





## ORIGINAL ARTICLE

# High frequency of acute decompensation and cancer in patients with compensated cirrhosis due to nonalcoholic fatty liver disease: A retrospective cohort study

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## Abstract

The natural history of compensated cirrhosis due to nonalcoholic fatty liver disease (NAFLD) has not been completely characterized. The aim of the present study was to assess the incidence and risk factors of acute decompensation of cirrhosis, hepatocellular carcinoma, and extrahepatic cancers. This was a multicenter, retrospective, cohort study including 449 patients with compensated cirrhosis due to NAFLD. We calculated cumulative incidences and used competitive risk analysis to determine the risk factors associated with decompensation and cancer development. Over a median of 39 months of follow-up, 124 patients (28%) presented acute decompensation. The most

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frequent decompensation was ascites (21%) followed by hepatic encephalopathy (15%), variceal bleeding (9%), and spontaneous bacterial peritonitis (3%). Acute-on-chronic liver failure was diagnosed in 6% of patients during follow-up. Liver function parameters and specifically an albumin level below 40g/L were independently associated with an increased risk of decompensation. The presence of ischemic heart disease was independently associated with acute decompensation. Seventy-eight patients (18%) developed hepatocellular carcinoma or extrahepatic cancers during follow-up (51 and 27, respectively). *Conclusion:* Patients with compensated cirrhosis due to NAFLD are at high risk of severe liver complications, such as the development of acute decompensation, in a relative short follow-up time. This population is at high risk of hepatic and extrahepatic cancers.

## INTRODUCTION

Cirrhosis is the end stage of chronic liver diseases (CLDs) and is associated with high morbidity and mortality. Mortality due to cirrhosis has increased by 15% from 2007 to 2017<sup>[1]</sup> and is expected to increase even further in the future due to an increased prevalence of nonalcoholic fatty liver disease (NAFLD). NAFLD is the most common cause of CLD worldwide, and recent data suggest that NAFLD will be responsible for most liver-related complications, including hepatocellular carcinoma (HCC) and death, in the near future.<sup>[2]</sup> We know from studies with paired-liver biopsies that fibrosis stage is the most important predictor of mortality and progression to cirrhosis.<sup>[3–5]</sup> However, there is a paucity of information on the natural history of advanced NAFLD and the main risk factors for clinical decompensation when cirrhosis is already established, mostly because studies in the field have mainly focused on early stages of the disease.

Compensated cirrhosis is usually a long-standing and asymptomatic phase followed by a decompensated stage that usually leads to a dramatic increase in morbidity and mortality.<sup>[6]</sup> Few studies address the natural history of advanced NAFLD, and these have been hampered by low sample size, short follow-up, and inclusion of highly selected populations that are not representative of the actual population with NAFLD at advanced stages.<sup>[3,7–9]</sup> A recent and high-quality study regarding the natural history of NAFLD has confirmed that patients with fibrosis stages F3 and F4 are those with the highest risk of decompensation. However, in this prospective analysis, the population with cirrhosis was limited.<sup>[10]</sup> Most studies include patients at different stages of advanced fibrosis (F3 and F4), which have different prognosis as recently demonstrated.<sup>[3,4,8,9]</sup> Therefore, there is a lack of data regarding the natural history of NAFLD in a real-life setting and when cirrhosis is already established. The identification of

risk factors for disease progression and decompensation is needed. Also, there is a lack of information about the risk of cancer development in this population with advanced disease because most of the research in the field has been performed in low and intermediate stages of fibrosis. Moreover, NAFLD is considered the hepatic expression of the metabolic syndrome, a condition that can affect many organs. For that reason, patients with NAFLD and cirrhosis could be at increased risk of acute-on-chronic liver failure (ACLF), a syndrome characterized by systemic inflammation, organ failure, and high mortality.<sup>[11]</sup> There are data indicating that NAFLD is the fastest rising etiology of cirrhosis associated with ACLF among patients listed for liver transplantation.<sup>[12]</sup> No clinical study has so far addressed the incidence of ACLF or analyzed its predictive factors in this population.

The aims of the present study were (1) to describe the natural history of compensated cirrhosis due to NAFLD in a real-life setting; and (2) to determine the risk factors of acute decompensation (AD), ACLF, survival, development of HCC, and extrahepatic cancers during follow-up.

## MATERIALS AND METHODS

Investigators of an association of academic and specialized liver units designed a multicenter observational study involving a cohort of patients diagnosed with compensated cirrhosis secondary to NAFLD from nine centers in Spain (see [Supporting Materials](#)).

### Study population

The study population included all patients diagnosed with compensated cirrhosis due to NAFLD from January 2009 to December 2018. Patients were

identified retrospectively from electronic records at each center. We searched for a combination of “steatosis,” “steatohepatitis,” “nonalcoholic fatty liver disease,” and “cirrhosis.” Matching data were individually analyzed by investigators to account for the fulfillment of the inclusion and exclusion criteria (see below). Demographic and clinical characteristics; laboratory, ultrasound, or computed tomography scan; and endoscopic and histologic data were recorded. The inclusion date was the date of cirrhosis diagnosis by the reference hepatologist; this determined the start of follow-up time. The maximum time difference accepted between all baseline data and the inclusion date was 6 months. We included only patients that were followed up by a hepatologist of the same center after diagnosis. Investigators examined their electronic records in search of clinical events after the diagnosis of cirrhosis, ensuring that all patients had a minimum of 1 year of follow-up. Diagnosis, screening, and follow-up of cirrhosis was performed using international guidelines.<sup>[13]</sup> The primary outcome was the development of the first acute decompensation of cirrhosis during follow-up as defined by the recent expert recommendations detailed below.<sup>[14]</sup> Secondary outcomes were the occurrence of ACLF, death, and liver transplantation. Follow-up lasted until the patient died, received a transplant, was lost to follow-up, or at the end of the study follow-up in December 2018.

