

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

Grazia Pennisi, Gabriele Di Maria, Vincent Wai-Sun Wong, Victor de Ledinghen, Giada Sebastiani, Mauro Viganò, Anna Ludovica Fracanzani, Luca Miele, Elisabetta Bugianesi, Mattias Ekstedt, Roberta D'Ambrosio, Federico Ravaioli, Filippo Schepis, Fabio Marra, Alessio Aghemo, Gianluca Svegliati-Baroni, Marcello Persico, Luca Valenti, Annalisa Berzigotti, Jacob George, Angelo Armandi, Patrik Nasr, Stergios Kechagias, Antonio Liguori, Dario Saltini, Yuly P. Mendoza, Vincenza Calvaruso, Marco Enea, Huapeng Lin, Giuseppe Infantino, Mario Masarone, Nicola Pugliese, Adele Tulone, Vito Di Marco, Calogero Cammà, Salvatore Petta

Table of contents

Supplementary tables.....	2
Supplementary figures.....	7

Supplementary tables

Table S1. 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).

Table S2. 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
<i>cACLD</i>	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
<i>First decompensation</i>	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)

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 %.

Table S3. 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
cACLD	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/mm³, diabetes, albumin <3.6 g/dL
Abbreviations: cACLD, compensated advanced chronic liver disease; MASLD, metabolic-dysfunction associated steatotic liver disease; PLT, platelets.

Table S4. 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
<i>First acute decompensation</i>	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)
<i>First non-acute decompensation</i>	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
<i>Further acute decompensation</i>	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)	-	-
<i>Further non-acute decompensation</i>	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)	-	-

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

Table S5. 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
<i>cACLD with occurrence of first decompensation</i>	Male	1.39	0.97-1.98	0.069
	Age >60 years	4.70	2.59-8.51	<0.001
	PLT <150/mm ³	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
<i>cACLD with occurrence of first AD and NAD</i>	Male	1.66	1.09-2.53	0.01
	Age >60 years	4.76	2.51-9.03	<0.001
	PLT <150/mm ³	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
<i>First decompensation with occurrence of further decompensation</i>	NAD*	19.4	9.66-40.35	<0.001
	Male	1.43	0.96-2.13	0.07
	Age >60 years	3.85	1.96-7.57	<0.001
	Diabetes	0.84	0.56-1.25	0.40
	HCC*	1.43	1.03-2.00	0.03
<i>First decompensation with occurrence of further AD and NAD</i>	Further decompensation*	1.52	1.02-2.34	0.04
	Male	1.56	0.98-2.51	0.06
	Age >60 years	3.35	1.65-6.81	0.001
	Diabetes	1.04	0.67-1.62	0.84
	HCC*	1.63	1.14-2.33	0.006
	AD*	1.24	1.01-2.04	0.04
	NAD*	1.27	1.02-2.01	0.04

*Included as time-dependent covariate.

Abbreviations: cACLD, compensated advanced chronic liver disease; MASLD, metabolic-dysfunction associated steatotic liver disease; AD, acute decompensation; NAD, non-acute decompensation; HCC, hepatocellular carcinoma; PLT, platelets.

Supplementary figures

Fig. S1. The Sankey Plot reporting the major outcomes that occurred in the clinical history of MASLD cACLD patients.

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.

