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FIB-4 predicts events in compensated advanced chronic liver disease and type 2 diabetes treated with GLP-1-receptor-agonists

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ABSTRACT

Background & aims: Patients with compensated advanced chronic liver disease (cACLD) and treated type 2 diabetes have an increased risk for liver-related events, but data regarding this population is lacking, particularly, taking into account novel treatments. We assessed the role of Fibrosis-4 index and other variables to predict events.

Methods: First hepatic decompensation, liver transplantation (OLT), death, hepatocellular carcinoma (HCC) and bacterial infections over a follow-up period of 28.7 (16–49.4) months were retrospectively identified from 106 patients with treated type 2 diabetes and liver stiffness measurement >10 kPa suggesting ACLD. We identified predictors of events using Cox regression. Additionally, we evaluated treatment effect with add-on GLP-1 receptor agonists (GLP-1-RA) compared to other antidiabetic medications.

Results: FIB-4 was associated with hepatic decompensation, OLT and death (HR 1.517, 95%CI 1.226–1.879, $p \leq 0.001$), HCC (HR 1.369, 95%CI 1.046–1.791, $p = 0.022$) and bacterial infections (HR 1.379, 95%CI 1.118–1.702, $p = 0.003$). Propensity score adjusted analysis for GLP-1-RA treatment did not show an effect (HR 0.240, 95%CI 0.044–1.315, $p = 0.1$). Survival was worse in those with more advanced disease defined by FIB-4 > 2.67 ($p = 0.02$).

Conclusion: FIB-4 is a strong prognostic tool to screen patients and refer them to specialists, in cACLD patients and pharmacologically treated type 2 diabetes, irrespective of treatment.

1. Introduction

Advanced chronic liver disease (ACLD) is the eleventh cause of global mortality, with 1.3 million deaths in 2019.[1] This is mainly due to hepatic decompensation in the form of variceal bleeding, ascites, hepatic encephalopathy or spontaneous bacterial peritonitis and hepatorenal syndrome because of portal hypertension, which decreases median survival from 10 to 12 years to 1–2 years.[2] Type 2 diabetes (T2DM) has been identified as a risk factor for progression and development of liver fibrosis and cirrhosis. On a cellular level, glucose and insulin have profibrogenic effects on hepatic stellate cells, inducing connective tissue growth.[3] This is in line with findings from clinical studies, where patients with liver cirrhosis and concomitant T2DM have a higher rate of decompensation, compared to those without T2DM.[4] Especially in patients with metabolic dysfunction-associated steatotic liver disease (MASLD), T2DM has been identified as an accelerator of the disease.[5] Additionally, there is evidence that T2DM increases the risk of hepatocellular carcinoma (HCC) in the general population.[6]

Abbreviations: ACLD, advanced chronic liver disease; T2DM, type 2 diabetes mellitus; NAFLD, non-alcoholic fatty liver disease; HCC, hepatocellular carcinoma; OLT, orthotopic liver transplantation; LSM, liver stiffness measurement; FIB-4, Fibrosis-4 score; MELD, model of end stage liver disease; BMI, body mass index; LI-RADS, liver imaging reporting and data system; HR, hazard ratio; GLP-1-RA, Glucagon-like Peptide-1 receptor agonist; PS, propensity score; MASLD, metabolic dysfunction-associated steatotic liver disease; ALD, alcohol-related liver disease; BL, baseline; AUD, alcohol use disorder; CAP, controlled attenuation parameter; NSBB, non-selective beta-blockers; HbA1c, haemoglobin A1c; SGLT-2i, Sodium-Glucose Cotransporter-2 inhibitors; DPP4i, Dipeptidyl Peptidase 4 inhibitors; NITs, non-invasive tests; HBV, hepatitis B virus; HCV, hepatitis C virus.

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Non-invasive tests (NITs) such as liver stiffness measurement (LSM) have been studied as surrogates for portal hypertension to stratify patient risk and predict liver-related events in patients with compensated ACLD (cACLD).[7–9] Similarly, fibrosis-4 score (FIB-4) showed the ability to predict the development of a first event of hepatic decompensation.[10]

However, there are no studies assessing NITs or other markers predicting liver-related events in the specific population with cACLD and pharmacologically treated T2DM, not merely T2DM as a factor. Furthermore, most studies include patients with MASLD without other aetiologies and fail to report glycaemic control and its impact on outcomes. Studies assessing the effect of antidiabetic treatment such as glucagon-like peptide 1-receptor agonists (GLP-1-RA) on liver-related events show a reduction of decompensation in those patients.[11,12]

We designed this retrospective cohort study to identify prognostic factors for hepatic decompensation, HCC, bacterial infection, OLT and death in patients with cACLD and pharmacologically treated T2DM.

2. Methods

2.1. Study design and patient population

The study was performed retrospectively at the Department of Visceral Surgery and Medicine, Bern University Hospital, Switzerland. We collected data of outpatients with cACLD defined as a LSM by FibroScan >10kPa[13] or histological fibrosis grade F3 and F4, with no previous or current decompensation (ascites, variceal bleeding, hepatic encephalopathy), no previous HCC, and pharmacologically treated T2DM in the period between January 2012 and June 2022. The LSM were carried out in patients with chronic liver disease for fibrosis staging. The first valid LSM >10 kPa and/or liver biopsy >F3 in patients with T2DM were considered the baseline time point and all lab values and clinical information (medication and comorbidities) within 3 months of this LSM were the baseline values.

