Research Article
Cirrhosis and Liver Failure

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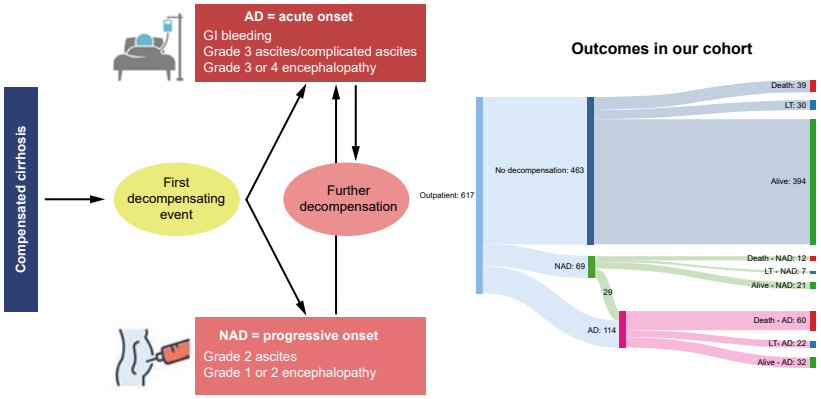
Graphical abstract



Highlights

- In clinical practice, patients can develop complications progressively (NAD) rather than acutely (AD).
- The unfavorable impact of AD in patients with cirrhosis is well known, while the role of NAD is still to be proven.
- NAD accounted for 45% of decompensations and 42% of patients with NAD developed AD during follow-up.
- Mortality in patients with NAD is higher than in compensated patients.
- Patients with NAD should be monitored closely to prevent the development of AD.

Impact and implications

This multicenter study is the first to investigate the role of non-acute decompensation (NAD) in patients with cirrhosis. In fact, while the unfavorable impact of acute decompensation is well known, there is currently a dearth of evidence on NAD, despite it being a common occurrence in clinical practice. Our data show that almost half of decompensations in patients with cirrhosis can be considered NAD and that such events are associated with a higher risk of mortality than no decompensation. This study has important clinical implications because it highlights the need to carefully consider patients who develop NAD, in order to prevent further decompensation and reduce mortality.

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A new clinical and prognostic characterization of the patterns of decompensation of cirrhosis☆

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Background & Aims: The prognostic impact of acute decompensation (AD), *i.e.* the development of complications that require hospitalization, has recently been assessed. However, complications of cirrhosis do not necessarily require hospitalization and can develop progressively, as in the recently defined non-acute decompensation (NAD). Nevertheless, there is no data regarding the incidence and prognostic impact of NAD. The aim of the study was to evaluate the incidence and the prognostic impact of NAD and AD in outpatients with cirrhosis.
Methods: A total of 617 outpatients with cirrhosis from two Italian tertiary centers (Padua and Milan) were enrolled from January 2003 to June 2021 and followed prospectively until the end of the study, death or liver transplantation. The complications registered during follow-up were considered as AD if they required hospitalization, or NAD if managed at the outpatient clinic.
Results: During follow-up, 154 patients (25.0% of total patients) developed complications, 69 patients (44.8%) developed NAD and 85 (55.2%) developed AD, while 29 patients with NAD (42.0%) developed a further episode of AD during follow-up. Sixty-month survival was significantly higher in patients with no decompensation than in patients with NAD or AD. On multivariable analysis, AD (hazard ratio [HR] 21.07, p <0.001), NAD (HR 7.13, p <0.001), the etiological cure of cirrhosis (HR 0.38, p <0.001) and model for end-stage liver disease score (HR 1.12, p = 0.003) were found to be independent predictors of mortality.
Conclusions: The first decompensation is non-acute in almost 50% of outpatients, though such events are still associated with decreased survival compared to no decompensation. Patients who develop NAD must be treated with extreme care and monitored closely to prevent the development of AD.

