**Research Article**
MASLD and Alcohol-Related Liver Diseases

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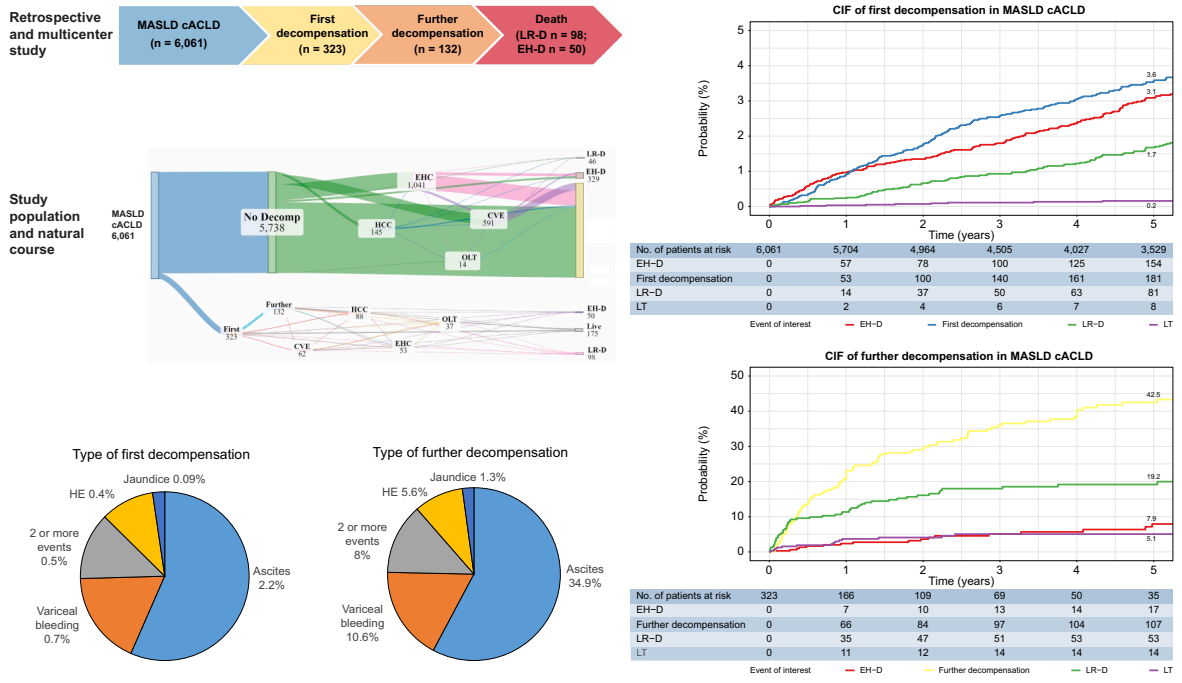
## Authors

**Grazia Pennisi, Gabriele Di Maria,** Vincent Wai-Sun Wong, …, Vito Di Marco, Calogero Cammà, Salvatore Petta

## Correspondence

grazia.pennisi@unipa.it (G. Pennisi).

## Graphical abstract




## Highlights

- First and further decompensation in MASLD-cACLD increased liver-related mortality by 18.9- and 1.52-fold, respectively.
- Ascites was the most common form of decompensation and had the greatest impact on liver-related mortality in MASLD-cACLD.
- Both acute and non-acute decompensation similarly raise liver-related death risk in MASLD-related cACLD.
- Extrahepatic death accounted for a high mortality burden at 5 years due to the high metabolic risk of patients with MASLD.
- HCC further raises liver-related mortality risk post-decompensation in MASLD-cACLD by up to 2.95-fold.

## Impact and implications

In this large international multicenter cohort of 6,061 patients with compensated advanced chronic liver disease (cACLD) due to metabolic dysfunction-associated steatotic liver disease (MASLD), we examined the clinical impact of first and further decompensation events. At 5 years, the cumulative incidences of first and further decompensation were 3.5% and 43.9%, respectively, each significantly increasing the cause-specific hazard of liver-related death (18.9-fold and 1.52-fold). Ascites, more so than variceal bleeding, was the predominant and most impactful event. Both acute and non-acute decompensation similarly contributed to liver-related mortality. Additionally, hepatocellular carcinoma independently increased the hazard of liver-related death, even post-decompensation. Notably, extrahepatic deaths also represented a considerable burden, reflecting the high metabolic risk of MASLD. These findings highlight key prognostic inflection points in MASLD-related cACLD.

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# Impact of first and further decompensation in patients with compensated ACLD due to MASLD

**Grazia Pennisi**[1,*,†], **Gabriele Di Maria**[2,†], Vincent Wai-Sun Wong[3], Victor de Ledinghen[4], Giada Sebastiani[5], Mauro Viganò[6], Anna Ludovica Fracanzani[7,8], Luca Miele[9], Elisabetta Bugianesi[10], Mattias Ekstedt[11], Roberta D'Ambrosio[12], Federico Ravaioli[13,14], Filippo Schepis[15], Fabio Marra[16], Alessio Aghemo[17,18], Gianluca Svegliati-Baroni[19], Marcello Persico[20], Luca Valenti[7,21], Annalisa Berzigotti[22], Jacob George[23], Angelo Armandi[10], Patrik Nasr[11], Stergios Kechagias[11], Antonio Liguori[9], Dario Saltini[15], Yuly P. Mendoza[22], Vincenza Calvaruso[1], Marco Enea[2], Huapeng Lin[3], Giuseppe Infantino[1], Mario Masarone[19], Nicola Pugliese[17,18], Adele Tulone[1], Vito Di Marco[1], Calogero Cammà[1], Salvatore Petta[1]

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**Background & Aims:** First and further decompensation events mark key transitions in the natural history of cirrhosis and significantly influence mortality risk. We assessed the cumulative incidence of first and further (acute and non-acute) decompensation and evaluated their impact on liver-related death (LR-D) in patients with compensated advanced chronic liver disease (cACLD) due to metabolic dysfunction-associated steatotic liver disease (MASLD).

**Methods:** We conducted an international, multicenter (17 centers), retrospective study involving 6,061 consecutive patients with cACLD due to MASLD, diagnosed either clinically (liver stiffness measurement >10 kPa) or histologically (F3–F4 fibrosis). Decompensation events were defined according to the Baveno VII criteria. Cumulative incidence functions and cause-specific Cox models (with baseline and time-dependent variables) were used to analyze competing risks. A multistate model was developed to better describe the clinical trajectory of cACLD due to MASLD.

**Results:** The 5-year cumulative incidence of first decompensation was 3.5% (95% CI 3.0–4.1), which was associated with an 18.9-fold increase (95% CI 10.8–32.9) in the cause-specific hazard of LR-D. Among patients who experienced a first decompensation, the 5-year cumulative incidence of further decompensation was 43.9% (95% CI 37.2–50.2), further increasing the hazard of LR-D by 1.52-fold (95% CI 1.02–2.34). Ascites, followed by variceal bleeding, were the most common decompensation events. Hepatocellular carcinoma independently increased the cause-specific hazard of LR-D by 2.95-fold (95% CI 2.02–4.31) in the overall cohort and by 1.43-fold (95% CI 1.03–2.00) in patients who had experienced a first decompensation.

**Conclusions:** First and subsequent decompensation events are major inflection points in the clinical progression of cACLD due to MASLD, increasing the cause-specific hazard of LR-D by 18.9- and an additional 1.52-fold, respectively. Hepatocellular carcinoma is an independent predictor of LR-D and further exacerbates mortality risk when present alongside decompensation.



## Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as one of the most significant global health challenges, with a worldwide prevalence of 38% according to recent estimates,[1] and a concerning upward trend driven by the growing epidemics of diabetes and obesity.[2]

The widespread impact of MASLD is compounded by its potential to progress from simple steatosis to steatohepatitis (MASH), and ultimately to cirrhosis, which may be further complicated by hepatic decompensation and hepatocellular carcinoma (HCC), often culminating in liver-related death (LR-D) or the need for liver transplantation (LT).[2]

It is well established that the first decompensation – defined as ascites, hepatic encephalopathy (HE), variceal bleeding, and jaundice – is a pivotal event in terms of prognosis and marks the transition from the compensated, also known as compensated advanced chronic liver disease (cACLD), to the decompensated stage of cirrhosis.[3] Although only a small fraction of patients die following the first decompensation episode, the risk of developing further decompensation increases and the median survival dramatically decreases.[4] The

* Corresponding author. Address: Grazia Pennisi, Section of Gastroenterology and Hepatology, PROMISE, Policlinico Universitario Paolo Giaccone, Piazza delle Cliniche, 2, 90127 Palermo, Italy. Tel.: +39 091 23890673. Fax +39 091 6552156.
*E-mail address:* grazia.pennisi@unipa.it (G. Pennisi).
† These authors equally contributed to the study.
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occurrence of a further decompensation event – defined according to the Baveno VII consensus[5] as either the recurrence of the initial event or the development of a second decompensation event – represents a crucial turning point in the natural history of the liver disease, markedly increasing the risk of LR-D in these patients.

