation and relevant clinical events was assessed by competing risks analysis (19), with death and LT as competing events. Differences in survival probabilities were assessed using the log-rank test, while differences in CIFs were assessed using Gray's test (20,21). Time zero for analyses of the time to further decompensation and death was the date of first decompensation. Five-year incidence plots are shown to achieve homogeneous follow-up time across centers. Probabilities are

expressed as percentages throughout the text and figures. To investigate the impact of further decompensation on mortality adjusted for known prognostic factors, a multivariable explorative analysis was performed by the cause specific Cox model (22) to allow for LT as a competing risk. Robust (sandwich) variance estimation was used in all the analyses (23,24). Candidate predictors included further decompensation, age, sex, etiology, serum albumin, serum bilirubin, INR, serum creatinine, platelets, esophagogastric varices, HE, ascites, variceal bleeding, jaundice, comorbidity, diagnostic criteria. Missing values for albumin, bilirubin, creatinine, and Child-Pugh score (in a total of 264 patients) were replaced with multiple imputations (20 imputations) (25–28). The imputation model included the following variables: MELD, age, sex, INR, platelet count, etiology of cirrhosis, disease stage at first decompensation, ascites, bleeding, hepatic encephalopathy, jaundice. We did not impute missing values for hemoglobin, missing in 368/2028 patients (18%) and did not include it in multivariable analyses. However, a complete case analysis was also performed and shown in the supplementary material. The variable "further decompensation" was included in all the models as a time-varying covariate to allow for appropriate interpretation of the relevant hazard ratio (29). All analyses were stratified by the center and year of patient inclusion to allow for heterogeneity between centers and different inclusion periods. Non automated stepwise backward analysis was performed by selecting covariates according to clinical judgement/ known prognostic value and statistical significance ($p < 0.05$). Separate models were performed by including the MELD (30) or the Child-Pugh (31) scores and excluding the corresponding components to avoid redundancy (shown in the supplementary material). Moreover, since the majority of HCV positive patients had not been treated for HCV infection, we performed a separate analysis by excluding these patients to explore a potentially confounding effect of the lack of anti HCV treatment. To assess the robustness of the results based on the time of patient inclusion in the study, the cumulative incidence of further decompensation and its impact on mortality were also separately assessed in subsets of patients included before or after 1999. A four-state model including first decompensation, further decompensation, LT and death has been built (32). Intensity of transitions across disease states are derived by the corresponding competing risks analyses for transitions from first and further decompensation, while transition rate from LT to death is derived by the

corresponding Kaplan Meier survival analysis. The probability of disease state occupation in the multistate model has been computed by using the routine *mslt* in STATA. All the statistical analyses were performed using STATA 16.1 (©2019 Stata Corporation, College Station, TX).

Results

Patient characteristics for the whole cohort and for patients included before and after 1999 are shown in Table 1, including patients with compensated cirrhosis who developed decompensation during follow-up and were included in the study as of the time of their decompensation. Etiology was mostly from alcohol (44%), hepatitis C virus (28%), and NASH (9%). Among patients included with decompensated cirrhosis 1036 had ascites, 651 variceal bleeding, 133 HE, and 314 jaundice. Significant comorbidities, predominantly diabetes, were present in nearly one-third of the patients. Since most patients were included before the introduction of direct antiviral agents (DAA) for HCV, only 88 of 561 HCV-positive patients received antiviral treatment (mostly interferon-based), while 20 of 57 HBV- positive were given viral suppressive therapy (mostly interferon and lamivudine-based).

Among 989 patients with compensated cirrhosis at inclusion, 85 died and 2 were transplanted before decompensation, 282 remained with compensated cirrhosis, and 622 developed decompensations. Of these, 74 died at decompensation, 2 were transplanted soon after decompensation, and 3 had no further follow-up, leaving a total of 543 patients available for analysis of further decompensation from this group. Among 1517 patients with decompensated cirrhosis at inclusion 30 died at decompensation and 2 were lost to follow-up, leaving 1485 patients available for analysis of further decompensation . Therefore, a total of 2028 patients were included in the present analysis of the incidence and outcome of further decompensation: 543 who developed decompensation during follow-up and 1485 included at first decompensation (Figure 1, left panel).