Introduction

There is a universal agreement that the occurrence of clinical complications, such as ascites, hepatic encephalopathy, gastrointestinal bleeding, and jaundice mark the transition from the compensated to the decompensated stage of cirrhosis.[1] Decompensation is associated with a substantial worsening of patient prognosis and is therefore considered the most important stratification variable for the risk of death. Our current classification of decompensated cirrhosis is based on the findings of a retrospective cohort study showing that the 5-year mortality risk is 20% for patients decompensating with bleeding alone, 30% with any non-bleeding event, mostly ascites, and 88% with any combination of more than two events. In accordance with these findings, these three scenarios have been designated as states 3, 4 and 5, with states 1 and 2 pertaining to compensated cirrhosis: the absence of varices defines state 1 while the presence of varices state 2, with a 5-year risk of death of 1.5% and 10%, respectively.[2] However, this classification does not consider the modalities of onset and the severity of decompensating events. With regard to this matter, one of the most recent achievements was the description of "acute decompensation" (AD) as a condition that can predispose to the development of acute-on-chronic liver failure (ACLF) according to the EASL-CLIF criteria. AD was defined first in the CANONIC study, and then in the PREDICT and ACLARA studies, as "a distinct clinical presentation of decompensation of cirrhosis defined by the acute development of at least one major complication: first or recurrent grade 2 or 3 ascites within less than 2 weeks, first or recurrent acute hepatic encephalopathy (HE) in patients with previously normal consciousness, acute gastrointestinal bleeding, and any type of acute bacterial infection".[3–5] Beyond the introduction of bacterial infections among the complications, and therefore among the decompensating events, on which a heated doctrinal debate is still underway, the great innovative element of the

Keywords: decompensated cirrhosis; acute decompensation; non-acute decompensation; complicated ascites; hepatic encephalopathy; gastrointestinal bleeding.
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definition of AD is the emphasis on the importance of the pathway by which decompensation occurs. The rapidity of onset of the complications of cirrhosis is the pillar of the AD definition; to such an extent the term “acute” was repeated four times in the definition and, most importantly, all the patients included in the CANONIC study and in the PREDICT study were hospitalized. Now, without wishing to enter a sterile debate about the variability of hospitalization criteria between countries, regions, and hospitals, it is a matter of fact that in a prospective series of thousands of patients with cirrhosis, the acute presentation of one or more than one decompensating event has a deep negative impact on the prognosis of patients with cirrhosis. So, once established that AD is the clinical pathway of decompensation of cirrhosis based on the strongest scientific evidence, the main question is: "How to harmonize the concept of AD in the current classification of decompensated cirrhosis?” Recently, the Experts in Baveno VII in the attempt to increase the granularity of the definition of decompensation have proposed to include patients with a very advanced course of decompensation in a “further decompensation state”, defined by any of the following events: a) development of a second portal hypertension-driven decompensating event (ascites, variceal hemorrhage or HE) and/or jaundice; b) development of recurrent variceal bleeding, recurrent ascites (requirement of ≥3 large-volume paracenteses within 1 year), recurrent HE, development of spontaneous bacterial peritonitis and/or hepatorenal syndrome-acute kidney injury.[6] However, this is not a valid answer to the main question because 1) AD may develop as the first decompensation of cirrhosis in at least 20-25% of the cases, and 2) none among stages 3, 4, and 5 considers the modalities of onset of the characterizing decompensating events. Now, in the attempt to find a valid answer to the main question, it could be useful to look back at our daily clinical practice. All over the world there are millions of patients with cirrhosis who gradually developed grade 2 or 3 ascites or grade 1 or 2 HE or jaundice and are treated as outpatients. Some experts have recently proposed the definition of this pathway of decompensation as “non-acute decompensation (NAD)”.[7] Although it appears reasonable and shareable that both AD and NAD may occur in patients with cirrhosis with potentially different effects on their clinical outcomes, AD and NAD represent at this time only a working hypothesis certainly supported by clinical experience, but never tested. In order to test this hypothesis many questions should be addressed. How many patients with compensated cirrhosis develop AD or NAD? How many patients develop AD on top of NAD? What is the impact of these conditions on survival? What are the main differences between patients with NAD or AD?

The present prospective study represents a first attempt at answering these questions, favoring the construction of a univocal classification that can help future research, overcoming current shortcomings and/or overlaps.

Patients and methods

Protocol

In this study, we considered all outpatients who attended two tertiary centers in Italy, *i.e.* the Care Management Program[8] from the University Hospital of Padua, and the Outpatients’ Clinic from Foundation IRCCS Ca’ Granda Ospedale Maggiore Policlinico in Milan. In the Padua group, the authors enrolled all the patients attending the Care Management Program from January 2003 to January 2021, while in the Milan group outpatients were enrolled from January 2003 to June 2021.

Inclusion criteria were the following: a) age >18 years; b) cirrhosis diagnosed by histological findings on biopsy, or by the evidence of clinical, biohumoral or instrumental data (endoscopic, ultrasound or liver stiffness measured by transient elastography); c) no current or known previous decompensation of cirrhosis in the 6 months before inclusion; d) ability and will to provide written informed consent.