Recently, some experts have reasonably suggested defining the decompensation pathway occurring in patients with cirrhosis as either "acute" (AD) or "non-acute" decompensation (NAD).[6] Although they can potentially influence the clinical outcomes of cirrhosis differently, AD and NAD currently remain theoretical constructs among patients with decompensated cirrhosis.

Although the natural course of liver disease has been extensively studied across various settings and etiologies, the impact of initial and subsequent decompensation –whether acute or non-acute – has not been specifically assessed in patients with MASLD. This scenario is particularly complex due to the dual risks involved: LR-D and a well-documented risk of extrahepatic death (EH-D) from cardiovascular events and extrahepatic cancers.[7]

The aim of our study was to assess the cumulative incidence of first and further decompensation events, acute and non-acute, and to evaluate their impact on both LR-D and EH-D in a large cohort of patients with cACLD secondary to MASLD.

## Patients and methods

### Study design and patient selection

This retrospective study used prospectively collected data from patients with cACLD secondary to MASLD, enrolled between 1988 and 2023 across 17 tertiary centers in Italy, France, Sweden, Canada, and China. All patients provided informed consent, and the study received approval from the respective local ethics committees. These cohorts have previously been described in studies on the natural history of MASLD.[8,9]

Consecutive patients with either a clinical or biopsy-proven diagnosis of cACLD due to MASLD were included. cACLD was defined by a liver stiffness measurement (LSM) >10 kPa using FibroScan or by histological evidence of F3–F4 fibrosis using the Kleiner score, in accordance with Baveno VII criteria.[5] In patients without histologic examinations, the diagnosis of MASLD required ultrasonographic detection of steatosis plus at least one criterion of the metabolic syndrome. Only patients with a follow-up of ≥6 months were included.

Exclusion criteria included age <18 years, previous history of decompensated cirrhosis and/or HCC, other liver disease etiologies (chronic hepatitis B/C, HIV infection, autoimmune hepatitis, hereditary hemochromatosis, alpha-1 antitrypsin deficiency), excessive alcohol intake (>30 g/day for men, >20 g/day for women), and extrahepatic malignancy.

Follow-up assessments included laboratory testing every 6–12 months, abdominal ultrasound or HCC screening every 6 months, and upper endoscopy according to current recommendations.[5,10]

### Decompensation definition

First decompensation was defined as the simultaneous development of ≥1 of the following events: portal hypertension-driven events (ascites, overt HE, variceal bleeding)[5] and/or jaundice.[6] Ascites was diagnosed by compatible clinical signs and confirmed with ultrasound and/or diagnostic paracentesis; overt HE was classified according to West-Haven classification;[11] variceal bleeding was identified by upper endoscopy; jaundice was defined as bilirubin >3 mg/dl.[12]

Further decompensation was defined as the recurrence or *de novo* development of a second portal hypertension-driven decompensating event (ascites, HE or variceal bleeding) and/or jaundice.[5]

AD was defined as the development of ≥1 major complication(s): first or recurrent grade 2 or 3 ascites within less than 2 weeks, first or recurrent acute HE in patients with previously normal consciousness, and acute variceal bleeding.[6]

NAD was defined as slow ascites formation, mild grade 1 or 2 HE, or progressive jaundice in non-cholestatic cirrhosis.[6]

Patients who developed events during follow-up were evaluated for available therapies and/or for LT, as appropriate.[13–15]

### Patient evaluation

Clinical and metabolic data were collected at enrollment. The diagnosis of type 2 diabetes (T2D) was made according to the American Diabetes Association criteria,[16] using a value of fasting blood glucose ≥126 mg/dl. In patients with a previous diagnosis of T2D, current medications and their changes were documented and used to confirm the diagnosis of T2D. Arterial hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, or use of blood pressure-lowering agents.[17] A 12-hour overnight fasting blood sample was drawn to determine serum levels of alanine aminotransferase, albumin, and bilirubin, as well as platelet count, and international normalized ratio.

### Extrahepatic events and mortality assessment

Extrahepatic events and mortality were recorded during the entire follow-up in both groups. Extrahepatic events were defined as cardiovascular events – stroke, transient ischemic attack, myocardial infarction, unstable angina – or extrahepatic cancers not including non-melanomatous skin cancers. Evidence of extrahepatic events was provided by clinical charts from emergency areas and/or hospitalization. Death was also recorded during the follow-up and classified according to associated events (liver-related, defined as LR-D, or extrahepatic-related, defined as EH-D).

### Statistical analysis

Continuous variables were summarized using the median (IQR), while categorical variables were presented as frequencies and percentages. Sankey plots were utilized to illustrate the flow of major outcomes throughout patients' clinical histories, categorized by the presence and type of decompensation.

A competing risk analysis was performed to estimate the occurrence of the first decompensation, considered the event of interest, with LR-D, EH-D and LT treated as competing events. A second competing risk analysis was conducted on the subset of patients experiencing a first decompensation, with subsequent decompensation as the primary event and

LR-D, EH-D and LT as competing events. Cumulative incidence function (CIF) estimates were calculated and group comparisons were carried out using Gray's test.[18]

Additional CIFs were generated by stratifying the main and competing events based on several factors:

1. Splitting both first and subsequent decompensations into AD and NAD.
2. Further categorizing first and subsequent decompensations into ascites, HE, jaundice, and variceal bleeding.
3. Differentiating deaths into liver-related and extrahepatic causes within the context of both first and subsequent decompensations.
4. Subdividing liver-related deaths due to cACLD secondary to MASLD within the framework of both first and subsequent decompensations.

The analysis of time to first decompensation began at the date of the initial diagnosis of cACLD, while the analysis of time to subsequent decompensation started from the date of the first decompensation. To ensure uniform follow-up periods across centers, 5-year CIFs were presented, with probabilities expressed as percentages throughout the text and figures.

To assess the impact of first and subsequent decompensations on LR-D – with EH-D and LT treated as competing events – and accounting for known prognostic factors and potential confounders, a multivariable analysis was performed using a cause-specific proportional hazards model with time-dependent covariates. The occurrence of the first decompensation was included as a time-dependent covariate in the linear predictor of the cACLD model, while the occurrence of subsequent decompensation was included in the model for patients who had already experienced a first decompensation. Results were expressed as hazard ratios (HRs) with 95% CIs. Additionally, the occurrence of HCC was incorporated as a time-dependent covariate in both models.

Beyond the time-dependent covariates, the cACLD model included sex, age, platelet count, albumin levels, and diabetes. In contrast, the model for first decompensation included only sex, age, and diabetes, due to the unavailability of platelet and albumin data at the time of the first decompensation.

A seven-state model was constructed, comprising cACLD as the initial state, first decompensation and subsequent decompensation as transient states, and LT, HCC-related death, LR-D, and EH-D as absorbing states. The probabilities of occupying each disease state within the multistate model were estimated using the *mstate* package in R.

All analyses were performed using R statistical software (version 4.3.3). In addition to the base R packages, the following libraries were used: *tidyverse, survival, readxl, gridExtra, grid, cr17, gtable, mstate*, and *cmprsk*.

