Università degli Studi di Palermo

AREA RICERCA E TRASFERIMENTO TECNOLOGICO
SETTORE DOTTORATI E CONTRATTI PER LA RICERCA
U. O. DOTTORATI DI RICERCA

Dottorato Medicina Molecolare e Clinica
Promozione della Salute, Materno-Infantile, di Medicina Interna e Specialistica di Eccellenza "G. D'Alessandro" (PROMISE), Università degli Studi di PALERMO
Settore Scientifico Disciplinare BIOS-10/A

THE IMPACT OF FIRST AND FURTHER DECOMPENSATION IN PATIENTS WITH METABOLIC-DYSFUNCTION ASSOCIATED COMPENSATED ADVANCED CHRONIC LIVER DISEASE

IL DOTTORE
DOTT.SSA CLAUDIA LA MANTIA

IL COORDINATORE
PROF. A . TUTTOLOMONDO

IL TUTOR
PROF. STEFANIA GRIMAUDO

CICLO _XXXVIII__
ANNO CONSEGUIMENTO TITOLO _2025/2026 -

INDEX

1. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) represents the leading cause of chronic liver disease worldwide, affecting nearly 38% of the adult population, and its prevalence is expected to rise in parallel with global epidemics of obesity, metabolic syndrome, and type 2 diabetes mellitus (T2DM)[1–3]. Once considered a benign hepatic manifestation of metabolic dysfunction, MASLD is now recognized as a progressive disease that can evolve toward advanced fibrosis, cirrhosis, and hepatocellular carcinoma (HCC), leading to liver-related death (LR-D) or the need for liver transplantation (LT) [4]. The burden of MASLD extends beyond hepatic morbidity, as patients often suffer from cardiovascular and extrahepatic metabolic complications contributing to increased overall mortality [5]. In Europe, MASLD has become a leading cause of liver transplantation, surpassing viral hepatitis in several cohorts [6] , and similar trends are seen in Italy, highlighting the disease as a major public health challenge [7] .

Over the past decade, the terminology describing fatty liver disease has evolved to better reflect its metabolic pathogenesis. Historically defined as non-alcoholic fatty liver disease (NAFLD), this term excluded patients with significant alcohol intake or other secondary causes but failed to emphasize metabolic dysfunction as the central feature [8]. In 2023, an international consensus redefined the condition as metabolic dysfunction-associated steatotic liver disease (MASLD), with metabolic dysfunction-associated steatohepatitis (MASH) referring to the inflammatory and fibrosing phenotype [3]. This reclassification underscores the importance of metabolic risk factors such as obesity, insulin resistance, dyslipidemia, and hypertension while acknowledging potential overlap with other etiologies. The change aligns MASLD with the broader concept of metabolic syndrome as a systemic, multi-organ disorder.

The pathogenesis of MASLD involves complex metabolic, inflammatory, and fibrogenic mechanisms. Insulin resistance plays a central role by promoting hepatic fat accumulation through enhanced lipolysis and increased free fatty acid flux to the liver [9]. Excess lipid accumulation induces lipotoxicity, oxidative stress, and mitochondrial and endoplasmic reticulum dysfunction, resulting in hepatocellular injury [10]. Kupffer cell activation and cytokine release (TNF-α, IL-6, IL-1β) drive hepatic inflammation and activate stellate cells, leading to fibrosis [11]. Alterations in the gut–liver axis, such as dysbiosis and increased intestinal permeability, contribute to chronic inflammation through microbial translocation [12] . Genetic and epigenetic factors, including variants in PNPLA3, TM6SF2, MBOAT7,

and HSD17B13, modulate susceptibility to fibrosis and HCC [13,14], while epigenetic mechanisms like microRNAs and DNA methylation further refine fibrogenic pathways [15].

MASLD progresses from steatosis to MASH, fibrosis, cirrhosis, and decompensated liver disease. The compensated advanced chronic liver disease (cACLD) stage reflects significant structural remodeling and portal hypertension, though patients may remain asymptomatic or show only mild biochemical changes [16]. Non-invasive tools such as transient elastography (liver stiffness >10 kPa) are now widely used to detect cACLD and predict outcomes [17]. Decompensation marks a pivotal transition in disease progression, defined by the onset of complications like ascites, variceal bleeding, hepatic encephalopathy, or jaundice [18]. According to Baveno VII criteria, median survival decreases from over 12 years in compensated stages to about 2 years following first decompensation [16]. In MASLD-cACLD, this event is less frequent than in other etiologies but has major prognostic significance [19].

Recent studies, including CANONIC and PREDICT, distinguish between acute (AD) and non-acute decompensation (NAD). AD is a sudden deterioration often triggered by infection or alcohol intake, while NAD develops gradually due to systemic decline.[20–22]

MASLD-related cirrhosis is frequently associated with extrahepatic comorbidities—particularly T2DM, obesity, and cardiovascular disease that influence outcomes and often exceed liver-related causes of death[5,23]. This dual burden necessitates comprehensive cardiometabolic management, as “multisystem metabolic failure” is increasingly recognized as a key determinant of prognosis [4]. Moreover, HCC represents one of the most severe complications, with incidence rates of 2–3% per year in advanced stages [1] .HCC can occur even in non-cirrhotic MASLD, reflecting systemic metabolic and inflammatory carcinogenesis [24]. Within cACLD, HCC worsens survival independently of decompensation and serves as a competing risk for liver-related death [19]. Despite its importance, adherence to surveillance programs remains low. [25]

In light of these challenges, the present research investigates the prognostic impact of first and subsequent decompensation in MASLD-cACLD, using a large, international cohort. By examining cumulative incidence, decompensation type, and outcomes, and by considering interactions between hepatic and extrahepatic mortality as well as HCC, this study aims to refine prognostic models and optimize clinical management strategies.

2 Materials e Method

2.1 Study Design and Objectives

This doctoral research is based on a multicenter, retrospective cohort study designed to evaluate the incidence, characteristics, and prognostic implications of first and further decompensation events in patients with compensated advanced chronic liver disease (cACLD) due to metabolic dysfunction-associated steatotic liver disease (MASLD). The study also investigates the interaction between hepatic and extrahepatic causes of death, as well as the modifying effect of hepatocellular carcinoma (HCC) on patient outcomes.

The principal objectives were:

- To estimate the cumulative incidence of first and subsequent decompensation in MASLD-related cACLD.
- To distinguish acute versus non-acute decompensation patterns and determine their prognostic significance.
- To identify independent predictors of decompensation and liver-related death (LR-D)
- To explore the competing risks of extrahepatic death (EH-D) and liver transplantation (LT).
- To evaluate the influence of HCC development on overall prognosis and survival trajectories.

2.2 Study Population

2.2.1 Inclusion Criteria

Patients were enrolled from 17 hepatology centers across Europe, Asia, and North America between 2005 and 2023. Inclusion criteria were: - Age ≥ 18 years at enrollment. - Diagnosis of MASLD according to international consensus criteria [3]. Evidence of compensated advanced chronic liver disease (cACLD), defined by one or more of the following: - Histological fibrosis stage F3–F4. - Liver stiffness measurement (LSM) > 10 kPa on transient elastography. - Clinical or imaging findings consistent with advanced fibrosis without prior decompensation. - Availability of longitudinal follow-up data (minimum 12 months or until death/transplantation).

2.2.2 Exclusion Criteria

Exclusion criteria included:

- History of hepatic decompensation before enrollment.

- Alternative or coexisting liver diseases as predominant etiology (viral hepatitis, autoimmune, cholestatic, or genetic liver disorders). Excessive alcohol consumption (>30 g/day for men, >20 g/day for women).

- Active malignancy other than HCC.

- Inadequate clinical data or loss to follow-up before first outcome event.

2.2.3 Definition of MASLD Etiology

MASLD diagnosis required evidence of hepatic steatosis (by imaging or histology) in combination with at least one cardiometabolic risk factor: obesity (BMI ≥ 25 kg/m²), type 2 diabetes mellitus, dyslipidemia, or hypertension [3]. Alcohol consumption within moderate limits was not exclusionary if metabolic dysfunction was the primary driver of liver disease.

2.3 Clinical and Laboratory Assessment

Baseline assessments included demographic data, anthropometric parameters, metabolic comorbidities, biochemical profiles, and non-invasive fibrosis markers. The following parameters were collected at enrollment:

- Demographics: age, sex, ethnicity.
- Anthropometrics: BMI, waist circumference, blood pressure.
- Metabolic parameters: fasting glucose, HbA1c, insulin, lipid profile.
- Liver function tests: ALT, AST, ALP, GGT, bilirubin, albumin, INR.
- Renal function: creatinine, estimated glomerular filtration rate (eGFR).
- Non-invasive markers: LSM (transient elastography), FIB-4 index, APRI.
- Comorbidities: T2DM, arterial hypertension, dyslipidemia, coronary artery disease.

All patients were followed according to standardized clinical protocols, with visits every 6–12 months or as clinically indicated. Follow-up data included liver-related events, HCC occurrence, death (categorized as liver-related or extrahepatic), and liver transplantation.

2.4 Definition of Clinical Events

2.4.1 Decompensation

Decompensation was defined according to Baveno VII consensus [16]: the first occurrence of any of the following events:

- Ascites (confirmed by ultrasound or requiring diuretic therapy/paracentesis).

- Variceal bleeding (endoscopically confirmed).

- Hepatic encephalopathy (clinically diagnosed or requiring therapy).

- Jaundice (bilirubin >3 mg/dL in the absence of other causes).

2.4.2 Acute vs. Non-Acute Decompensation

Based on PREDICT and CANONIC study definitions [20,21]:

- Acute Decompensation (AD): rapid onset of symptoms and hospitalization within 30 days of precipitating events (e.g., infection, alcohol intake, bleeding, or renal failure).

- Non-Acute Decompensation (NAD): gradual clinical deterioration without an identifiable acute trigger.

2.4.3 Hepatocellular Carcinoma (HCC)

HCC was diagnosed according to EASL guidelines based on imaging criteria or histological confirmation [European Association for the Study of the Liver, 2018].

2.4.4 Death and Liver Transplantation

- Liver-Related Death (LR-D): mortality directly attributable to hepatic failure, portal hypertension complications, or HCC.
- Extrahepatic Death (EH-D): death due to cardiovascular, renal, or oncologic causes unrelated to liver function.
- Liver Transplantation (LT): considered as a competing endpoint to death in statistical modeling.

2.5 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 inci dence function (CIF) estimates were calculated and group comparisons were carried out using Gray's test. [42] 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 subse quent decompensations.

4. Subdividing liver-related deaths due to cACLD secondary to MASLD within the framework of both first and subse quent 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 de compensations 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 occur rence 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 gender, age, platelet count, albumin levels, and dia betes. In contrast, the model for first decompensation included only gender, 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, grid Extra, grid, cr17, gtable, mstate, and cmprsk.

2.6 Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Boards (IRB) of all participating centers. Informed consent was obtained from all patients at enrollment or, for retrospective data, waived by local ethics committees where appropriate. Data confidentiality and anonymization procedures were strictly followed under the European General Data Protection Regulation (GDPR, 2016/679).

2.7 Data Management and Quality Control

A centralized database was established to collect de-identified clinical and laboratory data. Data quality was ensured through double-entry verification, range checks, and random audits. Missing data were handled using multiple imputation methods where applicable. Data analysis and manuscript preparation followed STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.

3. Results

3.1 Baseline Characteristics of the Study Population

The study included a large cohort of patients with compensated advanced chronic liver disease (cACLD) due to metabolic dysfunction-associated steatotic liver disease (MASLD). At baseline, participants exhibited demographic and clinical characteristics consistent with the typical MASLD-cACLD phenotype. The median age of the cohort was approximately 58 years, with a slight predominance of male patients. Metabolic comorbidities were highly prevalent, with the majority of individuals presenting obesity, type 2 diabetes mellitus (T2DM), arterial hypertension, and dyslipidemia. More than a half of patients enrolled had metabolic comorbidities: T2D and obesity were present in 41.5 % and 52.4% of the patients, respectively. Only 3.8% of the patients developed HCC; CVE and EHC were found in 10.8% and 18.1% of patients, respectively. The median follow-up was 6.45 (range 3.02-9.04) years.

Liver stiffness measurement (LSM) values, assessed by transient elastography, indicated a median stiffness of around 16–18 kPa, confirming the presence of advanced fibrosis or cirrhosis. Platelet counts were moderately reduced, and biochemical tests reflected compensated liver function, with normal or mildly elevated transaminases and preserved albumin and bilirubin levels. These findings confirm that the study population represented a well-compensated stage of chronic liver disease, prior to any clinical decompensation (**Table 1**).

During the median follow-up period of approximately 4–5 years, a substantial proportion of patients experienced hepatic and extrahepatic events, including first and subsequent decompensation, hepatocellular carcinoma (HCC) development, and mortality. The comprehensive design and longitudinal nature of the cohort allowed a detailed evaluation of the timing, frequency, and prognostic impact of these events.

Baseline demographic and clinical characteristics are also summarized in Table 1. There were no major differences between centers regarding age, sex, or metabolic comorbidities, confirming the external validity of the pooled cohort. Patients were predominantly European (71%), with the remainder from Asia (21%) and North America (8%). 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).

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. Baseline features of 6.061 patients with cACLD due to MASLD.

Age (*)	58 (49.8 - 65.5)
Male gender	53.9%
Obesity	52.4%
Diabetes	41.5%
Arterial Hypertension	36.3%
Fasting glucose - mg/dL (*)	110 (93.6 - 139.6)
Total Cholesterol - mg/dL (*)	180 (153.8 - 210.3)
Triglycerides - mg/dL (*)	136.4 (98.3 - 194)
HDL - mg/dL (*)	46.4 (39- 56)
Platelets – mmc (*)	220 (172 - 266)
INR (*)	1 (0.9 - 1.1)
Albumin - g/dL (*)	4.3 (4 - 4.5)
Bilirubin - mg/dL (*)	0.6 (0.4 - 0.8)
AST - UI/L (*)	39 (26 - 57)
ALT - UI/L (*)	37 (24 - 63)
GGT - UI/L (*)	77 (44 - 152.2)
ALP - UI/L (*)	90 (70 - 121)
First decompensation (n=315) Single Multiple Acute Non-acute	 72.2% 27.8% 61.7% 38.3%
Type of first decompensation Ascites 2 or more events HE Variceal bleeding Jaundice	 3.1% 0.51% 0.6% 0.8% 0.07%
Further decompensation (n=126) Single Multiple Acute Non-acute	 63.3% 36.6% 46.4% 53.6%
Type of further decompensation Ascites 2 or more events HE Variceal bleeding Jaundice	 0.7% 0.6% 0.7% 0.1% 0.08%
Portal trombosis	1.3%
LT	0.8%
TIPS	0.4%
HCC	3.8%
CVE	10.8%
EHC	18.1%

cACLD, compensated advanced chronic liver disease; MASLD, metabolic-dysfunction associated steatotic liver disease; HDL, high-density lipoprotein; INR, international normalized ratio; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; HE, hepatic encephalopathy; LT, liver trasplantation; TIPS, transjugular intrahepatic portosystemic shunt; HCC, hepatocellular carcinoma;; CVE,

cardiovascular events; EHC, extra-hepatic cancers; CV-D, cardiovascular death; HCC-D, hepatocellular carcinoma-related death; LR-D, liver-related death; EH-D, extra-hepatic death.

Data are given as (*) median (interquartile range).

3.2 Incidence and Characteristics of First Decompensation

Among the total cohort, the cumulative incidence of first hepatic decompensation was significant, reflecting the natural progression from the compensated to the decompensated stage of MASLD-related cirrhosis.

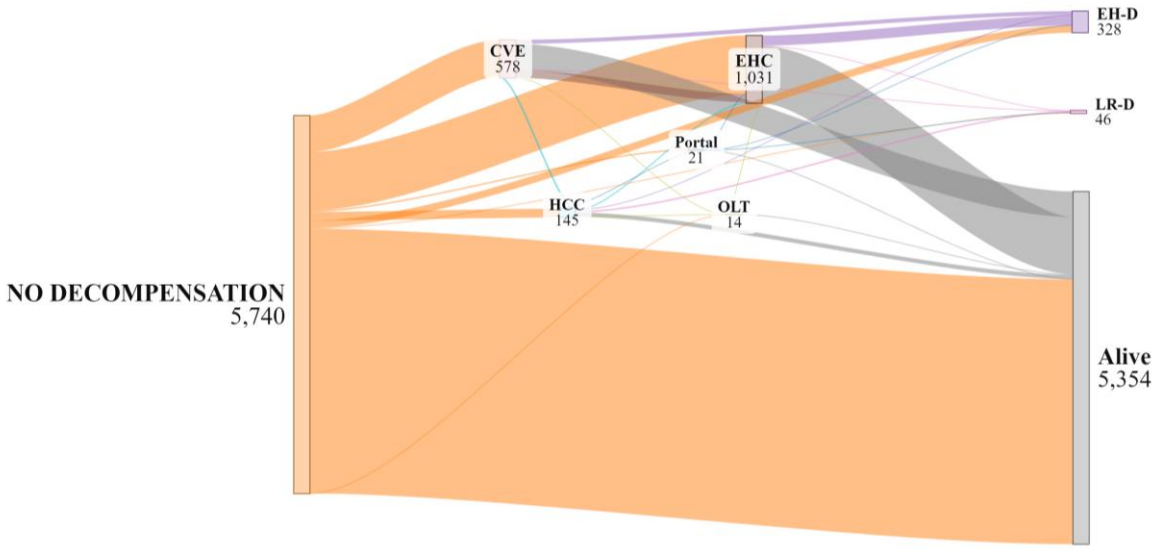


Figure 1A

The Sankey Plot (**Figure 1A**) The Sankey Plot reporting the major outcomes occurred in the clinical history of MASLD cACLD patients according to the absence (A) or the presence and the type of decompensation (**B**). cACLD, compensated advanced chronic liver disease; LT, liver transplantation; HCC, hepatocellular carcinoma; CVE, cardiovascular events; EHC, extra-hepatic cancer; LR-D, liver-related death; EH-D, extra-hepatic death.

