

Mortality Risk According to Different Clinical Characteristics of First Episode of Liver Decompensation in Cirrhotic Patients: A Nationwide, Prospective, 3-Year Follow-Up Study in Italy

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- OBJECTIVES:** The occurrence of decompensation marks a crucial turning point in the course of cirrhosis. The purpose of this study was to assess the risk of mortality according to the clinical characteristics of first decompensation, considering also the impact of acute-on-chronic liver failure (AoCLF).
- METHODS:** We conducted a prospective nationwide inception cohort study in Italy. Decompensation was defined by the presence of ascites, either overt or detected by ultrasonography (UD), gastroesophageal variceal bleeding (GEVB), and hepatic encephalopathy (HE). AoCLF was defined according to the Asian Pacific Association for the Study of the Liver criteria. Multivariable Cox proportional hazards regression was used to analyze the risk of failure (death or orthotopic liver transplantation (OLT)).
- RESULTS:** A total of 490 consecutive cirrhotic patients (314 males, mean age 60.9±12.6 years) fulfilled the study criteria. AoCLF was identified in 59 patients (12.0%). Among the remaining 431 patients, ascites were found in 330 patients (76.6%): in 257 (77.8%) as overt ascites and in 73 (22.2%) as UD ascites. GEVB was observed in 77 patients (17.9%) and HE in 30 patients (7.0%). After a median follow-up of 33 months, 24 patients underwent OLT and 125 died. The cumulative incidence of failure (death or OLT) after 1, 2, and 3 years was, respectively, 28, 53, and 62% in patients with AoCLF; 10, 18, and 25% in patients with UD ascites; 17, 31, and 41% in patients with overt ascites; and 8, 12, and 24% in patients with GEVB ($P < 0.0001$).
- CONCLUSIONS:** AoCLF is responsible for a relevant proportion of first decompensation in cirrhotic patients and is associated with the poorest outcome. Patients with UD ascites do not have a negligible mortality rate and require clinical monitoring similar to that of patients with overt ascites.

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at <http://www.nature.com/ajg>

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INTRODUCTION

The disease course of cirrhosis, one of the worldwide leading causes of death, is characterized by an initial symptomless period of variable extent (1). However, during this chronic process, increasing portal pressure and decreasing liver function over time result in the development of hepatic decompensation that corresponds to a crucial turning point of this condition because it is associated with over 50% risk of further complications or death within a relatively short period of time (2–4). This decompensated stage deeply affects both the clinical management and the follow-up strategies (5–7). Despite the magnitude of the problem, a survey that assessed the outcome of patients with cirrhosis since the onset of decompensation according to its clinical features, namely inception cohort study, is still lacking.

In the attempt to overcome the weaknesses of the available information, D'Amico *et al.* (8) carried out a systematic review. Based on its results, they proposed to categorize cirrhotic patients by a multiple-step classification that identifies two stages of decompensated cirrhosis according to the characteristics of complications at presentation, and to their different rates of mortality. Nevertheless, the quoted systematic review suffers from several important methodological flaws as a consequence of being modeled by data collected retrospectively and obtained from studies carried out in a period when treatment of portal hypertension-related complications was still in its infancy. Furthermore, the suggested stage system (8) did not distinguish patients at their first decompensation from those who had already experienced it. Moreover, the authors did not consider the clinical impact of the acute deterioration upon a preexisting liver disease (acute-on-chronic liver failure (AoCLF)), the definition of which was only recently stated by the Asian Pacific Association for the Study of the Liver (APASL) (9). Finally, one more interesting issue on this topic, which has never been investigated so far, refers to the prognostic importance and the clinical outcome of ascites detectable only by ultrasonography since its first occurrence.

The aim of this prospective nationwide inception cohort study (EPA-SCO) was to evaluate the disease course of cirrhosis since the onset time of the first complication. The enrolled patients were allocated in distinct subcohorts according to the different characteristic of decompensation at study entry.

METHODS

The EPA-SCO study was carried out on behalf of the Italian Association for the Study of the Liver Disease (AISF).

Study population

Between October 2007 and October 2008, we enrolled all consecutive patients with cirrhosis (either followed by periodically surveillance as outpatients or after in-hospital admission) in whom a first episode of liver decompensation defined as (i) ascites (overt or ultrasound detected alone (UD)), (ii) gastroesophageal variceal bleeding (GEVB), (iii) hepatic encephalopathy (HE), (iv) jaundice, and (v) hepatorenal syndrome (HRS), has occurred. A total of 29 centers scattered throughout Italy agreed to participate.

The collection of personal data was made in full compliance with the Italian law on personal data protection, and each patient gave his/her consensus in participating. Inclusion criteria were age >18 years and diagnosis of cirrhosis, whereas all patients with previous episodes of liver decompensation, diagnosis of hepatocellular carcinoma (HCC), HIV co-infection, drug addiction, concomitant extrahepatic neoplasm, hemodialysis, and solid organ or bone marrow transplantation were excluded.

Diagnostic criteria for inclusion

At baseline, demographic, etiologic, and biochemical variables were set up. Diagnosis of previous compensated cirrhosis (either by histology or based on clinical ground) was available in all patients who had undergone periodical follow-up. For those who were unaware of a preexisting liver disease, diagnosis was obtained by the evaluation of clinical certification/record (when available) and/or confirmed during hospitalization by ultrasound, computed tomography scan, and upper endoscopy. In the latter group of patients, a detailed history of the prior clinical course of their disease was accurately investigated at study entry in order to confirm the inclusion criteria.