Exclusion criteria were: a) diagnosis of hepatocellular carcinoma (HCC) or extrahepatic malignancies at the time of inclusion; b) other highly disabling pathologies of extrahepatic origin at the time of inclusion (*e.g.* heart failure [NYHA class ≥3] or GOLD chronic obstructive pulmonary disease grade ≥3); c) recurrence of cirrhosis after liver transplantation (LT); d) refusal, or inability of the patient to provide informed consent. The protocol was approved by the local Ethics Committees (218n/AO/2022). Data were collected prospectively and all patients gave informed consent according to local regulations for this kind of study. All patients were followed until the end of the observation period (August 2021), or until death or LT.

Demographic and clinical data were collected at inclusion. An ultrasound evaluation of the upper abdomen was performed for all patients at the time of inclusion or within the following 2 months. During follow-up patients underwent an abdominal ultrasound every 6 months. Esophagogastroduodenoscopy was performed in all patients within 6 months after inclusion, and subsequently repeated according to the temporal indications suggested by the guidelines existing at the time of evaluation.[9–11] Patients under the age of 70 who had model for end-stage liver disease (MELD) values greater than 15, or an HCC inside the Milan criteria[12] were evaluated for LT according to the modalities and scores existing at the time of observation.[13,14]

The occurrence of complications of cirrhosis was recorded and complications were treated according to the guidelines that existed at the time of the evaluation.[15–17] The following were considered as complications of cirrhosis: a) development of grade 2 or 3 ascites according to the definition of the International Club of Ascites;[18] b) gastrointestinal (GI) bleeding from rupture of esophageal varices; c) overt HE according to the definition based on the West Haven classification.[19]

Unlike in the CANONIC study, a bacterial infection at the time of hospitalization was considered as a precipitating rather than a decompensating event, with the only exception being spontaneous bacterial peritonitis, which was included in the definition of AD.

The acute occurrence of GI bleeding, grade 3 or 4 HE, grade 3 ascites, and/or complicated ascites (with superimposed spontaneous bacterial peritonitis and/or acute kidney injury) requiring emergency hospitalization was defined as AD. The non-acute occurrence of grade 2 ascites and/or grade 1-2 HE manageable in the outpatient clinic was defined as NAD. Whenever a patient managed as NAD was hospitalized within 30 days from the development of decompensation, they were included directly as AD. Patients who developed neither NAD nor AD during follow-up were grouped as patients with no decompensation (ND).

For the purpose of the study an "effective etiological treatment" was considered the elimination of the etiological cause of the liver disease by a specific treatment (*i.e.* a sustained

virological response after antiviral treatment for patients with HCV, undetectable HBV DNA for patients with HBV during treatment with nucleos(t)ide analogues, achievement of complete abstinence from alcohol) at any time during follow-up. Recompensation was calculated according to Baveno VII criteria.[6]

Statistical analysis

Continuous variables were reported as mean (SD) and compared with Student's *t* test or with ANOVA with multiple comparison according to the Tukey's test (when normally distributed), or as median (IQR) and compared with the Wilcoxon's, Mann-Whitney or Kruskal-Wallis tests (when not normally distributed). Categorical variables were reported as proportions and compared with the Chi Square test or Fisher's exact test, if indicated.

Association between variables and risk of mortality were assessed using a Cox proportional-hazards model. The hazard ratios and their 95% CIs were calculated. Notably, the development of AD or NAD was considered a time-dependent covariate to avoid immortal time bias for patients who developed complications of cirrhosis throughout their follow-up time. We did not use a competing risk analysis because the use of time-dependent covariates can lead to distorted results with the Fine and Gray method.[20] All the parameters that were judged as clinically relevant according to the literature were included in a multivariable model: MELD, prophylaxis with non-selective beta-blockers (NSBBs), effective etiologic treatment, NAD, AD, and ND. MELD components were not included in the multivariable analyses in order to avoid multicollinearity.

The analysis was performed with SPSS (version 27.0; SPSS, Inc. Chicago, IL) and R 4.2.1 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria, 2021). Considering R, the following packages were used: survival (Therneau T, 2023, package version 3.5-5), RcmdrPlugin.EZR (Kim J, 2022, package version 1.61) and Rcmdr software (Fox J, Bouchet-Valat M 2022, package version 2.8-0).