Further decompensation. The mean follow-up (±SD) after the first decompensation in the 2028 patients included in this analysis was 43.3±71.6 months. Overall, 1192 patients (58.8%) developed further

decompensation, of whom 649 (54.4%) died [149 (12.5%) within 28 days after further decompensation] and 96 were transplanted [2 of whom died at the time of transplantation]. Among 836 patients who did not develop further decompensation, 481 were still alive at the end of follow-up, 314 died, and 41 were transplanted.

Clinical presentation of further decompensation is shown in Table 2 according to the clinical presentation of the first decompensation. Five-year cumulative incidence of further decompensation was 52%; further decompensation and death within 28 days 7.3%; death before further decompensation 16%; LT 2.3% (Figure 2, left panel). Cumulative incidence of the different further decompensating events over a 5-year period is shown in supplementary Figure 2: ascites 15% and complications of ascites 7.5% were the most frequent causes of further decompensation (22.5%), while (re)bleeding accounted for 11% of cases and jaundice and hepatic encephalopathy for 9% each.

The cumulative incidence of events in patients included before and after 1999 were, respectively, further decompensation 46.3 % vs 55.2%, death 17.6% vs 14.7%, death within 28 days of decompensation 9.1% vs. 6.0%, and liver transplantation 1.1% vs 2.9% (supplementary Figure 3). A direct comparison of the cumulative incidence of further decompensation between the two subgroups is shown in supplementary Figure 4. Sensitivity analyses by excluding HCV patients showed similar findings (supplementary Figure 5).

Five-year cumulative incidences of death and LT after further decompensation were 55% and 9.7%, respectively (Figure 2, right panel). Overall, 649 of 1192 (54%; 95% CI 51-57%) who developed further decompensation died. The median survival time after further decompensation was 273 days (IQ range 15-974).

Multistate model. To assess the impact of further decompensation on the clinical course of cirrhosis we built up a 4-state model including decompensation, further decompensation, liver transplant and death (Figure 3, left). Intensity of transitions across disease states are derived by the relevant competing risks analyses shown in Figure 2; transition from LT to death is derived by the corresponding Kaplan Meier analysis (supplementary Figure 6). The 5-year model shows that nearly 60% of patients experiencing a first

decompensation develop further decompensation and that less than 16% died without further decompensation while the majority of patients died after further decompensation. Corresponding 5-year probability of state occupation were the following: alive with first decompensation 24%, alive after further decompensation 21%, alive with liver transplant 7%, dead after first decompensation 16%, dead after liver transplant <1%, dead after further decompensation 31%. The five-year cumulative incidences of further decompensation, LT and death according to the initial stage of decompensated cirrhosis are summarized in Figure 4.

In 721 patients presenting first decompensation with variceal bleeding either alone (n=408) or with another complication (n=313), 294 developed further decompensation within 5 days of bleeding and 160 from day 6 to 42 after bleeding. Interestingly, the survival of patients who developed further decompensation soon after bleeding (≤ 5 days) was almost identical, in the first year, to that of patients who remained free of other complications at the episode of bleeding, while patients who developed a further decompensating event >5 days after bleeding had a significantly worse survival (Figure 5).

The impact of further decompensation, as a time varying covariate, on mortality was assessed by the multivariable cause-specific Cox model analysis adjusting for known predictors of death (LT competing). The hazard ratio for death in patients who experienced further decompensation was 1.53 (95% CI 1.31-1.81) in the whole cohort, 1.40 (1.10-1.71) in patients included before and 1.91(1.52-2.40) after 1999 (Table 3). Corresponding findings by analyses including MELD or Child-Pugh score and excluding their components to avoid redundancy, confirmed the significant impact of further decompensation on mortality (supplementary Table 2). When excluding HCV positive patients (because only 88 of 561 received anti-viral treatment), the HR for death with further decompensation was 1.64 (95%CI 1.35 to 2.00) (supplementary Table 3).