As mentioned above, ascites was diagnosed both by clinical examination (overt ascites) and ultrasonography (UD ascites). The detection of UD ascites was systematically looked for and reported, if present, at study entry, and its presence has been confirmed by two independent physicians. UD ascites was ascertained prospectively in patients previously free of ascites who were on regular surveillance for their liver condition. For the remaining individuals we cannot exclude that UD ascites could have been already present. Diagnostic paracentesis was performed in all patients with overt ascites in order to establish its portal-hypertensive nature by serum-ascites albumin gradient and to assess the concomitant presence of spontaneous bacterial peritonitis (SBP) by a polymorphonuclear cell count in ascitic fluid >250 cell/mm³ (10). HRS and refractory ascites were diagnosed according to the International Ascites Club criteria (11). Bleeding was attributed to the rupture of GEVB by endoscopic report according to Baveno guidelines (12). HE was defined as an episode of neurological and neuropsychiatric abnormality (drowsiness, mental confusion, and disorientation) revertible after an effective ammonia-lowering treatment (13). Initially, patients were allocated in the above-mentioned subcohort categories. Patients with mixed synchronous complications at presentation (i.e., ascites + GEVB and ascites + HE) were categorized apart. Later, in the beginning of 2010, based on the availability of the AoCLF criteria developed by the consensus recommendations of APASL (14), which includes (i) jaundice (serum bilirubin ≥5 mg/dl), (ii) coagulopathy (international normalized ratio ≥1.5), and (iii) *de novo* occurrence of ascites and/or encephalopathy, the protocol was amended. Both the preexisting diagnosis of stable compensated cirrhosis and a possible/probable acute hepatic insult within a 4-week period before the onset of the above-mentioned concurrent conditions were carefully required to certify this diagnosis. A detailed report for intake of different drugs or infections over the past 3 months was also taken. Accordingly, all patients who fulfilled the APASL criteria at the time of study entry were

retrospectively *post hoc* allocated in this category. Hence, in order to follow the results more easily, patients were presented as AoCLF and non-AoCLF subcohorts.

Presence of HCC was assessed by two coincidental imaging techniques (15) and, in controversial cases, also by a fine needle biopsy.

The etiology of cirrhosis was based on viral markers (anti-HCV and hepatitis B surface antigen (HBsAg)), amount and duration of alcohol intake, confirmed by relatives, autoantibodies, markers of iron overload, and criteria of metabolic syndrome for non-alcoholic steatohepatitis (NASH). Cryptogenic cirrhosis was diagnosed in the absence of any viral, autoimmune, or metabolic etiology. The Child–Turcotte–Pugh (CTP) classification (16), the Model for End-Stage Liver Disease (MELD) (17), and the MELD–Na (18) scores were determined at the initial visit. Treatments of complications were carried out according to current guidelines in all centers (10–12). For patients with UD ascites, a low-salt diet was prescribed, and spironolactone was also administered on the basis of the Na^+/K^+ urinary excretion ratio. Patients with GEVB received injection sclerotherapy, endoscopic band ligation, or transjugular intrahepatic portosystemic shunt. All these patients were discharged with β -blocker secondary prophylaxis unless contraindications or subjective intolerance were present.

Schedule of follow-up

The follow-up schedules after hospital release were pre-established by the writing committee and they were based on 3-month intervals (clinical and biochemical ultrasonography). These schedules were not modified after the protocol amendment. However, each center could adapt the visit periodicity individually, as clinically required.

Statistical analysis

Data were collected in a pre-established electronic CRF database (web-based data collection, e-CRF provided by Air-Tel, Airon Telematica, Milan, Italy). Differences in the distribution of subject characteristics between groups were evaluated by the analysis of variance and the χ^2 analysis for continuous and categorical variables, respectively. In time-to-event analyses, the considered event of interest was death or orthotopic liver transplantation (OLT). HCC was considered as a competing event. The observation started from the time of first episode of decompensation. Data were censored on the date of the last follow-up visit. The cumulative incidences of death or OLT and HCC were calculated using the method of Kalbfleisch and Prentice (19) and compared across different subgroups using the Gray test (20). For multivariate analyses, Cox proportional hazard regression modeling was used to analyze the factors associated with the outcomes and hazard ratios and 95% confidence intervals (CIs) were calculated for the strength of association.

A direct comparison of a model that includes only MELD score as a covariate and a model including also the type of decompensation at baseline was carried out. To evaluate the incremental predictive information of the new disease definition, we used the likelihood ratio test (21). We also assessed the improvement in risk

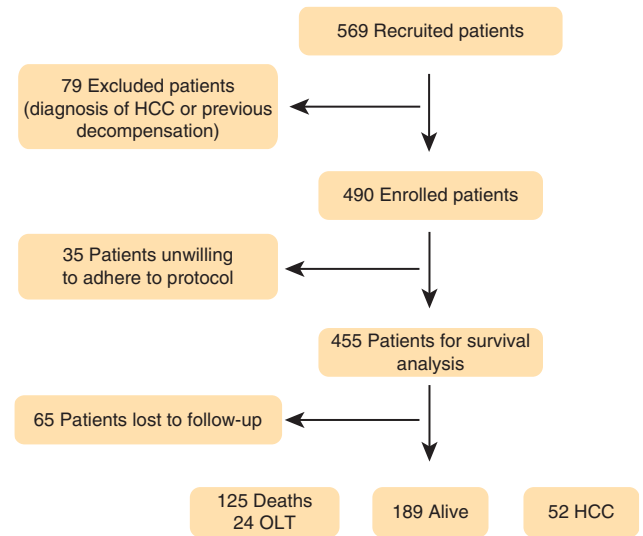


Figure 1. Flowchart of the study. HCC, hepatocellular carcinoma; OLT, orthotopic liver transplantation.

prediction when the covariates age, sex, body mass index, alanine transaminase, hemoglobin, sodium, and presence of diabetes were incorporated into the model.