Patient selection was performed by screening the electronic hospital database. Patients with a) cACLD and b) pharmacologically treated T2DM were included in this study. The patients included needed to be between 18 and 80 years old and have signed general informed consent. Patients with significant comorbidities, other causes of diabetes mellitus, pregnancy or no general informed consent were excluded.

The cohort entry date was the first visit at our outpatient clinic with F3/F4 diagnosed by LSM >10 kPa (IQR/med <0.3) plus pharmacologically treated T2DM according to hospital records. If there was never a LSM conducted or the stiffness was always <10 kPa, but a previously biopsy-proven advanced fibrosis (within 1 year), the patients were included irrespective of their LSM.

This study was approved by the Swiss Association of Research Ethics Committees (KEK 2018-00487).

2.2. Data collection

Clinical data recorded at baseline included demographic information, aetiology of liver disease, anthropometric data, duration of T2DM, bariatric surgery during follow-up, presence of arterial hypertension, alcohol consumption and presence of alcohol use disorder, NITs (ultrasound and liver stiffness measurement by Fibroscan results, Child Pugh score, MELD-Na score, FIB-4 score), laboratory values and records of prescribed medications. The diagnosis of arterial hypertension was given whenever it was listed as a diagnosis, or when the patient received antihypertensive medication. The diagnosis of alcohol use disorder was determined whenever it was listed as such or the patient had alcohol-related liver disease as the main diagnosis. FIB-4 score was calculated using an online readily available calculator and the following formula was used: Age ([yr] × AST [U/L]) / ((PLT [10(9)/L]) × (ALT [U/L])(1/2)).[14]

The patients were followed-up at least every 12 months or until occurrence of the primary outcome, occurrence of antidiabetic treatment discontinuation or the last appointment at our clinic. All of the patients were under HCC screening with 6-monthly ultrasounds.

All results of this cohort study were reported utilizing the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.[15]

2.3. Outcomes

The primary endpoint was a composite of first decompensation (ascites, variceal bleeding or hepatic encephalopathy), OLT and death. For secondary outcomes, we compared differences in BMI, HbA1c, LSM, FIB-4 score,[14] Child Pugh score and MELD-Na score at baseline and after 24 months. We further assessed HCC and bacterial infection rates.

First decompensation was defined using the Baveno VII criteria.[13] HCC was defined as a LI-RADS (Liver Imaging Reporting and Data System) 4 or LI-RADS 5 lesion detected by CT or MRI. Bacterial infections were defined by the ICD 10 code as "acute infectious disorder caused by gram positive or gram negative bacteria" (A49.9).

If the patient presented recurrent HCC or bacterial infection during follow-up, only the first event was considered for analysis. All of these outcomes were systematically searched in the patients' clinical reports as "variceal bleeding", "ascites", "hepatic encephalopathy" and "liver transplantation".

2.4. Statistical analysis

Continuous variables with normal distribution were presented as means ± standard deviation (SD) and all non-normal distributed variables as medians and interquartile ranges (IQR). Categorical data was expressed as counts and percentages. Dichotomous variables were compared by using the Chi-square test (χ^2-test). For continuous variables we used the unpaired *t*-test for parametric data and the Mann-Whitney-*U* test for non-parametric data.

Univariate Cox regression was used to establish variables that were predictive of the composite endpoint, HCC and bacterial infection and expressed as hazard ratio (HR) with 95 % confidence interval (CI). Significant variables were implemented in multivariate regression analysis.

Kaplan-Meier curves and log-rank test were used to display and compare cumulative incidences of first decompensation, OLT and death.

We performed two subgroup analyses. Firstly, we grouped patients according to whether treated with GLP-1-RA in addition to other antidiabetic treatments as the GLP-1-RA group, whereas patients treated exclusively with other antidiabetic medication were classified as the non-GLP-1-RA group. Groups were compared with regard to baseline variables and outcomes. We used propensity score (PS) to adjust for covariates. The propensity scores were calculated using logistic regression. The covariates included to generate the propensity score: baseline Child-Pugh, baseline FIB-4, baseline LSM, baseline BMI, gender, aetiology and total FU time. For propensity score, 90 patients were used (45 GLP, 45 non-GLP). Calibre matching was used to form the groups.

In the second subgroup analysis, we compared patients with a baseline FIB-4 > 2.67, suggestive of advanced fibrosis (stage F3-F4),[16] to patients with FIB-4 < 2.67.

Statistical analyses were performed using IBM SPSS version 28.0.1.1 (Chicago, IL, United States). A *p*-value of <0.05 was considered as statistically significant.

3. Results

3.1. Baseline demographic and clinical characteristics

We included 106 patients. The baseline characteristics are displayed in Table 1. The majority of patients were male (59 %) and median age was 61.5 (IQR 54–68) years. Obese patients with MASLD (58.5 %) composed the majority of the cohort, with an additional 17.9 %

Table 1
Baseline characteristics of the cohort.