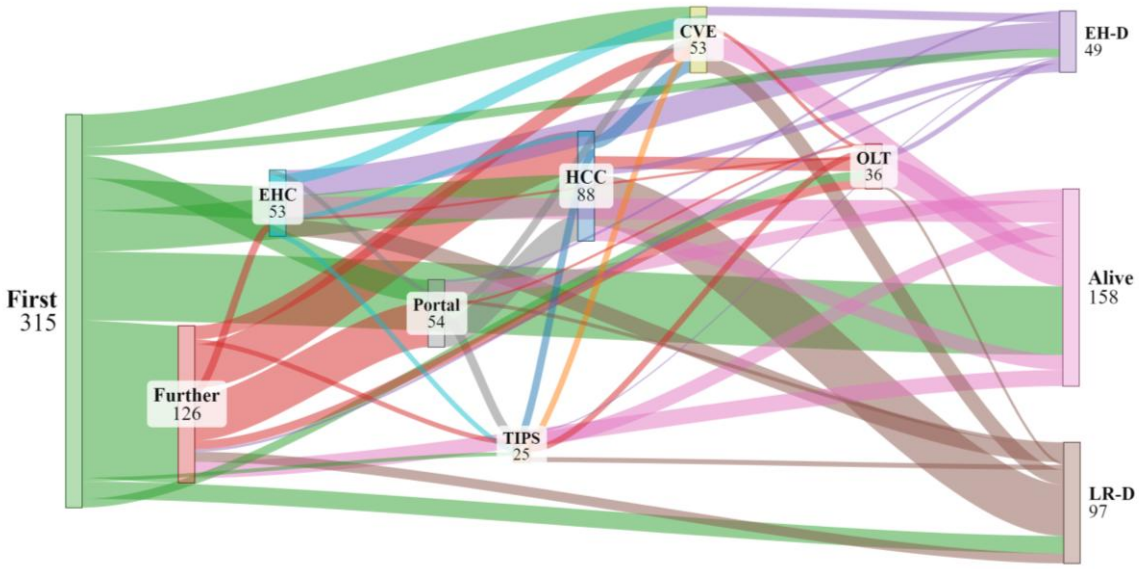


Figure 1B

The first decompensating events were predominantly represented by ascites, which accounted for about 60–65% of cases. Variceal bleeding and hepatic encephalopathy occurred less frequently, each representing roughly 15–20% of first events. Jaundice was uncommon as an initial presentation. These proportions indicate that portal hypertension-related complications are the primary mode of transition to decompensation in MASLD-cACLD, mirroring patterns observed in other etiologies of cirrhosis but with a lower contribution of bleeding events.

The median age at first decompensation was higher than that typically reported for viral or alcohol-related cirrhosis, underscoring the older demographic and multisystemic burden of the MASLD population. Furthermore, patients with metabolic comorbidities such as T2DM and obesity exhibited a significantly greater incidence of first decompensation, suggesting a synergistic role of systemic metabolic dysfunction in accelerating hepatic deterioration.

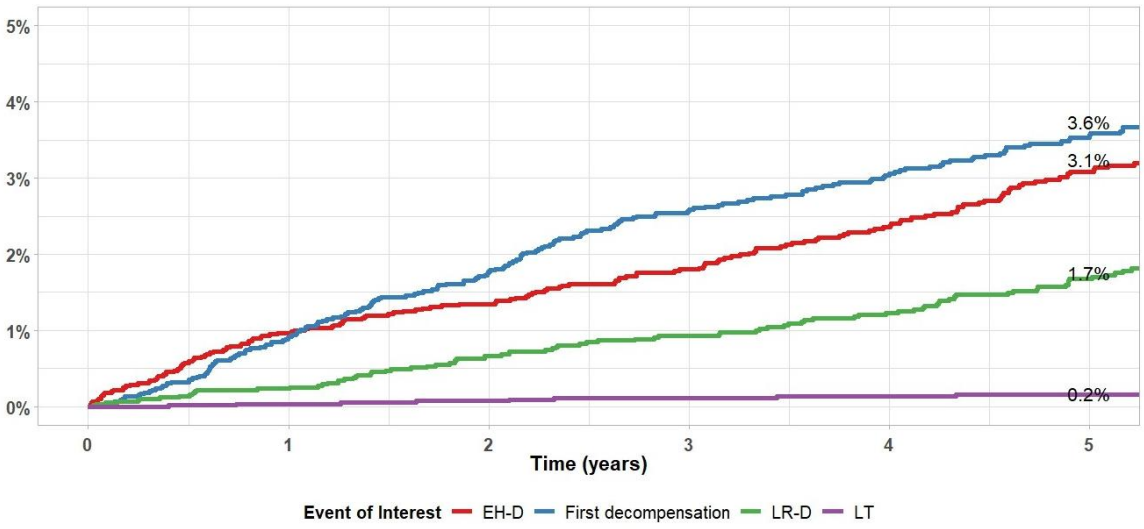


Figure 2A

Figure 2A illustrates the 5-year cumulative incidence of the first decompensation, considering death and liver transplantation (LT) as competing events. Specifically, the cumulative rates of first decompensation were 0.9% (95% CI 0.7–1.2) at 1 year, 2.6% (95% CI 2.2–3.0) at 3 years, and 3.6% (95% CI 3.0–4.1) at 5 years (see Table 2).

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

Setting	Years	Death	First decompensation	LT
First decompensation	**1**	1.7 (1.4-2)	0.9 (0.7-1.1)	0.03 (0-0.1)
	3	2.8 (2.4-3.2)	2.6 (2.2-3)	0.01 (0.004-0.02)
	5	4.7 (4.1-5.3)	3.5 (0.3-0.4)	0.02 (0.006-0.02)
Setting	**Years**	**Death**	**Further decompensation**	**LT**
Further decompensation	**1**	17 (12.9-21.6)	23.4 (18.6-28.6)	3.5 (1.8-6.2)
	3	25.1 (20-30.4)	37.7 (31.6-43.7)	4.8 (2.7-7.9)
	5	28.3 (22.1-33.2)	43.9 (37.2-50.2)	5.3 (3-8.5)

Abbreviations: cACLD, compensated advanced chronic liver disease; MASLD, metabolic-dysfunction associated steatotic liver disease; LT, liver transplantation.
Data are given as % (95% CI).

Importantly, the occurrence of first decompensation was associated with a sharp decline in survival probability, indicating a major prognostic inflection point in the natural history of the disease.

The cumulative incidences of different types of first decompensation over 5 years are shown in Fig. 2B: 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.

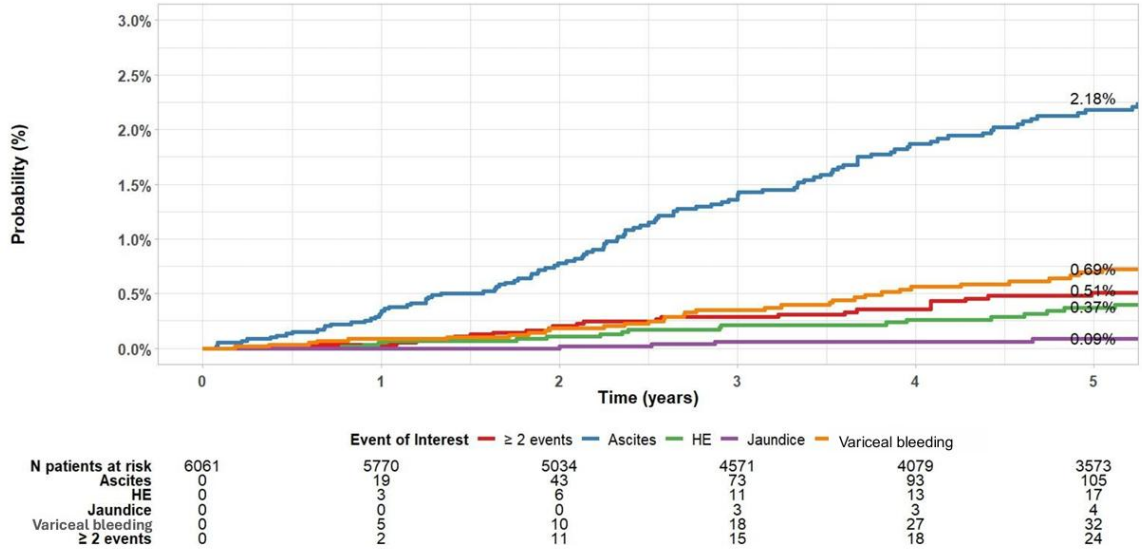


Figure 2B

Baseline characteristics of patients who had ascites as first decompensation, compared to those who experienced variceal bleeding, are reported in **Table 3**.

Table 3. Baseline features of patients with cACLD due to MASLD who experienced ascites and variceal bleeding

Variable	Ascites (n=187)	Variceal bleeding (n=50)
Age (*)	66.3 (60-73)	68.5 (60.5-74.8)
Male gender	110 (58.8%)	26 (52 %)
Obesity	83 (51.5%)	19 (44.2%)
Diabetes	118 (63.1%)	33 (66%)
Arterial Hypertension	114 (60.9%)	26 (52%)
Fasting glucose - mg/dL (*)	116 (99-142)	114 (91-139)
Total Cholesterol - mg/dL (*)	174 (145–206)	191 (153–202)
Triglycerides - mg/dL (*)	123 (89.1–156)	130 (112–180)
HDL - mg/dL (*)	45 (39–55)	41 (35–47.5)
Platelets – mmc (*)	128 (83–177)	113 (76.2–242)
INR (*)	1.16 (1.06–1.3)	1.13 (1.07–1.3)
Albumin - g/dL (*)	3.8 (3.48–4.17)	3.9 (3.6–4.1)
Bilirubin - mg/dL (*)	1.08 (0.697–1.4)	1 (0.7–1.21)
AST - UI/L (*)	46 (34.2–65)	41 (32–61)
ALT - UI/L (*)	40 (27–57)	40 (25–54)
GGT - UI/L (*)	15 (70-226)	84 (58–141)
ALP - UI/L (*)	130 (93.2-169)	108 (86.2–142)

cACLD, compensated advanced chronic liver disease; MASLD, metabolic-dysfunction associated steatotic liver disease; HDL, high-density lipoprotein; INR, international normalized ratio; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase.
Data are given as (*) median (interquartile range).

The analyses employing cumulative incidence functions (CIFs) to evaluate the probability of first decompensation stratified by liver stiffness measurement (LSM) categories, diabetes status, ancestry, and histological or clinical cACLD diagnosis — as well as the risk of hepatocellular carcinoma (HCC) according to LSM and diabetes, are presented in **Figures 3–8**. Corresponding cause-specific Cox regression models assessing first decompensation (using the same covariates) and HCC development (by LSM categories and diabetes) are summarized in **Table 4**.

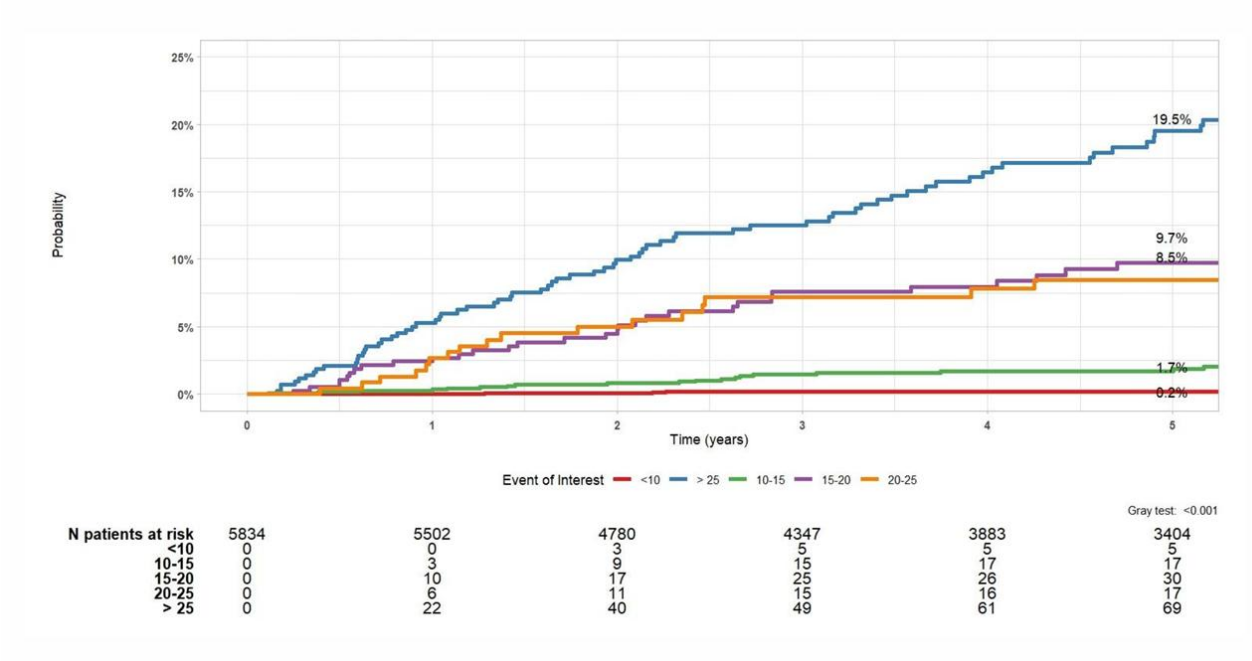
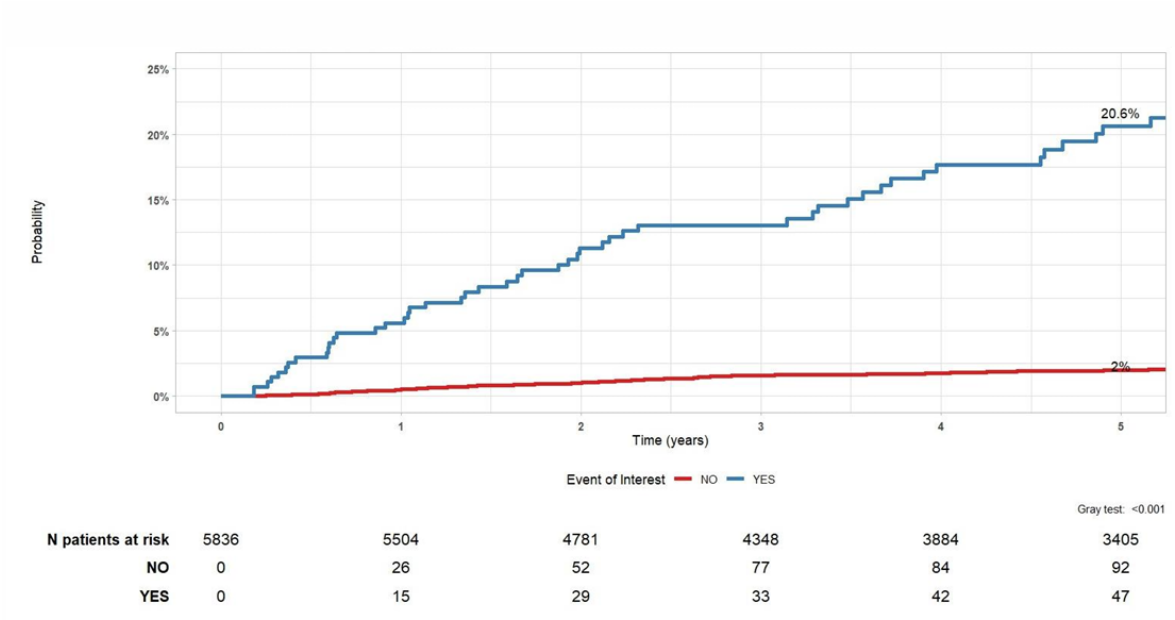
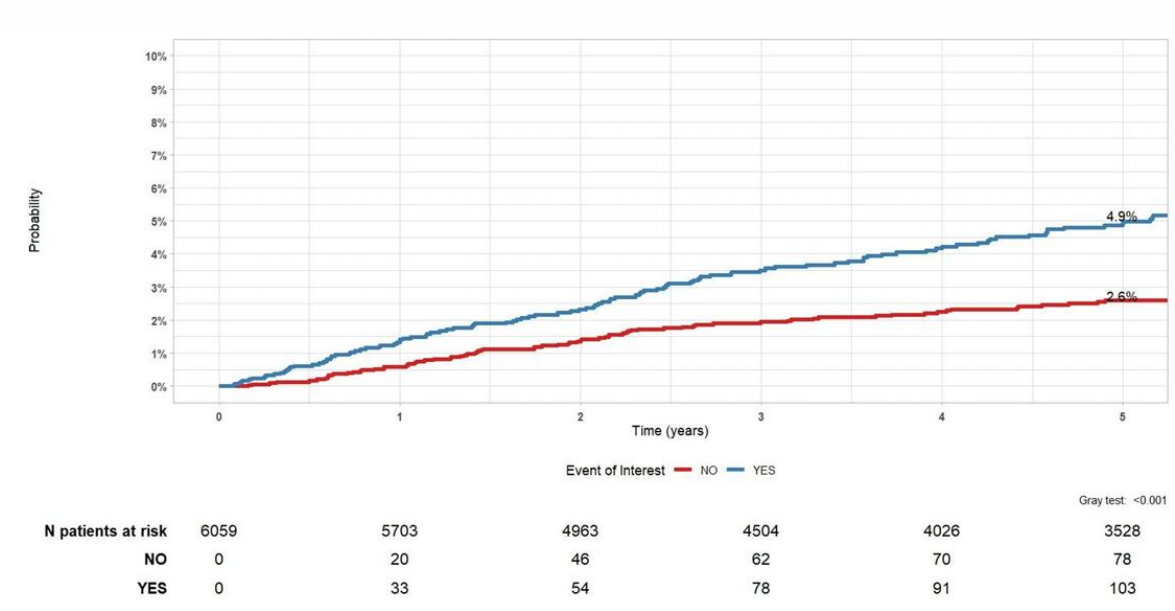