## Results

### Patients characteristics

Patient characteristics are listed in Table 1. Only 3.8% of patients developed HCC, while cardiovascular events and extrahepatic cancers were observed in 10.8% and 18.1% of

**Table 1. Features of 6,061 patients with cACLD due to MASLD and rates of event occurrence.**

| Baseline characteristics of 6,061 patient with cACLD due to MASLD | |
|---|---|
| **Variable** | **Value [missing data]** |
| Age (*) | 58 (49.8-65.5) [0] |
| Male sex | 3,268 (53.9%) [0] |
| Diabetes | 2,518 (41.5%) [2] |
| Arterial hypertension | 2,201 (36.3%) [6] |
| Platelets – $mm^3$ (*) | 220 (172-266) [197] |
| INR (*) | 1 (0.9-1.1) [165] |
| Albumin - g/dl (*) | 4.3 (4-4.5) [120] |
| Bilirubin - mg/dl (*) | 0.6 (0.4-0.8) [117] |
| ALT - IU/L (*) | 37 (24-63) [105] |
| Histological diagnosis | 528 (8.7%) |
| **Rates of event occurrence during follow-up** | |
| First decompensation (n = 323) | |
| Data available on discrimination between single or multiple decompensation | 313 (96.9%) |
| Single | 226 (70.0%) |
| Multiple | 87 (26.9%) |
| Data available on discrimination between acute or non-acute decompensation | 274 (84.8%) |
| Acute | 169 (61.7%) |
| Non-acute | 105 (38.3%) |
| Type of first decompensation | |
| Data available on type of decompensating event | 308 (95.4%) |
| Ascites | 187 (3.1%) |
| ≥2 events | 31 (0.51%) |
| HE | 36 (0.6%) |
| Variceal bleeding | 50 (0.8%) |
| Jaundice | 4 (0.07%) |
| Further decompensation in the 323 patients who experienced first decompensation (n = 132) | |
| Data available on discrimination between single or multiple decompensation | 128 (96.9%) |
| Single | 69 (53.9%) |
| Multiple | 59 (46.1%) |
| Data available on discrimination between acute or non-acute decompensation | 125 (94.7%) |
| Acute | 58 (46.4%) |
| Non-acute | 67 (53.6%) |
| Type of further decompensation | |
| Data available on type of decompensating event | 131 (99.2%) |
| Ascites | 42 (0.7%) |
| 2 or more events | 34 (0.6%) |
| HE | 42 (0.7%) |
| Variceal bleeding | 8 (0.1%) |
| Jaundice | 5 (0.08%) |
| LT | 51 (0.8%) |
| HCC | 231 (3.8%) |
| CVE | 653 (10.8%) |
| EHC | 1,093 (18.1%) |
| Death | |
| Overall | 521 (8.6%) |
| CV-D | 56 (11.9%) |
| HCC-D | 110 (23.6%) |
| LR-D | 144 (30.6%) |
| EH-D | 158 (33.8%) |

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; cACLD, compensated advanced chronic liver disease; CV-D, cardiovascular death; CVE, cardiovascular events; EH-D, extrahepatic death; EHC, extrahepatic cancers; GGT, gamma-glutamyltransferase; HCC, hepatocellular carcinoma; HCC-D, HCC-related death; HDL, high-density lipoprotein; HE, hepatic encephalopathy; INR, international normalized ratio; LR-D, liver-related death; LT, liver transplantation; MASLD, metabolic dysfunction-associated steatotic liver disease; TIPS, transjugular intrahepatic portosystemic shunt.
(*)Data are given as median (IQR).

patients, respectively. The first patient was enrolled in October 1988 and the last in July 2023. The median follow-up was 77.4 months (IQR 36.2-108.4 months); when stratified by center, the shortest median follow-up was 9.7 months (IQR 9.4-12.3 months) and the longest was 100.6 months (IQR 46.9-111.8 months).

### Cumulative incidence of first decompensation

The Sankey Plot in Fig. S1 reports the major outcomes that occurred in the clinical history of patients according to the presence and the type of decompensation.

Three hundred and twenty-three patients experienced first decompensation in the whole cohort, 72.2% of those had a single decompensating event and 27.8% had multiple concomitant events; 61.7% experienced AD, while 38.3% experienced NAD (Table 1).

Fig. 1A shows the 5-year CIF of first decompensation, with death and LT considered as competing risks. Specifically, the cumulative incidences of first decompensation were 0.9% (95% CI 0.7-1.2), 2.6% (95% CI 2.2-3) and 3.6% (95% CI 3.0-4.1) at 1, 3 and 5 years, respectively (Table 2). The cumulative incidences of different types of first decompensation over 5 years are shown in Fig. 1B: 2.2% (95% CI 1.77-2.6) of patients experienced ascites, 0.7% (95% CI 0.48-0.97) experienced variceal bleeding and 0.5% (95% CI 0.31-0.71) experienced ≥2 events; HE and jaundice were reported less commonly. Baseline characteristics of patients who had ascites as first decompensation, compared to those who experienced variceal bleeding, are reported in Table S1.

Analyses using CIFs for the risk of first decompensation (according to LSM categories, presence of diabetes, ancestry, and histological/clinical diagnosis of cACLD) and for the risk of HCC (according to LSM categories and presence of diabetes) are shown in Fig. S2–7. Cause-specific Cox models for first decompensation (based on the same covariates) and for HCC occurrence (according to LSM categories and diabetes) are reported in Table S3.

### Cumulative incidence of first decompensation spilt as AD and NAD

When focusing on the pattern of first decompensation, *i.e.* AD or NAD, data were available in 274 out of 323 patients who experienced first decompensation. Fig. 1C shows the 5-year CIF of AD and NAD with death and LT considered as competing risks, in patients with cACLD due to MASLD experiencing first decompensation. The cumulative incidences of AD at 1, 3 and 5 years were 0.5% (95% CI 0.4-0.7), 1.3% (95% CI 1-1.7) and 1.8% (95% CI 1.5-2.2), respectively, and of NAD were 0.3% (95% CI 0.15-0.41), 0.9% (95% CI 0.63-1.13) and 1.3% (95% CI 1-1.6), respectively (Table S2).

### Cumulative incidence of further decompensation

Of 323 patients with cACLD due to MASLD with a first episode of decompensation, 132 developed further decompensation. Specifically, 53.9% had a single decompensating event and 46.1% had multiple events; 46.4% of patients with further decompensation experienced AD, while 53.6% experienced NAD (Table 1).

Fig. 2A shows the 5-year CIF of further decompensation, with death and LT considered as competing risks. The observed cumulative incidences of further decompensation were 23.4% (95% CI 18.6-28.6), 37.7% (95% CI 31.6-43.7) and 43.9% (95% CI 37.2-50.2) at 1, 3 and 5 years, respectively (Table 2). The cumulative incidences of different types of further decompensation over 5 years are shown in Fig. 2B: 34.9% (95% CI 29.21-39.94) of patients experienced ascites, 10.6% (95% CI 7.46-14.43) experienced variceal bleeding and 8% (95% CI 4.99-11.01) experienced ≥2 events; HE and jaundice were found less commonly.

### Cumulative incidence of further decompensation stratified by AD and NAD

When focusing on the pattern of further decompensation, *i.e.* AD or NAD, data were available in 114 out of 132 patients who experienced further decompensation. Fig. 2C shows the 5-year CIF of AD and NAD, with death and LT considered as competing risks, in patients with cACLD due to MASLD experiencing further decompensation. The cumulative incidences of AD at 1, 3 and 5 years were 7.9% (95% CI 5-11.5), 13.4% (95% CI 9.5-18.1) and 16.7% (95% CI 11.5-21.1), respectively, and of NAD were 12% (95% CI 8.4-16.3), 20% (95% CI 15.1-24.4) and 23.2% (95% CI 17.8-29), respectively (Table S2).

### Cumulative incidence of liver-related mortality at first decompensation

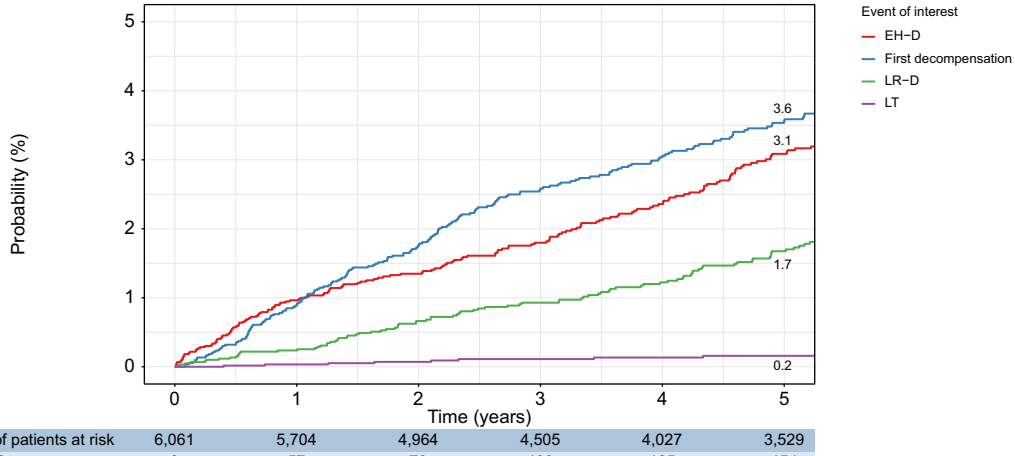
In patients who experienced a first decompensating event, median survival was 19.9 months (IQR 9.2-48.6). Patients who experienced ascites as a first decompensating event had a lower median survival (17.5 months; IQR 5.4–40.9) compared to those who experienced variceal bleeding (37.6 months; IQR 8.7–63.5). Fig. 3A shows the 5-year CIF of LR-D, with further decompensation, LT, and EH-D considered as competing risks. The competing risk analysis reported in Table 3 shows that LR-D occurred in 8.8% of patients (95% CI 5.9–12.3) at 1 year, 15% (95% CI 11–19.6) at 3 years, and 15.6% (95% CI 11.5–20.2) at 5 years. EH-D occurred in 5.2% of patients (95% CI 3–8.1) at 1 year, 8.2% (95% CI 5.3–11.9) at 3 years, and 12% (95% CI 7.5–15.9) at 5 years.