	Cohort ($N = 106$)
Sex	
Female, n (%)	43 (40.6)
Male, n (%)	63 (59.4)
Age (y), median (IQR)	61.5 (54–68)
BMI (kg/m^2), mean ± SD	31.1 ± 4.9
Obesity (BMI ≥ 30 kg/m^2), n (%)	61 (57.5)
Arterial hypertension, n (%)	86 (81.9)
AUD, n (%)	25 (23.6)
Alcohol consumption (g/week), median (IQR)	82.1 (30.6–258.5)
Bariatric surgery during follow-up, n (%)	6 (5.7)
Aetiology of ACLD	
MASLD, n (%)	62 (58.5)
ALD, n (%)	4 (3.8)
MetALD, n (%)	19 (17.9)
Viral hepatitis, n (%)	8 (7.5)
Autoimmune, n (%)	4 (3.8)
Other/ mixed aetiology, n (%)	9 (8.5)
MELD-Na score, median (IQR)[a]	7 (7–9)
Child-Pugh score, median (IQR)	5 (5–6)
Bilirubin (μmol/L), median (IQR)	10 (7–15)
Albumin (g/L), median (IQR)	38 (35–40)
INR, median (IQR)	1.04 (1.00–1.12)
Platelets, median (IQR)	179 (133–232)
Liver stiffness (kPa), median (IQR)	16.7 (12.4–26.7)
CAP (kPa), median (IQR)[b]	325 (254–374)
FIB-4, median (IQR)	2.20 (1.33–3.75)
Statin use, n (%)	51 (48.1)
NSBB use, n (%)	13 (12.3)
Duration of T2DM (years), median (IQR)[c]	7 (2–11)
HbA1c, median (IQR)[d]	7.0 (6.3–8.0)
GLP-1-RA, n (%)	45 (42.5)
Semaglutide, n (%)	34 (32.1)
Liraglutide, n (%)	11 (10.4)
Metformin, n (%)	65 (61.3)
SGLT-2i, n (%)	10 (9.4)
DPP4i, n (%)	4 (3.8)
Sulfonylurea, n (%)	18 (17.0)
Insulin, n (%)	58 (55.7)

Abbreviations: BMI, body mass index; AUD, alcohol use disorder; ACLD, advanced chronic liver disease; MASLD, metabolic-dysfunction associated steatotic liver disease, MetALD, MASLD and alcohol-related liver disease, ALD, alcohol-related liver disease; MELD, Model of End Stage Liver Disease; CAP, Controlled Attenuation Parameter; NSBB, non-selective beta-blockers; T2DM, type 2 diabetes mellitus; HbA1c, haemoglobin A1c; GLP-1-RA, Glucagon-like Peptide-1 Receptor Agonists; SGLT-2i, Sodium-Glucose Cotransporter-2 inhibitors; DPP4i, Dipeptidyl Peptidase 4 inhibitors.

[a] Available in $n = 93$.
[b] Available in $n = 79$.
[c] Available in $n = 57$.
[d] Available in $n = 89$.

presenting the combination of MASLD and alcohol-related liver disease ALD (MetALD).[17] The median Child-Pugh and MELD-Na scores were low, as expected in compensated patients. Median LSM was 16.7 (IQR 12.4–26.7) kPa.

Specifically regarding ALD, 3.8 % of patients were diagnosed with ALD, 17.9 % MetALD, and 23.6 % of all patients had alcohol use disorder. The median alcohol consumption was 82.1 (30.6–258.5) grams per week.

Concerning metabolic syndrome, the median duration of T2DM was 7 years (2−11). Regarding T2DM treatments, 42.5 % were treated with GLP-1-RA and 61.3 % with metformin. Median HbA1c was 7.0 % (6.3–8.0), and 7.5 % patients had an HbA1c >9.0 %. The mean BMI was 31.1 ± 4.9 kg/m^2 and 57.5 % were obese. Six patients (5.7 %) underwent bariatric surgery during follow-up. The majority of patients (81.9 %) had arterial hypertension and 48.1 % were treated with statins.

3.2. Outcomes

The median follow-up time was 28.7 (IQR 16–49.4) months. Eight patients (7.5 %) decompensated during this time; the majority (62.5 %) had ascites. Death or OLT occurred in four (3.8 %) and two (1.9 %) patients, respectively. During follow-up, eight (7.5 %) patients were diagnosed with HCC and 10 (9.4 %) had a first episode of bacterial infection. Infection location was most commonly in the urinary tract, occurring in five (50 %) patients. HCC and infections regression analyses are provided in Tables S3 and S4, respectively. After 24 months, there was a reduction in median LSM of −2.5 (−7.9–1.9) kPa. Changes in BMI, HbA1c and FIB-4, as well as, in Child-Pugh and MELD-Na score were recorded (Table S1). In the eight patients with HbA1c ≥ 9.0 % versus the remaining cohort with HbA1c <9 %, there were not more events of hepatic decompensation ($p = 0.59$).