We excluded patients with alcohol consumption of more than 21 standard drinks per week in men and 14 in women or with other concomitant causes of liver disease. We excluded all patients who had HCC or any decompensation of liver disease at the time of diagnosis of cirrhosis or previously. Patients with prior liver transplantation were also excluded as were patients with advanced extrahepatic diseases (metastatic cancer and advanced heart or respiratory failure) that would impact short-term survival.

## Definitions

Diagnosis of NAFLD cirrhosis was made according to any of the following: (1) liver biopsy with  $\geq 5\%$  steatosis and/or steatohepatitis and a nonalcoholic steatohepatitis Clinical Research Network score of 4 (F4)<sup>[15]</sup> or cryptogenic cirrhosis in a patient with obesity, type 2 diabetes, or metabolic syndrome and no other detectable etiology of liver disease; (2) radiologic or endoscopic signs of cirrhosis and portal hypertension in a patient with obesity, type 2 diabetes, or metabolic syndrome and no other detectable etiology of liver disease; (3) presence of steatosis by imaging techniques and liver stiffness measurement (LSM)  $\geq 18$  kPa in a patient with obesity, type 2 diabetes, or metabolic syndrome in the absence of other etiologies of cirrhosis and heart failure.<sup>[16]</sup>

We defined the signs of ultrasonographic portal hypertension as the presence of splenomegaly ( $\geq 13$  cm), portal-systemic collaterals, inversion of flow within the portal system, dilatation of the portal vein (diameter  $\geq 13$  mm), or reduced portal vein flow velocity  $< 10$  cm/second.<sup>[17,18]</sup> Endoscopic signs of portal hypertension were the presence of gastroesophageal varices or portal hypertensive gastropathy.<sup>[18]</sup> Hepatic vein catheterization and hepatic venous pressure measurement (HVPG) were available in 86 patients (19%), and we used clinically significant portal hypertension (CSPH), defined by HVPG value  $\geq 10$  mm Hg,<sup>[19]</sup> as a diagnostic criteria for portal hypertension.

The primary outcome was acute decompensation (AD), defined as new onset ascites; grade 2 hepatic encephalopathy (HE), according to the West-Haven classification<sup>[13]</sup>; portal-hypertension-related bleeding (PHB), confirmed by endoscopy due to the presence of bleeding attributed to gastroesophageal varices or hypertensive gastropathy and requiring hospital admission; or spontaneous bacterial peritonitis (SBP), defined as the presence of  $\geq 250$  polymorphonuclear leucocytes/mm<sup>3</sup> in ascitic fluid.<sup>[14]</sup> Secondary outcomes were development of HCC, ACLF, liver-related death,<sup>[20]</sup> death from any cause, cardiovascular events, and extrahepatic cancer, excluding nonmelanoma skin cancer. HCC was screened periodically and diagnosed by noninvasive dynamic images or by invasive criteria, according to European Association for the Study of the Liver (EASL) guideline recommendations.<sup>[21]</sup> ACLF was defined according to the EASL-Chronic Liver Failure (CLIF) Acute-on-Chronic Liver Failure in Cirrhosis (CANONIC) study criteria described elsewhere.<sup>[11,13]</sup> Cardiovascular event was defined as acute coronary syndrome or acute stroke. See [Supporting Materials](#) for further definitions.

When multiple decompensating events occurred in the same patient, the earliest event was adopted for the analysis.

The study was approved by the institutional review board at all participating centers and was conducted in compliance with the Declaration of Helsinki (Internal code HCP:2019/635).

## Statistical analysis

Normally distributed variables were reported as means  $\pm$  SD and non-normally distributed variables as median and interquartile range (IQR). We compared continuous variables using the two-tailed Student *t*-test. Categorical variables were compared using the chi-square test. We calculated incidence rate as the number of new events during the study follow-up divided by the sum of the years at risk for each patient. When analyzing the cumulative probability of presenting AD, we found liver transplantation and non-liver-related deaths were

considered as competing events. We used Fine and Gray's proportional subhazards for multivariate modeling. All variables clinically and statistically different ( $p < 0.1$ ) were considered for multivariate modeling. The number of variables included in the initial models followed the rule of one variable per 10 outcomes. To avoid collinearity, we did not include scores and variables included in those scores in the same model. We then chose the best predictive models, using a backward stepwise regression method that included competitive risk analysis. Significance levels to enter and drop model variables were adopted as 5% and 10%, respectively. Area under the receiver operating characteristic curves (AUROCs) were calculated using Youden index to choose the best cut-off point for discrimination. All confidence intervals (CIs) and significance tests were two sided with a level of significance of 0.05. We used STATA/IC v.15.1 software to perform all statistical analyses.

## RESULTS

### Characteristics of the study population

We identified 548 patients with NAFLD cirrhosis between 2009 and 2018. Of those, 99 were excluded: 84 due to the presence of previous hepatic decompensation or because the diagnosis was made at the time of the first decompensation and 15 because of the presence of HCC. Of the 449 patients included, 165 (37%) patients were diagnosed based on histologic criteria, 263 (58%) patients were diagnosed because they had signs of cirrhosis and endoscopic or ultrasonographic signs of portal hypertension, and 22 (5%) patients were diagnosed based on an LSM above 18 kPa. Baseline characteristics of patients at the time of diagnosis of cirrhosis (inclusion date) are shown in Table 1. Cardiometabolic risk factors were highly prevalent. Almost 10% of the cohort had previous ischemic heart disease. As expected for a cohort of patients with compensated cirrhosis, liver function tests were preserved and most patients (87%) were classified as Child-Pugh A. Patients had a median Model for End-stage Liver Disease (MELD) score of 8 (IQR, 2). Two thirds of the cohort had either endoscopic or ultrasonographic signs of portal hypertension (63% and 68%, respectively).

### Frequency and risk factors of AD

Median follow-up time of the cohort was 39 months (IQR, 22–66). During follow-up, 124 patients (28%) developed a first AD. Of the 124 patients who developed AD, 68 (55%) developed more than one AD either simultaneously with the first event or during follow-up. Ascites was the most frequent AD (21% of the overall patients) followed by HE (15%), PHB (9%), and SBP (3%) (Table 2).