A *P* value of <0.05 was considered statistically significant. All *P* values were two tailed. Statistical analyses were performed with the SAS software (version 9.3, Cary, NC), and the R software <http://www.R-project.org/>.

RESULTS

A total of 569 subjects were enrolled, and 79 were excluded, either because of diagnosis of concurrent HCC or because previously reported episodes of decompensation were found. The flowchart of the study is illustrated in **Figure 1**.

The clinical and laboratory characteristics of the 490 evaluated patients at inclusion are shown in **Table 1**. Approximately two-thirds of patients were men and the mean age was 60.9 years (range: 18–87 years). The mean values of biochemical parameters were consistent with the diagnosis of established cirrhosis. The distribution of CTP classes was: 19.4% class A, 61.0% class B, and 19.6% class C. Gastroesophageal varices were present in 218 patients (55 small, 79 medium, and 84 large varices) and, among them, 91 subjects (41.7%) took β -blockers (propranolol or nadolol) as a primary prophylaxis of variceal bleeding. The most frequent etiological factor was hepatitis C virus (HCV) infection (41.0%), followed by alcohol abuse (30.0%). The coexistence of HCV and alcohol abuse was ascertained in 11.4% of patients. Out of 244 HCV-positive patients, 82 (33.6%) have been previously unsuccessfully treated with α -interferon with or without ribavirin, whereas none of them received antiviral therapy during the study period. Of the patients, 11% had hepatitis B virus (HBV)–related cirrhosis. Out of 50 HBsAg-positive patients, 10 (20.0%) were taking a nucleoside analog therapy at the time of the enrollment into the study. Autoimmunity, iron overload, NASH, and cryptogenic

Table 1. Baseline characteristics of patients at first episode of decompensation at study entry and according to the presence or absence of AoCLF

Variable ^a	All patients (n=490)	AoCLF (n=59)	Non-AoCLF (decompensated cirrhosis) (n=431)	P value
Age (years)	60.9±12.6	55.1±13.7	61.7±12.3	<0.001
<i>Gender</i>				
Male	314 (64.1%)	42 (71.2%)	272 (63.1%)	0.2
Female	176 (35.9%)	17 (28.8%)	159 (36.9%)	
BMI	26.2±4.1	25.7±3.8	26.3±4.1	0.3
Serum bilirubin (mg/dl)	3.4±4.0	9.2±6.2	2.6±2.8	<0.001
Serum albumin (g/l)	31.7±6.0	28.7±5.1	32.7±6.1	<0.001
Prothrombin time (INR)	1.40±0.36	1.74±0.24	1.36±0.35	<0.001
ALT (u.l.n.)	2.2±1.3	2.1±1.3	2.2±1.3	0.5
Hb (g/dl)	11.7±2.2	11.2±2.1	11.8±2.3	0.07
Platelets (×10 ⁹ /l)	108.6±70.2	119.3±90.2	107.1±67.0	0.2
Creatinine (mg/dl)	0.92±0.45	0.90±0.53	0.93±0.44	0.6
Sodium (mEq/l)	137.0±4.6	134.8±4.8	137.3±4.5	<0.001
<i>Child–Turcotte–Pugh class</i>				
A5/A6	95 (19.4%)	0	95 (22.0%)	<0.001
B7/B9	302 (61.6%)	22 (37.3%)	280 (65.0%)	
C10/C15	93 (19.0%)	37 (62.7%)	56 (13.0%)	
MELD score (median, IQR)	13 (10–17)	20 (19–23)	13 (10–14)	<0.001
MELD-Na (median, IQR)	14 (10–19)	23 (19–28)	13 (10–17)	<0.001
<i>Gastroesophageal varices</i>				
Small	55 (25.3%)	6 (28.6%)	49 (24.9%)	0.9
Medium	79 (36.2%)	7 (33.3%)	72 (36.5%)	
Large	84 (38.5%)	8 (38.1%)	76 (38.6%)	
<i>Etiology</i>				
HBV	35 ^b (7.1%)	1 (1.7%)	34 (7.9%)	<0.001
HCV	201 ^c (41.0%)	11 (18.6%)	190 (44.1%)	
Alcohol	147 (30.0%)	35 (59.3%)	112 (26.0%)	
Alcohol/virus	56 (11.4%)	5 (8.5%)	51 (11.8%)	
Autoimmune (PBC, PSC, AIH)	14 ^d (2.9%)	3 (5.1%)	11 (2.6%)	
NASH/cryptogenic	37 (7.6%)	4 (6.8%)	33 (7.7%)	
In-hospital admission	423 (86.3%)	58 (98.3%)	375 (84.7%)	0.002
Outpatients	67 (16.7%)	1 (1.7%)	66 (15.3%)	
Regular follow-up before the study entry	178 (36.3%)	19 (32.2%)	159 (36.9%)	0.4

AIH, autoimmune hepatitis; ALT, alanine transaminase; AoCLF, acute-on-chronic liver failure; BMI, body mass index; Hb, hemoglobin; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D Virus; INR, international normalized ratio; IQR, interquartile range; MELD, Model for End-Stage Liver Disease; MELD-Na, MELD-serum sodium; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; u.l.n., upper limit of normal.

^aValues are number and percentage, mean ± s.d. or median and IQR.

^bIncluding 7 patients with HDV coinfection.

^cIncluding 5 hepatitis B surface antigen (HBsAg)-positive patients.