3.3. Factors associated with the composite endpoint

In univariate Cox regression, baseline FIB-4 was associated with a higher risk of the composite endpoint (HR 1.517, 95 % CI 1.226–1.879, $p < 0.001$). Other significant predictors were duration of T2DM, bilirubin, and non-selective beta-blocker (NSBB) use at baseline (Table 2). In multivariate analyses including all above-mentioned variables, the strongest independent predictors for the composite endpoint were baseline FIB-4 (HR 1.677, 95 % CI 1.147–2.541, $p = 0.008$) and duration of T2DM (HR 1.142, 95 % CI 1.031–1.265, $p = 0.011$). Baseline FIB-4 (HR 1.959, 95 % CI 1.396–2.751, $p < 0.001$) albumin, bilirubin and NSBB use were also significant predictors of the composite endpoint at 24 months.

Table 2
Univariate Cox regression for the primary composite endpoint.

Variable	Univariate HR (95 % CI)	*P* value
Age	1.065 (0.998–1.137)	0.06
Female	0.780 (0.268–2.269)	0.6
GLP-1-RA	0.593 (0.122–2.895)	0.5
BL MELD-Na score[a]	0.929 (0.662–1.302)	0.7
BL Child Pugh score	1.823 (0.922–3.604)	0.08
BL LSM	1.023 (0.993–1.055)	0.1
BL CAP[b]	0.994 (0.983–1.005)	0.3
BL FIB-4	1.517 (1.226–1.879)	**<0.001**
Aetiology MASLD	0.935 (0.295–2.963)	0.9
Aetiology MetALD	2.347 (0.596–9.243)	0.2
Aetiology ALD	1.572 (0.201–12.259)	0.7
Aetiology ALD + MetALD	2.213 (0.664–7.376)	0.2
BMI	1.044 (0.928–1.174)	0.5
Duration of T2DM[c]	1.140 (1.027–1.265)	**0.01**
BL HbA1c[d]	1.024 (0.674–1.555)	0.9
Statin use	0.838 (0.273–2.571)	0.8
NSBB use	4.399 (1.403–13.790)	**0.01**
BL Bilirubin	1.098 (1.023–1.180)	**0.01**
BL Albumin	0.836 (0.721–0.969)	0.8
Metformin use	0.698 (0.221–2.203)	0.5
BL LSM ≥25 kPa	2.550 (0.890–7.305)	0.08
BL BMI ≥30	1.373 (0.473–3.983)	0.6
BL FIB-4 ≥ 2.67	4.331 (1.201–15.621)	**0.03**
Alcohol consumption yes/no	1.200 (0.401–3.590)	0.7
Alcohol consumption g/week	1.001 (0.992–1.011)	0.8

Abbreviations: GLP-1-RA, Glucagon-like Peptide-1 Receptor Agonists; BL, baseline; MELD Model for End Stage Liver Disease; LSM, liver stiffness measurement; CAP, Controlled Attenuation Parameter; FIB-4, Fibrosis-4 score; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, MASLD and alcohol-related liver disease; ALD, alcohol-related liver disease; BMI, body mass index; T2DM, type 2 diabetes mellitus; HbA1c, haemoglobin A1c; NSBB, non-selective beta-blocker.

[a] Available in n = 93.
[b] Available in n = 79.
[c] Available in n = 57.
[d] Available in n = 89.

3.4. Factors associated with occurrence of HCC and bacterial infection

Baseline FIB-4 score (HR 1.369, 95 % CI 1.046–1.791, $p = 0.022$), age, albumin and ALD aetiology were significant predictors of HCC. For the bacterial infections, baseline FIB-4 score (HR 1.379, 95 % CI 1.118–1.702, $p = 0.003$) and age significantly predicted the outcome. (Tables S2 and S3). In multivariate analyses, no factors showed significance.

3.5. Subgroup analysis: prognostic value of FIB-4 score above 2.67

Among the cohort, 43 patients (41 %) had a FIB-4 score > 2.67 at baseline and 25 % had FIB-4 < 1.3. Compared to patients with FIB-4 < 2.67, baseline MELD-Na score, bilirubin, INR and LSM were significantly higher and CAP, platelets and BMI significantly lower (Table 3).

Most of the recorded events occurred in this high-risk population, with eight events of hepatic decompensation, two liver transplants and one death.

In univariate Cox regression for patients with a FIB-4 score > 2.67, a LSM above 25 kPa was able to predict the composite endpoint (HR 4.705, 95 % CI 1.196–18.508, $p = 0.03$).

Comparing the FIB-4 score >/<2.67 patients in a log-rank test regarding the composite endpoint, the difference between the two groups was significant ($p = 0.02$) (Fig. 1). In the population with FIB-4 score > 2.67 splitting into add-on GLP-1-RA treatment versus non-GLP-1-RA group after 36 months, no significant difference was found ($p = 0.616$) (Fig. 2).

3.6. Subgroup analysis: GLP-1-RA versus non-GLP-1-RA

There were 45 patients (42 %) treated with GLP-1-RA in addition to other antidiabetic medication (GLP-1-RA group). Patients in the GLP-1-RA group had lower LSM ($p = 0.05$) and FIB-4 ($p = 0.02$) and a higher CAP ($p = 0.02$), platelet count (p = 0.02) as well as BMI ($p = 0.04$) compared to patients in the non-GLP-1-RA group (Table 4). MELD-Na and Child-Pugh score did not differ between groups ($p = 0.28$ and 0.42, respectively).