Figure 3. Five-year CIF of first decompensation in cACLD due to MASLD according to LSM categories (<10 KPa, 10-15 KPa, 15-20 KPa, 20-25 KPa, > 25 KPa).cACLD, compensated advanced chronic liver disease; LSM, liver stiffness measurement.



N patients at risk	5836	5504	4781	4348	3884	3405
NO	0	26	52	77	84	92
YES	0	15	29	33	42	47

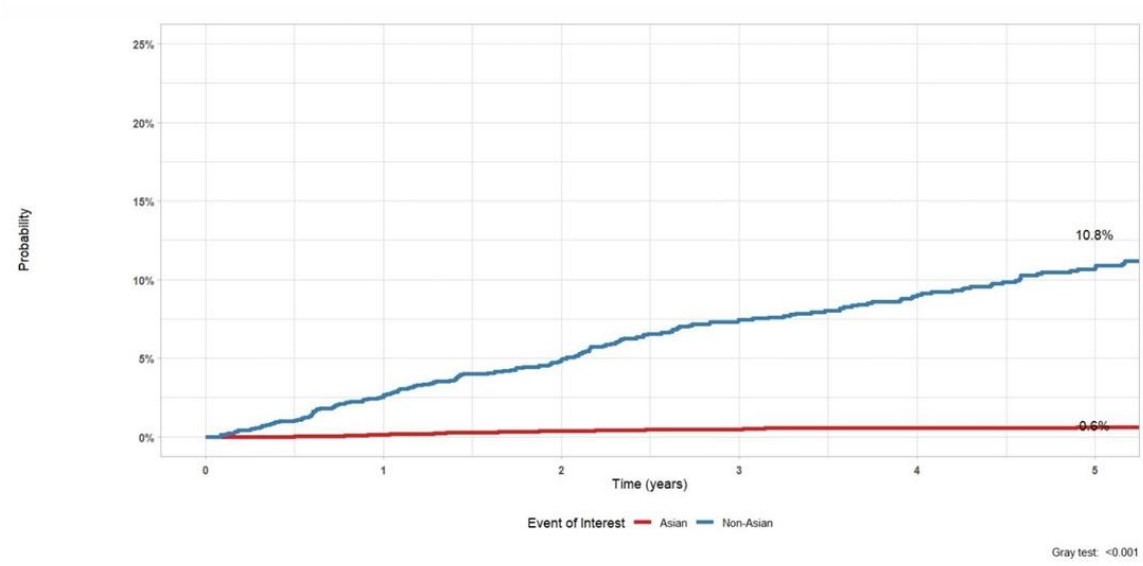
Figure 4. Five-year CIF of first decompensation in cACLD due to MASLD according to LSM >30.7 KPa. cACLD, compensated advanced chronic liver disease; LSM, liver stiffness measurement



N patients at risk	6059	5703	4963	4504	4026	3528
NO	0	20	46	62	70	78
YES	0	33	54	78	91	103

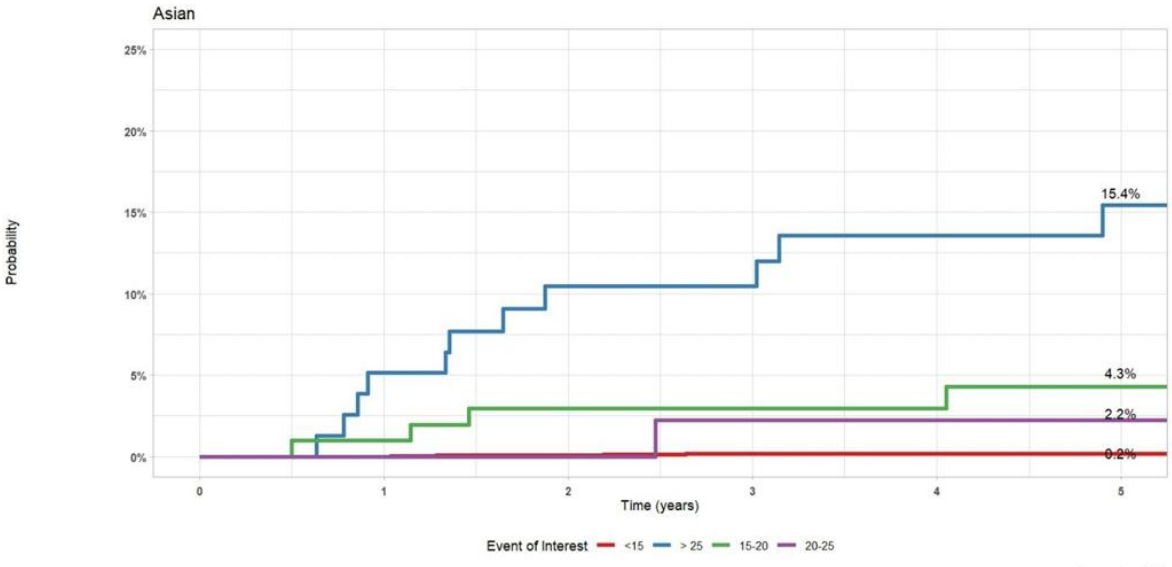
Figure 5. Five-year CIF of first decompensation in cACLD due to MASLD according to the presence or absence of diabetes. *cACLD, compensated advanced chronic liver disease.*

A

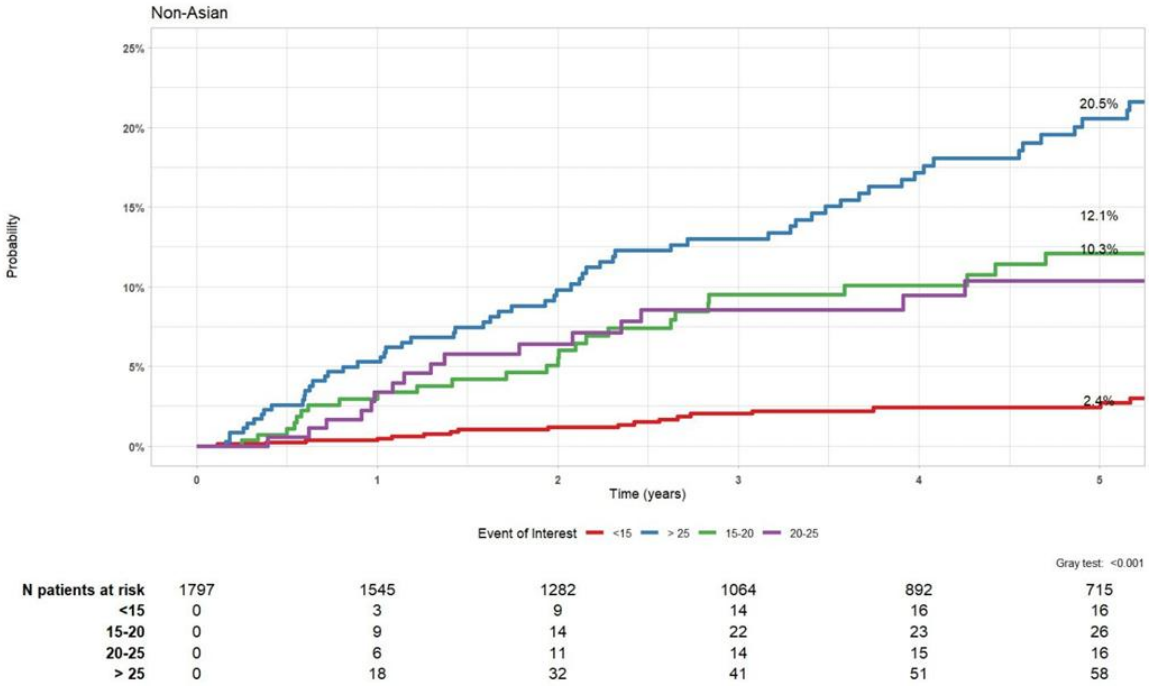


N patients at risk	6061	5704	4964	4505	4027	3529
Asian	0	5	14	18	20	22
Non-Asian	0	48	86	122	141	159

B

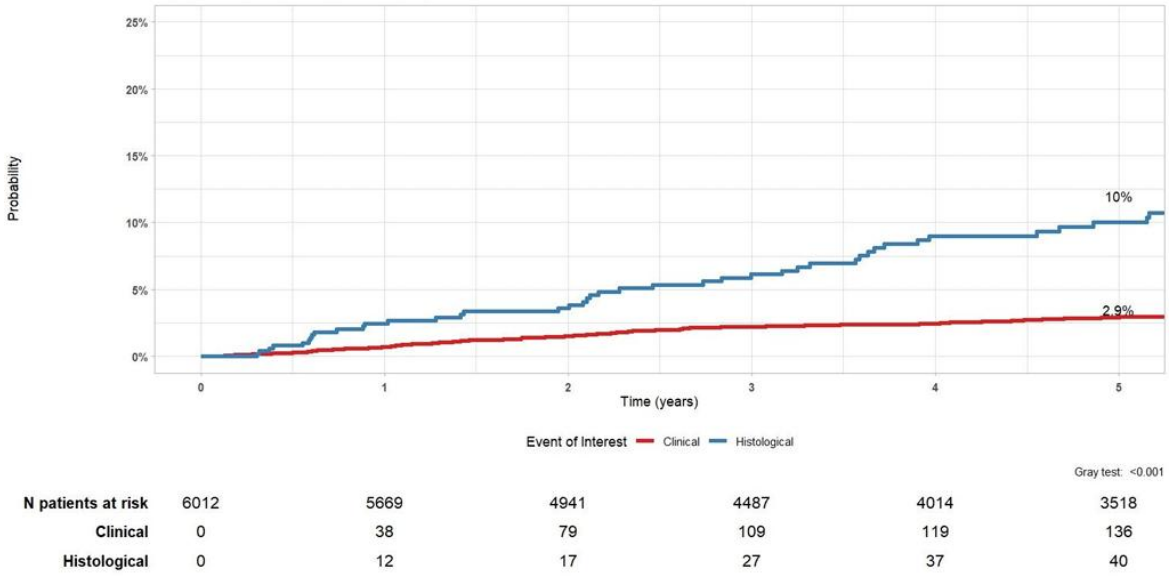


N patients at risk	4037	3957	3498	3284	2991	2690
<15	0	0	3	6	6	6
15-20	0	1	3	3	3	4
20-25	0	0	0	1	1	1
> 25	0	4	8	8	10	11



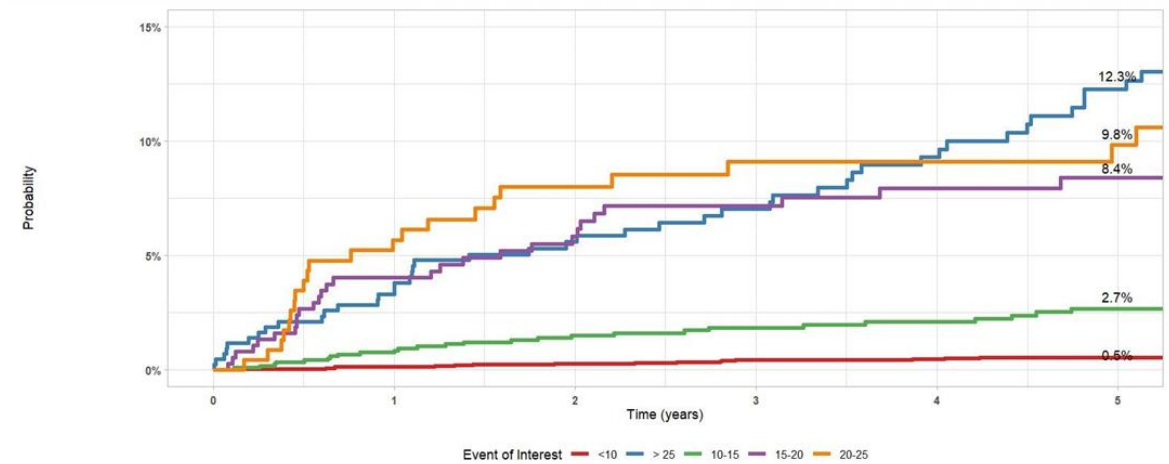
N patients at risk	1797	1545	1282	1064	892	715
<15	0	3	9	14	16	16
15-20	0	9	14	22	23	26
20-25	0	6	11	14	15	16
> 25	0	18	32	41	51	58

Figure 6. Five-year CIF of first decompensation in cACLD due to MASLD according to (A) ancestry and (B) both ancestry and LSM categories (<10 KPa, 10-15 KPa, 15-20 KPa, 20-25 KPa, ≥ 25 KPa).*cACLD, compensated advanced chronic liver disease; LSM, liver stiffness measurement.*



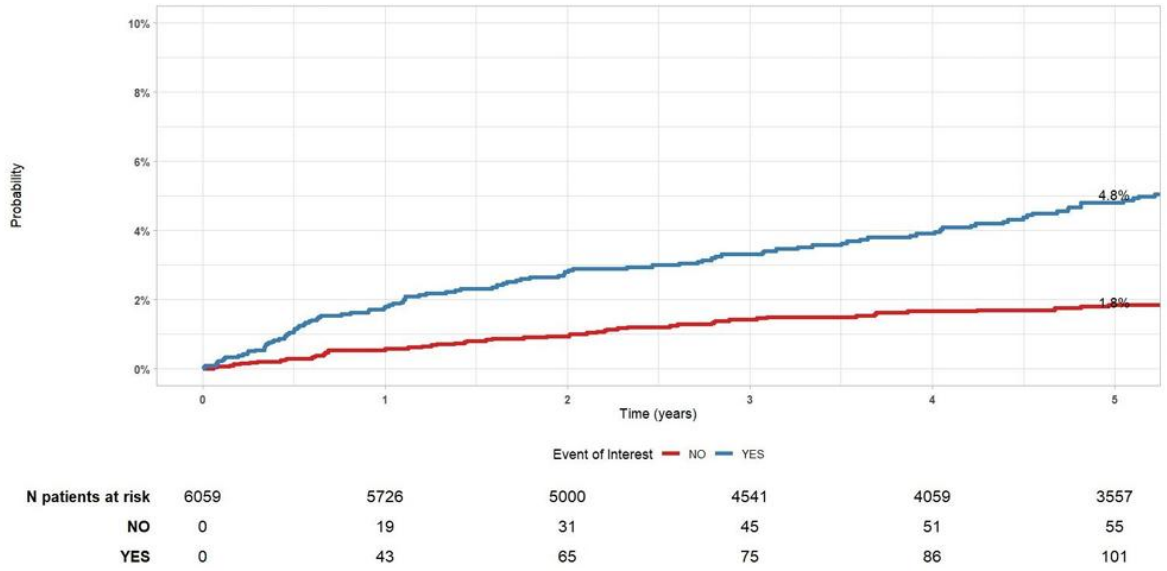
N patients at risk	6012	5669	4941	4487	4014	3518
Clinical	0	38	79	109	119	136
Histological	0	12	17	27	37	40

Figure 7. Five-year CIF of first decompensation in cACLD due to MASLD according to the histological or clinical diagnosis of the disease.*cACLD, compensated advanced chronic liver disease.*



N patients at risk	5834	5511	4800	4362	3894	3416
<10	0	4	8	13	14	16
10-15	0	9	17	20	22	26
15-20	0	15	21	25	27	28
20-25	0	13	18	20	20	21
> 25	0	16	23	28	35	43

A



B

Figure 8. Five-year CIF of HCC in cACLD due to MASLD according to (A) LSM categories (<10 KPa, 10-15 KPa, 15-20 KPa, 20-25 KPa, ≥ 25 KPa) and (B) the presence or absence of diabetes.

cACLD, compensated advanced chronic liver disease; HCC, hepatocellular carcinoma; LSM, liver stiffness measurement

Cause-specific Cox proportional hazards models were developed to evaluate the determinants of the first hepatic decompensation event and the occurrence of hepatocellular carcinoma (HCC). The model for decompensation included the same set of covariates used in the main analyses, while the model for HCC focused specifically on liver stiffness measurement (LSM) categories and the presence of diabetes as key predictors. The detailed results of these analyses are presented in **Table 4**.