Discussion.

Based on a large database collecting prospective data from 21 centers, including a total of 2028 patients with cirrhosis and first decompensation, this study demonstrates that further decompensation in cirrhosis occurs in more than half of patients within 5 years of a first decompensating event and increases mortality by approximately two times compared to first decompensation.

Ascites is the most frequent event causing further decompensation, although its incidence is relatively low (15% in 5 years) because a large majority of patients have ascites at their first decompensating event. In contrast, complications of ascites, such as SBP, AKI, and LVP, are important causes of further decompensation. Although this study lacks measures of HVPG and systemic arterial resistance, this finding is conceivably related to the progression of portal hypertension and worsening of hyperdynamic circulation with reduced renal perfusion and poorer response to diuretics requiring frequent LVP and increasing the risk of AKI, while increasing bacterial translocation increases the risk of SBP. With cumulative incidences of approximately 9% each, hepatic encephalopathy and jaundice are more frequent causes of further than first decompensation where they account each for approximately 3-4% of cases(33). As for first decompensation, variceal bleeding (either new or recurrent) is an important cause of further decompensation.

To assess the role of further decompensation in the context of the clinical course of the disease we built up a four-state model including first and further decompensation, LT and death. The multistate model provides a comprehensive description of the clinical course of the diseases from the first decompensation to death in this study cohort. The model clearly showed that further decompensation has a key role in determining the disease outcome with most patients transitioning through further decompensation before death. This is even more evident in the 5-year state occupation probability analysis, showing that the probability of dying after further decompensation is almost twice that of dying after the first decompensating event. In line with this finding, the 5-year probability of remaining alive after further decompensation (21%) is similar to that of remaining alive after further decompensation (24%). This finding is explained by the fact that the high intensity of transition from first to further decompensation is balanced by high intensity of transition from further decompensation to death.

The significant impact of further decompensation on mortality was confirmed in the multivariable cause specific Cox model where further decompensation was assessed as a time-varying covariate and its effect was adjusted for a number of well-known prognostic factors in cirrhosis. Notably the worsening effect of further decompensation on mortality, was confirmed in sensitivity analyses according to the time of inclusion in the study, and by excluding the HCV positive patients, mostly untreated in this cohort.

By using competing risks analysis, we were able to put further decompensation into the context of the previously proposed five clinical stages of cirrhosis (13) and to identify further decompensation as the more advanced stage of cirrhosis before death. In this representation, the most important outcome from stages 3, 4, and 5 is the transition to further decompensation, which is associated with the highest risk of death.

In patients with variceal bleeding, the effect of further decompensation seems to be related to timing. In fact, the development of further decompensating events within 5 days of bleeding had no impact on survival (at least in the first year) when compared to the few that remained free of further decompensation. In contrast, patients who developed further decompensation ≥6 days after bleeding had a significantly worse survival. This finding might reflect a transitory stress (bleeding)-induced further decompensation that resolves in patients with better liver function compared to a slower and persistent further decompensation in patients with more advanced liver dysfunction. The reliability of this observation is probably limited by the very small number of patients remaining free of other decompensating events after the first bleeding event; therefore, it requires validation in other independent cohorts. However, if confirmed, this finding might suggest that very early complications after bleeding are transitory events that do not accurately represent the true severity of liver dysfunction.

Recognizing that the full cohort had a large time span during which treatments for cirrhosis had evolved, a subgroup analysis based on the time of inclusion in the study was performed, based on a significantly better survival observed in patients included after 1999 compared to those included before. This probably reflects the progressive introduction of effective treatments for portal hypertension

complications, including endoscopic variceal ligation (8), its association with NSBB (9) and the use of covered instead of bare metal TIPS stents (10). Importantly, even given these differences in survival between an old and a more recent cohort, the development of a further decompensating event (independent of the time frame) was still a marker of a poorer prognosis. Additionally, all multivariable analyses performed to assess the impact of decompensation on mortality were stratified by center and year of inclusion to allow for the expected heterogeneity among centers on point estimates.