There were more events in the non-GLP-1-RA group than in the GLP-1-RA group with 26 versus six events ($p = 0.001$), respectively. Events consisted in one hepatic decompensation, one death, two HCC and two bacterial infections (Table S4). Differences in BMI and HbA1c after 24 months in the two treatment groups are reported in Table 5, with a significant difference in change of HbA1c between the groups ($p = 0.004$). Regarding NITs, the difference after the above-mentioned time period was not significant in the GLP-1-RA group.

Comparing semaglutide and liraglutide, there were 34 and 11 patients treated with these drugs, respectively. There were no differences in outcomes (one hepatic decompensation, two bacterial infections and two HCCs in the semaglutide group, versus one death in the liraglutide group). There was a reduction of values of HbA1c and BMI in these patients, although only the difference in delta BMI between the two groups was significant ($p = 0.009$).

We adjusted the Cox regression analysis for gender, platelet count, LSM, FIB-4, BMI and length of follow-up. Add-on GLP-1-RA treatment failed to reach statistical significance for the primary endpoint (HR 0.240, 95 % CI 0.044–1.315, $p = 0.1$).

4. Discussion

This cohort study aimed to identify prognostic factors for hepatic decompensation, OLT and death, as well as HCC and bacterial infections in patients with cACLD and pharmacologically treated T2DM.

Our results identified the FIB-4 score as the strongest predictor of the composite endpoint of first decompensation, OLT and death. In addition, FIB-4 predicted the occurrence of HCC and bacterial infections. This is consistent with a study of Boursier et al., where FIB-4 predicted hepatic

Table 3
Baseline characteristics split by FIB-4 above vs below 2.67.

	All patients (N = 106)	FIB-4 > 2.67 (N = 43)	FIB-4 < 2.67 (N = 63)	p-value
Length of follow-up period (m), median (IQR)	28.7 (16–49.4)	34.3 (18.3–52.4)	25 (15.6–44.2	0.2
Sex				
Female	43 (40.6)	20 (46.5)	23 (36.5)	0.3
Male	63 (59.4)	23 (53.5)	40 (63.5)	
BL age, median (IQR)	61.5 (54–68)	65 (58–70)	59 (51–65)	**<0.001**
Arterial hypertension, n (%)	86 (81.1)	36 (83.7)	50 (79.4)	0.6
AUD, n (%)	25 (23.6)	10 (23.3)	15 (23.8)	0.9
Alcohol consumption g/week, median (IQR)	82.1 (30.6–258.5)	100.8 (35.7–268.3)	63.4 (30–330.4)	1.0
Bariatric surgery, n (%)	6 (5.7)	3 (7)	3 (4.8)	0.7
Aetiology of ACLD, n (%)				
MASLD, n (%)	62 (58.5)	25 (58.1)	37 (58.7)	1.0
ALD, n (%)	4 (3.8)	1 (2.3)	3 (4.8)	0.6
MetALD, n (%)	19 (17.9)	9 (20.9)	10 (15.9)	0.5
Viral hepatitis, n (%)	8 (7.5)	4 (9.3)	4 (6.3)	0.7
Autoimmune, n (%)	4 (3.8)	2 (4.7)	2 (3.2)	1.00
Other/ mixed aetiology, n (%)	9 (8.5)	2 (4.7)	7 (11.1)	0.3
BL MELD-Na score, median (IQR)[a]	7 (7–9)	8 (7–10)	7 (6–8)	**0.002**
BL Child-Pugh score, median (IQR)	5 (5–6)	5 (5–6)	5 (5–5)	0.06
BL Bilirubin (μmol/L), median (IQR)	10 (7–15)	14 (10–17)	8 (6–11)	**<0.001**
BL Albumin (g/L), median (IQR)	38 (35–40)	38 (34–40)	38 (36–40)	0.5
BL INR, median (IQR)	1.04 (1.00–1.12)	1.12 (1.02–1.19)	1.02 (0.99–1.07)	**<0.001**
BL Platelets, median (IQR)	179 (133–232)	115 (91–146)	224 (181–256)	**<0.001**
BL Liver stiffness (kPa), median (IQR)	16.7 (12.4–26.7)	20.9 (14.8–30)	14.7 (11.5–21.4)	**0.003**
BL CAP (kPa), median (IQR)[b]	325 (254–374)	261 (233–347)	333 (303–375)	**0.01**
BL FIB-4, median (IQR)	2.20 (1.33–3.75)	4.09 (3.39–5.41)	1.43 (1.18–2.05)	**<0.001**
Statin use, n (%)	51 (48.1)	19 (44.2)	32 (50.8)	0.5
NSBB use, n (%)	13 (12.3)	11 (25.6)	2 (3.2)	**<0.001**
BL BMI, mean ± SD	31.1 ± 4.9	29.7 ± 4.4	32.1 ± 5	**0.01**
Obesity (BMI > 30 kg/m^2), n (%)	61 (57.5)	21 (48.8)	40 (63.5)	0.1
Duration of DMT2 (y), median (IQR)[c]	7 (2–11)	5 (1–14)	7.5 (2–11)	0.9
BL HbA1c, median (IQR)[d]	7.0 (6.3–8.0)	7.1 (6.4–8.3)	7.0 (6.2–8.0)	0.4