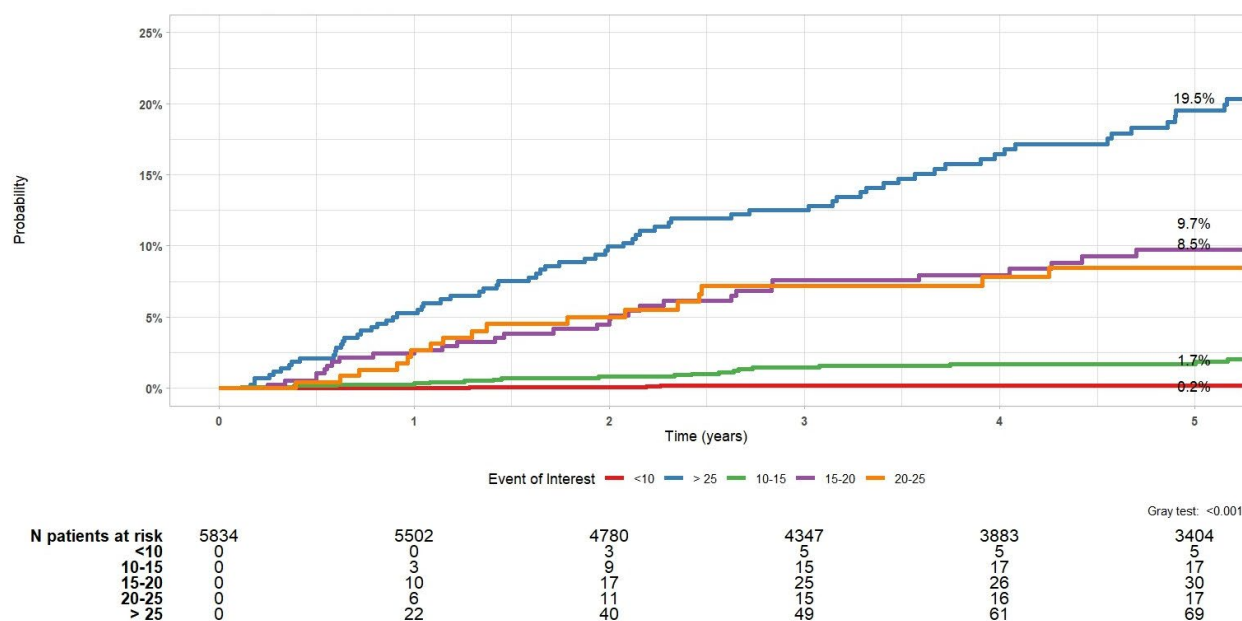


Fig. S2. Five-year CIF of first decompensation in cACLD due to MASLD according to LSM categories (<10 KPa, 10-15 KPa, 15-20 KPa, 20-25 KPa, ≥ 25 KPa).

cACLD, compensated advanced chronic liver disease; LSM, liver stiffness measurement.

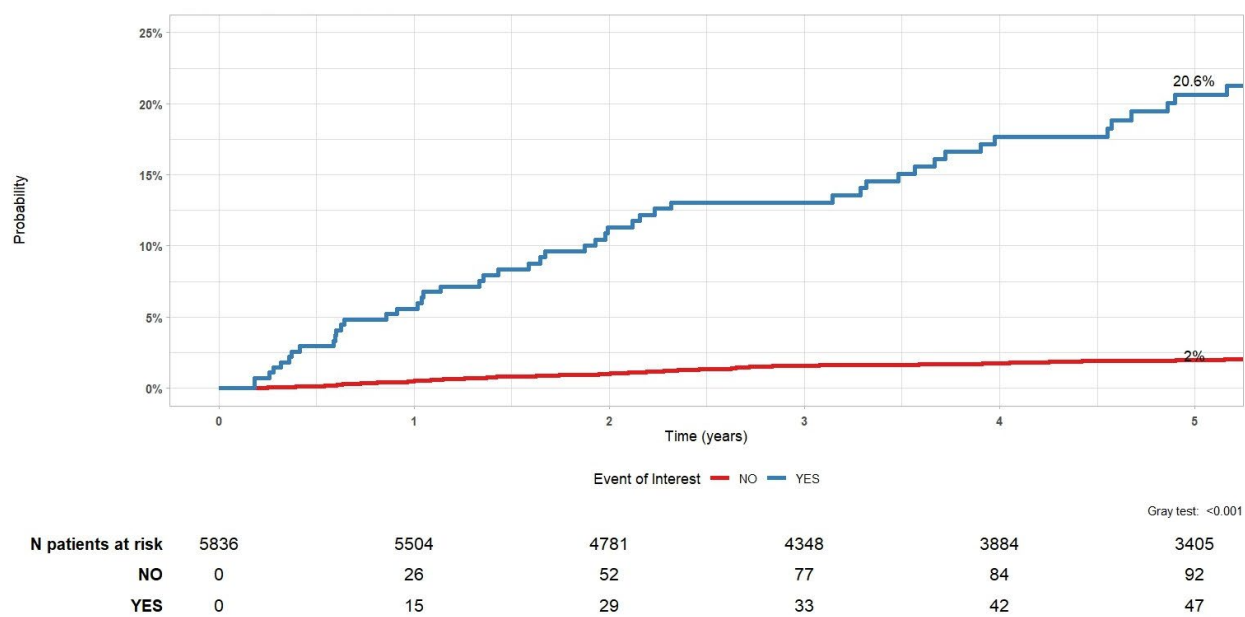


Fig. S3. Five-year CIF of first decompensation in cACLD due to MASLD according to LSM >30.7 KPa.

cACLD, compensated advanced chronic liver disease; LSM, liver stiffness measurement.