This study has a major limitation in the lack of antiviral treatment in most patients with viral etiology and, when given, they were mostly based on interferons and ribavirin for HCV and lamivudine for HBV. The expected impact of antiviral therapy would be a significant reduction in the incidence of decompensation in patients with viral cirrhosis (34), although it has been reported that clinically significant portal hypertension persists up to 2 years after HCV eradication in 53-65% of patients (35,36). Moreover, how much viral eradication in decompensated cirrhosis impacts the disease course, is still unclear (37). Therefore, the impact of HCV eradication in patients with already decompensated disease may be lower than expected and probably much less than that observed for first decompensation. However, to overcome this limitation, we performed a separate analysis by excluding HCV patients and did not find appreciable difference in the incidence and prognostic role of further decompensation, compared to the whole cohort.

Another potential limitation is the lack of information on alcohol withdrawal in patients with alcoholic cirrhosis. This, however, probably do not reduce the applicability of study results because any effort was always done at each center to achieve alcohol withdrawal according to guidelines and common medical practice.

Although alcohol was the main etiology in our cohort (and continues to be one of the most prevalent causes of cirrhosis), it included only a small number of patients with NASH, which is becoming the most prevalent cause of cirrhosis. Although the development of cirrhosis seems to be much longer in NASH cirrhosis (38), once decompensation occurs, the course appears to be similar to that of decompensated cirrhosis of other etiologies (39). In fact, a multistate model with state definitions, transitions across states,

and mortality from each state has recently been proposed (39) and is similar to the multistate model for viral and alcoholic cirrhosis (13).

Based on this study, we propose that further decompensation, as suggested at the Baveno VII meeting (6) is an additional more severe stage of cirrhosis. Until more data are available, the specific clinical events that should be used to define further decompensation are the following:

a) In patients with ascites as a single first decompensation, the development of need for LVP, SBP, AKI or a second decompensating event (bleeding, encephalopathy, or jaundice)
b) In patients with bleeding as a single first decompensation, the development of rebleeding, ascites (with or without complications of ascites), encephalopathy, or jaundice provided these events occurred > 5 days after the initial bleeding event.
c) In patients with encephalopathy as a single first decompensation, the development of recurrent encephalopathy, ascites (with or without complications), bleeding, or jaundice.
d) In patients with ≥2decompensating events occurring at first decompensation, the development of a new decompensation or complication of an event (e.g., rebleeding, need for LVP).
e) Patients presenting with jaundice should be considered further decompensated at presentation, independent of whether it is a first or second event.

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Figure legends

Figure 1. Flow diagram of patients through the study phases and patient selection for analysis of further decompensation (left panel) and cumulative survival of patients included before or after 1999 (right panel).

Figure 2. Five-year cumulative incidence function (CIF) of major events after first and further decompensation. Left panel: CIF of further decompensation, death within 28 days of further decompensation, death, and liver transplant in 2028 patients with decompensated cirrhosis. Right panel: CIF of death and liver transplant in patients with further decompensation. Time zero is first decompensation and, respectively, further decompensation. In each panel, numbers below the abscissa are the number of patients at risk per each time period.

Figure 3. Multistate model summarizing the 5-year outcome of the 2028 patients with decompensated cirrhosis. Assessed states are first decompensation, further decompensation, liver transplant and death. Left panel: multistate model. Arrows represent transitions across clinical states. The numbers close to arrows are the 5-year transition rates derived by the corresponding competing risks analysis. Time zero per each transition rate is the time when the patient entered the relevant state. For the state of liver transplant the only assessed transition was to death and the transition rate corresponds to 1-Kaplan Meier cumulative survival. Right panel: 5-year state occupation probability or the probability that one patient observed at his first decompensation will be in one of the assessed states along time. The subtle white area represents the probability of being dead after liver transplant which was <1% in this cohort. Numbers below the abscissa are the number of patients at risk per each time period. Numbers on the right side of the graph represent the computed 5-year probabilities of being in the relevant state. LT= liver transplant.