**TABLE 1** Baseline characteristics of the study population

| Variable   | n = 449 (%) |
|--|-------------|
| Age, years   | 65 (14)     |
| Sex, male  | 234 (52)    |
| Race (Caucasian/Black/Asian)                         | 430/10/9    |
| Ethnicity (White/Latino/African/Asian)               | 408/22/10/9 |
| Current alcohol consumption <sup>a</sup>             | 95 (21)     |
| Weekly standard drinks among consumers               | 7 (8)       |
| Current smoker                                       | 45 (10)     |
| BMI (kg/m <sup>2</sup> )                             | 31 (7)      |
| Obesity  | 286 (64)    |
| Overweight   | 134 (30)    |
| Arterial hypertension                                | 329 (73)    |
| Diabetes mellitus                                    | 338 (76)    |
| Dyslipidemia   | 250 (56)    |
| Previous stroke                                      | 11 (3)      |
| Ischemic heart disease                               | 39 (9)      |
| Bilirubin (mg/dl)                                    | 0.8 (0.6)   |
| Albumin (g/L)  | 41 (6)      |
| INR  | 1.1 (0.2)   |
| Platelets (10 <sup>9</sup> /L)                       | 126 (85)    |
| Glycated hemoglobin (%)                              | 6.5 (2)     |
| HDL-cholesterol (mg/dl)                              | 46 (19)     |
| Triglycerides  | 125 (85)    |
| ALT (U/L)  | 38 (31)     |
| Alkaline phosphatase (U/L)                           | 107 (71)    |
| Creatinine (mg/dl)                                   | 0.8 (0.3)   |
| Child-Pugh, A5/A6/B7/B8                              | 333/58/17/4 |
| MELD   | 8 (2)       |
| NAFLD fibrosis score                                 | 1.3 (1.8)   |
| FIB-4  | 3.5 (2.7)   |
| Liver stiffness <sup>b</sup>                         | 22 (17)     |
| CAP <sup>c</sup>                                     | 296 (98)    |
| Endoscopic signs of portal hypertension <sup>d</sup> | 192 (63)    |
| Gastroesophageal varices                             | 95 (31)     |
| Portal hypertensive gastropathy                      | 97 (31)     |
| Ultrasonographic signs of portal hypertension        | 293 (68)    |
| HVPG (mm Hg) <sup>e</sup>                            | 13 (7)      |
| Liver biopsy available                               | 175 (39)    |
| Steatosis grade 2–3 <sup>f</sup>                     | 60 (48)     |
| Ballooning grade 2                                   | 25 (20)     |
| Lobular inflammation grade 2                         | 24 (20)     |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; FIB-4, fibrosis-4; HDL, high-density lipoprotein; HVPG, hepatic venous pressure gradient; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; NAFLD, nonalcoholic fatty liver disease.

<sup>a</sup>Consumption inferior to 21 standard drinks per week in men and 14 in women. Higher consumption was an exclusion criterion as described in Materials and Methods.

<sup>b</sup>Available in 208 patients.

<sup>c</sup>Available in 127 patients.

<sup>d</sup>Screening for varices with gastroscopy within 1 year of admission in a total of 306 patients.

<sup>e</sup>Available in 86 patients.

<sup>f</sup>Individual data about steatosis, ballooning, and lobular inflammation grades were available in 126, 123, and 122 patients, respectively.



**TABLE 2** Acute decompensations of cirrhosis, deaths, and liver transplantation frequencies of the patients included

| Outcome                                  | <i>n</i> = 449 (%) |
|--|--------------------|
| Patients with any hepatic decompensation | 124 (28)           |
| Total acute decompensations <sup>a</sup> | 211                |
| Ascites                                  | 94                 |
| Hepatic encephalopathy                   | 61                 |
| Portal hypertension-related bleeding     | 41                 |
| Spontaneous bacterial peritonitis        | 15                 |
| Acute-on-chronic liver failure           | 26 (6)             |
| Grade 1/2/3                              | 13/7/6             |
| Deaths                                   | 68 (15)            |
| Cause of death                           |                    |
| Liver failure related                    | 26 (38)            |
| Hepatocellular carcinoma                 | 13 (19)            |
| Extrahepatic cancer                      | 9 (13)             |
| Cardiovascular related                   | 10 (15)            |
| Others <sup>b</sup>                      | 10 (15)            |
| Liver transplantation                    | 20 (5)             |

<sup>a</sup>Multiple decompensations occurred in some patients. Here, we report the total number of decompensating events (not patients) during follow-up.

<sup>b</sup>Other causes of death were acute infections not related to acute decompensation of cirrhosis, decompensation of chronic lung disease, and unknown.

The incidence rate of presenting a first AD event was 0.08 events per person-year of follow-up (95% CI, 0.07–0.10). Patients with Child A5 had an AD incidence rate of 0.06 events per person-year (95% CI, 0.05–0.08) compared to the rest of the cohort (Child A6 and Child B) with 0.16 events per person-year (95% CI, 0.12–0.21). The incidence rate ratio was 2.65 (95% CI, 1.81–3.84). Considering extrahepatic deaths and liver transplantation as competing events, the cumulative incidence of presenting an AD at 2 years of follow-up was 15% (95% CI, 12–18). The cumulative incidence of AD is shown in Figure 1, and the univariate description of the population categorized according to the development of AD is shown in Table 3. Sex differences in AD and HCC development are shown in Figure S1.

We found that fibrosis-4 (FIB-4) score and liver function as assessed by MELD score and albumin were independently associated with the development of AD. Interestingly, the presence of previous ischemic heart disease was also independently associated with AD development. On multivariable modeling (Table 4), the best predictive model of AD development included serum albumin, MELD score, FIB-4, and the presence of ischemic heart disease. Ischemic heart disease remained an independent predictor even after adjustment by the presence of diabetes mellitus (which was not associated with the development of AD). Albumin alone had the best discriminative capacity, with an AUROC of 0.70. The best cutoff to discriminate patients with AD was 40 g/L (95% CI, 38.2–41.4), with sensitivity and

specificity of 0.78 and 0.53, respectively. Comparison of cumulative incidences of developing AD categorized by the aforementioned predictors is shown in Figure 2.