In the multivariable Cause-specific Cox model, first decompensation as a time-varying covariate (HR 18.94, 95% CI 10.87-32.99, $p$ <0.001), age >60 years (HR 4.70, 95% CI 2.59-8.51, $p$ <0.001), occurrence of HCC (HR 2.95, 95% CI 2.02-4.31, $p$ <0.001), and baseline albumin <3.5 g/dl (HR 2.03, 95% CI 1.30-3.18, $p$ = 0.001) were independently associated with LR-D (Table S5).

### Cumulative incidence of liver-related mortality at first decompensation stratified by AD and NAD

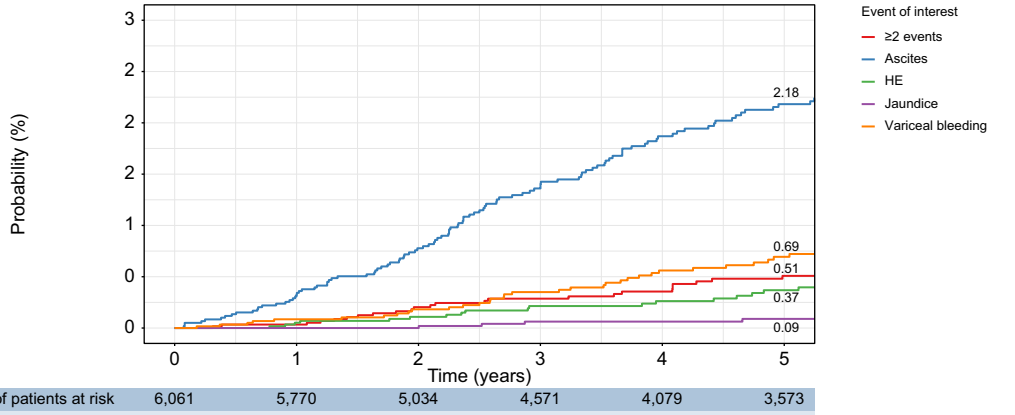
Fig. 3B shows the 5-year CIF of LR-D in patients with cACLD due to MASLD who experienced a first AD or NAD, with further decompensation, LT, and EH-D considered as competing risks. The cumulative incidences of LR-D at 1, 3 and 5 years were 8.1% (95% CI 4.4-13.3), 11.5% (95% CI 6.8-17.5) and 12.4% (95% CI 7.5-18.6), respectively, in patients experiencing AD, and 6.5% (95% CI 2.6-12.7), 17.1% (95% CI 9.7-

**A**



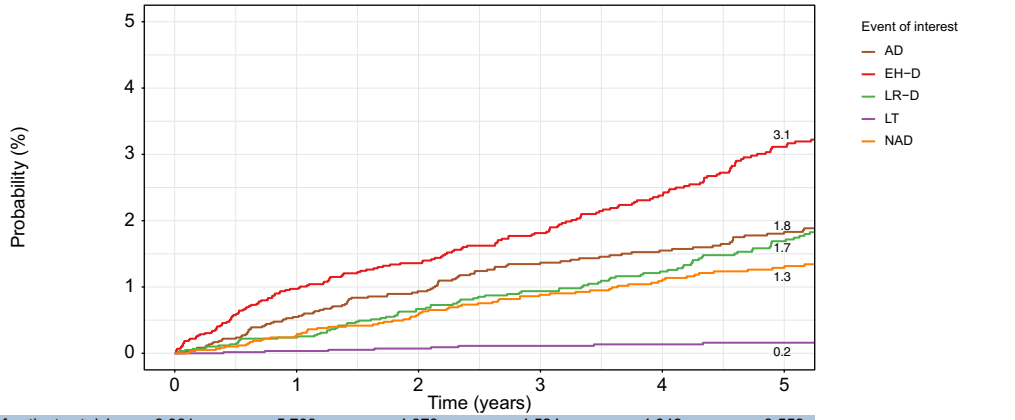

| No. of patients at risk | 6,061 | 5,704 | 4,964 | 4,505 | 4,027 | 3,529 |
|---|---|---|---|---|---|---|
| EH−D | 0 | 57 | 78 | 100 | 125 | 154 |
| First decompensation | 0 | 53 | 100 | 140 | 161 | 181 |
| LR−D | 0 | 14 | 37 | 50 | 63 | 81 |
| LT | 0 | 2 | 4 | 6 | 7 | 8 |

**B**




| No. of patients at risk | 6,061 | 5,770 | 5,034 | 4,571 | 4,079 | 3,573 |
|---|---|---|---|---|---|---|
| Ascites | 0 | 19 | 43 | 73 | 93 | 105 |
| HE | 0 | 3 | 6 | 11 | 13 | 17 |
| Jaundice | 0 | 0 | 0 | 3 | 3 | 4 |
| Varicel bleeding | 0 | 5 | 10 | 18 | 27 | 32 |
| ≥2 events | 0 | 2 | 11 | 15 | 18 | 24 |

**C**




| No. of patients at risk | 6,061 | 5,709 | 4,978 | 4,524 | 4,049 | 3,553 |
|---|---|---|---|---|---|---|
| AD | 0 | 32 | 53 | 74 | 82 | 93 |
| EH−D | 0 | 57 | 78 | 100 | 125 | 154 |
| LR−D | 0 | 14 | 37 | 50 | 63 | 81 |
| LT | 0 | 2 | 4 | 6 | 7 | 8 |
| NAD | 0 | 16 | 33 | 47 | 57 | 64 |

**Fig. 1. Five-year CIF of major events in the whole cohort with cACLD due to MASLD.** (A) Five-year CIF of first decompensation, death and LT as competing events. (B) CIF of the clinical presentation of the first decompensation. (C) CIF showing the "acute" or "non-acute" presentation of first decompensation. AD, acute decompensation; cACLD, compensated advanced chronic liver disease; CIF, cumulative incidence function; HE, hepatic encephalopathy; LT, liver transplantation; NAD, non-acute decompensation. (This figure appears in color on the web.)

**Table 2. Cumulative incidence of first and further decompensation at 1, 3 and 5 years, with liver-related death, extrahepatic death and LT as competing events in patients with cACLD due to MASLD.**

| Setting | Years | LR-D | EH-D | First decompensation | LT |
|---|---|---|---|---|---|
| cACLD | **1** | 0.2 (0.1.-0.4) | 0.9 (0.7-1.2) | 0.9 (0.7-1.1) | 0.03 (0-0.1) |
| | **3** | 0.9 (0.7-1.2) | 1.8 (1.4-2.1) | 2.6 (2.2-3) | 0.01 (0.004-0.02) |
| | **5** | 1.7 (1.3-2.1) | 3.1 (2.6-3.6) | 3.5 (3.0-4.1) | 0.02 (0.006-0.02) |
| **Setting** | **Years** | **LR-D** | **EH-D** | **Further decompensation** | **LT** |
| First decompensation | **1** | 11,4 (8.1-15.2) | 2.0 (0.8-4.1) | 23.4 (18.6-28.6) | 3.5 (1.8-6.2) |
| | **3** | 17.9 (13.7-22.8) | 4.6 (2.5-7.6) | 37.7 (31.6-43.7) | 4.8 (2.7-7.9) |
| | **5** | 19.2 (14.6-24.1) | 7.1 (4.1-11.2) | 43.9 (37.2-50.2) | 5.3 (3-8.5) |

cACLD, compensated advanced chronic liver disease; EH-D, extrahepatic death; LR-D, liver-related death; LT, liver transplantation; MASLD, metabolic dysfunction-associated steatotic liver disease.
Data are given as % (95% CI).

26.1) and 17.1% (95% CI 9.7-26.1), respectively, in patients experiencing NAD (Table S4).

In the multivariable cause-specific Cox model, both acute (HR 20.64, 95% CI 10.20–41.81; $p$ <0.001) and non-acute (HR 19.4, 95% CI 9.66–40.36; $p$ <0.001) first decompensation events, included as time-varying covariates, were independently associated with LR-D (Table S5).

### Cumulative incidence of liver-related mortality at further decompensation

When assessing mortality rates in patients with cACLD due to MASLD who experienced further decompensation, the cumulative incidences of LR-D at 1, 3 and 5 years were 41.3% (95% CI 29-53.2), 61.9% (95% CI 48.5-72.8) and 74.6% (95% CI 59.8-82.5), respectively, which were much higher than for EH-D (12.7% [95% CI 5.9-22.3], 19% [95% CI 10.4-29.7], 20.6% [95% CI 11.6-31.5] at 1, 3 and 5 years, respectively) (Table 3). Fig. 3C shows the 5-year CIFs of LR-D and EH-D. Notably, no patients were transplanted.