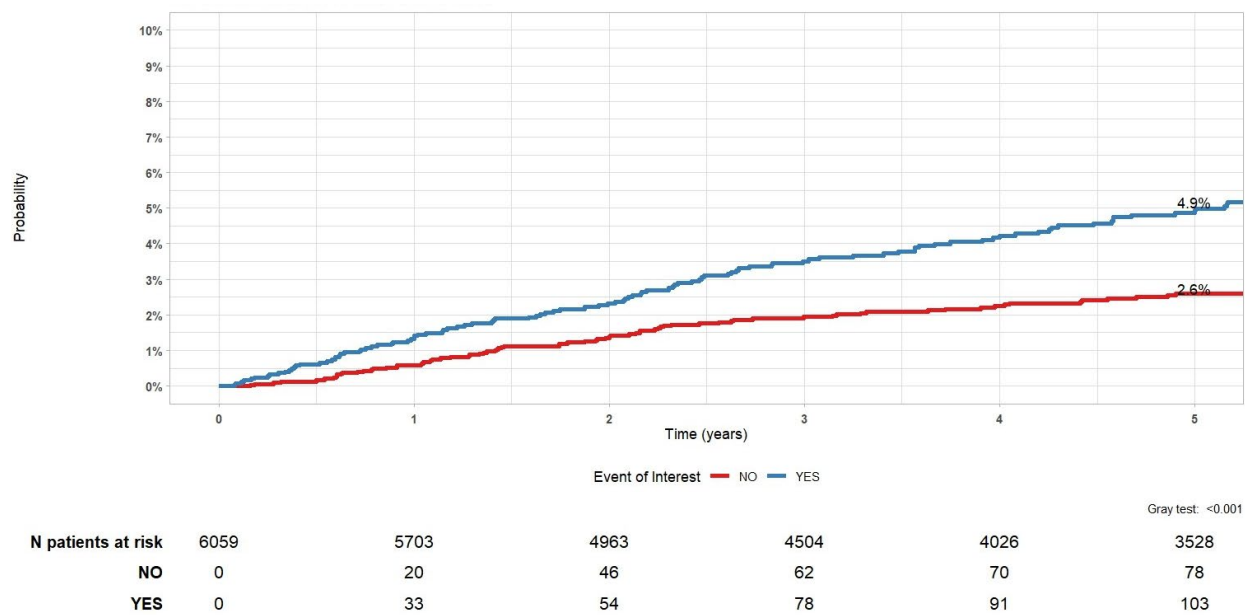
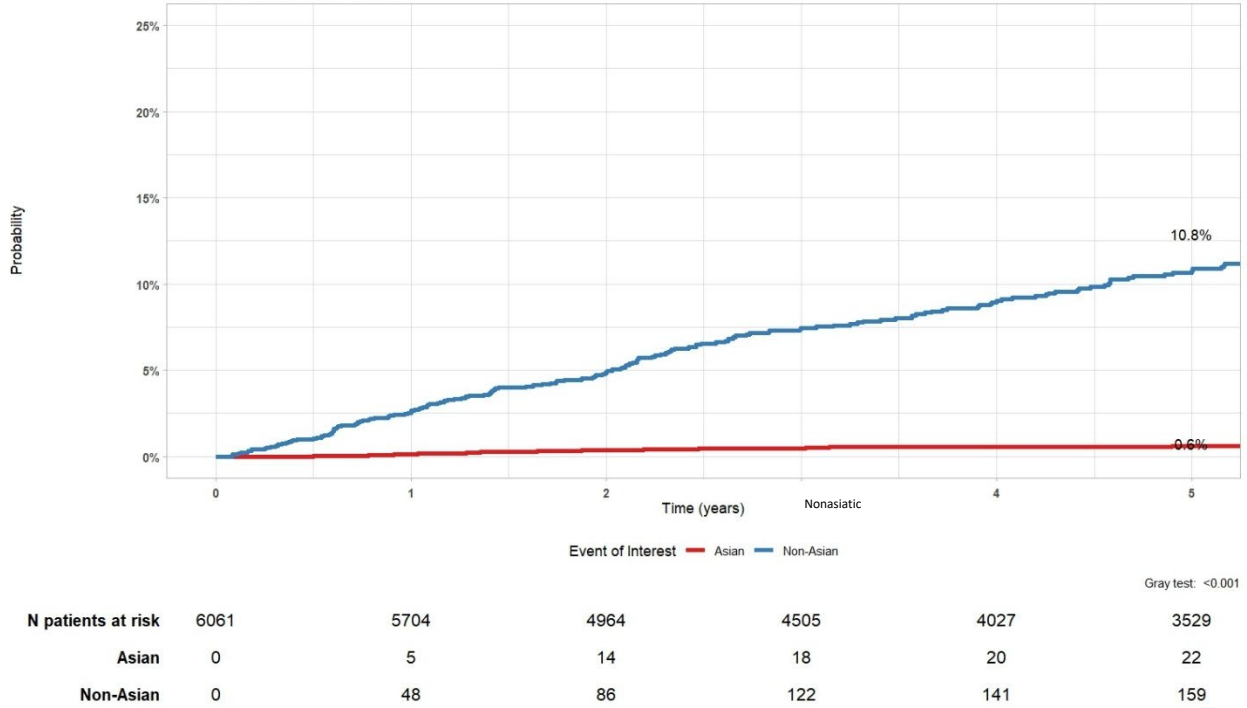


Fig. S4. Five-year CIF of first decompensation in cACLD due to MASLD according to the presence or absence of diabetes.

cACLD, compensated advanced chronic liver disease.