Table 4. Competing risk analysis (cause-specific Cox) assessing the effect of LSM, diabetes, race, and type of cACLD diagnosis on the cause-specific hazard of first decompensation, and of LSM and diabetes on the cause-specific hazard of HCC in patients with cACLD due to MASLD.

Setting	Variables	HR	95% C.I.	P value
Outcome: First decompensation*				
cACLD	LSM >15-20 KPa vs <15	5.72	(3.47-9.42)	<0.001
	LSM >20-25 KPa vs <15	5.24	(3.03-9.06)	<0.001
	LSM >25 KPa vs <15	7.41	(4.74-11.5)	<0.001
	LSM >30.7 KPa vs. ≤30.7 KPa	2.25	(1.58-3.21)	<0.001
	Diabetes	1.16	(0.88-1.54)	0.27
	Nonasiatic vs Asiatic population	6.15	(4.01-9.43)	<0.001
	Histological vs Clinical diagnosis	1.38	(1.00-1.91)	0.04
	LSM 15-20 KPa vs <15 in Asiatic patients	8.69	(2.52–29.9)	<0.001
	LSM >20-25 KPa vs <15 in Asiatic patients	9.70	(2.04-46.1)	0.004
	LSM >25 KPa vs <15 in Asiatic patients	20.3	(7.24–57.4)	<0.001
	LSM >30.7 KPa vs. ≤30.7 KPa in Asiatic patients	8.81	(3.15-24.6)	<0.001
	LSM >15-20 KPa vs <15 in nonasiatic patients	2.48	(1.44–4.23)	<0.001
	LSM >20-25 KPa vs <15 in nonasiatic patients	2.21	(1.24-3.93)	0.006
	LSM >25 KPa vs <15 in nonasiatic patients	3.05	(1.92-4.84)	<0.001
	LSM >30.7 KPa vs. ≤30.7 KPa in nonasiatic patients	1.55	(1.08-2.32)	0.01
Outcome: Hepatocellular carcinoma				
cACLD	Diabetes	1.63	(1.21-2.21)	0.001
	LSM 15-20 KPa vs <15	4.63	(3.02-7.12)	<0.001
	LSM >20-25 KPa vs <15	4.18	(2.53-6.90)	<0.001
	LSM >25 KPa vs <15	3.84	(2.54-5.81)	<0.001
	LSM >30.7 KPa vs ≤30.7	2.04	(1.39-3.00)	<0.001

* Models adjusted for the variables object of investigation and for age>60 years, PLT>150/mmc, diabetes, albumin <3.6 g/dL .Abbreviations: cACLD, compensated advanced chronic liver disease; MASLD, metabolic-dysfunction associated steatotic liver disease; PLT, platelets

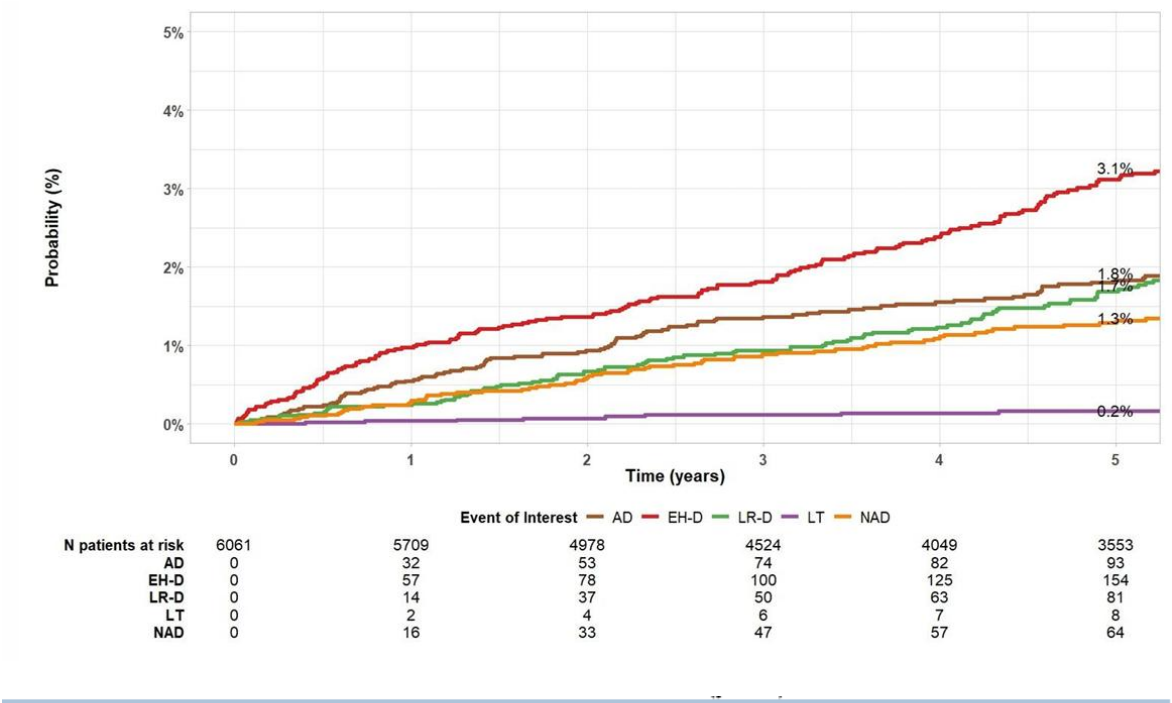
3.3 Patterns of Acute and Non-Acute Decompensation

The study further classified decompensating events into acute (AD) and non-acute (NAD) patterns, based on clinical presentation and triggering factors. Acute decompensation was characterized by the sudden onset of complications such as rapid ascites formation, acute variceal bleeding, or abrupt hepatic encephalopathy often precipitated by identifiable events like bacterial infection, gastrointestinal hemorrhage, or medication-related hepatotoxicity. In contrast, non-acute decompensation evolved gradually, reflecting progressive hepatic and systemic dysfunction without a clear precipitant.

In this cohort, NAD was more frequent than AD, representing approximately two-thirds of all first decompensation cases. Patients with NAD tended to have more advanced portal hypertension and worse metabolic and renal profiles, while those with AD often had lower baseline liver stiffness but were more susceptible to acute inflammatory or infectious triggers.

Despite these phenotypic differences, survival analyses revealed that both AD and NAD conferred a similarly poor prognosis, with comparable liver-related mortality rates after onset. This finding emphasizes that, in MASLD-related cACLD, the distinction between acute and non-acute modes of decompensation may have limited prognostic discrimination, as both mark a critical transition in disease trajectory.

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. (**Figure 2C**)



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

Figure 2C. A five years 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.

The analysis of cumulative incidence revealed that the probability of developing an acute decompensation (AD) event progressively increased over time. Specifically, the estimated cumulative incidences of AD at 1, 3, and 5 years were 0.5% (95% CI 0.4–0.7), 1.3% (95% CI 1.0–1.7), and 1.8% (95% CI 1.5–2.2), respectively. These data indicate a relatively low short-term risk, with a gradual but consistent rise in event rates over the study period.

Similarly, the cumulative incidence of non-acute decompensation (NAD) also showed a time-dependent increase, although with slightly lower values compared to AD. The estimated incidences were 0.3% (95% CI 0.15–0.41) at 1 year, 0.9% (95% CI 0.63–1.13) at 3 years, and 1.3% (95% CI 1.0–1.6) at 5 years (Table 5).Taken together, these findings suggest that while both AD and NAD remain relatively uncommon within the first few years of follow-up, their likelihood increases steadily over time, reflecting the progressive nature of liver disease in this population.

Table 5. Cumulative incidence at 1, 3 and 5 years of first and further decompensation split into AD and NAD, with death and LT as competing events in patients with cACLD due to MASLD.

Setting	Years	Death	LT	AD	NAD
First decompensation	**1**	0.17 (0.13-0.2)	0.03 (0.001-0.1	0.5 (0.4-0.7)	0.3 (0.15-0.41)
	3	2.8 (2.4-3.3)	0.11 (0.04-0.2)	1.3 (1-1.7)	0.9 (0.63-1.13)
	5	4.7 (4.2-5.4)	0.02 (0.06-0.27)	1.8 (1.5-2.2)	1.3 (1-1.6)
Setting	**Years**	**Death**	**LT**	**AD**	**NAD**
Further decompensation	**1**	18 (13.6-22.8)	3.76 (1.9-6.6)	7.9 (5-11.5)	12 (8.4-16.3)
	3	26.6 (21.2-32.2)	5.1 (2.8-8.3)	13.4 (9.5-18.1)	20 (15.1-24.4)
	5	30 (23.5-35.2)	5.6 (3.2-9)	16.7 (11.5-21.1)	23.2 (17.8-29)

Abbreviations: cACLD, compensated advanced chronic liver disease; MASLD, metabolic-dysfunction associated steatotic liver disease; LT, liver transplantation; AD, acute decompensation; NAD, non-acute decompensation. Data are given as %.

3.4 Further Decompensation and Disease Progression

Following the first decompensation, a notable proportion of patients developed further decompensation events, confirming the progressive nature of advanced MASLD-cACLD. 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**).

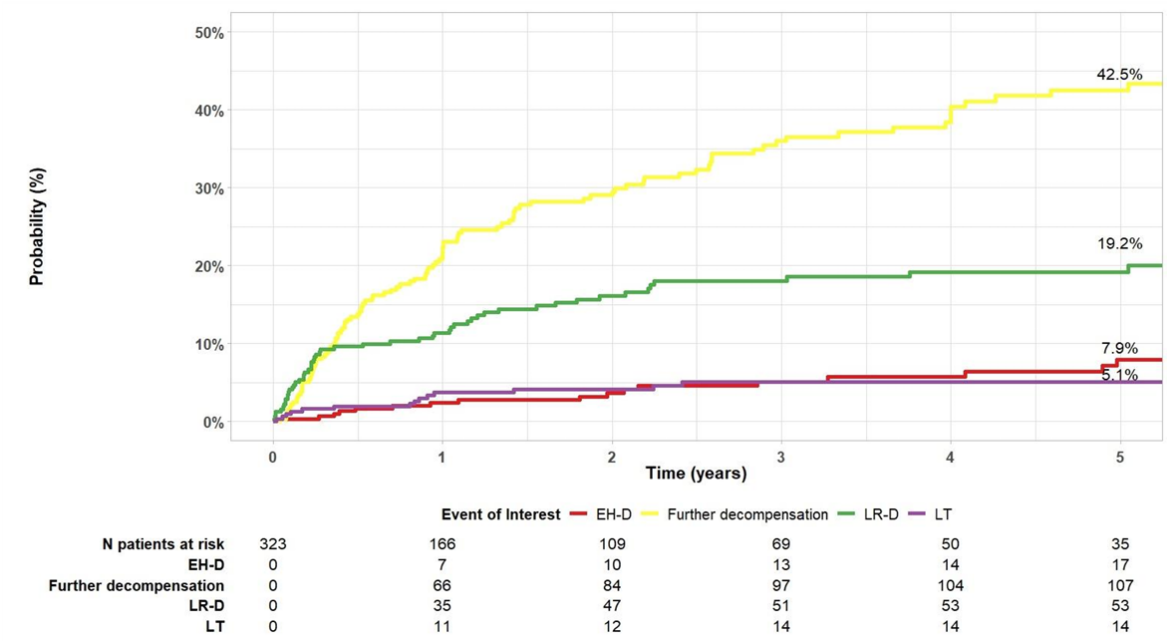


Figure 9A

The **figure 9A** 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**).

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	Death	First decompensation	LT
First decompensation	**1**	1.7 (1.4-2)	0.9 (0.7-1.1)	0.03 (0-0.1)
	3	2.8 (2.4-3.2)	2.6 (2.2-3)	0.01 (0.004-0.02)
	5	4.7 (4.1-5.3)	3.5 (0.3-0.4)	0.02 (0.006-0.02)
Setting	**Years**	**Death**	**Further decompensation**	**LT**
Further decompensation	**1**	17 (12.9-21.6)	23.4 (18.6-28.6)	3.5 (1.8-6.2)
	3	25.1 (20-30.4)	37.7 (31.6-43.7)	4.8 (2.7-7.9)
	5	28.3 (22.1-33.2)	43.9 (37.2-50.2)	5.3 (3-8.5)

Abbreviations: cACLD, compensated advanced chronic liver disease; MASLD, metabolic-dysfunction associated steatotic liver disease; LT, liver transplantation.
Data are given as % (95% CI).

The pattern of recurrent events varied according to the initial mode of presentation. Patients whose first decompensation was ascites were more likely to experience recurrent ascites, while those who initially presented with hepatic encephalopathy or variceal bleeding frequently developed multiple types of complications over time.

Notably, the presence of comorbid conditions such as chronic kidney disease or cardiovascular disorders significantly increased the likelihood of multiple decompensations, reflecting a state of multisystemic vulnerability. The interval between first and subsequent events shortened progressively, suggesting a decline in hepatic compensatory capacity and systemic resilience.

The cumulative incidences of the different types of further decompensation over a 5-year follow-up period are illustrated in **Figure 9B**. Overall, 34.9% (95% CI 29.21–39.94) of patients developed ascites, 10.6% (95% CI 7.46–14.43) experienced variceal bleeding, and 8% (95% CI 4.99–11.01) had more than two decompensating events. Hepatic encephalopathy (HE) and jaundice occurred less frequently, representing less common manifestations of disease progression within this timeframe.

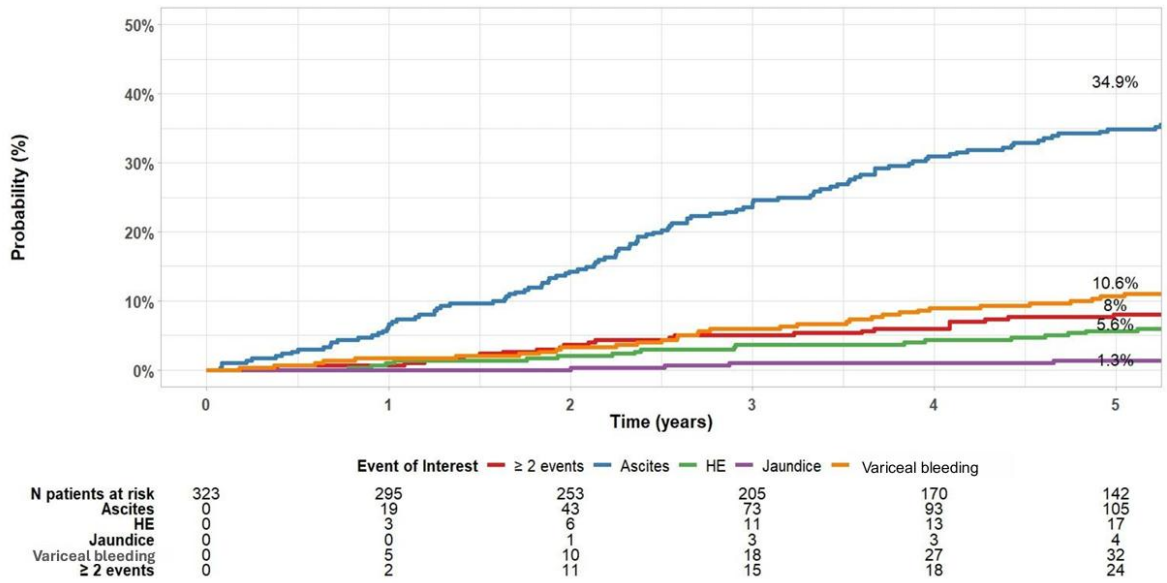


Figure 9B Five-year CIF of major events in cACLD due to MASLD after first decompensation. (B) CIF of the clinical presentation of the further decompensation.