We performed subgroup analysis of the prognostic impact of the presence of signs of portal hypertension by endoscopy (i.e., gastroesophageal varices and/or portal hypertensive gastropathy). We found a strong association between the presence of endoscopic signs of portal hypertension and the probability of decompensation after adjusting for MELD, serum albumin, and presence of ischemic heart disease (Figure S2; Table S2). Of the 449 included patients, 86 patients had an assessment of HVPG and 62 (72%) patients had CSPH. As expected, 27 (43%) patients among those with CSPH developed AD during follow-up compared to none of those without CSPH ( $p < 0.001$ ).

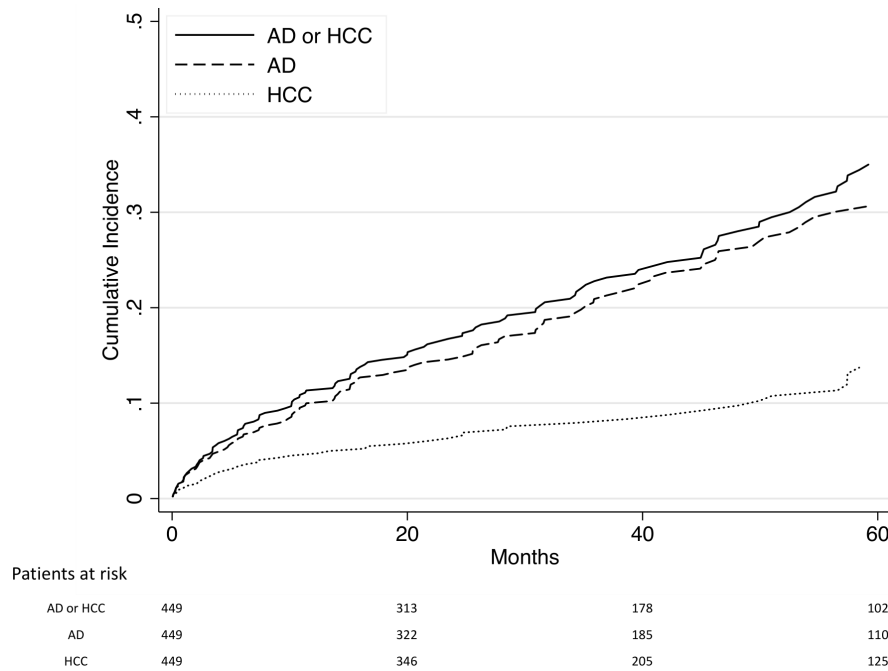
Two-hundred and eight patients had LSM available, and we found that higher values of liver stiffness were independently associated with the development of AD after adjusting for other covariates (Table S3). Interestingly, among the patients with controlled attenuation parameter (CAP) assessment ( $n = 127$ ), we found a negative association between CAP values and the probability of AD at follow-up after adjusting for other covariates. Consistently, the presence of histologic steatosis stage 2 or 3 at univariate analysis (Table 1) was associated with a lower probability of developing AD.

## Frequency and risk factors of HCC and other types of cancer

Fifty-one patients (12%) developed HCC during follow-up (Table S1; Figure S1). Most patients presented with early stages of HCC, mainly Barcelona Clinic Liver Cancer stages 0 and A. The only variable independently associated with an increased probability of HCC development was serum albumin after adjusting for MELD and age at diagnosis of cirrhosis. Besides HCC, 27 (6%) patients presented extrahepatic cancers during follow-up, colorectal cancer being the most frequent.

## Frequency and risk factors of ACLF development

During the study follow-up, 26 patients (6%) developed ACLF: 13 patients with grade 1, seven grade 2, and six grade 3. The incidence rate of ACLF development was low, namely 0.015 events per person-year (95% CI, 0.010–0.022). All patients but one presented AD before ACLF. The majority (70%) of patients who developed ACLF died. Variables independently associated with the development of ACLF were serum albumin and MELD score. Results of the multivariate modeling are shown in Table S4.



**FIGURE 1** Cumulative incidence of presenting HCC, AD alone, or a combination of HCC or AD. AD, acute decompensation; HCC, hepatocellular carcinoma.

## Survival analysis

During a median follow-up time of 39 months (IQR, 22–66), we observed 68 deaths (15%), 20 (5%) patients received liver transplants, and five were lost to follow-up. The detailed causes of mortality in our cohort are shown in Table 2. The majority of deaths were liver related (57%): 26 (38%) due to complications of cirrhosis and 13 (19%) due to HCC. The second most frequent cause of mortality was cardiovascular events ( $n = 10$ ; 15% of deaths) followed by extrahepatic cancer in nine patients (13%). Survival analysis is shown in Figure S3. Death incidence rate was 0.04 (95% CI, 0.03–0.05) events per person-year. Variables independently associated with mortality were age at diagnosis, serum albumin, and MELD score. Detailed results of the sub-hazards modeling are shown in Table S5.

## DISCUSSION

This study shows the natural history of NAFLD cirrhosis in a real-life setting with the largest cohort of patients with NAFLD with compensated cirrhosis analyzed to date. Our study has three main findings: (1) we found a significant frequency of AD and cancer development; (2) predictors of AD were mainly related to liver function; and (3) we described the frequencies of development and risk factors of ACLF in this population.