In the multivariable Cause-specific Cox model, further decompensation as a time-varying covariate (HR 1.52, 95% CI 1.02-2.34, $p$ = 0.04), age >60 years (HR 3.85, 95% CI 1.96-7.57, $p$ = 0.001) and occurrence of HCC (HR 1.43, 95% CI 1.03-2.00, $p$ = 0.03) were independently associated with LR-D (Table S5).

### Cumulative incidence of liver-related mortality at further decompensation stratified by AD and NAD

Fig. 3D shows the 5-year CIF of LR-D in patients with cACLD due to MASLD who experienced further AD or NAD, with EH-D considered as a competing risk. The cumulative incidences of LR-D at 1, 3 and 5 years were 20.8% (95% CI 7.3-39), 41.7% (95% CI 21.5-60.8) and 62.5% (95% CI 34.8-76), respectively, in patients experiencing AD, and 46.2% (95% CI 26.1-64.1), 69.2% (95% CI 46.6-83.8) and 80.8% (95% CI 57.6-92.1), respectively, in patients experiencing NAD (Table S4).

In the multivariable Cause-specific Cox model, both acute (HR 1.24, 95% CI 1.01-2.04, $p$ = 0.04) and non-acute (HR 1.27, 95% CI 1.02-2.01, $p$ = 0.04) further decompensation events were independently associated with LR-D (Table S5).

### Multistate model

To better appraise the impact of first and further decompensation on liver-related mortality in patients with cACLD due to MASLD, we built a multistate model. The model in Fig. S8A depicts the clinical course of those patients from the cACLD state to LR-D, EH-D and LT through first and further decompensation. Interestingly, nearly 30% of patients with cACLD due to MASLD died from EH-D without developing any decompensation event. After developing the first decompensation, EH-D was lower and nearly 43% died from LR-D and 19% underwent LT. Sixteen percent of patients with cACLD experienced a further decompensation and, as expected, the proportion of LR-D increased to 54% while that of EH-D decreased.

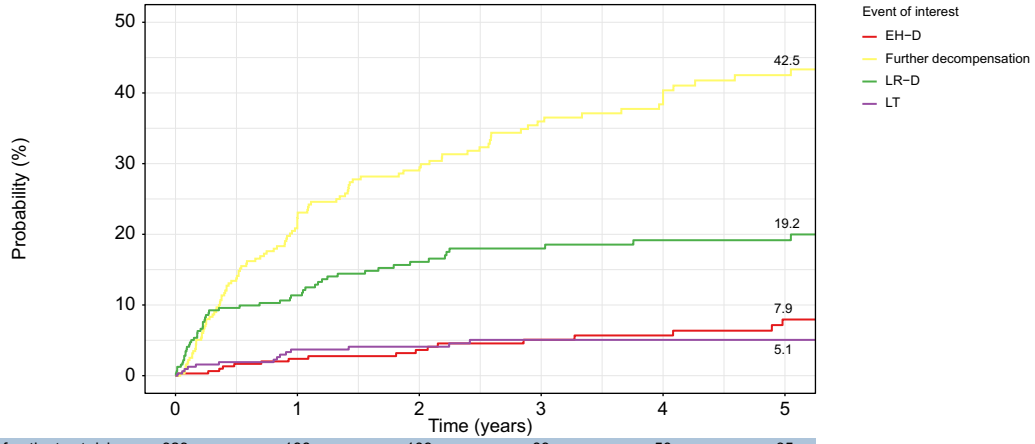
The corresponding 5-year probabilities of state occupation for patients with cACLD due to MASLD (Fig. S8B) were: cACLD 41% (95% CI 37.3-45.0), first decompensation 6.9% (95% CI 5.0-9.3), further decompensation 6.1% (95% CI 4.2-8.7), LT 4.1% (95% CI 2.7-6.3), LR-D 8.7% (95% CI 6.6-11.5), EH-D 29.9% (95% CI 26.4-33.8) and HCC-D 3.2% (95% CI 2.0-4.9). Fig. S8C depicts the corresponding 5-year probabilities of state occupation after first decompensation: first decompensation 4.8% (95% CI 2.8-7.8), further decompensation 16.2% (95% CI 10.7-24.4), LT 19.4% (95% CI 12.5-30), LR-D 42.7% (95% CI 33.8-53.8), EH-D 17% (95% CI 11.0-26.0). Finally, among patients who experienced further decompensation, the 5-year probabilities of state occupation were: further decompensation 19% (95% CI 10.9-33.1), LT 14.5% (95% CI 7.2-29.1), LR-D 54% (95% CI 39.0-74.4) and EH-D 12.5% (95% CI 5.3-29.1) (Fig. S8D).

## Discussion

This multicenter study, which included 6,061 patients with cACLD due to MASLD, demonstrates that the 5-year cumulative incidence of first decompensation was approximately 3.5%. This event was associated with an 18.9-fold increase in the cause-specific hazard of LR-D. Among patients who experienced a first decompensation, the 5-year risk of further decompensation was about 44%, which conferred a 1.52-fold increase in the cause-specific hazard of LR-D. For both first and further decompensation, ascites was the most frequent event, and the pattern of decompensation (AD *vs.* NAD) showed a similar impact on mortality. Additionally, the occurrence of HCC independently increased the cause-specific hazard of LR-D, regardless of hepatic decompensation.

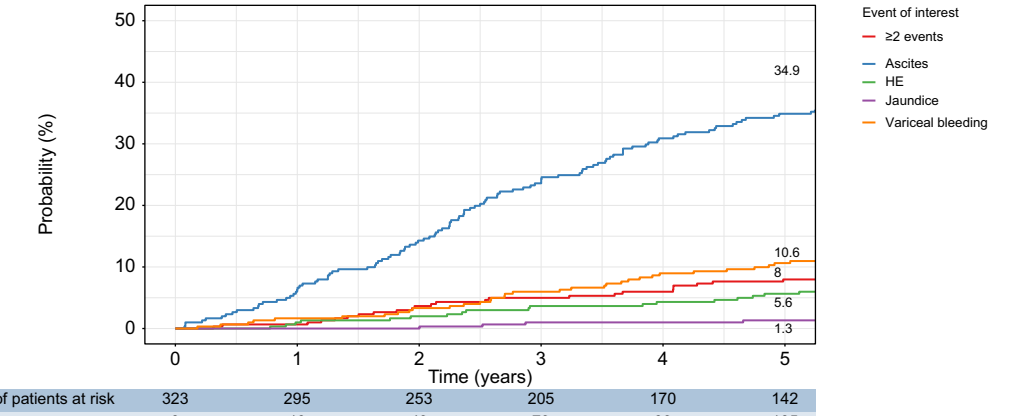
Current literature indicates that the latency period from MASH to the appearance of cACLD may be longer than in other etiologies.[19] However, once the first decompensation event occurs, the progression seems comparable to other etiologies.[20] Recent evidence has underscored the differing

**A**



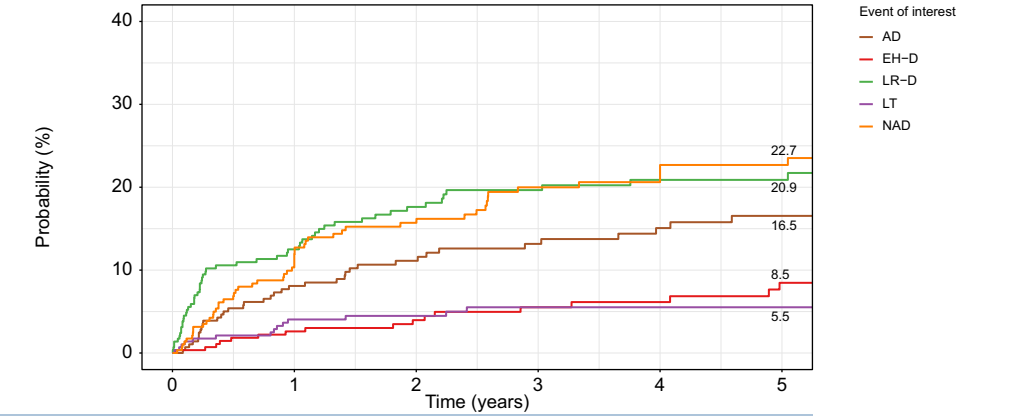

| No. of patients at risk | 323 | 166 | 109 | 69 | 50 | 35 |
|---|---|---|---|---|---|---|
| EH−D | 0 | 7 | 10 | 13 | 14 | 17 |
| Further decompensation | 0 | 66 | 84 | 97 | 104 | 107 |
| LR−D | 0 | 35 | 47 | 51 | 53 | 53 |
| LT | 0 | 11 | 12 | 14 | 14 | 14 |