BL, baseline; BMI, body mass index; AUD, alcohol use disorder; ACLD, advanced chronic liver disease; MASLD, metabolic-dysfunction associated steatotic liver disease, MetALD, MASLD and alcohol-related liver disease, ALD, alcohol-related liver disease; MELD, Model of End Stage Liver Disease; CAP, Controlled Attenuation Parameter; NSBB, non-selective beta-blockers; T2DM, type 2 diabetes mellitus; HbA1c, haemoglobin A1c.

[a] Available in n = 93.

[b] Available in n = 79.

[c] Available in n = 57.
[d] Available in n = 89.

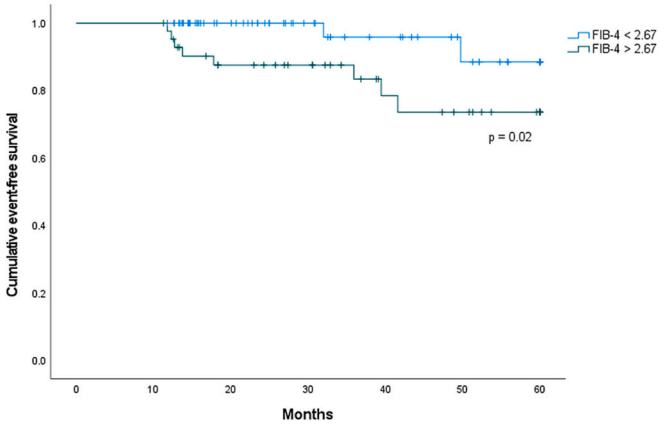

Fig. 1. event-free survival of all patients with FIB-4 > 2.67 versus <2.67.

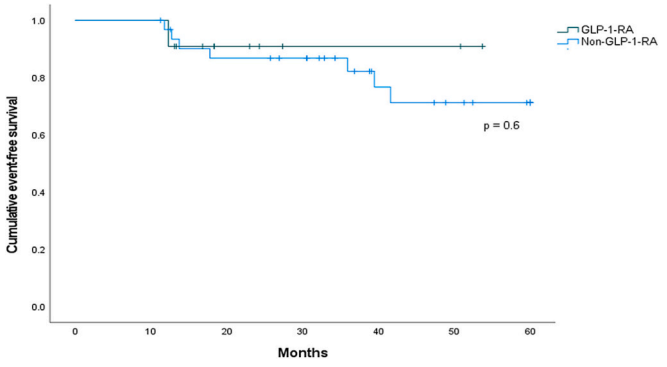

Fig. 2. event-free survival of high-risk group (FIB-4 > 2.67) with GLP-1-RA add-on treatment versus non-GLP-1-RA.

decompensation, HCC and death in patients with NAFLD.[18] Additionally, among patients with cirrhosis, Guha et al. showed that FIB-4 strongly predicted first decompensation.[10] Previously, we demonstrated that adding FIB-4 enhances the predictive ability of LSM for first decompensation in overweight or obese patients with ACLD.[19] Furthermore, a FIB-4 score > 2.67 also predicted the composite endpoint in our population. These findings are consistent with a study of Angulo et al. showing that patients with NAFLD and FIB-4 scores >2.67 had a higher risk of developing liver-related events than patients with lower scores.[20] Similarly, studies in patients with chronic hepatitis B[21] and hepatitis C[22] (with around 30 % of patients with cACLD) found that a FIB-4 score > 3.25 was associated with worse 5-year survival. However, notably, only part of the population in the above-mentioned studies had T2DM or ACLD.

LSM did not predict outcomes in our cohort, although in regards to the composite endpoint, it showed a positive trend. This can be due to the low number of events observed in this cohort. Moreover, when only considering the high-risk population of patients with FIB-4 > 2.67, where most of the events occurred, a LSM >25 kPa did predict the composite endpoint, which is in line with recent studies where LSM appears as a strong predictor of hepatic decompensation in patients with cACLD.[9,23,24] Semmler et al. showed that an increase of 20 % in LSM was associated with a 50 % increase in risk of developing hepatic decompensation.[9] Liver-related mortality was also linked LSM change over time. In contrast, a single LSM had a lower prognostic accuracy when predicting hepatic decompensation and death,[9] similarly in our study.

Table 4
Baseline characteristics split by drug type.