A



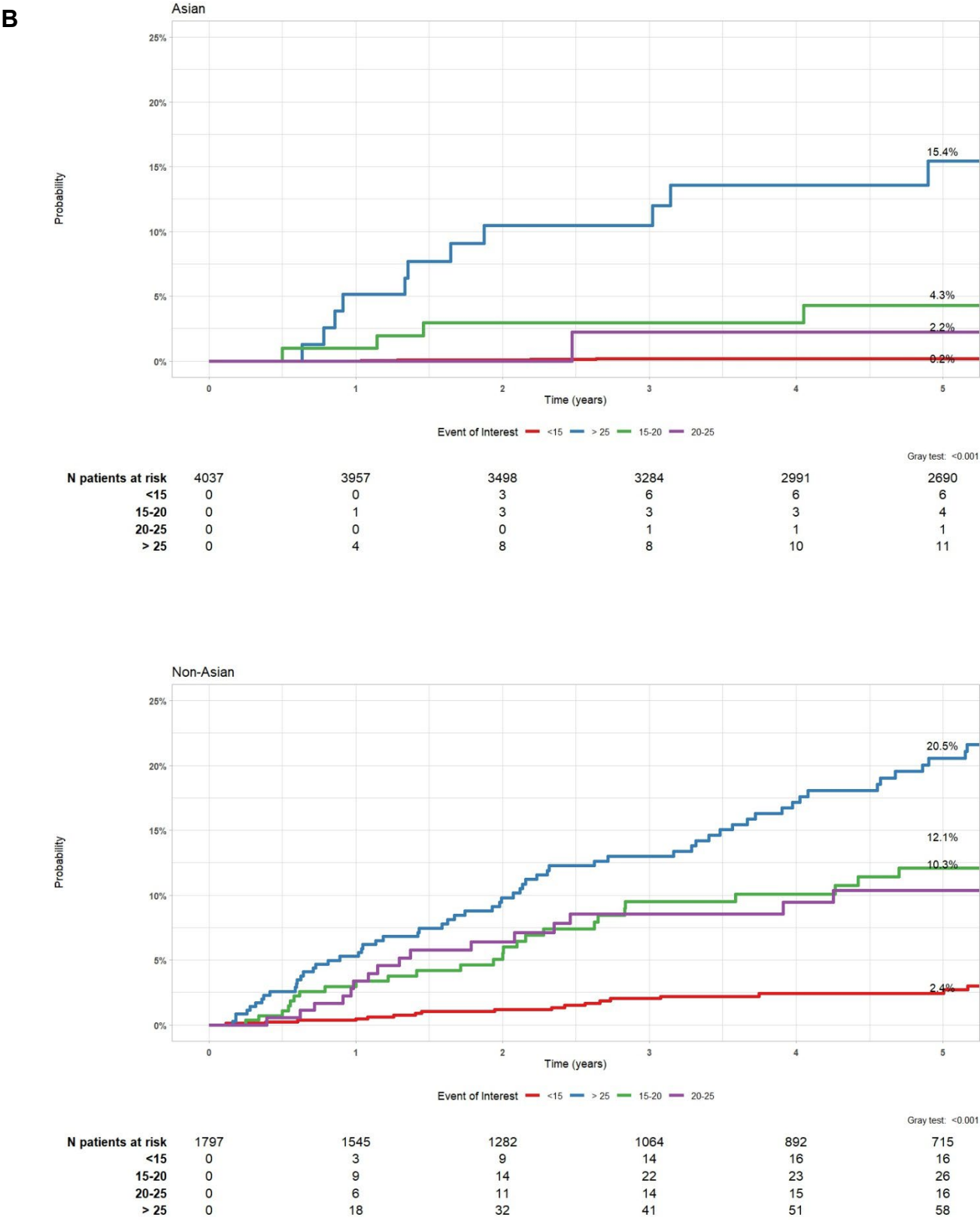


Fig. S5. Five-year CIF of first decompensation in cACLD due to MASLD according to (A) ancestry and (B) both ancestry and LSM categories (<10 KPa, 10-15 KPa, 15-20 KPa, 20-25 KPa, \geq 25 KPa). *cACLD*, compensated advanced chronic liver disease; *LSM*, liver stiffness measurement.