Results

Characteristics of patients at inclusion and decompensation assessment

During the enrollment period, 1,017 outpatients were evaluated for inclusion in the study, 749 from the Padua center and 268 from the Milan center. However, 376 patients in the Padua cohort and 24 in the Milan cohort already had decompensated cirrhosis at the time of the first evaluation or had an episode of decompensation in the last 6 months. Therefore, 617 patients were included in the study, 373 in the Padua cohort, and 244 in the Milan cohort. Fig. 1 summarizes the inclusion and exclusion criteria. The characteristics of patients at inclusion are shown in Table 1 while a comparison between patients from Padua and Milan is displayed in Table S1.

During follow-up, 463 patients (75.0% of the total number of patients) did not develop any decompensation. Among the 154 patients who developed complications, there were 69 (44.8%) episodes of NAD, and 85 (55.2%) episodes of AD. Among the 69 patients whose first episode of decompensation could be characterized as NAD, 54 (78.2%) developed ascites, 13 (18.8%) HE, and two (2.9%) a combined episode of ascites and HE. Among the 85 patients with AD as first decompensation, 29 (34.1%) had ascites, 28 (32.9%) HE, 23 (27.1%) GI bleeding and five (5.9%) combined episodes of ascites and HE or ascites and GI bleeding. Twenty-nine out of the 69 patients with a first episode of NAD (42.0%) developed AD after a median follow-up of 11 months (IQR 4-20.3).

Clinical and laboratory characteristics of patients at inclusion according to the pattern of decompensation are shown in

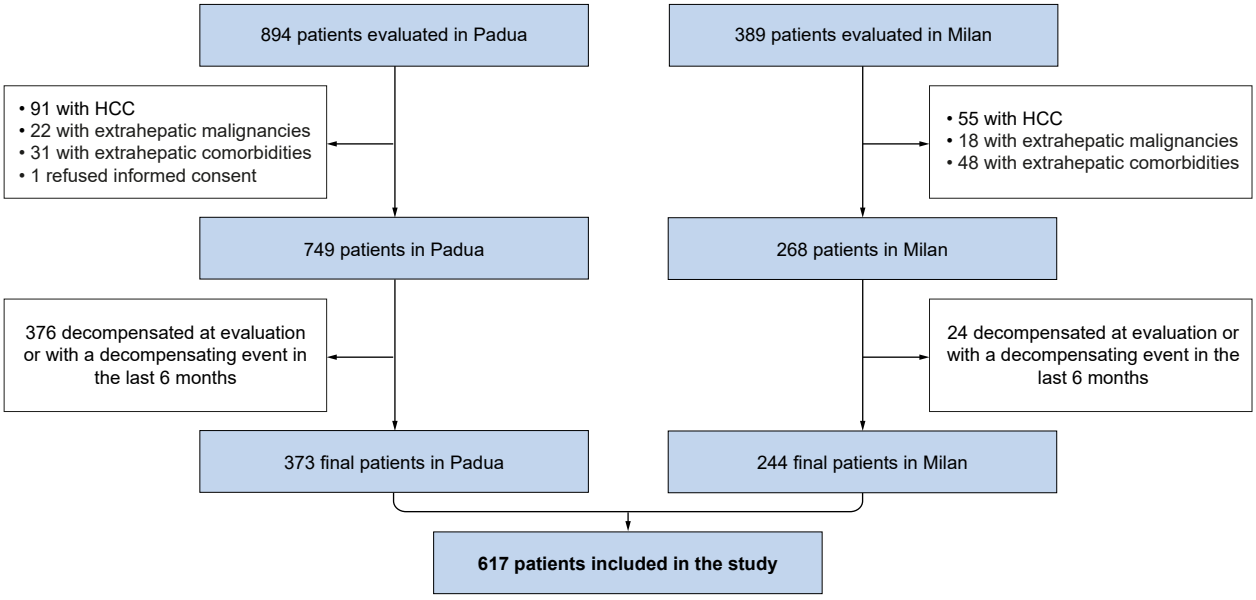

Fig. 1. Flow chart of patients included in the study. HCC, hepatocellular carcinoma.

Table 1. Characteristics of patients at inclusion.