	All patients (N = 106)	GLP (*N* = 45)	Non-GLP (*N* = 61)	p-value
Length of follow-up period (m), median (IQR)	28.7 (16–49.4)	20.1 (14.2–29.4)	38.8 (26.3–60.4)	**<0.001**
Sex				
Female	43 (40.6)	13 (28.9)	30 (49.2)	**0.04**
Male	63 (59.4)	32 (71.1)	31 (50.8)	
BL age, median (IQR)	61.5 (54–68)	61 (55–67.5)	62 (54–68)	0.92
Arterial hypertension, n (%)	86 (81.1)	38 (84.4)	48 (78.7)	0.45
AUD, n (%)	25 (23.6)	10 (22.2)	15 (24.6)	0.78
Alcohol consumption g/week, median (IQR)	82.1 (30.6–258.5)	151.2 (40–436.8)	63.4 (14.4–224)	0.26
Bariatric surgery, n (%)	6 (5.7)	3 (6.7)	3 (4.9)	0.7
Aetiology of ACLD, n (%)				
MASLD, n (%)	62 (58.5)	30 (66.7)	32 (52.5)	0.14
ALD, n (%)	4 (3.8)	1 (2.2)	3 (4.9)	0.64
MetALD, n (%)	19 (17.9)	8 (17.8)	11 (18.0)	0.97
Viral hepatitis, n (%)	8 (7.5)	1 (2.2)	7 (11.5)	0.13
Autoimmune, n (%)	4 (3.8)	1 (2.2)	3 (4.9)	0.64
Other/ mixed aetiology, n (%)	9 (8.5)	4 (8.9)	5 (8.2)	1.00
BL MELD-Na score, median (IQR)[a]	7 (7–9)	7 (7–9)	7 (6–8)	0.28
BL Child-Pugh score, median (IQR)	5 (5–6)	5 (5–6)	5 (5–6)	0.42
BL Bilirubin (μmol/L), median (IQR)	10 (7–15)	9 (7–14)	10 (7–15)	0.25
BL Albumin (g/L), median (IQR)	38 (35–40)	38 (35–41)	38 (35–40)	0.77
BL INR, median (IQR)	1.04 (1.00–1.12)	1.06 (1.02–1.14)	1.02 (0.99–1.12)	0.12
BL Platelets, median (IQR)	179 (133–232)	196 (160–240)	164 (105–220)	**0.02**
BL Liver stiffness (kPa), median (IQR)	16.7 (12.4–26.7)	14.8 (11–21.8)	18.2 (12.9–27.6)	**0.05**
BL CAP (kPa), median (IQR)[b]	325 (254–374)	342 (303–382)	294 (237–351)	**0.02**
BL FIB-4, median (IQR)	2.20 (1.33–3.75)	1.57 (1.28–2.68)	2.78 (1.37–4.17)	**0.02**
Statin use, n (%)	51 (48.1)	26 (57.8)	25 (41)	0.09
NSBB use, n (%)	13 (12.3)	5 (11.1)	8 (13.1)	0.76
BL BMI, mean ± SD	31.1 ± 4.9	32.2 ± 4.4	30.3 ± 5.1	**0.04**
Obesity (BMI ≥ 30 kg/m^2), n (%)	61 (57.5)	31 (68.9)	30 (49.2)	**0.04**
Duration of T2DM (y), median (IQR)[c]	7 (2–11)	8 (4.3–11)	5 (1–13)	0.46
BL HbA1c, median (IQR)[d]	7.0 (6.3–8.0)	7.2 (6.5–8.0)	6.8 (6.3–8.2)	0.56

BL, baseline; BMI, body mass index; AUD, alcohol use disorder; ACLD, advanced chronic liver disease; MASLD, metabolic-dysfunction associated steatotic liver disease, MetALD, MASLD and alcohol-related liver disease, ALD, alcohol-related liver disease; MELD, Model of End Stage Liver Disease; CAP, Controlled Attenuation Parameter; NSBB, non-selective beta-blockers; T2DM, type 2 diabetes mellitus; HbA1c, haemoglobin A1c.
[a] Available in n = 93.
[b] Available in n = 79.
[c] Available in n = 57.
[d] Available in n = 89.

Table 5
Differences at 24 months split by drug type.

	All (N = 106)	GLP (N = 45)	Non-GLP (N = 61)	p-value
ΔBMI[a]	−0.5 (−1.4–1.0)	−0.6 (−1.9–0.6)	−0.3 (−1.0–1.3)	0.062
ΔHbA1c[b]	−0.2 (−0.8–0.5)	−0.5 (−1.3–0.0)	0.2 (−0.4–0.9)	**0.004**
ΔLSM[c]	−2.5 (−7.9–1.9)	−2.6 (−8.0–1.0)	−1.5 (−8.4–3.8)	0.494
ΔFIB-4[d]	−0.04 (−0.46–0.45)	−0.07 (−0.55–0.23)	−0.00 (−0.28–0.65)	0.285
ΔChild-Pugh score[e]	0 (0–0)	0 (0–0)	0 (0–0)	0.302
ΔMELD score[f]	0 (0–1)	0 (−1–0.75)	0 (0–1)	0.056

[a] Available for 91 patients.
[b] Available for 62 patients.
[c] Available for 88 patients.
[d] Available for 100 patients.
[e] Available for 91 patients.
[f] Available for 87 patients.