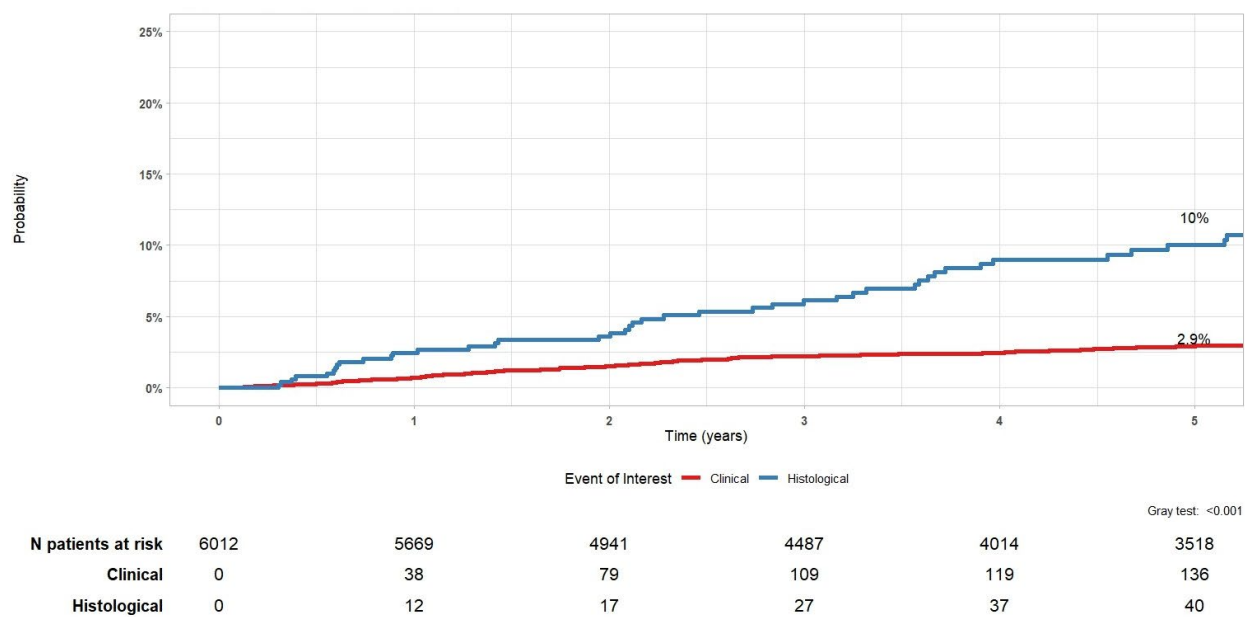
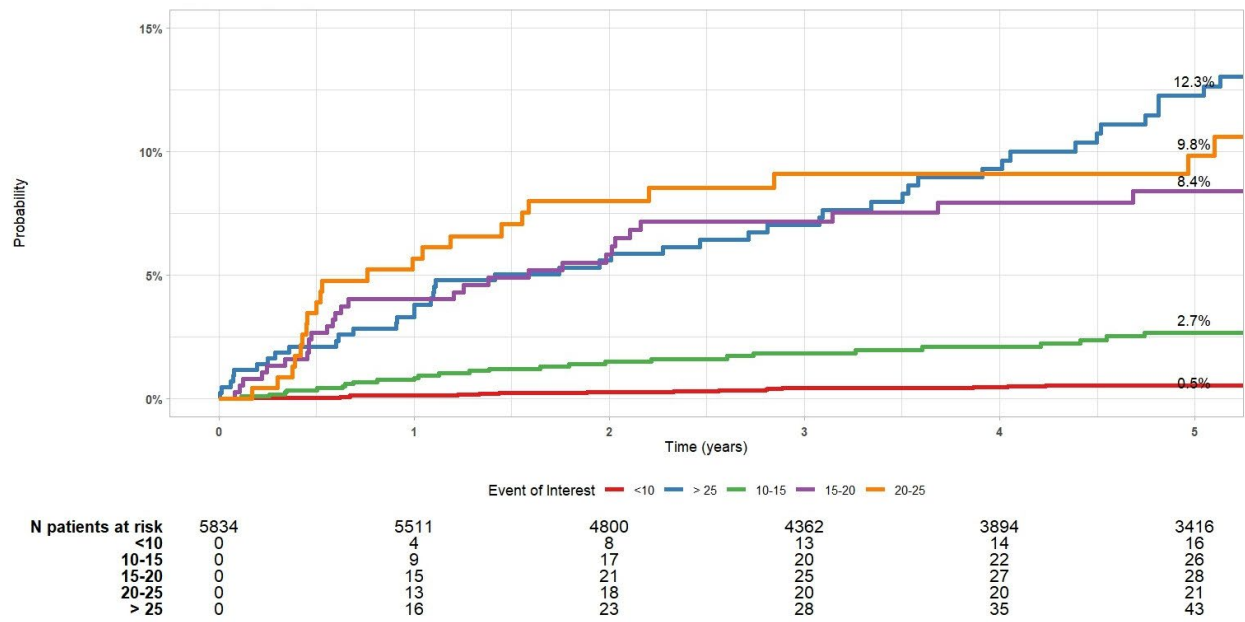


Fig. S6. Five-year CIF of first decompensation in cACLD due to MASLD according to the histological or clinical diagnosis of the disease.

cACLD, compensated advanced chronic liver disease.