	Patients (N = 617)
Age (years), mean (SD)	57.1 (12.2)
Sex (M *vs.* F), n (%)	401 (65.0)
Etiology, n (%)	
HCV	273 (44.2)
HBV	97 (15.7)
Alcohol	186 (30.1)
NASH	142 (2,306)
Autoimmune/cholestatic	39 (6.3)
Other	21 (3.4)
MAP (mmHg), median (IQR)	96.8 (90–105)
HR (bpm), median (IQR)	68.5 (64–78)
CTP score, median (IQR)	5 (5–6)
MELD score, median (IQR)	8 (7–11)
Serum albumin (g/L), median (IQR)	40.0 (36.2–43.0)
Sodium (mmol/L), median (IQR)	140 (138–142)
Creatinine (μmol/L), median (IQR)	71.0 (62.0–83.0)
WBC (/μl), median (IQR)	4,900 (3,780–6,410)
Hb (g/dl), median (IQR)	13.7 (12.1–15.0)
Bilirubin (μmol/L), median (IQR)	15.7 (10.7–25.1)
CRP (mg/dl), median (IQR)	3.9 (2.9–7.5)
BMI (kg/m^2) –median (IQR)	26.3 (23.7–29.0)
Diabetes (yes *vs.* no), n (%)	170 (27.6)
Varices at inclusion (yes *vs.* no), n (%)	240 (38.9)
Collateral circulation (yes *vs.* no), n (%)	126 (20.4)
NSBBs at inclusion (yes *vs.* no), n (%)	176 (28.5)

CRP, C-reactive protein; CTP, Child Turcotte Pugh score; Hb, hemoglobin; HR, heart rate; MAP, mean arterial pressure; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; NSBBs, non-selective beta-blockers; WBC, white blood cells.

Table 2. A high MELD score and prophylaxis with NSBBs were associated with a higher risk of NAD or AD, while an effective etiological treatment was associated with a lower risk of both NAD and AD (Tables 3 and 4).

Survival, predictors of mortality and secondary outcomes

One hundred and thirty-three patients (21.6%) were lost during follow-up. In the course of follow-up (a median of 60 months, IQR 32-114), 111 patients (18.0%) died; 39 patients had ND (8.4% of all patients with ND), 31 patients had NAD (44.9% of all patients with NAD), and 41 patients had AD (48.2% of all patients with AD, p <0.001). Death was due to hepatic causes in 17 patients with ND (43.6% of all deaths in this group), 18 with NAD (58.1% of all deaths in this group) and 31 with AD (75.6% of all deaths in this group, p = 0.014).

Among all patients, 59 (9.5%) underwent LT; 30 patients had ND (6.5% of all patients with ND), 12 patients had NAD (17.4% of all patients with NAD) and 17 had AD (20.0% of all patients with AD, p <0.001). Ninety-seven patients (15.7%) developed HCC, 60 in the ND group, 14 in the NAD group and 23 in the AD group (p = 0.003). As far as ACLF is concerned, one patient with ND (0.1%), 16 with NAD (23.5%) and 27 with AD (31.4%) developed ACLF during follow-up (p <0.001, comparison between NAD and AD is not significant). The major clinical outcomes in the three groups of patients are reported in Fig. 2.

Cox proportional-hazards model identified AD (*vs.* ND), NAD (*vs.* ND), MELD, an effective etiological treatment, and prophylaxis with NSBBs as independent predictors of mortality (Table 5). Considering NAD as the reference instead of ND in a multivariable model, AD was still associated with a higher risk of mortality (hazard ratio 2.92, 95% CI 1.40-6.08, p = 0.004).

According to Baveno VII criteria, four patients in the group with NAD (5.8% of patients in this group), and eight with AD (9.4% of patients in this group) achieved recompensation. The comparison between the two groups was not significant (p = 0.405).

Table 2. Characteristics of patients at inclusion, according to the development of complications of cirrhosis.