This is in accordance with our findings, since we used baseline LSM values to predict liver-related events. Moreover, Pons et al.[25] reported that LSM was a less accurate predictor in obese patients with cACLD. Since the mean BMI in our population was 31.1 kg/m^2, with a majority of patients with MASLD and obesity, this may have contributed to the decreased predictive ability of LSM. Finally, it is important to note that in the above-mentioned studies, only 30–50 % of the included patients had T2DM; there was no information on if, and how they were treated. Since evidence suggests that T2DM decreases the accuracy of several NITs, including LSM, this could further explain the findings in our population.[26]

Regarding antidiabetic treatment effect on liver-related events, add-on GLP-1-RA seemed protective against occurrence of the composite endpoint in covariate adjustment using the propensity score, particularly after 36 months of follow-up, although the results did not reach statistical significance. This could be, in part, due to the small sample size and short follow-up time. Additionally, when looking specifically at high-risk patients with FIB-4 > 2.67, a trend towards less liver-related events in the GLP-1-RA group was observed. Indeed, GLP-1-RA have shown, in previous trials, in patients with metabolic dysfunction-associated steatohepatitis (MASH) with or without T2DM, to reduce hepatic steatosis, resolve MASH, and mitigate fibrosis progression.[27–29] As such, one would expect, that over time, GLP-1-RA could decrease liver-related events. A retrospective study by Simon et al. was the first to link GLP-1-RA use to a reduction of liver related events in patients with compensated and decompensated cirrhosis and concomitant T2DM when compared to DPP-4i, sulfonylurea and SGLT-2i.[11] Similar results were generated by other studies when comparing GLP-1-RA users to non-users.[12,30] Therefore, our results are in line with existing literature.

In the overall cohort, we recorded eight events of hepatic decompensation over a median of 2.4 years, which equates to 7.5 % of the patients in our population. This is at the lower end of the estimated 5–11 %, reported in other studies with cirrhosis patients.[2,31] Of note, inclusion in our study was not based on a diagnosis of cirrhosis, but on a liver stiffness >10 kPa or grade 3–4 fibrosis on histology, which may result in including less severe patients. Moreover, 48.1 % of our patients were treated with statins. Statin therapy is linked to preventing liver disease development[32] and decompensation in patients with cirrhosis, although this has been particularly studied in patients with viral- and alcohol-related cirrhosis.[33,34] Nevertheless, this might be a partial explanation for the low rate recorded in our study. Additionally, it is important to discuss our results regarding NSBB use. It was linked to an increased risk of liver-related outcomes, including HCC and bacterial infections. This is likely because the main indication for NSBBs was the presence of clinically significant portal hypertension, which is the main risk factor of a hepatic decompensation in cACLD patients.[35]

In our population, T2DM was well-controlled with a median HbA1c of 7.0 % at baseline. Although HbA1c was not a significant predictor of events, there seemed to be a tendency for higher HbA1c levels to predict hepatic decompensation, OLT and death. A study by Huang et al. showed that HbA1c was a predictor for hepatic decompensation in diabetic patients with NAFLD.[5] Labenz et al. described HbA1c as a risk factor of covert and overt hepatic encephalopathy in patients with cirrhosis and concomitant T2DM.[36] Consequently, the fact that most of our patients had HbA1c <8 % could have further contributed to the low rate of liver-related events in our cohort. All patients were treated with at least one type of oral or injected antidiabetic medication. Data regarding this factor is conflicting. On one hand, Liu et al. documented an association between the type of diabetic treatment and the likelihood of a hepatic decompensation in cirrhosis patients, with insulin use as the strongest predictor of decompensation.[4] On the other hand, Calzadilla-Bertot et al. reported that adjusting their results for severity of diabetes, defined as using insulin as treatment, did not change the risk of decompensation and mortality in patients with T2DM and HCV-related cirrhosis.[37]

This study has some limitations. Firstly, it is a retrospective, monocentric cohort study, and thereby prone to selection bias and residual uncontrolled confounding bias. Secondly, our cohort consists of a small sample size, a relatively short follow-up for cACLD patients, and six patients submitted to bariatric surgery were not censored. Furthermore, there was relatively low number of events, which limits the evaluation of the impact of different antidiabetic medications. We did not have a registry of side effects of antidiabetic therapy in cirrhosis patients; thus, we cannot delineate which drugs could lead to a greater number of adverse effects. Lastly, we used covariate adjustment using the propensity score as a way to determine the effect of add-on GLP-1-RA therapy, which has a greater risk of residual confounding than propensity score matching. Due to our small sample size, matching was not possible. The above limitations call for caution when interpreting our results.

In conclusion, patients with cACLD and concomitant T2DM are an important patient group and at risk for liver-related events. FIB-4 appears as a strong predictor of liver-related outcomes including decompensation, HCC and bacterial infections. These findings apply to patients on GLP-1-RAs, making it a valuable tool for general practitioners, diabetologists and hepatologists to easily screen and stratify their patients. More prospective studies are needed to verify the roles of glycaemic control and antidiabetic therapies on liver-related events in patients with cACLD and T2DM.

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CRediT authorship contribution statement

Wiebke van Beurden: Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Yuly P. Mendoza:** Writing – review & editing, Data curation. **Naomi F. Lange:** Writing – review & editing, Data curation. **Jaime Bosch:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Conceptualization. **Annalisa Berzigotti:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Formal analysis, Conceptualization. **Susana G. Rodrigues:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors disclose no conflicts.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jdiacomp.2025.108978.

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