Figure **4**. Summary of 5-year outcome according to the disease stage at first decompensation in the whole cohort (N=2028). Here the multistate model depicted in Figure 3 is exploited according to the clinical presentation of the first decompensation. Arrows represent transitions across stages and the numbers next to the arrows are the transition rates. Stage 3 = variceal bleeding alone at first decompensation; stage 4=

any non-bleeding event (ascites, encephalopathy or jaundice) at first decompensation; stage 5= any combination of 2 or more events at first decompensation.

Figure 5. Survival of patients with variceal bleeding alone or combined with other events at their first decompensation according to whether further decompensation did not occur or occurred within 5 days of variceal bleeding or within 6 to 42 days. fdeco denotes further decompensation. Numbers below the abscissa are numbers of patients at risk. P value by the log-rank test is reported.

Table 1. Patient characteristics at inclusion, including 543 patients with compensated cirrhosis who developed decompensation during follow-up.

Characteristics	Whole cohort		Subgroups according to inclusion period			
			<1999		≥1999	
	value	missing	value	missing	value	missing
Demographics						
N patients (%)	2028 (100)		766 (38)		1262 (62)	
Age *	56.8 (12.4)	0	55.3 (12.3)	0	57.8 (12.3)	0
Female/Male	737/1291	0	302/464	0	435/827	0
Etiology, N (%)						
Anti-HCV +	561 (28)	0	293 (38)	0	268 (21)	0
HBsAg +	57 (3)	0	18 (2)	0	39 (3)	0
Anti-HCV and HBsAg+	20 (1)	0	17 (2)	0	3 (0.2)	0
Alcohol	899 (44)	0	253 (33)	0	646 (51)	0
Alcohol & virus	215 (11)	0	104 (14)	0	111 (9)	0
Autoimmune/CBP	94 (5)	0	17 (2)	0	77 (6)	0
NASH	182 (9)	0	64 (8)	0	118 (9)	0
Laboratory						
Albumin, g/L *	29.9 (9.8)	169	32.9(7.5)	14	27.9 (10.7)	155
Bilirubin, mg/dL*	3.0 (4.3)	151	2.5 (3.5)	4	3.4 (4.7)	147
Prothrombin% *	67.6 (17.7)	8	68.3 (17.5)	0	67.2 (17.8)	8
INR *	1.4 (0.4)	8	1.4 (0.4)	0	1.4 (0.4)	8
AST, IU *	88.1 (108.5)	40	89.1 (104.8)	6	87.4 (110.8)	34
ALT, IU *	68.3 (93.6)	41	81.9 (102.2)	11	60.0 (86.9)	30
Creatinine, mg/dl	0.97 (0.49)	94	1.01 (0.45)	24	0.94 (0.51)	70
Platelet count x10^9/L *	119.8 (68.8)	40	118.7 (67.3)	15	120.4 (69.6)	25
Hemoglobin, g/dL	11.5 (2.6)	368	11.8 (2.7)	154	11.3 (2.5)	214
Clinical presentation						
Compensated cirrhosis	543 (27)	0	271 (35)	0	272 (22)	0
Child-Pugh class, A/B/C, %	39/48/23	180	36/46/18	14	24/49/26	166
Child-Pugh score *	7.9 (1.9)	180	7.5 (1.9)	14	8.1 (1.9)	166
MELD *	12.8 (5.5)	46	12.4 (5.1)	0	13.1(5.7)	0
Esophageal Varices, ǂ	1689 (83)	0	676 (88)	0	1013 (80)	0
Ascites ǂ	1010 (49.8)	0	317 (41)	0	693 (55)	0
Bleeding ǂ	631 (31)	0	235 (30)	0	396 (31)	0
Encephalopathy ǂ	122 (6)	0	38 (5)	0	84 (7)	0
Jaundice ǂ	288 (14)	0	56 (7)	0	232 (18)	0
HCC ǂ	60 (3.0)	0	28 (3.7)	0	32 (2.5)	0
Stage 1 ǂ	237 (12)	0	138 (18)	0	99 (8)	0
Stage 2 ǂ	306 (15)	0	133 (17)	0	173 (14)	0
Stage 3 ǂ	358 (18)	0	151 (20)	0	207 (16)	0
Stage 4 ǂ	648 (32)	0	207 (27)	0	441 (35)	0
Stage 5 ǂ	479 (24)	0	137 (18)	0	342 (27)	0
Comorbidity, N (%)						
Chronic heart disease	100 (5)	0	36 (5)	0	64 (5)	0
Chronic lung disease	136 (7)	0	55 (7)	0	81 (6)	0
Diabetes	358 (18)	0	125 (16)	0	233 (18)	0
≥ 2 comorbidities	87 (4)	0	30 (4)	0	57 (4)	0
Total	6781 (34)	0	246 (32)	0	435 (35)	0