A



B

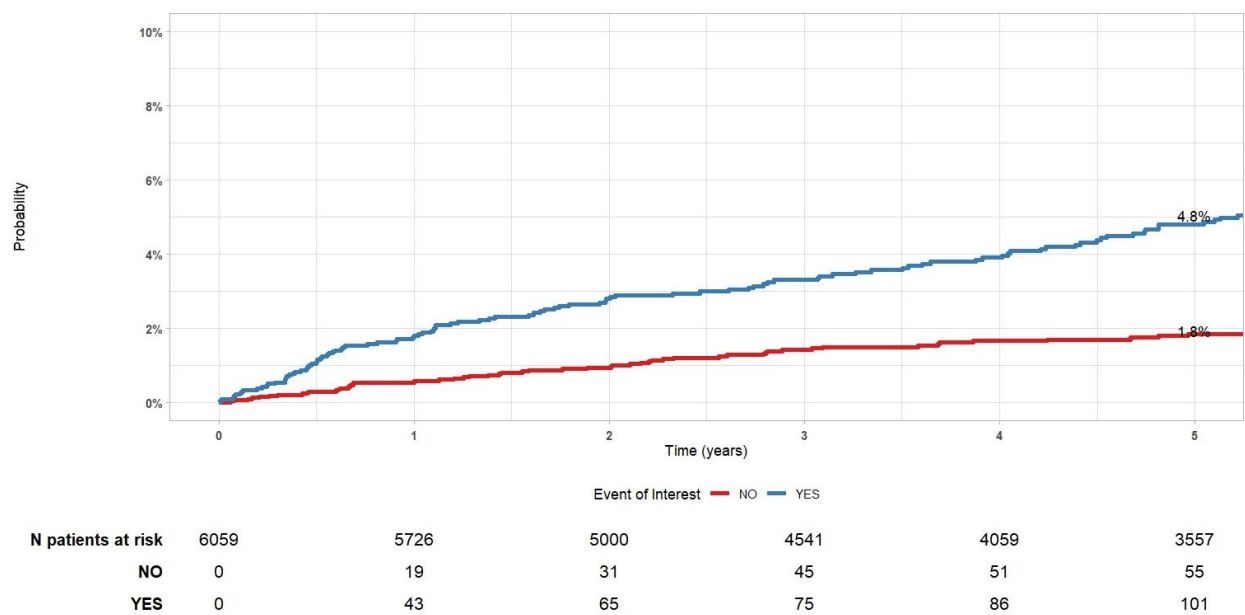