3.5 Cumulative incidence of further decompensation stratified by AD and NAD

When examining the pattern of further decompensation, either in the form of acute decompensation (AD) or non-acute decompensation (NAD), complete data were available for 114 out of the 132 patients who experienced an additional decompensating event. **Figure 9C** illustrates the 5-year cumulative incidence functions (CIF) of AD and NAD, taking into account death and liver transplantation (LT) as competing risks, in patients with compensated advanced chronic liver disease (cACLD) secondary to MASLD.

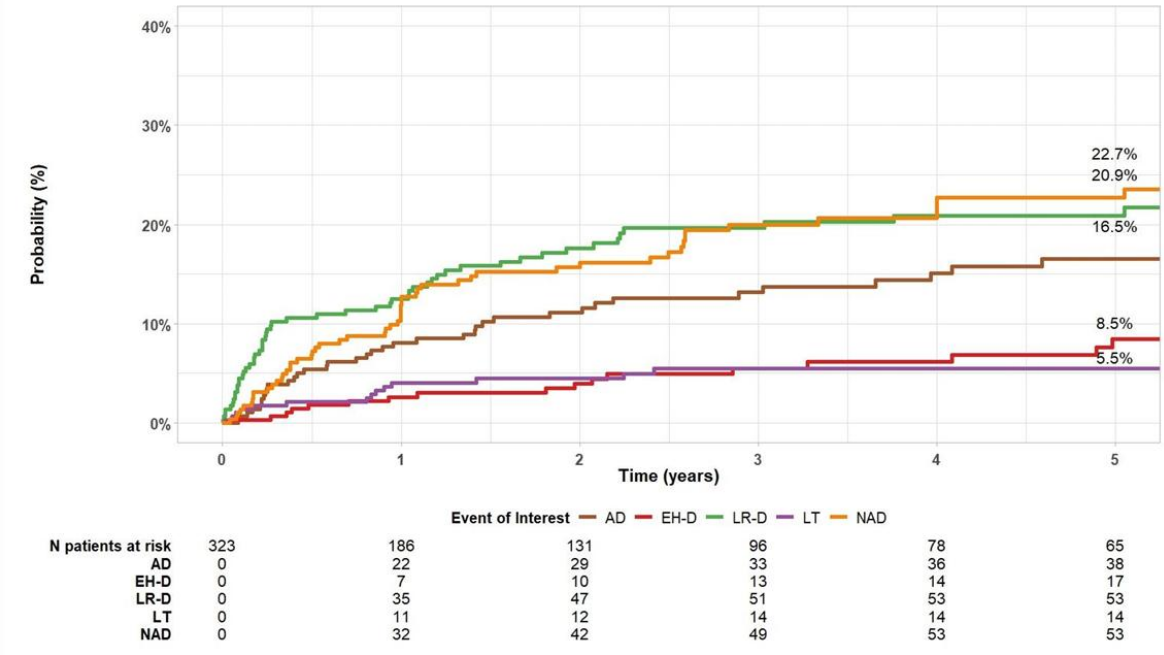


Figure 9C Five-year CIF of major events in cACLD due to MASLD after first decompensation. Showing the "acute" or "non-acute" presentation of further decompensation. AD, acute decompensation

Over the follow-up period, the cumulative incidence of AD was 7.9% (95% CI 5.0–11.5) at 1 year, 13.4% (95% CI 9.5–18.1) at 3 years, and 16.7% (95% CI 11.5–21.1) at 5 years. In comparison, the cumulative incidence of NAD was slightly higher, with values of 12% (95% CI 8.4–16.3), 20% (95% CI 15.1–24.4), and 23.2% (95% CI 17.8–29.0) at 1, 3, and 5 years, respectively (Supplementary Table 2). These findings highlight the progressive nature of liver dysfunction in this cohort, with a steady increase in both AD and NAD events over time, and a somewhat greater likelihood of NAD compared to AD throughout the study period.

Table 5. Cumulative incidence at 1, 3 and 5 years of first and further decompensation split into AD and NAD, with death and LT as competing events in patients with cACLD due to MASLD

Setting	Years	LR-D	EH-D	LT	AD	NAD
cACLD	**1**	0.2 (0.1-0.3)	0.9 (0.7-0.12)	0.03 (0.001-0.1)	0.5 (0.4-0.7)	0.3 (0.15-0.41)
	3	0.9 (0.7-1.2)	1.8 (1.4-2.2)	0.11 (0.04-0.2)	1.3 (1-1.7)	0.9 (0.63-1.13)
	5	1.7 (1.3-2.1)	3.1 (2.6-3.6)	0.02 (0.06-0.27)	1.8 (1.5-2.2)	1.3 (1-1.6)
Setting	**Years**	**LR-D**	**EH-D**	**LT**	**AD**	**NAD**
First decompensation	**1**	12.5 (8.9-16.7)	2.2 (0.9-4.5)	3.76 (1.9-6.6)	7.9 (5-11.5)	12 (8.4-16.3)
	3	19.6 (14.9-24.7)	4.9 (2.7-8.2)	5.1 (2.8-8.3)	13.4 (9.5-18.1)	20 (15.1-24.4)
	5	20.8 (16.0-26.2)	7.6 (4.4-11.9)	5.6 (3.2-9)	16.7 (11.5-21.1)	23.2 (17.8-29)

3.6 Liver-Related Mortality and Competing Risks

Over the course of the follow-up period, liver-related death (LRD) emerged as one of the most common adverse outcomes, affecting approximately 15–20% of the overall study population. This finding underscores the significant impact of hepatic complications on the long-term prognosis of patients with compensated advanced chronic liver disease (cACLD) due to MASLD. However, it is noteworthy that extrahepatic deaths (EHD) predominantly attributable to cardiovascular events and various malignancies represented a comparable, and in some cases even greater, proportion of total mortality.

This observation points to the complex interplay between liver-specific and systemic factors in determining patient outcomes. While progressive hepatic dysfunction remains a major driver of morbidity and mortality, the coexistence of metabolic comorbidities, such as diabetes, obesity, and cardiovascular disease, substantially contributes to the overall risk profile of these individuals. Consequently, the clinical course of MASLD-related cACLD cannot be understood solely in terms of liver disease progression; rather, it reflects a broader multisystem involvement characteristic of metabolic dysfunction.

Taken together, these findings highlight the dual burden of hepatic and extrahepatic mortality in this population, emphasizing the need for an integrated approach to patient management. Strategies aimed not only at preventing hepatic decompensation but also at mitigating cardiovascular and oncological risks are essential to improve long-term outcomes.

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).The figure 10A shows the 5-year CIF of LR-D, with further decompensation, LT, and EH-D considered as competing risks.

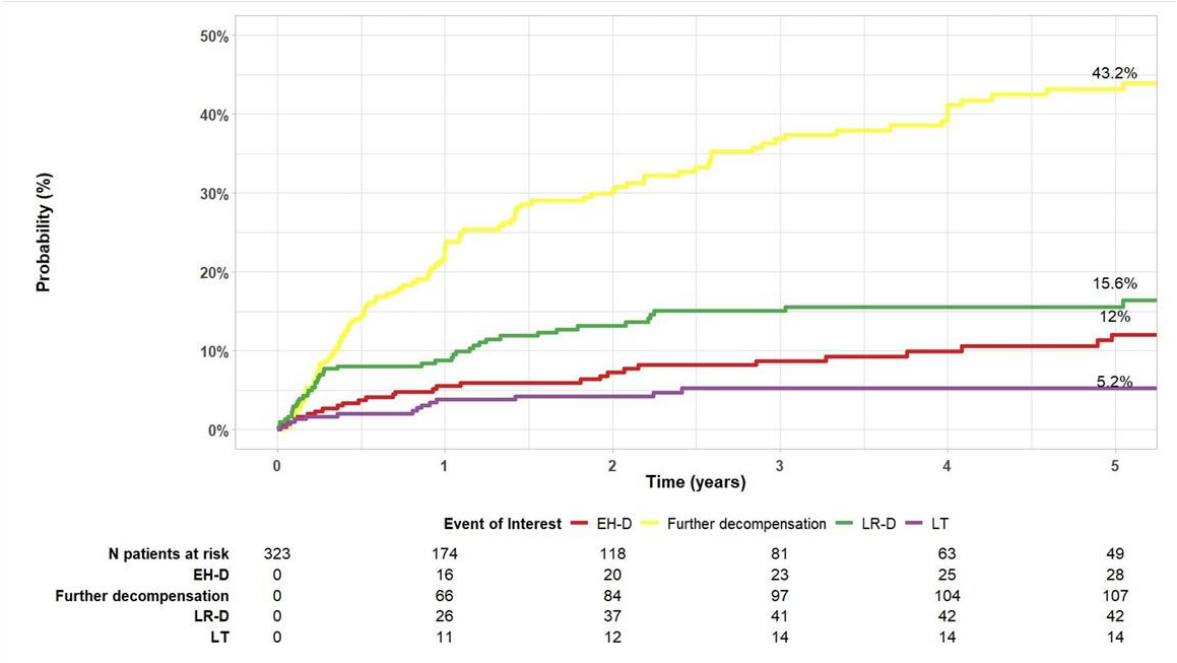


Figure 10A . Five-year CIF of death. (A) Five-year CIF of further decompensation, death (LR-D and EH-D) and LT in MASLD cACLD with first decompensation.

The competing risk analysis reported in **Table 6** 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.

Table 6. Cumulative incidence of LR-D at 1, 3 and 5 years.

Setting	Years	LR-D	EH-D	Further decompensation	LT
First decompensation	**1**	10	6.1	23.7	3.6
	3	15.1	8.7	38.1	4.9
	5	15.5	11.2	44.3	5.4
Setting	**Years**	**LR-D**	**EH-D**	**-**	**-**
Further decompensation	**1**	44.4	14.3	-	-
	3	61.9	19	-	-
	5	74.6	20.6	-	-

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).

In the multivariable Cause-specific Cox model, first decompensation as a time-varying covariate (HR 18.94, 95% CI 10.87-32.99, p 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 7**).

Table 7 . Competing risk analysis (cause-specific Cox) of variables associated with the cause specific hazard of LR-D at first and further decompensation and both split into AD and NAD in cACLD due to MASLD.

Setting	Variables	HR	95% C.I.	P value
First decompensation	Male	1.39	0.97-1.98	0.069
	Age >60 years	4.70	2.59-8.51	<0.001
	PLT <150/mmc	0.85	0.54-1.32	0.47
	Diabetes	0.95	0.67-1.36	0.81
	HCC	2.95	2.02-4.31	<0.001
	Albumin <3.5 g/dL	2.03	1.30-3.18	0.001
	First decompensation	18.94	10.87-32.99	<0.001
First decompensation split into AD and NAD	Male	1.66	1.09-2.53	0.01
	Age >60 years	4.76	2.51-9.03	<0.001
	PLT <150/mmc	0.69	0.40-1.17	0.17
	Diabetes	0.92	0.61-1.36	0.68
	HCC	3.64	2.33-5.66	<0.001
	Albumin <3.5 g/dL	1.94	1.21-3.10	0.005
	AD	20.64	10.19-41.81	<0.001
	NAD	19.4	9.66-40.35	<0.001
Further decompensation	Male	1.33	0.89-1.99	0.15
	Age >60 years	3.09	1.59-5.98	<0.001
	PLT <150/mmc	0.70	0.45-1.09	0.12
	Diabetes	0.92	0.61-1.38	0.69
	HCC	1.57	1.11-2.20	0008
	Albumin <3.5 g/dL	1.71	1.05-2.78	0.02
	Further decompensation	1.62	1.03-2.54	0.03
Further decompensation split into AD and NAD	Male	1.45	0.91-2.30	0.11
	Age >60 years	2.87	1.40-5.87	0.003
	PLT <150/mmc	0.60	0.37-0.97	0.04
	Diabetes	1.05	0.68-1.63	0.79
	HCC	1.74	1.21-2.50	0.002
	Albumin <3.5 g/dL	1.77	1.07-2.94	0.02
	AD	1.48	0.87-2.51	0.04
	NAD	1.44	0.83-2.47	0.04

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

The cumulative incidence of liver-related mortality (LRD) following the first episode of decompensation, stratified according to the type of event—acute (AD) or non-acute (NAD)—is illustrated in **Figure 10B**.

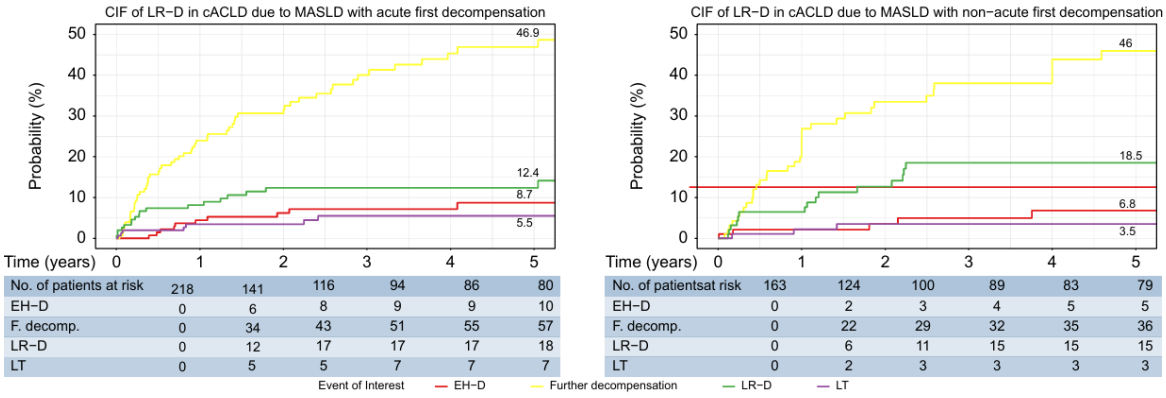


Fig 10B. Fiveyear CIF showing the "acute" or "non-acute" presentation of first decompensation, death (LR-D and EH-D) and LT in MASLD cACLD.

This analysis was conducted in patients with compensated advanced chronic liver disease (cACLD) secondary to MASLD, considering further decompensation events, liver transplantation (LT), and extrahepatic death (EHD) as competing risks. Over the 5-year observation period, patients who experienced an acute decompensation had cumulative incidences of LRD of 8.1% (95% CI 4.4–13.3) at 1 year, 11.5% (95% CI 6.8–17.5) at 3 years, and 12.4% (95% CI 7.5–18.6) at 5 years. In comparison, among those with a first non-acute decompensation, the corresponding incidences were 6.5% (95% CI 2.6–12.7) at 1 year and increased to 17.1% (95% CI 9.7–26.1) at both 3 and 5 years (**Table 8**).

Table 8. Cumulative incidence at 1, 3, and 5 years of LR-D, with further decompensation, EH-D, and LT as competing events in patients with cACLD due to MASLD who experienced first decompensation, stratified by AD and NAD (upper panel). 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, stratified by AD and NAD (bottom panel).

Setting	Years	LR-D	EH-D	LT	Further decompensation
First acute decompensation	**1**	8.1 (4.4-13.3)	3.7 (1.4-7.9)	2.7 (0.9-6.4)	23.2 (16.6-30.5)
	3	11.5 (6.8-17.5)	6.2 (2.9-11.3)	4.5 (1.8-9.1)	40.1 (31.2-48.8)
	5	12.4 (7.5-18.6)	8.7 (4.3-15.1)	5.5 (2.4-10.6)	46.9 (37-56.2)
First non-acute decompensation	**1**	6.5 (2.6-12.7)	2.1 (0.4-6.8)	1.1 (0.1-5.3)	23.4 (15.2-32.6)
	3	17.1 (9.7-26.1)	5 (1.6-11.4)	2.2 (0.4-7)	36.5 (26.1-46.9)
	5	17.1 (9.7-26.1)	5 (1.6-11.4)	2.2 (0.4-7)	43.9 (32.1-55)
Setting	**Years**	**LR-D**	**EH-D**	**LT**	**Further decompensation**
Further acute decompensation	**1**	20.8 (7.3-39)	20.8 (7.3-39.1)	-	-
	3	41.7 (21.5-60.8)	29.2 (12.5-48.2)	-	-
	5	62.5 (34.8-76)	33.3 (15.3-52.6)	-	-
Further non-acute decompensation	**1**	46.2 (26.1-64.1)	0	-	-
	3	69.2 (46.6-83.8)	7.7 (1.2-22.5)	-	-
	5	80.8 (57.6-92.1)	11.5 (2.6-27.9)	-	-

These findings indicate that the risk of liver-related death remains considerable in both groups, although patients with NAD appear to reach similar or even higher cumulative risks over time.