Data from nine centers provided insight into the incidence of AD of cirrhosis during a median follow-up time of 39 months (IQR, 44). Nearly one third of our

patients (28%) developed AD during the follow-up. Our data contrast with previous studies where the incidence of AD reported was lower. Sanyal et al.<sup>[9]</sup> reported a proportion of 19% of liver-related events (LREs) in patients with compensated cirrhosis during 30.9 months of follow-up (range, 0.1–45.5); Angulo et al.,<sup>[8]</sup> in the Prognostic Relevance of Liver Histology in NAFLD (PREHLIN) study, detected 24% of LREs in 12.6 years with a sample enriched with patients at low and intermediate stages of fibrosis; and Bhala et al.<sup>[7]</sup> detected 19% of LREs in patients with advanced fibrosis during a median follow-up of 86 months. All these studies were performed in highly selected populations excluding patients with advanced liver dysfunction. Indeed, Calzadilla-Bertot and colleagues,<sup>[22]</sup> in a recent predictive study including patients with compensated cirrhosis due to NAFLD, found 27% of events in 5.6 years (range, 2.4–14.1). Moreover, analyzing a derivation cohort to validate their model using less stringent exclusion criteria in liver function, they found 54% of events during a follow-up time similar to that of the current study.<sup>[22]</sup> In a recent prospective study of the full spectrum of NAFLD with a median follow-up time of 4 years, the authors found 37 hepatic decompensating events, 17 events among patients with F4 stage, and 17 among F3.<sup>[10]</sup> This latter study reported only three events among patients with lower fibrosis stages, underlining the importance of fibrosis stage as a predictive factor. However, the relatively low number of patients with cirrhosis ( $n = 167$ ) and the low number of total events hampered the development of a predictive analysis of hepatic decompensation in this important study.

**TABLE 3** Baseline characteristics of patients who developed acute decompensation of cirrhosis during follow-up compared to patients who did not

| Variables  | Acute decompensation | No decompensation | p-value <sup>a</sup> |
|--|----------------------|-------------------|----------------------|
|  | n = 124 (%)          | n = 325 (%)       |                      |
| Age, years   | 67 (14)              | 64 (13)           | 0.101                |
| Sex, female  | 55 (44)              | 160 (49)          | 0.291                |
| Current alcohol consumption <sup>b</sup>                   | 23 (19)              | 72 (22)           | 0.558                |
| Weekly standard drinks among consumers                     | 7 (5)                | 7 (9)             | 0.627                |
| Current smoker   | 10 (8)               | 35 (11)           | 0.643                |
| BMI (kg/m <sup>2</sup> )                                   | 31 (6)               | 32 (8)            | 0.494                |
| Obesity  | 78 (63)              | 208 (64)          | 0.963                |
| Arterial hypertension                                      | 91 (73)              | 238 (74)          | 0.434                |
| Diabetes mellitus  | 97 (78)              | 241 (75)          | 0.321                |
| Dyslipidemia   | 63 (50)              | 187 (58)          | 0.287                |
| Ischemic heart disease                                     | 17 (14)              | 22 (7)            | 0.008*               |
| Bilirubin (mg/dl)  | 0.9 (0.7)            | 0.7 (0.5)         | <0.001*              |
| Albumin (g/L)  | 38 (7)               | 42 (6)            | <0.001*              |
| INR  | 1.2 (0.2)            | 1.1 (0.2)         | 0.005*               |
| Platelets (10 <sup>9</sup> /L)                             | 107 (56)             | 135 (84)          | 0.022*               |
| Glycated hemoglobin (%)                                    | 6.4 (1.6)            | 6.5 (2)           | 0.517                |
| HDL-cholesterol (mg/dl)                                    | 44 (19)              | 46 (18)           | 0.539                |
| Triglycerides (mg/dl)                                      | 115 (64)             | 129 (93)          | 0.135                |
| AST (U/L)  | 47 (27)              | 40 (25)           | <0.001*              |
| ALT (U/L)  | 36 (30)              | 38 (32)           | 0.043*               |
| Creatinine (mg/dl)   | 0.8 (0.4)            | 0.8 (0.3)         | 0.915                |
| Child-Pugh Class, A5/A6/B7/B8                              | 74/25/10/4           | 259/33/7/0        | <0.001*              |
| MELD   | 9 (4)                | 8 (2)             | <0.001*              |
| NAFLD fibrosis score                                       | 1.8 (1.5)            | 1.1 (1.8)         | <0.001*              |
| FIB-4  | 4.7 (3.3)            | 3.0 (2.5)         | <0.001*              |
| Liver stiffness <sup>c</sup>                               | 24 (31)              | 21 (12)           | 0.003*               |
| CAP <sup>d</sup>   | 255 (128)            | 309 (88)          | <0.001*              |
| Endoscopic signs of portal hypertension <sup>e</sup>       | 73 (81)              | 119 (55)          | <0.001*              |
| Gastroesophageal varices                                   | 38 (42)              | 59 (27)           |                      |
| Portal hypertensive gastropathy                            | 35 (39)              | 60 (28)           |                      |
| Ultrasonographic signs of portal hypertension <sup>f</sup> | 78 (77)              | 170 (67)          | 0.163                |
| HVPG (mm Hg) <sup>g</sup>                                  | 15 (8)               | 11 (8)            | <0.001*              |
| Histologic diagnosis                                       | 53 (35)              | 134 (41)          | 0.153                |
| Steatosis grade ≥2   | 12 (34)              | 51 (53)           | 0.014 <sup>*,h</sup> |
| Ballooning grade 2   | 5 (14)               | 21 (22)           | 0.207                |
| Lobular inflammation grade 2                               | (17)                 | 21 (22)           | 0.317                |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; FIB-4, fibrosis-4; HDL, high-density lipoprotein; HVPG, hepatic venous pressure gradient; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; NAFLD, nonalcoholic fatty liver disease.

<sup>a</sup>p-values calculated in univariate Fine and Gray's regression analysis.

<sup>b</sup>Consumption inferior to 21 standard drinks in men and 14 in women.

<sup>c</sup>Available in 208 patients.

<sup>d</sup>Available in 127 patients.

<sup>e</sup>Available in a total of 306 patients.

<sup>f</sup>Available in 353 patients.

<sup>g</sup>Available in 86 patients.