	ND (n = 463)	NAD (n = 69)	AD (n = 85)	*p* value
Age (years), mean (SD)	57.3 (12.0)	56.4 (12.5)	56.4 (12.5)	0.717
Sex (M *vs.* F), n (%)	297 (64.1)	47 (69.1)	57 (66.3)	0.699
Etiology, n (%)				
HCV	100 (43.2)	29 (42.6)	44 (51.2)	0.378
HBV	78 (16.8)	10 (14.7)	9 (10.5)	
Alcohol	135 (29.2)	25 (36.8)	26 (30.2)	
NASH	105 (22.7)	16 (23.5)	21 (24.4)	
Autoimmune/cholestatic	24 (5.2)	7 (10.3)	8 (9.5)	
Other	18 (3.9)	2 (2.9)	1 (1.2)	
MAP (mmHg), median (IQR)	97 (90-107)	97 (87-103)	93 (87-95)	0.026
HR (bpm), median (IQR)	70 (64-78)	68 (64-76)	68 (64-80)	0.862
CTP score, median (IQR)	5 (5-6)	6 (5-7)	6 (5-7)	<0.001
MELD score, median (IQR)	8 (7-10)	10 (9-12)	9 (8-12)	<0.001
Serum Albumin (g/L), median (IQR)	41.0 (37.9 -44.0)	37.0 (33.0-40.0)	36.6 (32.0-40.0)	<0.001
Sodium (mmol/L), median (IQR)	140 (139-142)	139 (138-141)	139 (137-141)	0.001
Creatinine (μmol/L), median (IQR)	71.0 (62.0-84.0)	72.0 (59.0-80.0)	69.5 (61.8-83.3)	0.854
WBC (/μl), median (IQR)	5,100 (4,100-6,810)	4,040 (2,900-5,530)	4,280 (3,120-5,340)	<0.001
HB (g/dl), median (IQR)	13.9 (12.4-15.1)	13.0 (11.5-14.0)	12.8 (10.7-14.4)	<0.001
Bilirubin (μmol/L), median (IQR)	14.3 (10.4-22.2)	22.1 (14.1-31.5)	20.8 (13.0-34.6)	<0.001
CRP (mg/dl), median (IQR)	3.3 (2.9-6.8)	5.6 (2.9-11.7)	4.7 (3.0-9.7)	0.067
BMI (kg/m^2), median (IQR)	26.0 (23.6-28.7)	27.1 (23.9-29.8)	27.3 (24.6-31.0)	0.004
Diabetes (yes *vs.* no), n (%)	119 (25.7)	24 (35.3)	27 (3142)	0.176
Varices at inclusion (yes *vs.* no), n (%)	139 (30.4)	46 (67.6)	55 (64.0)	<0.001
Collateral circulation (yes *vs.* no), n (%)	75 (15.3)	22 (31.3)	29 (32.9)	<0.001
NSBBs at inclusion (yes *vs.* no), n (%)	105 (22.7)	35 (51.5)	36 (41.9)	<0.001*
Effective etiological treatment (yes *vs.* no), n (%)	277 (59.8)	30 (44.1)	39 (45.3)	0.005

Normally distributed continuous variables presented as mean (SD) and compared with ANOVA with multiple comparison according to the Tukey's test. Non-normally distributed variables presented as median (IQR) and compared with Wilcoxon's, Mann-Whitney *U* or Kruskal-Wallis tests. Categorical variables presented as proportions and compared with Chi square or Fisher's exact test.

AD, acute decompensation; CRP, C-reactive protein; CTP, Child Turcotte Pugh score; Hb, hemoglobin; HR, heart rate; MAP, mean arterial pressure; MELD, model for end-stage liver disease; NAD, non-acute decompensation; ND, no decompensation; NASH, non-alcoholic steatohepatitis; NSBBs, non-selective beta-blockers; WBC, white blood cells.

*The comparison between patients with NAD and AD is statistically significant.

Table 3. Predictors of non-acute decompensation on multivariable analysis.

	HR (95% CI)	*p* value
MELD	1.16 (1.09-1.24)	<0.001
NSBBs at inclusion (yes *vs.* no)	3.05 (1.89-4.97)	<0.001
Effective etiological treatment (yes *vs.* no)	0.48 (0.29-0.79)	0.004

Association between variables and development of NAD assessed using a Cox proportional-hazards model, considering NAD a time-dependent covariate to avoid immortal time bias.
HR, hazard ratio; MELD, model for end-stage liver disease; NSBBs, non-selective beta-blockers.

Table 4. Predictors of acute decompensation on multivariable analysis.

	HR (95% CI)	*p* value
MELD	1.10 (1.04-1.17)	0.002
NSBBs at inclusion (yes *vs.* no)	2.04 (1.31-3.20)	0.002
Effective etiological treatment (yes *vs.* no)	0.44 (0.28-0.69)	<0.001

Association between variables and development of AD assessed using a Cox proportional-hazards model, considering AD a time-dependent covariate to avoid immortal time bias.
HR, hazard ratio; MELD, model for end-stage liver disease; NSBBs, non-selective beta-blockers.

Discussion

The introduction of the definition of "AD" by the CANONIC study in 2013,[3] reaffirmed in the PREDICT study,[4] has contributed to the disruption of the old categorization of decompensation as "first decompensation" and "further or late decompensation", since AD can occur as both first decompensation and further decompensation. The definition of AD and the consequent possibility of developing ACLF has placed the emphasis on the acute nature of decompensation rather than on the nature of the decompensating event or its temporal location in the course of liver disease. The acute nature of decompensation, as emphasized in the definition of AD, is proven by the fact that all patients in the CANONIC[3] and PREDICT[4] studies were hospitalized. It can be argued that hospitalization probably followed different criteria from center to center and was not always based on the acute and urgent nature of the individual complications. This objection is certainly fair for those patients who were hospitalized for Grade 2-3 uncomplicated ascites. However, for all the other complications hospitalization was a hallmark of acuteness and seriousness. It is an equally solid fact that, in clinical practice, millions of patients with cirrhosis develop decompensation in a non-acute form, such as a progressive development of grade 2 ascites or grade 1 or 2 HE, to the point of being optimally manageable as outpatients. In the attempt to recompose the occurrence and evolution of decompensation in a common, contemporary, and shared vision, some experts have proposed, on the basis of their clinical expertise, a distinction between AD and NAD as different settings for the development of the first episode of decompensation.[7] The first and main