*Mean± standard deviation. ǂ N (%)

Table 2.

Clinical presentation of further decompensation according to the type of first decompensating events. Number and type of events presenting as further decompensation are shown according to the type of events which characterized the first decompensation.

Clinical presentation of first decompensation	Clinical presentation of further decompensation							
	No further decompensation	Ascites	Bleeding	HE	Jaundice	Rebleeding	LVP/AKI/ SBP	Total
Ascites	374	-	44	66	71	0	93	648
Bleeding	40	216	0	16	29	98	9	408
HE	14	27	5	0	6	0	1	53
jaundice	20	58	4	5	0	0	4	91
Ascites + bleeding	65	0	0	12	25	87	11	200
Ascites plus LVP/AKI/SBP*	210	-	28	69	53	11	21	392
Any combination of ≥2 of the above events	113	39	10	19	17	15	23	236
Total	836	340	91	187	201	211	162	2,028

HE, hepatic encephalopathy; LVP, large-volume paracentesis; AKI, acute kidney injury; SBP, spontaneous bacterial peritonitis.

*All patients had ascites with or without other events.

Table 3. Significant death risk indicators by cause specific Cox proportional hazards model (OLT competing) in patients with decompensated cirrhosis at inclusion in the whole series and in subgroups included before and after 1999. *¶

Variable	Score	Hazard Ratio	Robust Standard Error	p	95% Confidence Interval	
Whole cohort: N= 2028						
further decompensation	0=no, 1=yes	1.53	.126	<0.001	1.31	1.81
age	years	1.04	.003	<0.0001	1.03	1.04
s-albumin	g/L	0.98	.006	0.035	0.97	0.99
s-bilirubin	mg/dL	1.04	.008 9	<0.0001	1.03	1.06
INR	continuous	1.38	.142	0.002	1.12	1.68
s-creatinine	mg/dL	1.15	.069	0.017	1.02	1.30
Patients included before 1999: N=766						
further decompensation	0=no, 1=yes	1.36	.156	0.008	1.09	1.70
age	years	1.04	.005	<0.0001	1.03	1.05
s-bilirubin	mg/dL	1.04	.0128	<0.0001	1.02	1.07
sex	0=female; 1=male	1.26	.119	0.015	1.05	1.52
clinical stage	3=bleeding alone; 4=nonbleeding decompensation; 5=≥ events	1.23	.088	0.004	1.07	1.42
Patients included after 1999: N=1262						
further decompensation	0=no, 1=yes	1.91	.224	<0.0001	1.52	2.40
age	years	1.04	.005261	<0.001	1.03	1.05
s-albumin	g/L	0.98	.009	0.020	0.96	0.99
s-bilirubin	mg/dL	1.05	.0105519	<0.0001	1.03	1.07
s-creatinine	mg/dL	1.18	.087	0.028	1.02	1.36
sex	0=female; 1=male	1.27	.148	0.038	1.01	1.60

* The analyses included MELD and Child-Pugh score components but not the scores to avoid redundancy. The corresponding analyses, including the scores but not their components, are reported in the supplementary materials.

¶ Missing data were replaced by multiple imputations to avoid reducing the number of patients available for analysis (see methods and Table 1).