^dIncluding one anti-HCV positive patient.

etiologies accounted for the remaining 17.6% of cases. Before study entry, 178 (36.3%) patients had undergone regular surveillance by their referral centers.

AoCLF subcohort at presentation

In all, 59 (12.1%) patients fulfilled the criteria of AoCLF diagnosis. **Table 1** (middle column) shows their clinical and laboratory

features at study entry. At time 0, 46 patients had ascites alone, whereas HE was found in 13 patients. In six cases, the combination of ascites and HE was found. More than two-thirds of patients reported alcohol abuse as main determinant of their liver disease. Precipitating events of AoCLF were: (i) active alcoholism in 40 (5 with coexisting infections from urinary tract, two from lung, 10 without clear acute insult); (ii) drug-induced liver damage in 10 (nonsteroidal anti-inflammatory drugs in 4, amoxicillin-clavulanate in 4, hypericum perforatum and other unidentified herbal drugs in 2); (iii) active bleeding in 4 cases; and (iv) bacterial infections alone in 4 patients. Hepatitis reactivation was found to be the precipitating factor in one case due to HBV. Four patients had renal failure (creatinine > 1.5 mg/dl). No patient underwent mechanical ventilation or renal replacement. A severe hepatic impairment was very frequent: 62.7% of these subjects belonged to CTP class C and overall median value of MELD was 20. In hospital, the mortality rate was 3.4%.

Non-AoCLF subcohort at presentation

In **Table 1**, the right column shows the principal clinical and laboratory features of 431 patients with non-AoCLF decompensated cirrhosis. In comparison with previous subjects, these patients were significantly older, with less severe liver impairment. Viral infection predominates as etiological factor for cirrhosis.

The main features of this population according to the etiology of their liver disease are shown in **Supplementary Table S1** online. Patients with HCV-related cirrhosis were the oldest, whereas patients with dual etiology (virus plus alcohol) were the youngest. Patients with HBV infection or alcohol abuse were predominantly men, whereas female gender was highly represented in autoimmune and NASH/cryptogenic diseases. Compared with patients with HCV etiology, subjects with alcohol-related disease showed a more advanced stage of their condition (CTP class C: 19.6% vs. 11.1%, $P < 0.001$; median MELD: 14 vs. 12, $P < 0.001$). As expected, diabetes was present across all groups of patients, with the highest prevalence in the NASH/cryptogenic group (42.4%).

Table 2 shows the clinical and laboratory features of 416 non-AoCLF patients according to the type of clinical complication at presentation. In this group of patients, overt ascites was the most common cause of decompensation (246 cases, 59.1%). Among them, 8 patients had concomitant mild or moderate HE. In addition, 37 patients (15.0%) had leg edema. Sixteen patients (6.5%) had SBP 8 (13 of them were discharged from the hospital after starting an antibiotic prophylaxis). HRS was diagnosed in only one patient. Gastroesophageal varices were discovered in 77 patients (31.3%) with overt ascites. Interestingly, no difference in the occurrence of ascites was seen between patients who were receiving or not prophylactic β -blocker treatment for variceal bleeding (77.4% vs. 81.1, $P = 0.5$). GEVB alone was observed in 66 (15.9%) patients, but in only 1 patient with concomitant moderate HE. GEVB and overt ascites were concomitantly present in 11 patients (3.1%; **Table 2**). At hospital admission, 43 patients received sclerotherapy and 30 endoscopic band ligation, whereas in 7 cases vasoactive therapy

was used. Three patients had insertion of transjugular intrahepatic portosystemic shunt because of the failure of a stable control of the bleeding.

UD ascites was identified in 73 cases (17.7%; **Table 2**). Among them, only 10 patients (13.4%) were found to have gastroesophageal varices. Female gender was much more prevalent in comparison with the previous two subgroups.

Among the remaining 35 patients, mild-to-moderate HE was diagnosed in 20 cases (**Table 2**). Eight patients had acute cholangitis and isolated portal vein thrombosis was found in 7 subjects.

Overall, the in-hospital mortality rate of this subcohort of patients was 1.2%.

Follow-up and survival analysis

The median follow-up observed in 455 of 490 (92.9%) patients (AoCLF and non-AoCLF pooled together) who agreed to be regularly followed after hospital discharge was of 33 months (range 1–48), for a total of 872 person-years of observation. No significant difference of baseline characteristics was found between patients who adhered or refused to be followed-up (data not shown). During the time of observation, 125 patients died, 24 received OLT, and 52 developed HCC (overall incidence 23.0 per 100 person-years, HCC incidence 5.96 per 100 person-years). Sixty-five patients lost to follow-up were also included in the survival analysis. For these patients, follow-up was censored at the time of last observation (median follow-up of 12.3 months, range 1–29) and their clinical features (age, sex, etiology, and type of first decompensation) did not differ from those patients who were still on follow-up at the end of the study.

Transition to *de novo* complications by type of hepatic decompensation at presentation in non-AoCLF patients is reported in **Supplementary Material** online.

The cumulative incidence of failure (death or OLT) after the first episode of decompensation was 16% (95% CI: 13–20%) at 1 year, 28% (95% CI: 24–32%) at 2 years, and 37% (95% CI: 32–42%) at 3 years. The 3-year cumulative incidence of HCC was 13% (95% CI: 10–17%; **Figure 2**). The 3-year cumulative incidence of failure was 62% (95% CI 45–75%) in AoCLF cohort and 34% (95% CI 28–39%) in the non-AoCLF cohorts. The main causes of death for 125 patients were the following: liver failure ($n = 77$), GEVB ($n = 19$), sepsis ($n = 12$), HRS ($n = 8$), and other causes unrelated to liver disease ($n = 9$; **Table 3**).