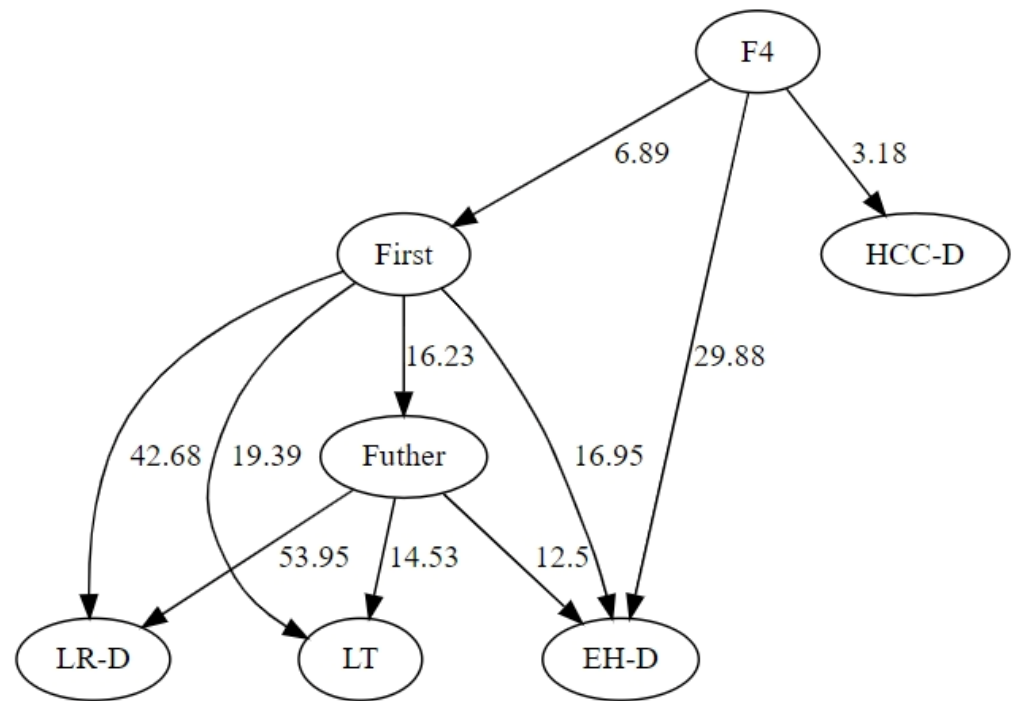
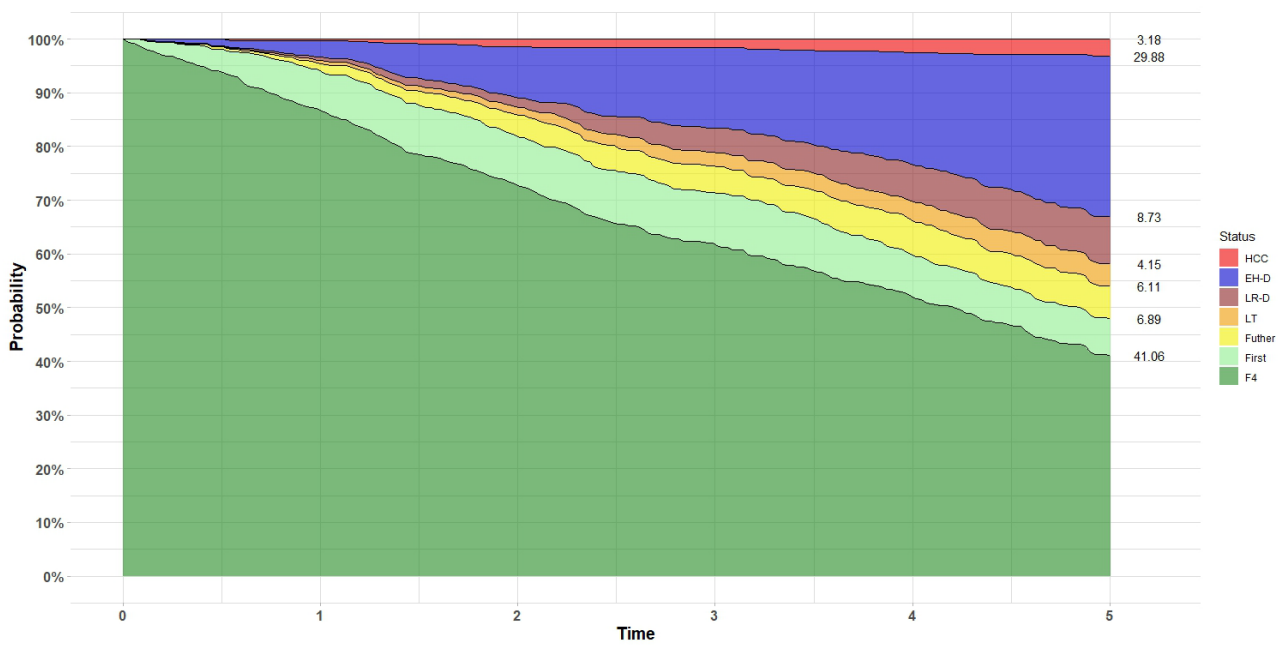