Multivariable cause-specific Cox regression analysis further confirmed the prognostic significance of the first decompensating event. Both acute and non-acute decompensation, when included as time-varying covariates, were independently associated with an increased risk of LRD. Specifically, the hazard ratio (HR) was 20.64 (95% CI 10.20–41.81; $p < 0.001$) for AD and 19.4 (95% CI 9.66–40.36; $p < 0.001$) for NAD (**Table 7**).

These results underscore the pivotal role of the first decompensation—regardless of its clinical presentation—as a critical turning point in the natural history of MASLD-related cACLD, marking a substantial shift toward higher mortality risk and poorer long-term prognosis.

3.8 Cumulative incidence of liver-related mortality at further decompensation

When evaluating mortality outcomes among patients with cACLD secondary to MASLD who experienced further episodes of decompensation, a marked increase in liver-related deaths (LRD) over time was observed. The cumulative incidences of LRD were 41.3% (95% CI 29.0–53.2) at 1 year, 61.9% (95% CI 48.5–72.8) at 3 years, and 74.6% (95% CI 59.8–82.5) at 5 years. These figures are substantially higher than those observed for extrahepatic deaths (EHD), which accounted for 12.7% (95% CI 5.9–22.3), 19% (95% CI 10.4–29.7), and 20.6% (95% CI 11.6–31.5) at the same time points, respectively (**Table 6**).

Figure 10C graphically illustrates the divergence between the 5-year cumulative incidence functions (CIF) of LRD and EHD. It is worth noting that, within this subgroup, no patients underwent liver transplantation during follow-up, highlighting the absence of this potential life-saving intervention.

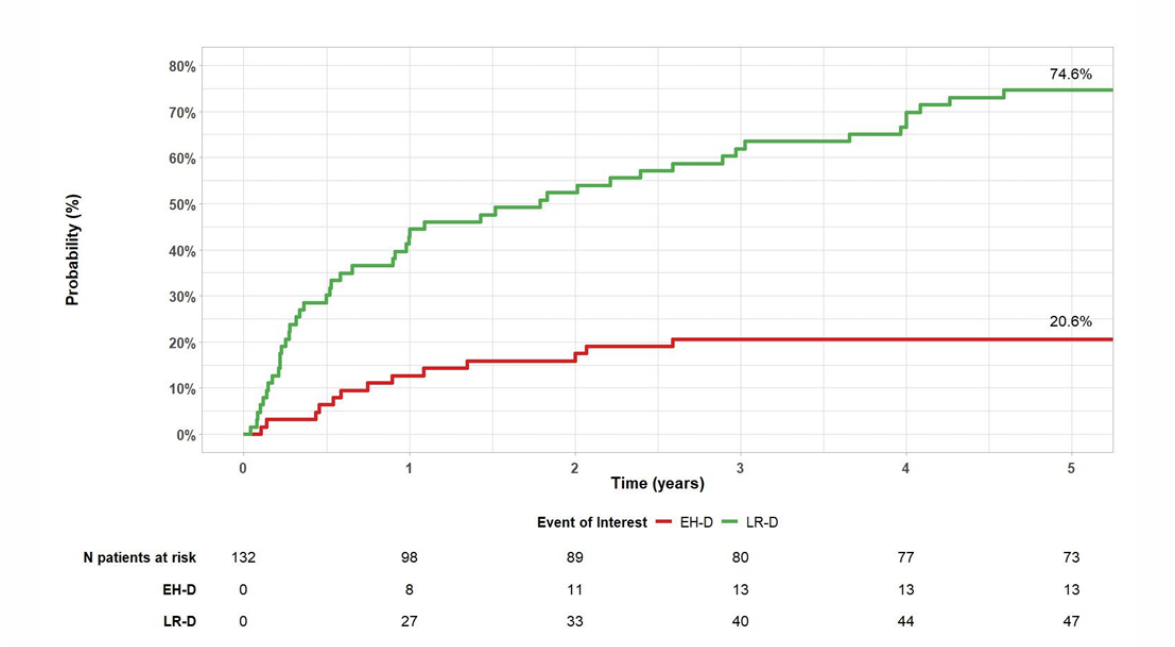


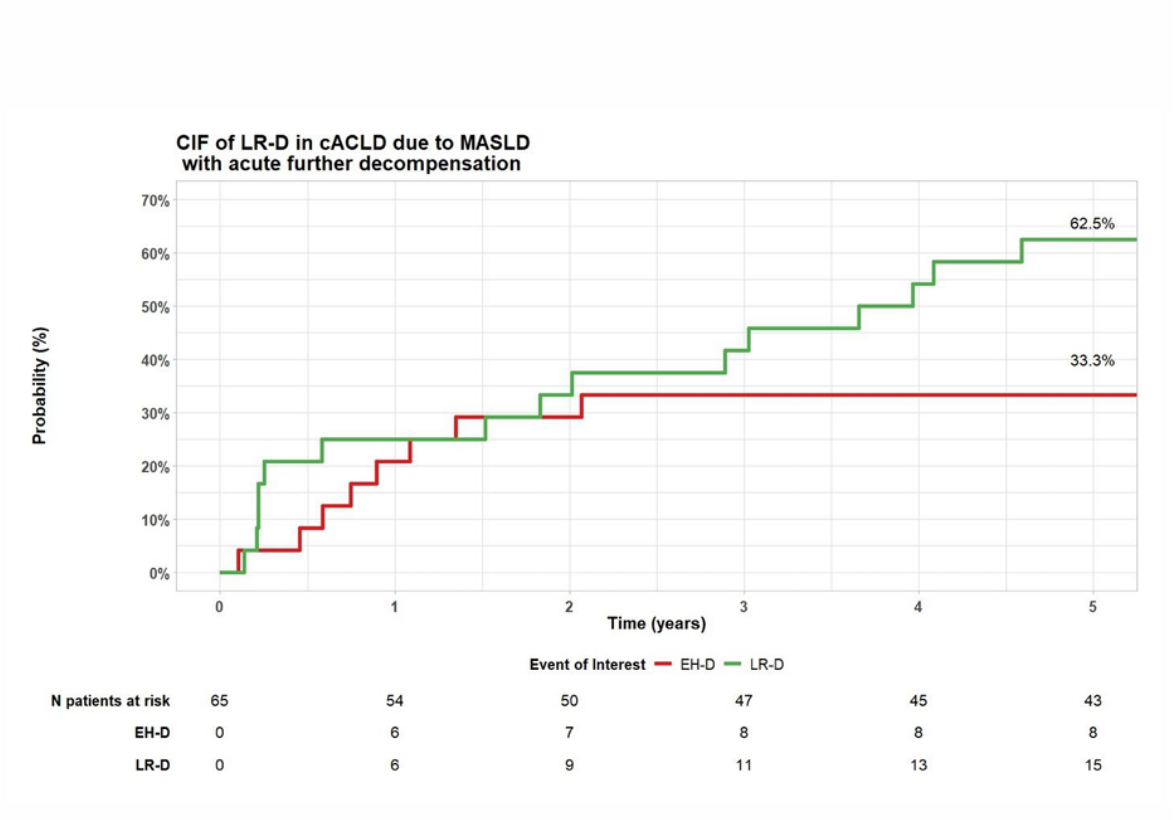
Figure 10C. Five-year CIF of LR-D and EH-D in MASLD cACLD with further decompensation.

In the multivariable cause-specific Cox regression model, several factors were identified as independent predictors of liver-related mortality. The occurrence of further decompensation, included as a time-varying covariate, was significantly associated with an increased risk of LRD (HR 1.52, 95% CI 1.02–2.34; p = 0.04). In addition, age greater than 60 years (HR 3.85, 95% CI 1.96–7.57; p = 0.001) and the development of hepatocellular carcinoma (HCC) (HR 1.43, 95% CI 1.03–2.00; p = 0.03) emerged as strong and independent prognostic factors (**Table 7**).

Taken together, these results underscore the severe prognostic implications of further decompensation in MASLD-related cACLD. The steep rise in liver-related mortality over time emphasizes how recurrent or progressive decompensating events mark a critical turning point in disease trajectory. Moreover, the association with older age and HCC highlights the multifactorial nature of mortality risk in this population, in which both hepatic and systemic factors contribute to the overall clinical outcome.

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

The analysis of liver-related mortality (LRD) following further episodes of decompensation, stratified by the type of event—acute (AD) or non-acute (NAD)—provides important insights into the prognosis of patients with MASLD-related cACLD. As illustrated in **Figure 10D**, the 5-year cumulative incidence functions (CIF) of LRD were estimated while considering extrahepatic death (EHD) as a competing risk.



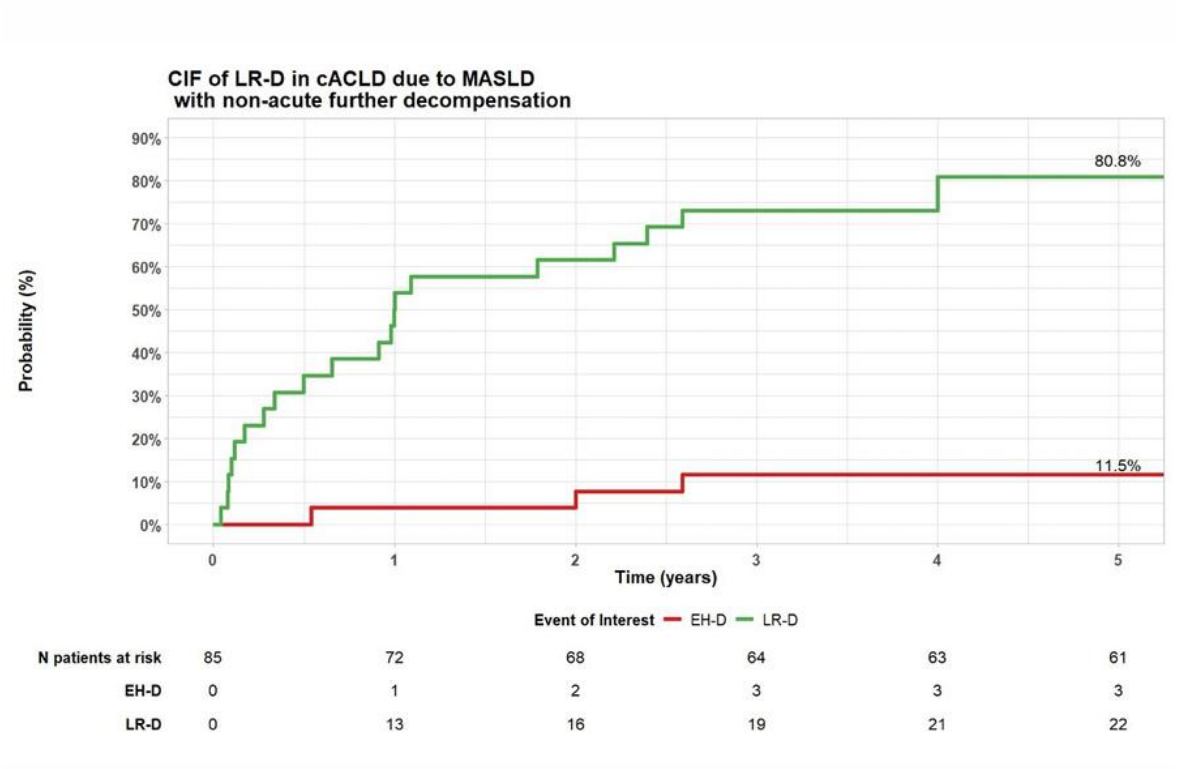


Figure 10D - Five-year CIF showing the "acute" or "non-acute" presentation of further decompensation, death (LR-D and and EH-D in MASLD cACLD with further decompensation.

Among patients who experienced further acute decompensation, the cumulative incidence of LRD progressively increased from 20.8% (95% CI 7.3–39.0) at 1 year, to 41.7% (95% CI 21.5–60.8) at 3 years, and reached 62.5% (95% CI 34.8–76.0) at 5 years. In contrast, those who underwent further non-acute decompensation showed even higher rates, with cumulative incidences of 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) at 1, 3, and 5 years, respectively (**Table 8**).

These findings indicate that, while both patterns of further decompensation carry a substantial risk of liver-related death, NAD is associated with a particularly unfavorable long-term outcome, suggesting a more insidious yet relentless progression of liver dysfunction in these patients.

In the multivariable cause-specific Cox regression model, both acute and non-acute further decompensation events emerged as independent predictors of liver-related mortality.

Specifically, the occurrence of acute decompensation was associated with an increased risk of LRD (HR 1.24, 95% CI 1.01–2.04; p = 0.04), as was non-acute decompensation (HR 1.27, 95% CI 1.02–2.01; p = 0.04) (**Table 7**).

Overall, these results reinforce the prognostic weight of recurrent decompensating events in the natural history of MASLD-related cACLD. Regardless of their clinical presentation, further decompensation episodes represent a major turning point that significantly worsens survival prospects, highlighting the need for early identification and proactive management of patients at risk of repeated liver deterioration.

4. Multistate Prognostic Model

The multistate model integrated the sequence of transitions between key clinical states: compensation, first decompensation, further decompensation, and death (either hepatic or extrahepatic). This dynamic framework allowed a nuanced understanding of the temporal relationships among events and their cumulative impact on prognosis.

The analysis confirmed that once decompensation occurred, the probability of returning to a compensated state was virtually negligible. The transition probability from first to further decompensation was high, underscoring the irreversible and self-reinforcing progression of the disease.

Importantly, the model revealed that extrahepatic mortality remained substantial at every disease stage, with cardiovascular deaths particularly prominent among those with preserved liver function but severe metabolic dysfunction.

Collectively, these results illustrate the multifaceted natural history of MASLD-related cACLD, in which hepatic decompensation, systemic comorbidities, and HCC interact dynamically to shape long-term outcomes.

The model in **Figure 11A** depicts the clinical course of those patients from the cACLD state to LR-D, EH-D and LT through first and further decom pensation. Interestingly, nearly 30% of patients with cACLD due to MASLD died from EH-D without developing any decompensation event. After developing the first decompen sation, 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.

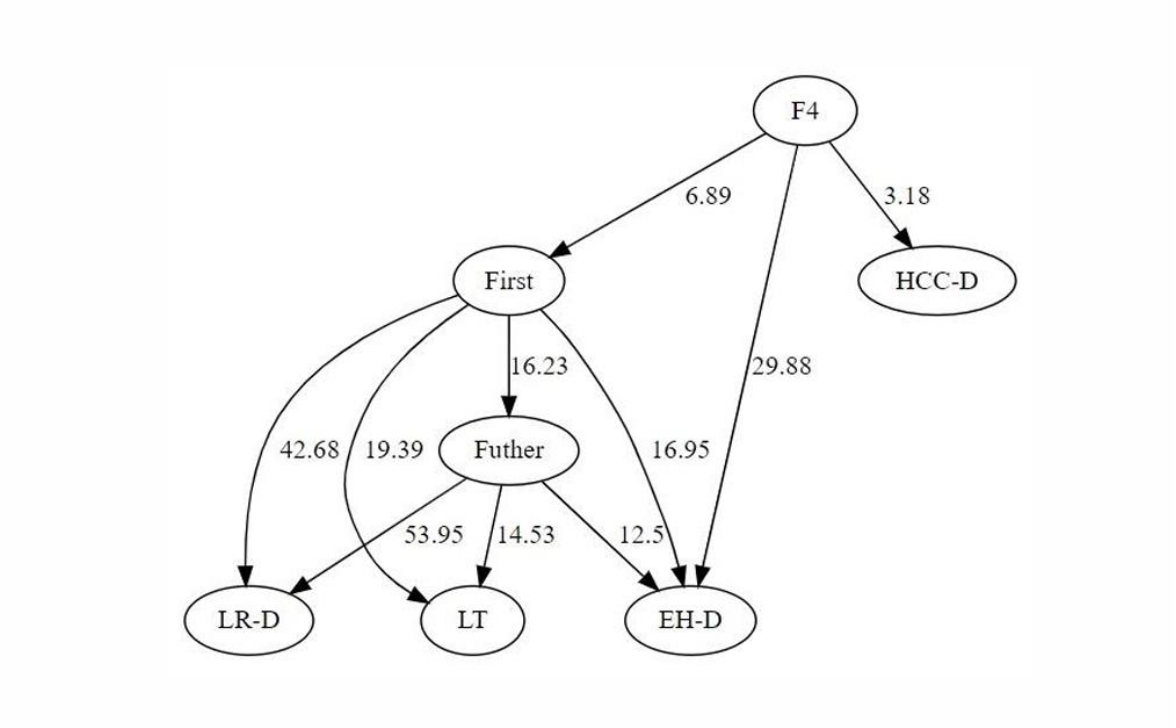


Figure 11. (A) Multistate model summarizing the clinical course in patients with cACLD due to MASLD. Arrows represent transitions across the clinical states. Numbers close to the arrows are the 5-years transition rate assessed by competing risk analysis. **(B)** Five-year occupation probability of state occupation of patients with cACLD due to MASLD. **(C)** Five-year occupation probability of state occupation of patients with cACLD due to MASLD at first decompensation. **(D)** Five-year occupation probability of state occupation of patients with cACLD due to MASLD at further decompensation. *cACLD, compensated advanced chronic liver disease; LT, liver transplantation; HCC-D, hepatocellular carcinoma-related death; LR-D, liver-related death; EH-D, extra-hepatic death.*

The corresponding 5-year probabilities of state occupation for patients with cACLD due to MASLD (**Figure 11B**) 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).