Figure 3 shows the curves of cumulative incidence of death/OLT according to the above-mentioned criteria. A significant difference of survival across the different subgroups was observed (Gray test, $P < 0.0001$). **Table 3** shows the cumulative incidence of failure (death and OLT) by type of decompensation at baseline.

Among 225 HCV patients with available information, 81 (36.0%) have been previously treated with antiviral therapy. The two survival curves of treated and untreated subjects were equivalent ($P = 0.9$ by log-rank test; data not shown). As for HBV, the number of patients was too low to be reliable. During follow-up, 41 patients continued to be alcohol abusing. Their overall survival rate was lower but not

Table 2. Baseline clinical and laboratory characteristics of 431 patients with non-AoCLF decompensated cirrhosis according to the features of first decompensation

Variable ^a	Overt ascites (n=246)	GEVB (n=66)	UD ascites (n=73)	Other ^b (n=35)	GEVB and ascites (n=11)	P value
Age (years) range	62.0±12.3	57.4±13.3	63.1±10.5	65.5±12.6	58.7±10.6	0.011
<i>Gender</i>						
Male	165 (67.1%)	42 (63.6%)	34 (46.6%)	22 (62.9%)	9 (81.8%)	0.018
Female	81 (32.9%)	24 (36.4%)	39 (53.4%)	13 (37.1%)	2 (18.2%)	
BMI	26.5±4.5	25.8±3.1	25.9±3.9	26.4±3.5	27.9±3.5	0.4
Serum bilirubin (mg/dl)	2.9±3.0	2.0±1.6	1.4±0.9	4.1±4.9	2.3±1.2	<0.001
Serum albumin (g/l)	30.9±5.9	31.9±5.4	35.1±5.7	35.1±7.0	29.2±4.8	<0.001
Prothrombin time (INR)	1.37±0.32	1.32±0.21	1.34±0.55	1.30±0.27	1.59±0.31	0.13
ALT (u.l.n.)	2.2±1.3	2.2±1.3	2.6±1.4	2.2±1.4	2.0±1.3	0.05
Hb (g/dl)	12.1±2.0	9.4±2.3	12.7±1.7	13.0±1.8	9.6±1.4	<0.001
Platelets (×10 ⁹ /l)	119.5±77.8	79.3±34.1	91.8±47.1	104.7±50.3	106.3±40.4	<0.001
Creatinine (mg/dl)	0.97±0.55	0.84±0.26	0.84±0.24	0.91±0.18	1.0±0.35	0.075
Sodium (mEq/l)	136.4±4.8	138.6±3.0	138.7±3.3	138.8±3.7	136.3±6.0	<0.001
<i>Child–Turcotte–Pugh class</i>						
A5/A6	22 (8.9%)	29 (43.9%)	30 (41.1%)	13 (37.1%)	1 (9.1%)	<0.001
B7/B9	180 (73.2%)	33 (50.0%)	43 (58.9%)	18 (51.4%)	6 (54.5%)	
C10/C15	44 (17.9%)	4 (6.1%)	0	4 (11.4%)	4 (36.4%)	
MELD score (median, IQR)	13 (11–16)	11 (10–14)	10 (8–12)	13 (9–17)	16 (11–19)	<0.001
MELD-Na (median, IQR)	14 (11–18)	11.5 (10–14)	10 (8–12.5)	13 (10–19)	18 (11–27)	<0.001
<i>Etiology</i>						
HBV	18 (7.3%)	6 (9.1%)	6 (8.2%)	4 (11.4%)	0	0.03
HCV	106 (43.1%)	21 (31.8%)	45 (61.6%)	17 (48.6%)	1 (9.1%)	
Alcohol	76 (30.9%)	15 (22.7%)	9 (12.3%)	5 (14.3%)	7 (63.6%)	
Alcohol/virus	26 (10.6%)	11 (16.7%)	7 (9.6%)	5 (14.3%)	2 (18.2%)	
Autoimmune	4 (1.6%)	4 (6.1%)	3 (4.1%)	0	0	
NASH/cryptogenic	16 (6.5%)	9 (13.6%)	3 (4.1%)	4 (11.4%)	1 (9.1%)	
Regular follow-up before the study entry	80 (32.5%)	21 (31.8%)	40 (54.8%)	17 (48.6%)	1 (9.1%)	0.003

ALT, alanine transaminase; AoCLF, acute-on-chronic liver failure; BMI, body mass index; GEVB, gastroesophageal variceal bleeding; Hb, hemoglobin; HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; IQR, interquartile range; MELD, Model for End-Stage Liver Disease; MELD-Na, MELD-serum sodium; NASH, nonalcoholic steatohepatitis; UD, ultrasonography detected; u.l.n., upper limit of normal.

^aValues are number and percentage or mean ± s.d.

^bHepatic encephalopathy, portal vein thrombosis, and cholangitis.

statistically significant ($P=0.075$ by log-rank test; data not shown) in comparison with that of abstinent individuals.

Predictive model for death/OLT

The likelihood of the Cox model including only MELD score was -773 (Table 4, model 1). The hazard ratio associated with a 5-point increase estimated from model 1 was 1.52 (95% CI 1.31–1.76). When the type of decompensation (categorized as AoCLF, overt ascites, GEVB, and UD) was added to model 1, the likelihood increased significantly to -769 (Table 4, model 2;

likelihood ratio test P value = 0.021). In model 2, the type of decompensation remained a statistically significant prognostic factor after adjusting for MELD score: when compared with GEVB patients, the hazard ratio for AoCLF, overt ascites, and UD patients were, respectively, 2.35 (95% CI: 1.11–4.99), 2.05 (95% CI: 1.11–3.77), and 1.28 (95% CI: 0.61–2.68).