**B**



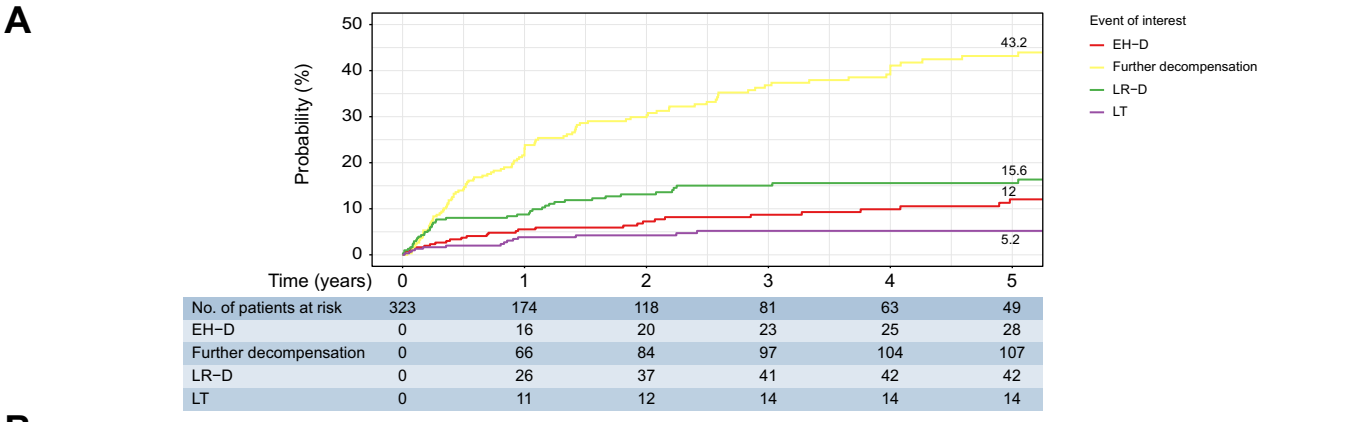

| No. of patients at risk | 323 | 295 | 253 | 205 | 170 | 142 |
|---|---|---|---|---|---|---|
| Ascites | 0 | 19 | 43 | 73 | 93 | 105 |
| HE | 0 | 3 | 6 | 11 | 13 | 17 |
| Jaundice | 0 | 0 | 1 | 3 | 3 | 4 |
| Varicel bleeding | 0 | 5 | 10 | 18 | 27 | 32 |
| ≥2 events | 0 | 2 | 11 | 15 | 18 | 24 |

**C**

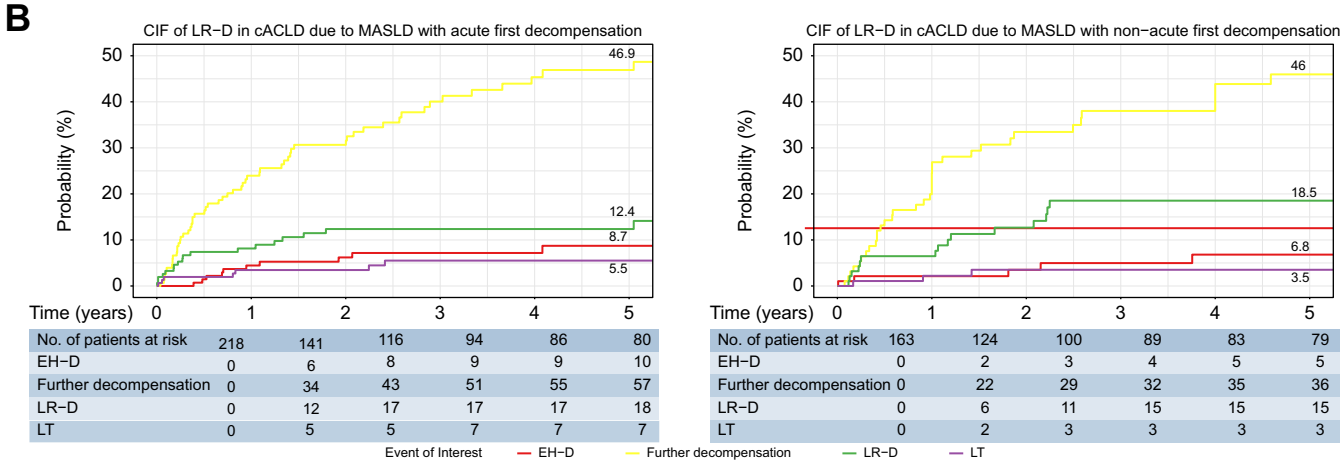



| No. of patients at risk | 323 | 186 | 131 | 96 | 78 | 65 |
|---|---|---|---|---|---|---|
| AD | 0 | 22 | 29 | 33 | 36 | 38 |
| EH−D | 0 | 7 | 10 | 13 | 14 | 17 |
| LR−D | 0 | 35 | 47 | 51 | 53 | 53 |
| LT | 0 | 11 | 12 | 14 | 14 | 14 |
| NAD | 0 | 32 | 42 | 49 | 53 | 53 |

**Fig. 2. Five-year CIF of major events in cACLD due to MASLD after first decompensation.** (A) Five-year CIF of further decompensation, death and LT as competing events. (B) CIF of the clinical presentation of the further decompensation. (C) CIF showing the "acute" or "non-acute" presentation of further decompensation. AD, acute decompensation; cACLD, compensated advanced chronic liver disease; CIF, cumulative incidence function; HE, hepatic encephalopathy; LT, liver transplantation; NAD, non-acute decompensation. (This figure appears in color on the web.)

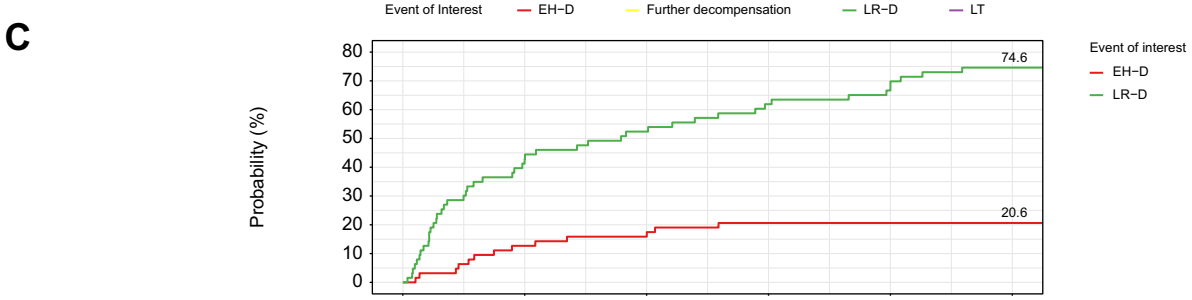



| No. of patients at risk | 323 | 174 | 118 | 81 | 63 | 49 |
|---|---|---|---|---|---|---|
| EH−D | 0 | 16 | 20 | 23 | 25 | 28 |
| Further decompensation | 0 | 66 | 84 | 97 | 104 | 107 |
| LR−D | 0 | 26 | 37 | 41 | 42 | 42 |
| LT | 0 | 11 | 12 | 14 | 14 | 14 |