<sup>h</sup>Grades 2–3 compared to combined steatosis grade 1 and no steatosis.

\*Significant at p < 0.05 in univariate analysis.

**TABLE 4** Univariate and multivariate competing risk analysis for acute decompensation development

| Univariate analysis                      |                   |         | Multivariate analysis          |                  |         |
|--|-------------------|---------|--------------------------------|------------------|---------|
| Variable                                 | sHR (95% CI)      | p-value | Variables                      | sHR (95% CI)     | p-value |
| Age, years                               | 1.02 (1.00–1.04)  | 0.101   | Model 1                        |                  |         |
| Current alcohol consumption <sup>a</sup> | 0.88 (0.56–1.36)  | 0.558   | Ischemic heart disease         | 2.45 (1.35–4.45) | 0.001*  |
| Weekly standard drinks among consumers   | 0.99 (0.93–1.05)  | 0.627   | Bilirubin (mg/dL)              | 1.15 (0.94–1.41) | 0.183   |
| BMI (kg/m <sup>2</sup> )                 | 0.99 (0.96–1.02)  | 0.494   | Albumin                        | 0.90 (0.87–0.93) | <0.001* |
| Obesity                                  | 1.01 (0.75–1.35)  | 0.963   | INR                            | 1.51 (0.95–2.41) | 0.078   |
| Arterial hypertension                    | 1.18 (0.78–1.78)  | 0.434   | Platelets (10 <sup>9</sup> /L) | 0.99 (0.99–1.00) | 0.278   |
| Diabetes mellitus                        | 1.25 (0.81–1.92)  | 0.321   | AST                            | 1.02 (1.01–1.03) | 0.003*  |
| Dyslipidemia                             | 0.83 (0.58–1.17)  | 0.287   | ALT                            | 0.99 (0.98–1.01) | 0.092   |
| Ischemic heart disease                   | 2.12 (1.23–3.65)  | 0.007*  | Model 2                        |                  |         |
| Bilirubin (mg/dL)                        | 1.48 (1.22–1.81)  | <0.001* | Ischemic heart disease         | 2.08 (1.15–3.77) | 0.015*  |
| Albumin (g/L)                            | 0.89 (0.87–0.92)  | <0.001* | Albumin                        | 0.90 (0.87–0.93) | <0.001* |
| INR                                      | 1.65 (1.16–2.35)  | 0.005*  | MELD                           | 1.07 (1.01–1.13) | 0.017*  |
| Platelets (10 <sup>9</sup> /L)           | 0.996 (0.99–1.00) | 0.022*  | FIB-4 score                    | 1.05 (1.01–1.08) | 0.010*  |
| Glycated hemoglobin (%)                  | 0.940 (0.78–1.13) | 0.517   | Model 3                        |                  |         |
| HDL-cholesterol (mg/dL)                  | 0.995 (0.98–1.01) | 0.539   | Ischemic heart disease         | 2.17 (1.23–3.82) | 0.007*  |
| Triglycerides (mg/dL)                    | 0.997 (0.99–1.01) | 0.135   | NAFLD fibrosis score           | 1.31 (1.13–1.51) | <0.001* |
| ALT (U/L)                                | 1.01 (1.00–1.01)  | <0.001* | Child-Pugh score               | 2.02 (1.56–2.63) | <0.001* |
| AST (U/L)                                | 1.003 (1.00–1.01) | 0.043*  |                                |                  |         |
| Creatinine (mg/dL)                       | 1.03 (0.59–1.82)  | 0.915   |                                |                  |         |
| Child-Pugh score                         | 2.16 (1.79–2.67)  | <0.001* |                                |                  |         |
| MELD                                     | 1.10 (1.05–1.15)  | <0.001* |                                |                  |         |
| NAFLD fibrosis score                     | 1.44 (1.26–1.65)  | <0.001* |                                |                  |         |
| FIB-4                                    | 1.08 (1.05–1.11)  | <0.001* |                                |                  |         |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; CI, confidence interval; FIB-4, fibrosis-4; HDL, high-density lipoprotein; HVPG, hepatic venous pressure gradient; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; NAFLD, nonalcoholic fatty liver disease; sHR, subhazard ratio.

<sup>a</sup>Consumption inferior to 21 standard drinks in men and 14 in women.

\*Significant at  $p < 0.05$  in univariate analysis.