Furthermore, when age, sex, body mass index, alanine transaminase, hemoglobin, sodium, and presence of diabetes were added to the model, the likelihood increased significantly to -734 (Table 4, model 3; likelihood ratio test P value < 0.0001). In addition, from

this final multivariable model, AoCLF patients and overt ascites patients remained at a significantly higher risk of event compared with GEVB patients.

Because of the low number of patients belonging to the subgroups, overt ascites plus GEVB, HE, portal vein thrombosis, and cholangitis categories were not included in the multivariable analyses.

DISCUSSION

The present nationwide inception cohort study illustrates the epidemiology, clinical features, and disease outcome of patients with cirrhosis after the onset of their first episode of liver decompensation. Although lack of data from other countries limits the

generalization of our results, it provides original information about the occurrence of AoCLF and subclinical (or UD detected) ascites, two interesting clinical entities for which available data are scarce.

First of all, we wish to emphasize some methodological aspects of our survey. The prospective enrollment of consecutive patients starting from their first complication has reduced potential selection bias. Moreover, the participation of both tertiary and peripheral centers have also minimized referral and recruitment biases because of local issues, and the participation of hospitals scattered all over the Country provided a representative picture of patients with cirrhosis in Italy.

At present, HCV is the main etiological cause of cirrhosis in patients. This does not surprise, considering both the high prevalence of this infection in Italy (22) and the unsatisfactory rates of response achieved with current interferon-based treatment regimen. In contrast, the number of patients with HBV infection was much lower, confirming that this condition has decreased over the past 20 years in our country, mainly because of the national vaccination plan and efficacy of antiviral therapy. Patients with alcohol-related etiology showed a more severe condition of the disease at presentation, irrespective of their younger age.

The observed findings are somewhat different from the results of a study performed during years 1988–1996, which enrolled 462 cirrhotic patients referring to 23 Italian hospitals for liver decompensation (23). In that study, ~40% of decompensated cirrhosis was attributable to alcohol consumption, whereas a little more than half of the subjects were infected by HCV. The discrepancy may be attributed to different characteristics of the enrolled patients. As a matter of fact, in the aforementioned study, all subjects were unaware of their condition and received the first diagnosis of cirrhosis at the time of decompensation, whereas in our survey only one-third of subjects were unaware of their illness before decompensation.

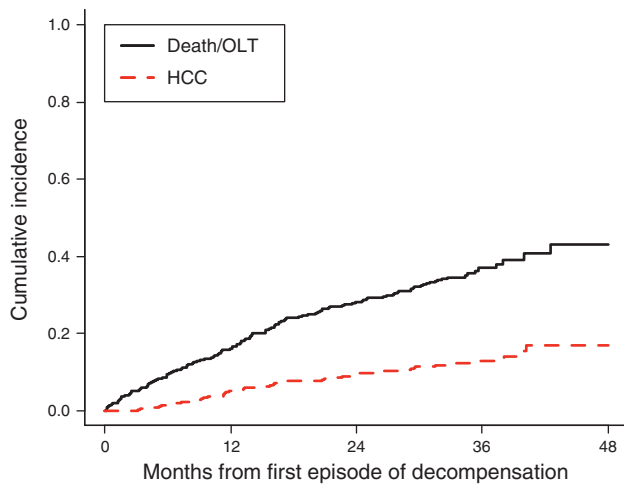


Figure 2. Cumulative incidence of death/OLT and HCC in the overall cohort (455 patients). HCC, hepatocellular carcinoma; OLT, orthotopic liver transplantation.

Table 3. Description of observed first clinical events and estimated cumulative incidence of failure by type of decompensation at baseline

Category	At risk	Cause of death					Total deaths	OLT	HCC	Cumulative incidence of failure (death and OLT) (95% CI)		
		Hepatic failure	Bleeding	Sepsis	HRS	Nonhepatic				1 Year	2 Years	3 Years
AoCLF	53	16	4	1	3	2	26	4	2	28% (16–41%)	53% (38–66%)	62% (45–75%)
UD ascites	71	12	1	1	—	1	15	2	4	10% (4–19%)	18% (10–28%)	25% (15–36%)
Overt ascites	230	39	8	5	5	5	65	17	30	17% (13–23%)	31% (25–37%)	41% (33–48%)
GEVB	60	5	4	1	—	1	11	1	8	8% (3–17%)	12% (5–22%)	24% (12–38%)
GEVB + overt ascites	8	—	—	—	—	1	1	0	2	—	16% (0–55%)	—
Other ^a	33	4	1	1	1	—	7	0	6	20% (8–35%)	23% (10–40%)	—

AoCLF, acute-on-chronic liver failure; CI, confidence interval; GEVB, gastroesophageal variceal bleeding; HCC, hepatocellular carcinoma; HRS, hepatorenal syndrome; OLT, orthotopic liver transplantation; UD, ultrasonography detected.

^aHepatic encephalopathy, portal vein thrombosis, and cholangitis.

In this study, HCV subjects were significantly older than alcoholics, suggesting that the disease route would be more indolent in this population. Additionally, the finding that the coexistence of HCV and alcohol was associated with the youngest age provides

solid evidence about the synergistic role of both factors in accelerating the progression of the disease (24–27). Finally, the observation that a relevant proportion of the etiologies of these patients may be attributed to NASH confirms that this disorder is not infrequently associated with progression to end-stage liver disease (28,29). The reliability of our diagnosis of NASH (still lacking a reliable marker) was certified by the fact that the prevalence of diabetes, which is strictly linked to the metabolic syndrome, was significantly higher in this group of subjects.