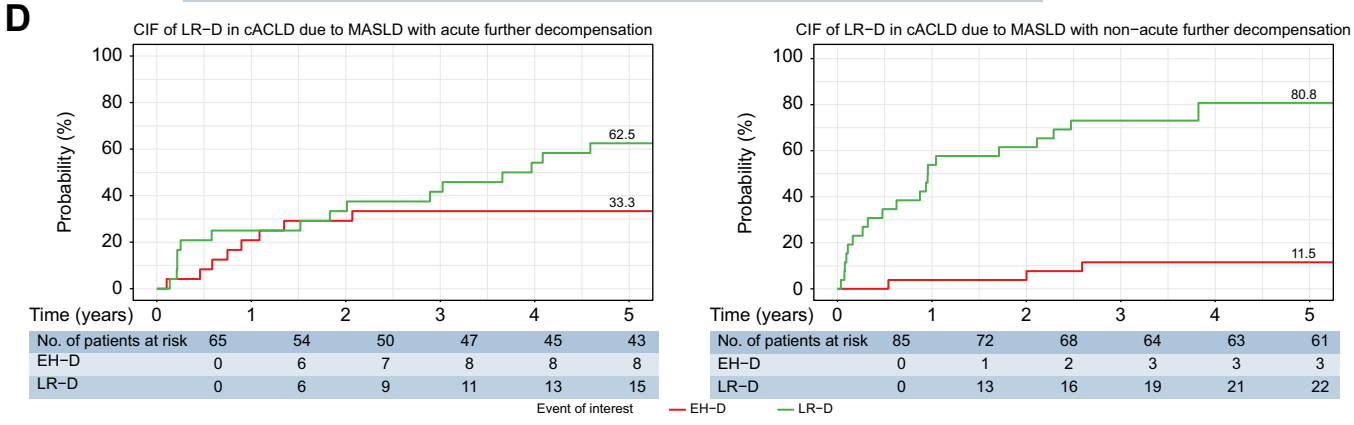



| No. of patients at risk | 218 | 141 | 116 | 94 | 86 | 80 |
|---|---|---|---|---|---|---|
| EH−D | 0 | 6 | 8 | 9 | 9 | 10 |
| Further decompensation | 0 | 34 | 43 | 51 | 55 | 57 |
| LR−D | 0 | 12 | 17 | 17 | 17 | 18 |
| LT | 0 | 5 | 5 | 7 | 7 | 7 |

| No. of patients at risk | 163 | 124 | 100 | 89 | 83 | 79 |
|---|---|---|---|---|---|---|
| EH−D | 0 | 2 | 3 | 4 | 5 | 5 |
| Further decompensation | 0 | 22 | 29 | 32 | 35 | 36 |
| LR−D | 0 | 6 | 11 | 15 | 15 | 15 |
| LT | 0 | 2 | 3 | 3 | 3 | 3 |




| No. of patients at risk | 132 | 98 | 89 | 80 | 77 | 73 |
|---|---|---|---|---|---|---|
| EH−D | 0 | 8 | 11 | 13 | 13 | 13 |
| LR−D | 0 | 27 | 33 | 40 | 44 | 47 |




| No. of patients at risk | 65 | 54 | 50 | 47 | 45 | 43 |
|---|---|---|---|---|---|---|
| EH−D | 0 | 6 | 7 | 8 | 8 | 8 |
| LR−D | 0 | 6 | 9 | 11 | 13 | 15 |

| No. of patients at risk | 85 | 72 | 68 | 64 | 63 | 61 |
|---|---|---|---|---|---|---|
| EH−D | 0 | 1 | 2 | 3 | 3 | 3 |
| LR−D | 0 | 13 | 16 | 19 | 21 | 22 |

**Fig. 3. Five-year CIF of death.** (A) Five-year CIF of further decompensation, death (LR-D and EH-D) and LT in MASLD cACLD with first decompensation. (B) Five-year CIF showing the "acute" or "non-acute" presentation of first decompensation, death (LR-D and EH-D) and LT in MASLD cACLD. (C) Five-year CIF of LR-D and EH-D in MASLD cACLD with further decompensation. (D) Five-year CIF showing the "acute" or "non-acute" presentation of further decompensation, death (LR-D and EH-D) and LT in MASLD cACLD. AD, acute decompensation; cACLD, compensated advanced chronic liver disease; CIF, cumulative incidence function; EH-D, extrahepatic death; LR-D, liver-related death; LT, liver transplantation; NAD, non-acute decompensation. (This figure appears in color on the web.)

**Table 3. Cumulative incidence of LR-D at 1, 3 and 5 years.**

| Setting | Years | LR-D | EH-D | Further decompensation | LT |
|---|---|---|---|---|---|
| First decompensation | **1** | 8.8 (5.9-12.3) | 5.2 (3-8.1) | 23.7 (18-27.7) | 3.6 (1.8-6) |
| | **3** | 15 (11-19.6) | 8.2 (5.3-11.9) | 38.1 (30.9-42.8) | 4.9 (2.6-7.7) |
| | **5** | 15.6 (11.5-20.2) | 12 (7.5-15.9) | 44.3 (36.6-49.6) | 5.4 (3-8.4) |
| **Setting** | **Years** | **LR-D** | **EH-D** | – | – |
| Further decompensation | **1** | 41.3 (29-53.2) | 12.7 (5.9-22.3) | – | – |
| | **3** | 61.9 (48.5-72.8) | 19 (10.4-29.7) | – | – |
| | **5** | 74.6 (59.8-82.5) | 20.6 (11.6-31.5) | – | – |

cACLD, compensated advanced chronic liver disease; EH-D, extrahepatic death; LR-D, liver-related death; LT, liver transplantation; MASLD, metabolic dysfunction-associated steatotic liver disease.
Data are given as % (95% CI).
Cumulative incidence of LR-D at 1, 3 and 5 years, with further decompensation, EH-D and LT as competing events in patients with cACLD due to MASLD who experienced first decompensation (upper). Cumulative incidence at 1, 3 and 5 years of LR-D, with EH-D as a competing event in patients with cACLD due to MASLD who experienced further decompensation (bottom).

prognostic implications of first *vs.* further decompensation and of AD *vs*. NAD in patients with cACLD, but data specifically addressing these dynamics in MASLD remain limited.

Our study, conducted on a large, international cohort with purely metabolic etiology, provides new insights. Prior studies addressing similar outcomes often involved cohorts with mixed etiologies, frequently driven by alcohol or viral hepatitis.[12,21] In our setting, competing risk analysis over 5 years revealed a low incidence (3.5%) of first decompensation, predominantly ascites, which significantly increased the hazard of LR-D – with a cumulative 5-year LR-D rate of 15.6% in these patients. Comparatively, D'Amico *et al.* reported a 5-year decompensation risk of 3% in patients without baseline varices and 28% in those with varices.[21] These higher rates may reflect differences in etiology and disease severity, as our cohort was limited to patients with cACLD, not all cirrhotic stages. D'Amico *et al.* also reported overall 5-year mortality rates of 20% and 30% in patients without and with varices, respectively – figures comparable to the 27% cumulative 5-year LR-D and EH-D observed in our cohort following first decompensation.

We also examined further decompensation, observing a cumulative 5-year incidence of 43.9% (again, mainly ascites), which further increased the hazard of LR-D to 74.6%. This is consistent with the 52% incidence reported by D'Amico *et al.*[12] and the 39.5% found by Noureddin *et al.*[22] in MASLD-related cirrhosis. However, our higher LR-D rate may stem from the low representation of viral etiology (only 9%) in our cohort, in contrast to cohorts where antiviral therapy could have improved prognosis.[23–25] Additionally, the high burden of metabolic comorbidities may have contributed to accelerated liver disease progression and worse outcomes.[26]

Notably, among the decompensating events, ascites was the most frequent in both the first and the further decompensation settings followed by variceal bleeding, consistent with the current literature.[11,22] We observed a relatively low rate of HE, in contrast to a recent US cohort where HE was more prevalent[27] – possibly due to differences in baseline characteristics, including a higher prevalence of obesity in the US population, which may predispose to cerebrovascular events. The very low incidence of jaundice in our cohort may also inform ongoing debate, such as the Baveno VII recommendations regarding its exclusion from decompensating events.

To better depict the role of first and further decompensation in the natural history of cACLD due to MASLD, a multistate model was built. Specifically, the model showed that among patients who experienced first decompensation, a higher proportion of them experienced liver disease progression depicted by a 5-year probability of state occupation of 4.7% for first decompensation, 16% for further decompensation, 42% for LR-D, and 19% for LT. Additionally, patients who experienced further decompensation had a poor liver-related prognosis with a 5-year probability of state occupation of 19% for further decompensation, 54% for LR-D, and 14% for LT.

A few years ago, the CANONIC[28] and PREDICT[29] studies introduced the concept of acute *vs.* non-acute decompensation. In our cohort, we assessed this distinction in cACLD due to MASLD, although unlike the CANONIC definition, our classification of AD excluded hospitalizations for sepsis or bacterial infection. We observed an even distribution of AD and NAD during both first and further decompensation. Notably, in first decompensation, both patterns increased the hazard of LR-D similarly, by about 20-fold, with no significant difference in risk during further decompensation. Our findings align with those by Tonon *et al.*, who also reported an even AD/NAD distribution in 617 patients with cACLD (secondary to various etiologies – only 23% had metabolic etiology).[30] However, unlike their study, which observed a higher impact of AD on mortality, we found a greater mortality risk associated with NAD. This may be attributed to increased patient frailty in our cohort, stemming from the presence of an active etiological trigger (as opposed to a treated/controlled viral etiology), along with a higher prevalence of metabolic comorbidities that may exacerbate liver disease progression.[26]

Another important finding was the independent impact of HCC on LR-D. Our cause-specific Cox models, both in the full cohort and among patients with first decompensation, showed that HCC significantly increased LR-D risk. These findings emphasize the need to consider HCC not merely as a separate complication but as a disease modifier when assessing prognosis in MASLD-related cACLD.