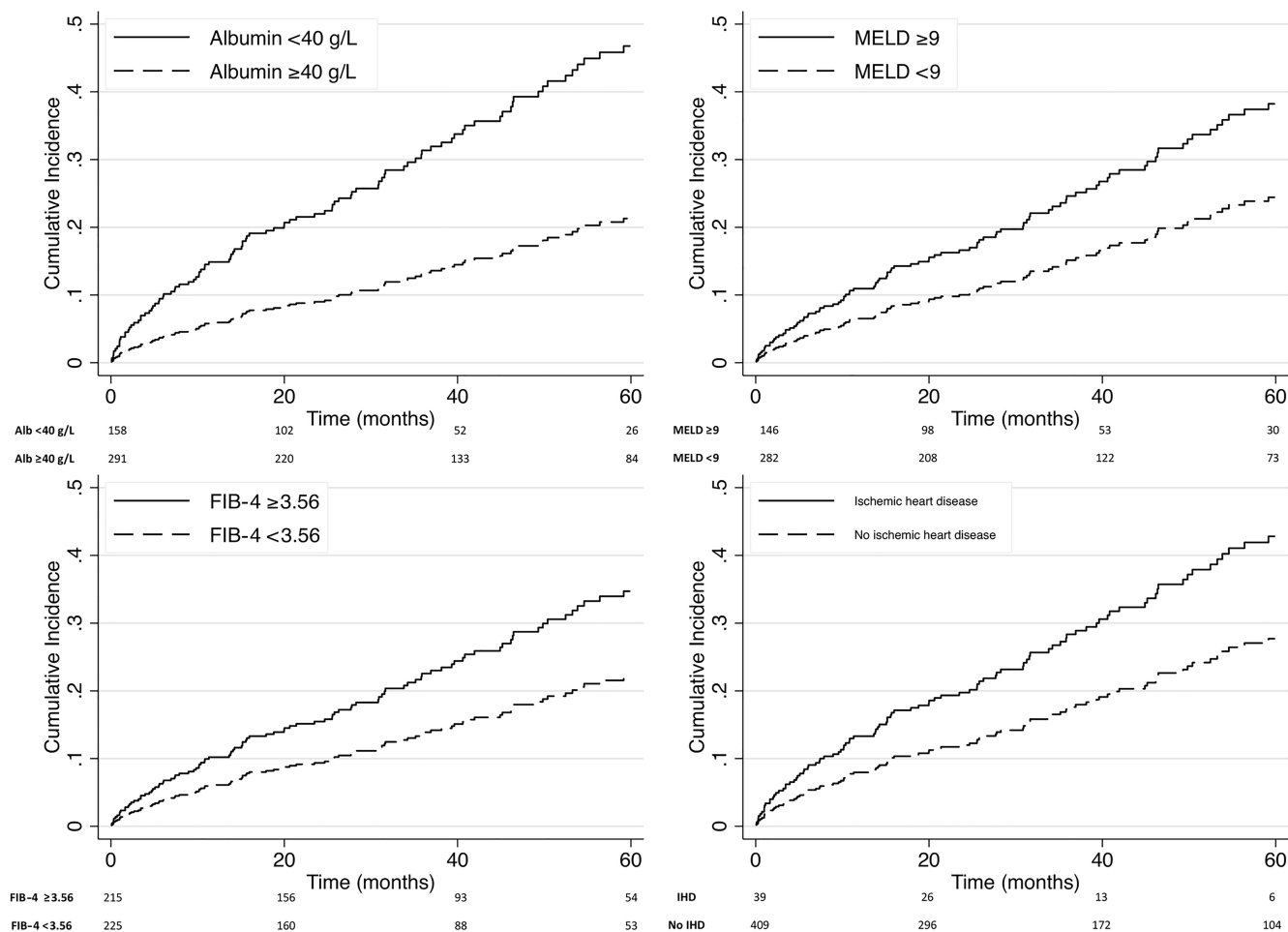
In our cohort, liver function as assessed mainly by albumin levels and MELD score was the best predictor of AD, as has been reported for other etiologies of cirrhosis.<sup>[6]</sup> In our real-life cohort, each drop of 1 g/L in serum albumin increased the risk of decompensation by 10%. Interestingly, we found that the presence of ischemic heart disease almost doubled the risk of presenting AD. However, individual parameters of cardiometabolic risk, such as the presence of diabetes mellitus, dyslipidemia, or arterial hypertension, were not found to be predictors of decompensation. This could be related to the high prevalence of these features in our cohort. A history of previous cardiovascular events may reflect more established cardiovascular damage in those patients that could therefore impact hepatic outcomes. More studies taking into account the dynamic changes in diabetes control and other metabolic parameters in patients with NAFLD

are needed to identify factors associated with worse hepatic outcomes.

Information about the development of ACLF in this population, which occurred in 6% of the cohort, is also described for the first time. Studies addressing the incidence of ACLF are mainly focused on patients with alcohol-related cirrhosis. We hypothesized that the burden of cardiometabolic disease of patients with NAFLD with cirrhosis could increase the risk of organ failure and thus ACLF development. However, we could not find any metabolic factors associated with the development of ACLF that were predicted only by liver function tests. More studies are needed to address the incidence of ACLF among patients with decompensated cirrhosis due to NAFLD.

Interestingly, we also found a high incidence of neoplastic events in this cohort of patients. Taken together, HCC or extrahepatic cancers were detected in 18% of





**FIGURE 2** Cumulative incidence of presenting AD according to the presence of low serum albumin, low MELD score, low FIB-4, and the presence of ischemic heart disease. AD, acute decompensation; Alb, albumin; FIB-4, fibrosis-4; MELD, Model for End-Stage Liver Disease.

the cohort, revealing a dramatic susceptibility to severe health issues in a relatively short follow-up time in this population.

The impact of alcohol use on the natural history of cirrhosis is a very interesting research topic in the NAFLD field. In our analysis, moderate alcohol consumption below the limits of the alcohol risk consumption definition to define patients with ALD<sup>[15,23]</sup> was not associated with a worse outcome. More studies are needed to address this important issue and establish the importance of any amount of alcohol consumption for decompensation risk in patients with NAFLD.

We are aware that our study has some limitations mainly related to its retrospective design and the relative short follow-up period. Our cohort is overrepresented by patients with compensated advanced cirrhosis as two thirds of our patients presented signs of portal hypertension. Whether our results can be extrapolated to patients with earlier stages of compensated cirrhosis is not known. On the other hand, 22 patients in our study were diagnosed based only on LSM criteria. Given the

limitations of this technique, we performed a sensitivity analysis excluding those patients from the analysis, but we observed no differences in the results. Moreover, data on LSM and HVP measurement were not available for the majority of patients, and potential confounding factors associated with the outcome, such as treatment with nonselective beta blockers, glucagon-like peptide-1 agonists, vitamin E, or statins, were not recorded. The probability of missing an AD event in our retrospective cohort is low because of the low rate of patients lost to follow-up.

In conclusion, patients with compensated cirrhosis due to NAFLD present a high risk of hepatic AD and cancer development, indicating that this population is at high risk of severe health issues in a relatively short follow-up period. A simple serum parameter, such as an albumin level below 40g/L, confers a higher risk of presenting AD compared to patients with values above this cut-off point. The presence of previous ischemic heart disease as well as FIB-4 and MELD scores also predict the development of hepatic decompensation. The incidence of ACLF in this population is no different

compared to published data from other etiologies and is predicted by MELD score and albumin levels.