This study first reports prevalence of AoCLF as determinant of first decompensation. By using the criteria proposed by APASL consensus meeting (9), which simply included a revisited version of the classical Child score, we found that at least 12% of the episodes of first complication in cirrhotic patients could be attributable to AoCLF. The fact that this information has not been available so far is not surprising, as although AoCLF should be always suspected in patients with cirrhosis showing sudden liver function deterioration, APASL criteria have not been universally accepted and a consensus for the definition of this entity has not been reached yet. This justifies the lower in-hospital mortality rate (3.4% vs. 10.4%) observed in our findings when compared with the one recently reported by Katoonizadeh *et al.* (30). Accordingly, despite the fact that APASL criteria to define AoCLF were also used in that study, the included patients were exclusively affected by alcohol-related cirrhosis and the proportion of subjects with systemic inflammatory response that emerged to be a main determinant of short-term mortality in that study was higher.

The bigger group of patients with HBV reactivation, concurrently with the more severe disease stage of patients at presentation

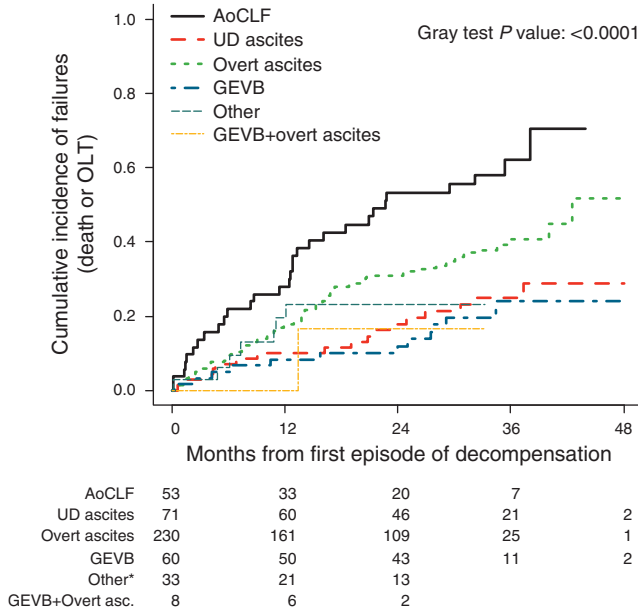


Figure 3. Cumulative incidence of death/OLT by type of decompensation at baseline. AoCLF, acute-on-chronic liver failure; GEVB, gastroesophageal variceal bleeding; OLT, orthotopic liver transplantation; UD, ultrasonography detected. *Hepatic encephalopathy, portal vein thrombosis, and cholangitis.

Table 4. Comparison between model considering only MELD score (model 1), model also including type of decompensation (model 2), and model also including type of decompensation, age, sex, BMI, ALT, Hb, sodium, and diagnosis of diabetes (model 3)

	Model 1		Model 2		Model 3	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
MELD score (5-point increase)	1.52 (1.31–1.76)	<0.0001	1.37 (1.13–1.66)	0.0014	1.32 (1.08–1.60)	0.0059
AoCLF vs. GEVB			2.35 (1.11–4.99)	0.0262	2.50 (1.11–5.65)	0.0272
Overt ascites vs. GEVB			2.05 (1.11–3.77)	0.0214	1.98 (1.02–3.84)	0.0452
UD vs. GEVB			1.28 (0.61–2.68)	0.5166	1.42 (0.63–3.17)	0.3985
Age (10-year increase)					1.41 (1.22–1.64)	<0.0001
Gender (male vs. female)					1.45 (1.00–2.12)	0.0501
BMI (5-unit increase)					0.80 (0.64–1.01)	0.0633
ALT (times u.l.n.; 1-unit increase)					1.26 (1.11–1.43)	0.0004
Hb (g/dl; 1-unit increase)					0.91 (0.83–0.99)	0.0306
Sodium (mEq/l; 1-unit increase)					0.94 (0.91–0.98)	0.0027
Diagnosis of diabetes (yes vs. no)					1.63 (1.10–2.41)	0.0141
Model 2 vs. model 1	LRT 8.7 (P=0.03)					
Model 3 vs. model 2	LRT 58.5 (P<0.0001)					

ALT, alanine transaminase; AoCLF, acute-on-chronic liver failure; BMI, body mass index; CI, confidence interval; GEVB, gastroesophageal variceal bleeding; Hb, hemoglobin; HR, hazard ratio; LRT, likelihood ratio test; MELD, Model for End-Stage Liver Disease; UD, ultrasonography detected; u.l.n., upper limit of normal.

(median MELD 29 vs. 20, high proportion of both HRS and multiorgan failure), may justify the different rates (63% vs. 25%) of 3-month mortality between our survey and another study carried out by Garg *et al.* (31) on 91 patients with APASL-AoCLF. In addition, the low number of multiorgan failure in our study also explains the lack of difference observed in in-hospital mortality between AoCLF and decompensated cirrhosis. Regarding this, whether patients with other multiple end-organ failures (as allowed by the EASL-Chronic Liver Failure (CLIF) Consortium Canonic study) should be included in AoCLF definition is still a matter of debate (32). Nevertheless, while waiting for the attainment of a general agreement, these criteria might be useful if applied in daily practice, as the main innovation that has emerged from our study is that the adoption of APASL criteria for AoCLF enables to infer a prospect of the long-term prognosis at the time of the patient's first complication.