Given the complexity of the clinical profile of patients with cACLD and MASLD, especially related to the increasing risk of extrahepatic complications (cardiovascular events and extrahepatic cancer),[7] we also evaluated the cumulative incidence of EH-D considered as a competing risk. Notably, in our multistate model with a 5-year follow-up, we found that in patients with cACLD, EH-D occurs in approximately 30% of cases and is the leading cause of death in this population. However, this proportion decreases to 16% in patients who experience a first decompensation and further decreases to

12% in those who experience subsequent decompensation(s). Conversely, LR-D progressively becomes the leading cause of death in these patients. These data highlight the need for a comprehensive clinical assessment of extrahepatic, primarily metabolic, comorbidities in patients with advanced liver damage due to MASLD. In a systemic disease like MASLD, these comorbidities can significantly affect the prognosis independently of liver-related risks.

Noureddin *et al.* recently reported crude rates of decompensation in ~2,000 patients with MASLD. Our study adds further depth by: (1) including a larger cohort focused exclusively on cACLD; (2) providing competing risk-based estimates rather than raw data; (3) modeling mortality using time-dependent decompensation and HCC variables in cause-specific Cox regression; and (4) evaluating the impact of AD and NAD separately.

The main limitation of this study stems from its retrospective nature. Although the patients enrolled in the present study were prospectively followed, the lack of a standardized protocol and uniform follow-up limit the availability of data on weight loss and control of metabolic comorbidities. The long enrollment period may have also introduced performance bias as well as a period effect. Additionally, the study relied on secondary data derived from larger databases aimed at evaluating non-invasive test changes, which may have resulted in missing cirrhosis-specific details. These include incomplete data on recompensation, hepatic venous pressure gradient, variceal status, therapy use (non-selective beta-blockers, statins, albumin), non-invasive portal hypertension tests, portal vein thrombosis, and TIPS (transjugular intrahepatic portosystemic shunt) placement – all of which could affect interpretation of the observed results. Another concern lies in the potentially limited external validity of our results for different populations and settings. We evaluated a cohort of patients with MASLD-related cACLD referred to tertiary referral centers and fulfilling the reported inclusion and exclusion criteria, this point being another potential source of bias. Another study limitation is the presence of missing data and potential attrition bias. Moreover, given the number of statistical tests and models performed, the possibility of false-positive findings due to multiplicity cannot be excluded. This should be considered when interpreting the significance of the associations reported. Furthermore, we did not perform separate analyses for patients with/without cirrhosis, as is common in MASH trials, while the relatively low LT rate in our cohort does not reflect the growing recognition of MASLD as a major indication for LT.[31] Finally, data on newer HCC treatments, which may impact survival, were lacking.[32]

In conclusion, our study delineates the natural history of patients with cACLD secondary to MASLD and underscores how, over a 5-year timeframe, most patients do not develop hepatic decompensation but primarily die due to extrahepatic comorbidities. Following the onset of the first decompensation, and even more after further decompensation, the risk of EH-D decreases, while the risk of LR-D progressively increases, especially in the presence of a concomitant HCC diagnosis. From a clinical standpoint, understanding the clinical course of patients with cACLD due to MASLD and profiling those patients based on the first/further decompensation and the presence or absence of HCC could prove valuable in enhancing patient care and tailoring follow-up for those at higher risk of developing complications and death.

**Affiliations**

[1]*Section of Gastroenterology and Hepatology, Dipartimento Di Promozione Della Salute, Materno Infantile, Medicina Interna e Specialistica Di Eccellenza (PROMISE), University of Palermo, Italy;* [2]*Dipartimento Di Promozione Della Salute, Materno Infantile, Medicina Interna e Specialistica Di Eccellenza (PROMISE), University of Palermo, Italy;* [3]*Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong;* [4]*Centre d'Investigation de la Fibrose Hépatique, INSERM U1053, Hôpital Haut-Lévêque, Bordeaux University Hospital, Pessac, France;* [5]*Division of Gastroenterology and Hepatology, McGill University Health Centre, Montreal QC, Canada;* [6]*Hepatology Unit, Ospedale San Giuseppe, University of Milan, Milan, Italy;* [7]*Department of Pathophysiology and Transplantation, University of Milan, Italy;* [8]*Unit of Medicine and Metabolic Disease, Fondazione IRCCS Ca' Granda Ospedale Maggiore, Policlinico, Italy;* [9]*DiSMeC-Department of Scienze Mediche e Chirurgiche, Fondazione Policlinico Gemelli IRCCS, 00168 Rome, Italy;* [10]*Division of Gastroenterology, Department of Medical Sciences, University of Torino, Torino, Italy;* [11]*Division of Diagnostics and Specialist Medicine, Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden;* [12]*Division of Gastroenterology and Hepatology, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy;* [13]*Division of Internal Medicine, Hepatobiliary and Immunoallergic Diseases, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy;* [14]*Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy;* [15]*Severe Liver Disease Unit, Azienda Ospedaliero-Universitaria di Modena and University of Modena and Reggio Emilia, Modena, Italy;* [16]*Dipartimento di Medicina Sperimentale e Clinica, University of Florence, Italy; Research Center DENOTHE, University of Florence, Italy;* [17]*Department of Biomedical Sciences, Humanitas University, Milan, Italy;* [18]*Division of Internal Medicine and Hepatology, Department of Gastroenterology, IRCCS Humanitas Research Hospital, Rozzano, Italy;* [19]*Liver Injury and Transplant Unit, Università Politecnica delle Marche, 60121 Ancona, Italy;* [20]*Department of Medicine and Surgery, "Scuola Medica Salernitana", Internal Medicine and Hepatology Unit, University of Salerno, Salerno, Italy;* [21]*Translational Medicine, Department of Transfusion Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico IRCCS, Milan, Italy;* [22]*Department of Visceral Surgery and Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland;* [23]*Storr Liver Centre, Westmead Institute for Medical Research, Westmead Hospital, University of Sydney, Westmead, New South Wales, Australia*

**Abbreviations**

AD, acute decompensation; cACLD, compensated advanced chronic liver disease; CIF, cumulative incidence function; EH-D, extrahepatic death; HCC, hepatocellular carcinoma; LR-D, liver-related death; LR-M, liver-related mortality; LT, liver transplantation; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; NAD, non-acute decompensation.

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## Conflict of interest

VW served as a consultant or advisory board member for AbbVie, Boehringer Ingelheim, Echosens, Gilead Sciences, Intercept, Inventiva, Novo Nordisk, Pfizer, Sagimet Biosciences, TARGET PharmaSolutions, and Visirna; and a speaker for Abbott, AbbVie, Echosens, Gilead Sciences, Novo Nordisk, and Unilab. He has received a research grant from Gilead Sciences and is a co-founder of Illuminatio Medical Technology. SP has acted as speaker and/or advisor for AbbVie, Echosens, Gilead, MSD, Pfizer, Novonordisk, Pfizer. LV has received speaking fees from: Viatris, Novo Nordisk, consulting fees from: Novo Nordisk, Pfizer, Boehringer Ingelheim, Resalis, and unrestricted grant support from: Gilead. RD has received speaking from AbbVie, Gilead, consulting fees from AbbVie, Gilead and Takeda. GS has acted as speaker for Merck, Gilead, Abbvie, Novo Nordisk, Pfizer, served as an advisory board member for Pfizer, Merck, Novo Nordisk, Gilead, and has received unrestricted research funding from Theratecnologies Inc. JG is supported by the Robert W. Storr Bequest to the Sydney Medical Foundation, University of Sydney; a National Health and Medical Research Council of Australia (NHMRC) Program Grant (APP1053206), Investigator and MRFF grants (APP2032407; NCRI000183; APP2016215; APP 2010795; APP1196492) and a Cancer Institute, NSW grant (2021/ATRG2028). FS as acted as speaker and/or consultant for W.L. GORE, COOK Medical, and Echosens.

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

## Authors' contributions

G.P., G.D.M., V.W.W., V.d.L., G.S., M.V., A.L.F., L.M., E.B., M.E., R.D., F.R., F.S., F.M., A.M.A., G.S–B, M.P., L.V., A.B., J.G., A.A., P.N., S.K., D.S., Y.P.M., V.C., M. E., L.H., G.I., M.M., N.P., A.T., V.D.M., C.C., S.P., had full control of the study design, data analysis, interpretation, and preparation of the article. All authors were involved in planning the analyses and drafting the article. The final draft article was approved by all the authors.

## Data availability

Data available on request due to privacy/ethical restrictions.

## Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2025.06.014.

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*Author names in bold designate shared co-first authorship*


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