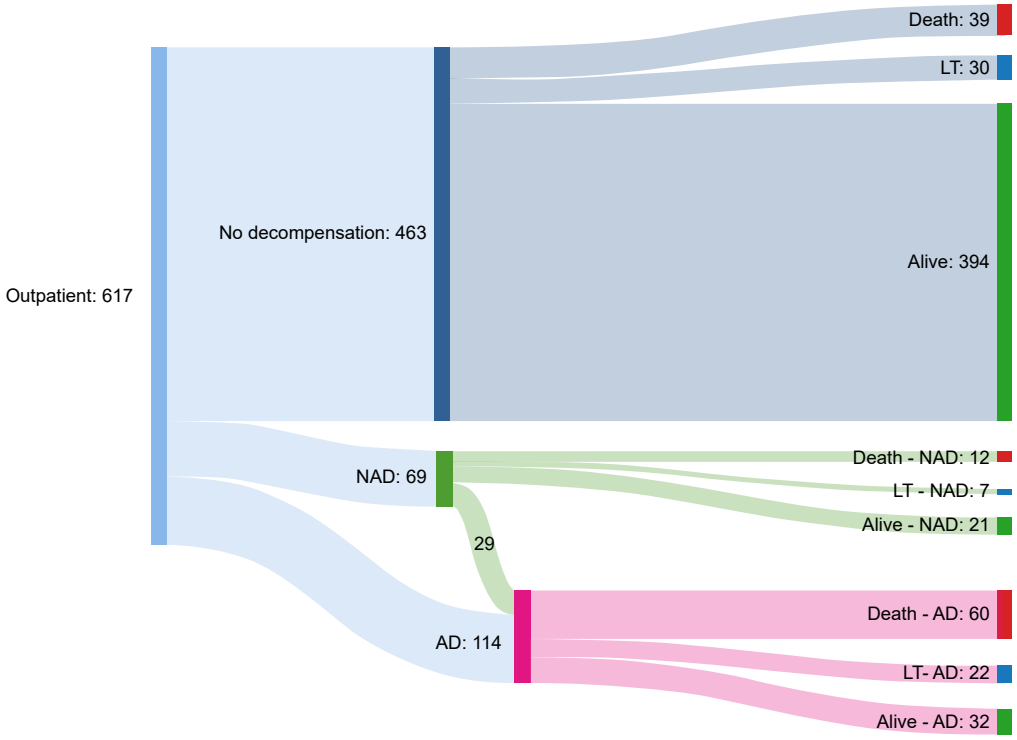

Fig. 2. Sankey plot reporting major clinical outcomes of the patients included in the study according to the type of decompensation. AD, acute decompensation; LT, liver transplantation; NAD, non-acute decompensation. (This figure appears in color on the web.)

Table 5. Predictors of mortality on multivariable analysis.

	HR (95% CI)	*p* value
MELD	1.12 (1.03-1.19)	0.004
NSBBs at inclusion (yes *vs*. no)	1.54 (0.88-2.67)	0.128
Effective etiological treatment (yes *vs*. no)	0.38 (0.21-0.68)	0.001
AD (*vs*. ND)	18.87 (10.24-34.75)	<0.001
NAD (*vs*. ND)	6.46 (2.85-14.66)	<0.001

Association between variables and mortality assessed using a Cox proportional-hazards model, NAD and AD were considered time-dependent covariates to avoid immortal time bias.

AD, acute decompensation; HR, hazard ratio; MELD, model for end-stage liver disease; NAD, non-acute decompensation; ND, no decompensation; NSBBs, non-selective beta-blockers.

finding of the present study is that AD and NAD are two different pathways of first decompensation that do not exist only in some experts' minds, but rather in daily clinical practice. Following the definition given by the aforementioned Expert Opinion,[7] our study demonstrates that in almost half of the 154 compensated outpatients who developed a first decompensating event, decompensation occurs as a slow, progressive process without any need for emergency hospitalization, thus perfectly intercepting the definition of NAD.