After exclusion of patients with AoCLF, ascites still remained the most frequent complication, and in a not-negligible number of cases it could be identified only by ultrasound examination. To our knowledge, no study has compared the survival rate of patients with UD ascites with that of patients with overt ascites so far. Regrettably, we did not compare a reference population of patients with compensated cirrhosis but we observed that the 3-year mortality rate of patients with UD ascites was approximately eightfold higher than the one reported by other previous investigations in patients with compensated disease (33,34). This finding, in addition to the rapid progression of overt ascites in approximately one-fifth of cases, is relevant from a clinical point of view and consistent with the assumption that UD ascites represents a very early stage of liver decompensation. Meanwhile, whether the practice of a salt-restricted diet and the expanding use of diuretics/albumin could be beneficial in these patients are matters of dedicated studies.

Survival rates in patients with overt ascites paralleled those reported by Planas *et al.* (35) in HCV patients and those described by Alvarez *et al.* (36) in alcohol-related cirrhosis. The lack of improvement of standard treatments of ascites over the past years, as well as the rapid transition to more severe conditions (refractory ascites, GEVB, SBP, and HRS), indicates that this complication, more accurately than bleeding, reflects a severe impairment of both circulatory and renal function, giving the justification of the concordance of our results with those obtained in the past (37).

Although the prevalence of subjects with concurrent SBP was low, this group of patients showed a significantly lower probability to survive over the first 6 months of follow-up, compared with those with ascites and no SBP. The finding that the vast majority of these cases received antibiotic prophylaxis according to international recommendations (38) indicates that the epidemiology of bacterial infections has changed over the years and that the level of efficacy of the available therapy schedule has lowered (39,40).

In comparison with previous estimates reported by D'Amico *et al.* (9), we found that both prevalence of GEVB as a first cause of decompensation and mortality rates of patients who have bled were extremely low. This discrepancy can be ascribed to several reasons: (i) current widespread use of primary prophylaxis with β -blockers

and/or endoscopic variceal ligation, (ii) use of prophylactic antibiotic and vasoactive therapy, (iii) a collection of prospective cases instead of retrospective cohorts (9), (iv) exclusive inclusion of patients at their first decompensation in spite of the presence of patients with previous decompensation, and (v) inclusion of patients with concurrent GEVB and ascites in the same subgroup, whereas in our study patients were considered separately.

We acknowledge that the results of this survey require an external validation, possibly performed in countries where the prevalence of some risk factors of cirrhosis is different. We also admit that the *post hoc* allocation of patients with AoCLF, as well as the negligible number of patients with multiorgan failure in this subgroup of subjects, may impair the strength of our study.

In conclusion, according to the APASL criteria, a substantial proportion of first decompensation in patients with cirrhosis in Italy may be attributable to AoCLF, a distinct syndrome that, irrespective of short-term outcome, had a very poor prognosis over a 3-year follow-up period. In addition, as the risk of mortality of patients who developed UD ascites was not negligible, subjects who developed this complication require a careful follow-up. Both prevalence and mortality rates of GEVB were extremely lower in comparison with those previously described in past surveys. Although the underlying liver functional status, as certified by MELD score, gives reason for diverse rates of mortality between the above-mentioned categories, other characteristics of patients, such as older age, sex male, obesity, and presence of diabetes across different types of first decompensation, were independently associated with the 3-year mortality risk in the single individual.

Both practicing specialists and general practitioners may use these results to (i) better categorize the population of cirrhotic patients at the time of their first complication, (ii) identify the subjects with worst prognosis at more urgent need for liver transplant, and (iii) standardize the criteria for including patients in future studies. Health-care systems may utilize these data to update the knowledge of the impact of this disease and to estimate the amount of economic investments that will be required to afford this condition.

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CONFLICT OF INTEREST

Guarantors of the article: Savino Bruno, MD and Piero Luigi Almasio, MD.

Specific author contributions: Savino Bruno and Piero L. Almasio conceived the study, coordinated data analysis, and were responsible for writing this report; Francesco Salerno, Simone Saibeni, Tommaso Stroffolini, and Patrick Maisonneuve supervised the study; Vincenzo Bagnardi performed statistical analysis; Carmen Vandelli, Massimo De Luca, Martina Felder, Anna Ludovica Fracanzani, Cleofe Prisco, Giovanna Vitaliani, Loredana Simone, Giovanni Battista Gaeta, Maria Stanzone, Caterina Furlan, and Marcello Persico collected and compiled the data.

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Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ During the disease course of liver cirrhosis, increasing portal pressure and decreasing liver function cause the development of hepatic decompensation.
- ✓ This clinical event marks a crucial turning point as it is associated with a higher risk of further complications and liver-related death.
- ✓ Predictive models of mortality based on clinical features of liver decompensation are widely accepted in daily practice.
- ✓ However, the above-mentioned estimates have been developed by a systematic review of literature that includes studies carried out when treatment of portal hypertension-related complications were still in its infancy and new emerging conditions such as acute-on-chronic liver failure (AoCLF) were not assessed.

WHAT IS NEW HERE

- ✓ AoCLF accounted for a relevant proportion of first decompensation in cirrhotic patients, the occurrence of which was associated with the poorest 3-year survival rate.
- ✓ On the basis of their not-negligible mortality rate, patients who develop ultrasound-detected (UD) ascites require clinical surveillance analogous to the one required by patients with overt ascites.
- ✓ In patients affected by gastroesophageal variceal bleeding (GEVB), the mortality rate was particularly lower in comparison with those previously reported.
- ✓ In the single individual affected by cirrhosis of any etiology, at the time of the onset of first episode of decompensation, a more accurate prognosis of 3-year mortality is enabled by combining multiple risk factors like type of complication, older age, male gender, obesity, diabetes, and Model for End-Stage Liver Disease (MELD) score.

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APPENDIX

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