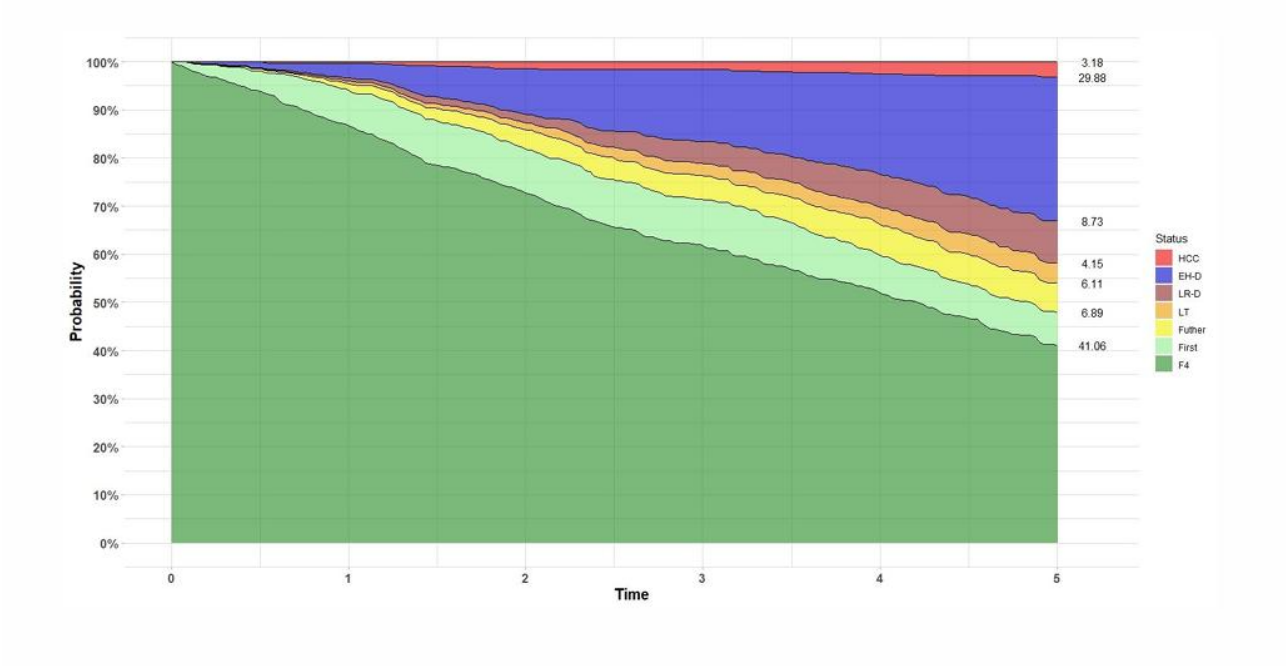


Figure 11B

Figure 11 C depicts the corresponding 5-year probabilities of state occupation after first decompensation: first decompen sation 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 decom pensation 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) (**Figure 11D**).

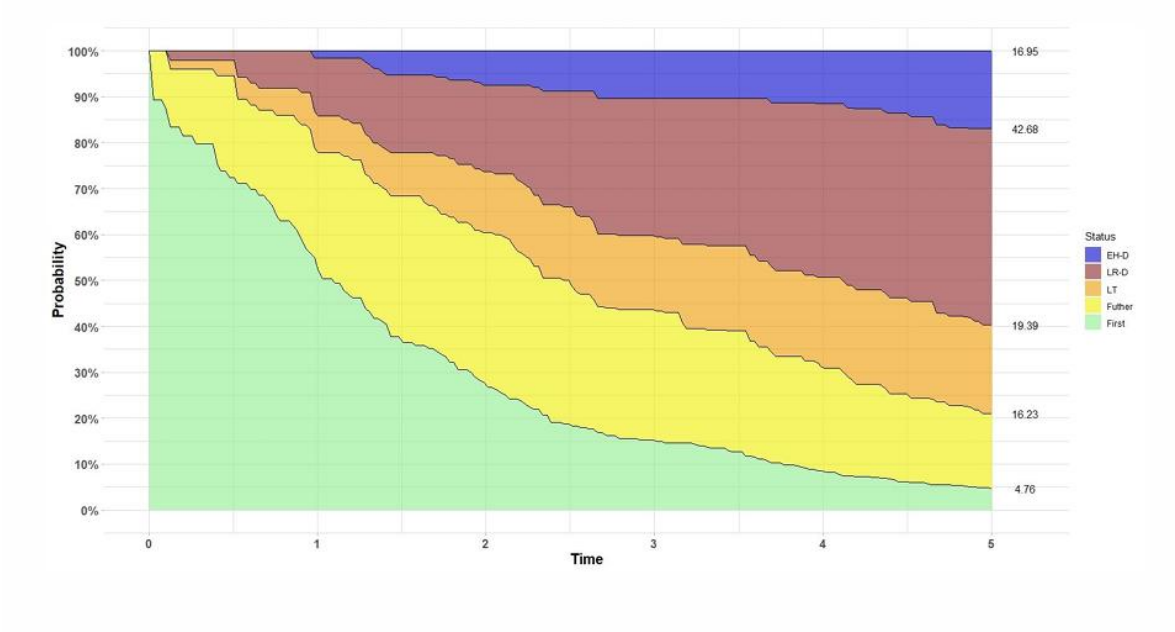


Figure 11C

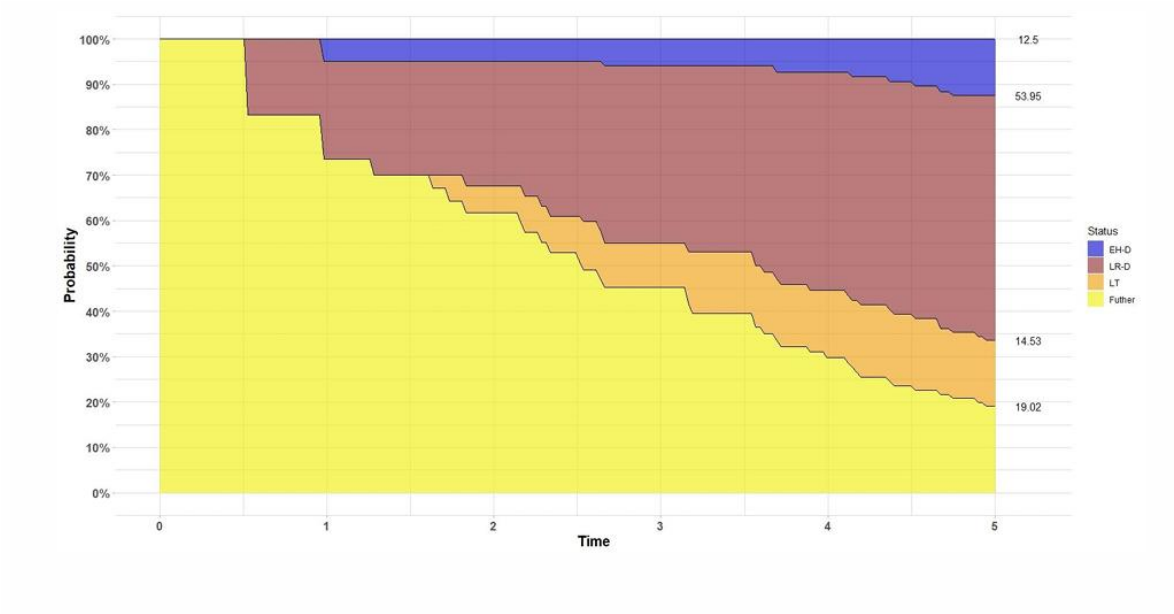

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Probability
0
1
2
3
4
5
Time
12.5
53.95
14.53
19.02
Status
EH-D
LR-D
LT
Futher

Figure 11D

5.Discussion

This multicenter study, which enrolled a total of 6,061 individuals with MASLD-related cACLD, provides a comprehensive overview of disease progression in this population. Over a 5-year period, the cumulative incidence of a first decompensation event was approximately 3.5%. Importantly, experiencing this initial decompensating episode was associated with a dramatic increase nearly 19-fold in the cause-specific hazard of liver-related mortality (LR-D).Among patients who did develop a first decompensation, almost half (44%) went on to experience further episodes within five years. These subsequent decompensation events were themselves associated with a significant worsening of prognosis, resulting in a 1.52-fold increase in the cause-specific hazard of LR-D. Across both first and recurrent episodes, ascites emerged as the most common clinical presentation, and the distinction between acute (AD) and non-acute (NAD) decompensation did not appear to substantially alter mortality risk, suggesting that both patterns reflect a similar underlying deterioration in hepatic function.
In addition, the development of hepatocellular carcinoma (HCC) was independently associated with an increased risk of liver-related death, irrespective of whether patients had previously experienced hepatic decompensation.

While existing literature suggests that the progression from MASH to clinically evident cACLD may occur more slowly compared with other etiologies, [31] once decompensation develops, the subsequent clinical trajectory appears to align with the pattern observed in other chronic liver diseases.[32] Recent studies have highlighted the prognostic differences between first and subsequent decompensation, as well as between AD and NAD, in patients with cACLD. However, evidence focusing specifically on MASLD has been scarce. By examining a large and exclusively metabolic cohort across multiple international centers, our study contributes important new insights into the natural history of MASLD-related cACLD. Previous research on similar outcomes has often involved heterogeneous cohorts, in which alcohol-related or viral hepatitis etiologies predominated, limiting the applicability of findings to patients with metabolic disease alone. [33, 34]

In our cohort, the competing risk analysis performed over a 5-year follow-up period showed that the incidence of a first decompensation event was relatively low (3.5%). Ascites represented by far the most frequent manifestation. Despite its low occurrence, the development of a first decompensation had important prognostic implications, leading to a

substantial rise in the hazard of liver-related death (LR-D). Indeed, among patients who decompensated, the cumulative 5-year LR-D rate reached 15.6%, highlighting how even a single decompensating episode signals a major shift in the clinical trajectory of MASLD-related cACLD.

When comparing these findings with the classical estimates reported by D'Amico et al., a few key differences emerge. Their study described a 5-year decompensation risk of 3% in patients without baseline varices and 28% in those with varices[34]. The higher rates observed in that setting likely reflect the inclusion of a broader spectrum of cirrhotic stages and etiologies, whereas our analysis was restricted to individuals already categorized within cACLD. Similarly, D'Amico et al. documented overall 5-year mortality rates of 20% and 30% in patients without and with varices, respectively—values that align closely with the combined 27% 5-year risk of LR-D and extrahepatic mortality (EH-D) observed in our cohort after first decompensation.

We also investigated the occurrence of further decompensation, which revealed a cumulative 5-year incidence of 43.9%, again with ascites as the most common event. These recurrent episodes had an even more profound prognostic impact, increasing the cumulative risk of LR-D to 74.6%. This pattern is consistent with the 52% rate of further decompensation reported by D'Amico et al. [33]and with the 39.5% incidence observed by Noureddin et al. in patients with MASLD-related cirrhosis [35].

However, some differences in liver-related mortality emerged when comparing our findings with previous studies. In our cohort, LR-D rates were higher, which may be explained partly by the low prevalence of viral etiologies (only 9%). In contrast, studies comprising a higher proportion of viral hepatitis often reported better outcomes, possibly due to the availability and effectiveness of antiviral therapies capable of modifying disease progression (36–38). Moreover, the significant burden of metabolic comorbidities in our cohort—such as diabetes, obesity, and cardiovascular disease—may have contributed to a faster progression of liver dysfunction and, consequently, to poorer long-term survival. [20]

An important observation emerging from our analysis is that ascites represented the most common manifestation of decompensation, both at the time of the first episode and in the context of subsequent events. This pattern was followed by variceal bleeding, aligning well with previous reports in the literature [39,35]. In contrast, hepatic encephalopathy (HE)

occurred less frequently in our cohort. This finding differs from that of a recent U.S. study, in which HE was reported as a more prevalent complication [31]. Such discrepancies may reflect differences in baseline characteristics between populations, including the higher prevalence of obesity in U.S. cohorts, a factor that has been associated with increased susceptibility to cerebrovascular dysfunction and may influence the onset of HE. Similarly, the remarkably low incidence of jaundice in our study population contributes to ongoing discussions—such as those reflected in the Baveno VII consensus—regarding whether jaundice should be formally considered a decompensating event.

In order to better illustrate how first and subsequent decompensation events shape the natural course of MASLD-related cACLD, we applied a multistate modeling approach. This methodology enabled us to follow patients as they moved through different clinical stages, thereby providing a dynamic view of disease progression. For individuals who experienced a first decompensation, the model showed that, at 5 years, the probabilities of occupying each state were as follows: 4.7% remained in the first-decompensation state, 16% had progressed to further decompensation, 42% had reached liver-related death (LR-D), and 19% had undergone liver transplantation (LT).

The outlook was even more concerning for patients who progressed to further decompensation. In this group, the 5-year probability of remaining in the further-decompensation state increased to 19%, while the probabilities of LR-D and LT rose to 54% and 14%, respectively. These results clearly highlight how recurrent decompensation represents a pivotal turning point in MASLD-related cACLD, marking a period of accelerated clinical decline. Once patients move beyond the first decompensating event, the trajectory of their disease becomes markedly more severe, reinforcing the need for close monitoring and targeted therapeutic strategies in this high-risk population.

A few years ago, the CANONIC [20] and PREDICT [21] studies proposed an important conceptual distinction between acute and non-acute decompensation, helping to refine our understanding of the different clinical trajectories in advanced chronic liver disease. Building on this framework, we examined the same distinction within our cohort of patients with MASLD-related cACLD. It is worth noting, however, that our definition of acute decompensation (AD) differed slightly from that used in the CANONIC study, as we did not consider hospitalizations due to sepsis or other bacterial infections as AD events.

In our population, AD and NAD occurred with similar frequency, both at the time of first decompensation and during subsequent episodes. Interestingly, during first decompensation,

both patterns were associated with a comparable and substantial increase—approximately 20-fold—in the hazard of liver-related death (LR-D). This similarity persisted even in the context of further decompensation, suggesting that, in MASLD-related cACLD, the type of decompensation may be less important than the occurrence of decompensation itself in shaping overall prognosis.

These findings are consistent with observations by Tonon et al. (30), who also reported an even distribution of AD and NAD in a cohort of 617 patients with cACLD of mixed etiologies (with only 23% of cases attributed to metabolic causes). However, our results diverge from theirs in one important respect: while Tonon et al. identified a stronger impact of AD on mortality, we observed a greater mortality risk associated with NAD. Several factors might explain this difference. In our cohort, patients may have been more frail, as they often had an active and ongoing etiological driver—unlike cohorts dominated by treated viral hepatitis—and carried a heavier burden of metabolic comorbidities, which are known to accelerate hepatic deterioration [40].

Another key observation from our analysis is the independent prognostic weight of hepatocellular carcinoma (HCC). In both the entire cohort and in the subgroup of patients who experienced a first decompensation, HCC significantly increased the risk of LR-D, as demonstrated by our cause-specific Cox models. This reinforces the idea that HCC should not be viewed merely as an isolated complication but rather as a major disease modifier that profoundly influences survival in MASLD-related cACLD.

Given the complex clinical profile of patients with MASLD-related cACLD—particularly the well-recognized increase in extrahepatic complications such as cardiovascular disease and extrahepatic malignancies[41] we also explored the cumulative incidence of extrahepatic death (EH-D), treating it as a competing risk. The multistate model developed for this study, with a 5-year follow-up, offers important insight into how mortality patterns shift across the disease course. Among all patients with cACLD due to MASLD, approximately 30% of deaths were attributed to extrahepatic causes, making EH-D the leading cause of mortality in the overall cohort.

However, this distribution changed markedly once hepatic decompensation occurred. In patients who experienced a first decompensation, the proportion of EH-D dropped to 16%, and it declined even further—to about 12%—in those who progressed to recurrent decompensation. In parallel, liver-related mortality (LR-D) became increasingly dominant as the disease advanced. These results emphasize how, although MASLD is a systemic

disorder in which metabolic and extrahepatic conditions play a substantial role, liver-related complications ultimately become the primary determinant of survival once decompensation sets in. This finding underscores the importance of managing metabolic comorbidities aggressively in earlier disease stages, as these factors may significantly influence the overall prognosis independent of hepatic deterioration.

Noureddin et al. recently published crude decompensation rates in a cohort of over 2,000 patients with MASLD, providing valuable insights into disease burden.