The probabilities of developing NAD or AD at 1 year were 7% and 17%, respectively. The validity and relevance of this observation is certified by the fact that the study was carried out in two centers that adopt the same strict criteria for urgent hospitalization of patients with decompensated cirrhosis. In particular, for patients presenting with ascites alone, urgent hospitalization was only provided in the case of complicated ascites. The existence of two different pathways of decompensation in patients with cirrhosis enables the validation of what has already emerged retrospectively in the CANONIC and PREDICT studies. While AD may represent a "first decompensation" in 21% of cases, in many others it develops in patients who had already developed NAD and can therefore be characterized as a form of "further decompensation", bringing some order to the formulation and use of the different definitions. Moreover, another main result of the study supports and gives solidity to the definition of NAD. In fact, the mortality rate in patients with NAD, although higher than in patients with ND, was found to be lower than in patients with AD (Fig. 2). It is important to highlight that almost half of the patients with NAD (42.0%) developed a further episode of AD, probably significantly worsening their prognosis, and increasing their risk of mortality. In order to better appreciate the relevance of this data, we must not overlook two considerations: a) about 44% of patients with NAD develop AD and b) it is known from the PREDICT study that over half of the patients who develop AD then develop stable decompensated cirrhosis, which appears very similar to NAD from a management point of view. Finally, a high MELD score, and the use of NSBBs at inclusion were both associated with a higher risk of decompensation. The data on MELD was largely predictable and required no interpretation. However, it may help to explain the higher incidence of decompensation at 1 year (25%) in the present series of patients with compensated cirrhosis compared to that previously observed in the PREDESCI study.[21] As far as NSBBs are concerned, it should be highlighted that more than half of the patients with both NAD and AD had varices at inclusion. Therefore, the use of NSBBs can be considered as an indirect sign of clinically significant portal hypertension. However, what makes the data on the use of NSBBs more intriguing is the fact that the percentage of patients on NSBBs was significantly higher in patients with NAD than in those with AD. It could be hypothesized that NSBBs may favor the development of NAD instead of AD. Nevertheless, it appears more probable that the development of AD requires an additional driver beyond portal hypertension, such as systemic inflammation. Unfortunately, the only raw parameter of systemic inflammation evaluated in the study, the level of C-reactive protein, did not show a difference between patients with NAD or AD. Finally, the observation that an effective etiological treatment was associated with a lower risk of development of both NAD and AD strengthens the concept that treating the causative agent of cirrhosis represents a disease-modifying approach that should be encouraged in as many patients as possible.[22–28] This data is even more evident if we consider that in both NAD and AD groups a consistent number of patients achieved recompensation according to Baveno VII criteria (5.8% in the NAD group and 9.4% in the AD group). The main limitation of the study that needs to be addressed is the limited number of patients that developed an episode of NAD (69 patients), or AD (85 patients). This limitation, as well as the lack of a deeper analysis of blood samples, prevented us from characterizing better the patients with NAD or AD. Further studies are certainly needed to strengthen the knowledge on NAD and its impact on clinical outcomes in patients with cirrhosis. Moreover, the cohort of patients have some characteristics that differ from other previous studies on decompensated cirrhosis, mainly regarding the distribution of the primary cause of liver disease. In fact, in our cohort, alcohol is less frequent than in other studies.[26] This could have an impact on the number of decompensating events and on the probability of achieving an effective etiologic treatment. However, etiology of liver disease was not found to be a predictor of development of either NAD or AD in our cohort.

In conclusion, decompensation of cirrhosis can occur in two different pathways, NAD and AD, which have a different impact on mortality. Patients who initially develop NAD should be monitored closely to prevent the further development of AD. Although our results need to be confirmed in a larger prospective observational study, they offer a first attempt at optimizing our understanding of decompensation and thereby developing improved strategies for management and prevention.

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Abbreviations

ACLF, acute-on-chronic liver failure; AD, acute decompensation; GI, gastrointestinal; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; LT, liver transplantation; MELD, model for end-stage liver disease; ND, no decompensation; NAD, non-acute decompensation; NSBBs, non-selective beta-blockers.

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Conflict of interest

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Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contribution

Study concept and design (MT, SP, PL, PA), data collection (MT, RDA, VC, GT, SI, CG, RG, MB, NZ), statistical analysis (AB), drafting of the manuscript (MT, RDA, PL, PA), revision for important intellectual content and approval of the final manuscript (all authors).

Data availability statement

The data relating to this study can be made available by the corresponding author via reasonable request.

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Supplementary data

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