## AUTHOR CONTRIBUTIONS

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**Data acquisition:** Octavi Bassegoda, Jesús Rivera-Esteban, Isabel Serra, Rosa Morillas, Teresa Broquetas, Mercedes Vergara, Adrià Rodriguez, Carles Aracil, Silvia Virolés, Jose A Carrión, Albert Pardo, Sergio Rodríguez-Tajes, Miquel Serra-Burriel, Juan M Pericàs, Pere Ginès, Salvador Augustin, Isabel Graupera. **Statistical analysis:** Octavi Bassegoda, Isabel Graupera. **Funding acquisition:** Isabel Graupera, Salvador Augustin, Pere Ginès. **Methodology:** Octavi Bassegoda, Jesús Rivera-Esteban, Albert Pardo, Salvador Augustin, Isabel Graupera. **Analysis and interpretation of data:** Octavi Bassegoda, Jesús Rivera-Esteban, Albert Pardo, Salvador Augustin, Isabel Graupera, Pere Ginès. **Writing original draft:** Octavi Bassegoda, Albert Pardo, Salvador Augustin, Isabel Graupera. **Review and editing:** Octavi Bassegoda, Jesús Rivera-Esteban, Isabel Serra, Rosa Morillas, Teresa Broquetas, Mercedes Vergara, Adrià Rodriguez, Carles Aracil, Silvia Virolés, Jose A Carrión, Albert Pardo, Sergio Rodríguez-Tajes, Miquel Serra-Burriel, Juan M Pericàs, Pere Ginès, Salvador Augustin, Isabel Graupera. **Study supervision:** Pere Ginès, Isabel Graupera. All authors reviewed and approved the final manuscript.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest with respect to this investigation.

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## REFERENCES

- GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392:1736–88. Erratum in: *Lancet*. 2018;392:2170.
- Younossi ZM, Stepanova M, Ong J, Trimble G, AlQahtani S, Younossi I, et al. Nonalcoholic steatohepatitis is the most rapidly increasing indication for liver transplantation in the United States. *Clin Gastroenterol Hepatol*. 2021;19:580–9.e5.
- Vilar-Gomez E, Calzadilla-Bertot L, Wai-Sun Wong V, Castellanos M, Aller-de la Fuente R, Metwally M, et al. Fibrosis severity as a determinant of cause-specific mortality in patients with advanced nonalcoholic fatty liver disease: a multi-national cohort study. *Gastroenterology*. 2018;155:443–57.e17.
- EKstedt M, Hagström H, Nasr P, Fredrikson M, Stål P, Kechagias S, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. *Hepatology*. 2015;61:1547–54.
- Taylor RS, Taylor RJ, Bayliss S, Hagström H, Nasr P, Schattenberg JM, et al. Association between fibrosis stage and outcomes of patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Gastroenterology*. 2020;158:1611–25.e12.
- D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol*. 2006;44:217–31.
- Bhala N, Angulo P, van der Poorten D, Lee E, Hui JM, Saracco G, et al. The natural history of nonalcoholic fatty liver disease with advanced fibrosis or cirrhosis: an international collaborative study. *Hepatology*. 2011;54:1208–16.
- Angulo P, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. *Gastroenterology*. 2015;149:389–97.e10.
- Sanyal AJ, Harrison SA, Ratziu V, Abdelmalek MF, Diehl AM, Caldwell S, et al. The natural history of advanced fibrosis due to nonalcoholic steatohepatitis: data from the simtuzumab trials. *Hepatology*. 2019;70:1913–27.
- Sanyal AJ, Van Natta ML, Clark J, Neuschwander-Tetri BA, Diehl A, Dasarathy S, et al. Prospective study of outcomes in adults with nonalcoholic fatty liver disease. *N Engl J Med*. 2021;385:1559–69.
- Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology*. 2013;144:1426–37.e1–9.
- Sundaram V, Jalan R, Shah P, Singal AK, Patel AA, Wu T, et al. Acute on chronic liver failure from nonalcoholic fatty liver disease: a growing and aging cohort with rising mortality. *Hepatology*. 2021;73:1932–44.
- European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. *J Hepatol*. 2018;69:406–60. Erratum in: *J Hepatol*. 2018;69:1207.
- Solà E, Pose E, Campion D, Piano S, Roux O, Simon-Talero M, et al. Endpoints and design of clinical trials in patients with decompensated cirrhosis: position paper of the LiverHope Consortium. *J Hepatol*. 2021;74:200–19.
- Chalasanani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. *Hepatology*. 2018;67:328–57.
- Eddowes PJ, Sasso M, Allison M, Tsochatzis E, Anstee QM, Sheridan D, et al. Accuracy of FibroScan controlled attenuation parameter and liver stiffness measurement in assessing steatosis and fibrosis in patients with nonalcoholic fatty liver disease. *Gastroenterology*. 2019;156:1717–30.
- Berzigotti A, Seijo S, Reverter E, Bosch J. Assessing portal hypertension in liver diseases. *Expert Rev Gastroenterol Hepatol*. 2013;7:141–55.

18. De Franchis R, Baveno VI Faculty. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. *J Hepatol.* 2015;63:743–52.
19. Bosch J, Abraldes JG, Berzigotti A, García-Pagan JC. The clinical use of HVPG measurements in chronic liver disease. *Nat Rev Gastroenterol Hepatol.* 2009;6:573–82.
20. Asrani SK, Larson JJ, Yawn B, Therneau TM, Kim WR. Underestimation of liver-related mortality in the United States. *Gastroenterology.* 2013;145:375–82.e1–2.
21. European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol.* 2018;69:182–236. Erratum in: *J Hepatol.* 2019;70:817.
22. Calzadilla-Bertot L, Vilar-Gomez E, Wong VW, Romero-Gomez M, Aller-de la Fuente R, et al. ABIDE: an accurate predictive model of liver decompensation in patients with non-alcoholic fatty liver-related cirrhosis. *Hepatology.* 2021;73:2238–50.
23. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL–EASD–EASO Clinical Practice Guidelines for the

management of non-alcoholic fatty liver disease. *J Hepatol.* 2016;64:1388–402.

## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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