Fig. S7. Five-year CIF of HCC in cACLD due to MASLD according to (A) LSM categories (<10 KPa, 10-15 KPa, 15-20 KPa, 20-25 KPa, \geq 25 KPa) and (B) the presence or absence of diabetes. *cACLD*, compensated advanced chronic liver disease; *HCC*, hepatocellular carcinoma; *LSM*, liver stiffness measurement

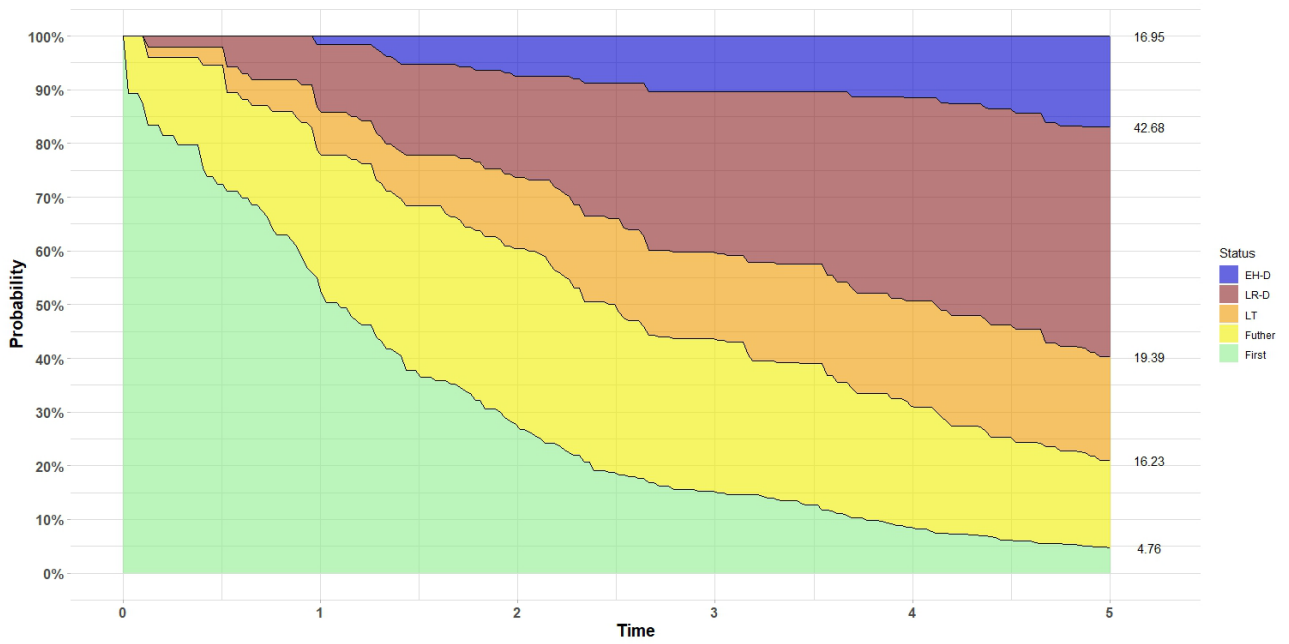
A



B



C



D

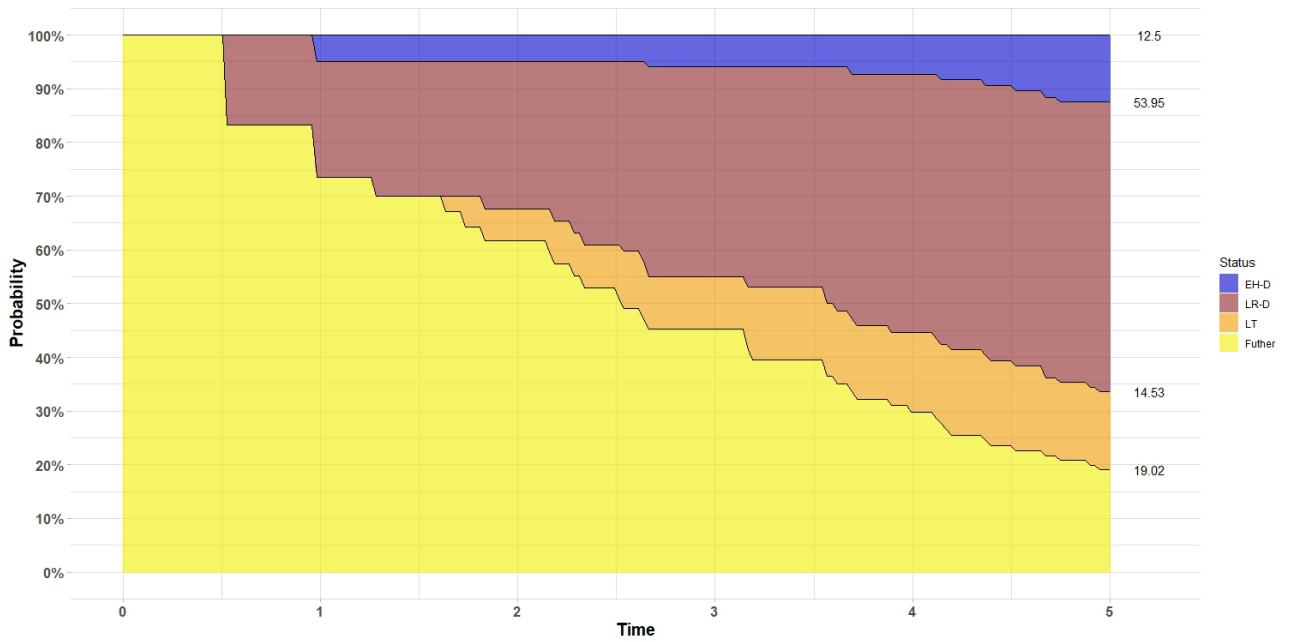


Fig. S8. (A) Multistate model summarizing the clinical course in patients with cACLD due to MASLD. Arrows represent transitions across the clinical states. Numbers close to the arrows are the 5-years transition rate assessed by competing risk analysis. (B) Five-year occupation probability of state occupation 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.