Our study expands on this evidence in several important ways:

- it includes a larger sample restricted exclusively to patients with cACLD;

- it offers cumulative incidence estimates derived through competing risk methodology rather than simple crude rates;

- it incorporates time-dependent variables—specifically decompensation events and HCC—within cause-specific Cox models to more accurately assess mortality risk; and
- it separately evaluates the prognostic significance of acute and non-acute decompensation patterns.

Together, these elements provide a more nuanced and clinically relevant understanding of the natural history of MASLD-related cACLD.

The principal limitation of our work relates to its retrospective design. Although the patients included were monitored prospectively in their respective centers, the absence of a unified protocol and of standardized follow-up procedures inevitably restricted the consistency and completeness of several clinical variables. In particular, information on weight loss, lifestyle changes, and management of metabolic comorbidities was not uniformly available. The long period of patient enrollment may have further introduced performance bias and potential time-related effects.

Moreover, our analyses were based on secondary data extracted from larger databases originally designed to investigate trends in non-invasive tests. As a consequence, certain details that are highly relevant in the context of cirrhosis were incompletely captured. Examples include limited information on recompensation, hepatic venous pressure gradient

measurements, variceal status, specific therapeutic interventions (such as non-selective beta-blockers, statins, or albumin administration), assessments of portal hypertension using non-invasive tools, and data on portal vein thrombosis or TIPS (transjugular intrahepatic portosystemic shunt) placement. The absence of these parameters may influence the interpretation of some findings and represents an intrinsic constraint of the study design.

Another aspect to consider concerns the generalizability of our results. The cohort consisted of patients with MASLD-related cACLD referred to tertiary care centers and selected according to specific inclusion and exclusion criteria. While this approach ensured a homogeneous study population, it also introduces a degree of selection bias and limits the external validity of the conclusions. Missing data and the possibility of attrition bias pose additional methodological limitations. Furthermore, given the large number of statistical tests and models used in our analyses, the risk of type I errors—i.e., false-positive associations—cannot be completely ruled out and should be kept in mind when interpreting the significance of the reported results.

Finally, this study did not separate analyses based on the presence or absence of cirrhosis, as commonly done in MASH clinical trials. Additionally, the relatively low number of liver transplants observed in our cohort does not fully reflect the increasing recognition of MASLD as an important and growing indication for liver transplantation, highlighting another potential limitation of the dataset.

Lastly, our study did not include detailed information on the use of newer therapeutic options for hepatocellular carcinoma (HCC), which may significantly influence patient survival and therefore represent an additional limitation.

In conclusion, this study provides a comprehensive overview of the natural history of MASLD-related cACLD. Over a 5-year period, the majority of patients do not experience hepatic decompensation; rather, mortality is predominantly driven by extrahepatic comorbidities. However, once the first decompensation event occurs—and even more so after subsequent episodes—the pattern of mortality shifts: the likelihood of extrahepatic death decreases, while liver-related mortality becomes increasingly predominant, particularly when HCC is also present.

From a clinical perspective, these findings highlight the importance of accurately characterizing the disease trajectory in patients with MASLD-related cACLD. Stratifying individuals according to the occurrence of first versus further decompensation and considering the presence or absence of HCC may help identify those at greatest risk of

complications and death. Such an approach could support more personalized clinical management, allowing healthcare providers to optimize surveillance strategies and allocate resources more effectively for higher-risk patients.

In summary, this large multicenter study demonstrated that in MASLD-cACLD:

- The **first decompensation** marks a pivotal prognostic transition, leading to a sharp decline in survival;
- **Further decompensations** occur frequently and cumulatively worsen prognosis;
- **Both acute and non-acute** decompensation patterns carry similarly adverse outcomes;
- **HCC and extrahepatic comorbidities** significantly modify mortality trajectories;
- Multistate modeling confirms the irreversible progression once decompensation occurs.

Together, these findings provide robust evidence that the clinical course of MASLD-cACLD is characterized by interconnected hepatic and systemic pathways of decline, reinforcing the need for integrated surveillance and early intervention strategies. The challenge in the coming years will be to transform this data into concrete clinical pathways. The research provides the scientific basis for implementing the development and application of guidelines that take into account the patient's overall risk, not just liver damage.

References

1. Younossi, Z. M., Stepanova, M., Ong, J. P., Jacobson, I. M., Bugianesi, E., Duseja, A., Eguchi, Y., George, J., Goodman, Z., Marchesini, G., & Negro, F. (2023). Global burden of MASLD and its outcomes: 2023 update. Nature Reviews Gastroenterology & Hepatology, 20(8), 555–570. https://doi.org/10.1038/s41575-023-00724-0

2. Huang, D. Q., El-Serag, H. B., & Loomba, R. (2024). Global epidemiology of MASLD and MASH: Implications for liver health. Nature Reviews Gastroenterology & Hepatology, 21(1), 40–56. https://doi.org/10.1038/s41575-023-00793-1

3. Eslam, M., Sanyal, A. J., George, J., & International Consensus Panel. (2023). MAFLD redefined as metabolic dysfunction-associated steatotic liver disease (MASLD): Consensus-driven update of nomenclature. Journal of Hepatology, 79(3), 472–488. https://doi.org/10.1016/j.jhep.2023.05.002

4. Anstee, Q. M., Reeves, H. L., Kotsiliti, E., Govaere, O., & Heikenwalder, M. (2019). From NASH to HCC: Current concepts and future challenges. Nature Reviews Gastroenterology & Hepatology, 16(7), 411–428. https://doi.org/10.1038/s41575-019-0214-1

5. Targher, G., Byrne, C. D., & Tilg, H. (2021). NAFLD and increased risk of cardiovascular disease: Clinical associations, pathophysiological mechanisms and pharmacological implications. Gut, 70(9), 1692–1709. https://doi.org/10.1136/gutjnl-2020-320622

6. Rowe, I. A., Parker, R., & Newsome, P. N. (2022). NAFLD and liver transplantation: Current burden and future challenges. Journal of Hepatology, 77(6), 1680–1692. https://doi.org/10.1016/j.jhep.2022.07.018

7. Petta, S., Di Marco, V., & Craxì, A. (2022). Non-alcoholic fatty liver disease pathogenesis: The present and the future. Digestive and Liver Disease, 54(9), 1157–1167. https://doi.org/10.1016/j.dld.2022.05.010

8. Eslam, M., Newsome, P. N., Sarin, S. K., Anstee, Q. M., Targher, G., Romero-Gomez, M., Zelber-Sagi, S., Wai-Sun Wong, V., Dufour, J. F., & George, J. (2020). A new definition for metabolic associated fatty liver disease: An international expert consensus statement. Journal of Hepatology, 73(1), 202–209. https://doi.org/10.1016/j.jhep.2020.03.039

9. Tilg, H., Adolph, T. E., & Moschen, A. R. (2021). Multiple parallel hits hypothesis in NAFLD revisited. Hepatology, 73(2), 833–842. https://doi.org/10.1002/hep.31518

10. Buzzetti, E., Pinzani, M., & Tsochatzis, E. A. (2016). The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). Metabolism: Clinical and Experimental, 65(8), 1038–1048. https://doi.org/10.1016/j.metabol.2015.12.012

11. Lefere, S., & Tacke, F. (2019). Macrophages in obesity and non-alcoholic fatty liver disease: Crosstalk with metabolism. Journal of Hepatology, 73(2), 484–495. https://doi.org/10.1016/j.jhep.2020.04.013

12. Aron-Wisnewsky, J., Vigliotti, C., Witjes, J., Le, P., Holleboom, A. G., Verheij, J., Nieuwdorp, M., & Clément, K. (2020). Gut microbiota and human NAFLD: Disentangling microbial signatures from metabolic disorders. Nature Reviews Gastroenterology & Hepatology, 17(5), 279–297. https://doi.org/10.1038/s41575-020-0269-9

13. Romeo, S., Kozlitina, J., Xing, C., Pertsemlidis, A., Cox, D., Pennacchio, L. A., Boerwinkle, E., Cohen, J. C., & Hobbs, H. H. (2008). Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. Nature Genetics, 40(12), 1461–1465. https://doi.org/10.1038/ng.257

14. Abul-Husn, N. S., Cheng, X., Li, A. H., Xin, Y., Schurmann, C., Stevis, P., Liu, Y., Kozlitina, J., Stender, S., Wood, G. C., … Dewey, F. E. (2018). A protein-truncating HSD17B13 variant and protection from chronic liver disease. New England Journal of Medicine, 378(12), 1096–1106. https://doi.org/10.1056/NEJMoa1712191

15. Sookoian, S., & Pirola, C. J. (2019). Genetic predisposition in nonalcoholic fatty liver disease. Clinical Molecular Hepatology, 25(3), 305–315. https://doi.org/10.3350/cmh.2019.0004

16. De Franchis, R., Bosch, J., Garcia-Tsao, G., Reiberger, T., & Ripoll, C. (2022). Baveno VII – Renewing consensus in portal hypertension. Journal of Hepatology, 76(4), 959–974. https://doi.org/10.1016/j.jhep.2021.12.022

17. Castera, L., Friedrich-Rust, M., & Loomba, R. (2022). Noninvasive assessment of liver disease in 2022: The dawn of precision hepatology. Journal of Hepatology, 77(4), 1021–1035. https://doi.org/10.1016/j.jhep.2022.05.005

18. D'Amico, G., Garcia-Tsao, G., & Pagliaro, L. (2018). Natural history and prognostic indicators of survival in cirrhosis: A systematic review of 118 studies. Journal of Hepatology, 69(5), 1163–1174. https://doi.org/10.1016/j.jhep.2018.07.018

19. Pennisi, G., Toniutto, P., Vilar-Gomez, E., et al. (2025). Prognostic impact of first and subsequent decompensation in MASLD-related compensated advanced chronic liver disease: A multicenter international study. Hepatology. (In press).

20. Moreau, R., Jalan, R., Gines, P., Pavesi, M., Angeli, P., Cordoba, J., Durand, F., Gustot, T., Saliba, F., Domenicali, M., … CANONIC Study Investigators. (2013). Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology, 144(7), 1426–1437.e9. https://doi.org/10.1053/j.gastro.2013.02.042

21. Trebicka, J., Fernandez, J., Papp, M., Caraceni, P., Laleman, W., Gambino, C., D'Amico, G., Bernardi, M., Arroyo, V., & PREDICT Study Group. (2021). PREDICT identifies three clinical courses of decompensated cirrhosis that have distinct pathophysiology. Journal of Hepatology, 75(4), 840–854. https://doi.org/10.1016/j.jhep.2021.05.005

22. Tonon, F., et al. (2023). Acute and non-acute decompensation in metabolic cirrhosis: Clinical patterns and outcomes. Hepatology Communications, 7(2), 214–228. https://doi.org/10.1002/hep4.2305

23. Vilar-Gomez, E., & Chalasani, N. (2023). Nonalcoholic fatty liver disease: The new burden of metabolic liver disease. Hepatology, 77(5), 1655–1669. https://doi.org/10.1002/hep.32760

24. Loomba, R., Friedman, S. L., & Shulman, G. I. (2021). Mechanisms and disease consequences of nonalcoholic fatty liver disease. Cell, 184(10), 2537–2564. https://doi.org/10.1016/j.cell.2021.04.015

25. Kanwal, F., Singal, A. G., & El-Serag, H. B. (2023). Hepatocellular carcinoma surveillance in patients with NAFLD/MASLD. Clinical Gastroenterology and Hepatology, 21(1), 21–29. https://doi.org/10.1016/j.cgh.2022.07.024

26. Angulo, P., Kleiner, D. E., Dam-Larsen, S., Adams, L. A., Bjornsson, E. S., Charatcharoenwitthaya, P., Mills, P. R., Keach, J. C., Lafferty, H. D., Stahler, A., & Haflidadottir, S. (2015). Liver fibrosis, but no other histologic features, associates with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology, 149(2), 389–397.e10 https://doi.org/10.1053/j.gastro.2015.04.043

27. Dulai, P. S., Singh, S., Patel, J., Soni, M., Prokop, L. J., Younossi, Z., Sebastiani, G., & Loomba, R. (2017). Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis. Hepatology, 65(5), 1557–1565. https://doi.org/10.1002/hep.29085

28. Taylor, R. S., Taylor, R. J., Anstee, Q. M., & Brown, R. M. (2020). Factors associated with progression or regression of fibrosis in nonalcoholic fatty liver disease: Systematic review and meta-analysis. Gastroenterology, 158(8), 1941–1956.e3. https://doi.org/10.1053/j.gastro.2020.01.043

29. Ripoll, C., Groszmann, R., Garcia-Tsao, G., Grace, N., Burroughs, A. K., Planas, R., Escorsell, À., Garcia-Pagán, J. C., Makuch, R., Patch, D., Matloff, D. S., Bosch, J., & Portal Hypertension Collaborative Group. (2007). Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology, 133(2), 481–488. https://doi.org/10.1053/j.gastro.2007.05.024

30. Colecchia, A., Ravaioli, F., Marasco, G., Colli, A., Dajti, E., Di Biase, A. R., Bacchi-Reggiani, M. L., Andreone, P., & Bernardi, M. (2018). A combined model based on spleen stiffness measurement and Baveno VI criteria to rule out high-risk varices in advanced chronic liver disease. Journal of Hepatology, 69(2), 308–317. https://doi.org/10.1016/j.jhep.2018.03.009

31. Sanyal AJ, Van Natta ML, Clark J, et al. Prospective study of outcomes in adults with nonalcoholic fatty liver disease. N Engl J Med 2021 Oct 21;385 (17):1559–1569. https://doi.org/10.1056/NEJMoa2029349. PMID: 34670043; PMCID: PMC8881985.

32. Allen AM, Therneau TM, Ahmed OT, et al. Clinical course of non-alcoholic fatty liver disease and the implications for clinical trial design. J Hepatol 2022 Nov;77(5):1237–1245. https://doi.org/10.1016/j.jhep.2022.07.004. Epub 2022 Jul 16. PMID: 35843374; PMCID: PMC9974107.

33. D'Amico G, Zipprich A, Villanueva C, et al. Further decompensation in cirrhosis: results of a large multicenter cohort study supporting Baveno VII statements. Hepatology 2024 Apr 1;79(4):869–881. https://doi.org/10.1097/HEP.0000000000000652. Epub 2023 Nov 2. PMID: 37916970.

34. D'Amico G, Pasta L, Morabito A, et al. Competing risks and prognostic stages of cirrhosis: a 25-year inception cohort study of 494 patients. Aliment Pharmacol Ther 2014 May;39(10):1180–1193. https://doi.org/10.1111/apt. 12721. Epub 2014 Mar 24. PMID: 24654740.

35. Noureddin N, Huang DQ, Bettencourt R, et al. Natural history of clinical outcomes and hepatic decompensation in metabolic dysfunction associated steatotic liver disease. Aliment Pharmacol Ther 2024 Jun;59 (12):1521–1526. https://doi.org/10.1111/apt.17981. Epub 2024 Apr 3. PMID: 38571305.

36. Krassenburg LAP, Maan R, Ramji A, et al. Clinical outcomes following DAA therapy in patients with HCV-related cirrhosis depend on disease severity. J Hepatol 2021 May;74(5):1053–1063. https://doi.org/10.1016/j.jhep.2020. 11.021. Epub 2020 Nov 23. PMID: 33242501.

37. Lens S, Alvarado-Tapias E, Mariño Z, et al. Effects of all-oral anti-viral therapy on HVPG and systemic hemodynamics in patients with hepatitis C virus-associated cirrhosis. Gastroenterology 2017 Nov;153(5):1273–1283. e1. https://doi.org/10.1053/j.gastro.2017.07.016. Epub 2017 Jul 20. PMID: 28734831.

38. Lens S, Baiges A, Alvarado-Tapias E, et al. Clinical outcome and hemo dynamic changes following HCV eradication with oral antiviral therapy in patients with clinically significant portal hypertension. J Hepatol 2020 Dec;73(6):1415–1424. https://doi.org/10.1016/j.jhep.2020.05.050. Epub 2020 Jun 12. PMID: 32535060

39. Ferenci P, Lockwood A, Mullen K, et al. Hepatic encephalopathy–definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. Hep atology 2002 Mar;35(3):716–721. https://doi.org/10.1053/jhep.2002.31250. PMID: 11870389.

40. Targher G, Byrne CD, Tilg H. MASLD: a systemic metabolic disorder with cardiovascular and malignant complications. Gut 2024 Mar 7;73(4):691– 702. https://doi.org/10.1136/gutjnl-2023-330595. PMID: 38228377.

41. Pennisi G, Enea M, Romero-Gomez M, et al. Liver-related and extrahepatic events in patients with non-alcoholic fatty liver disease: a retrospective competing risks analysis. Aliment Pharmacol Ther 2022 Mar;55(5):604–615. https://doi.org/10.1111/apt.16763. Epub 2022 Jan 5. PMID: 34988994.

42. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat 1988:1141–1154.