

# Dual Therapy With Metformin and Sodium Glucose Co-Transporter-2 Inhibitors (SGLT2-i) Improves Mortality in Cirrhotic Patients



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## Background

Metformin is the first-line treatment of type 2 diabetes mellitus (T2DM), though some patients require additional medications.

T2DM is a common comorbidity of cirrhosis, and studies show that chronic hyperglycemia can exacerbate liver disease progression.

There is limited research on the impact of dual anti-diabetic therapy on mortality and hepatic decompensation in cirrhosis, particularly in non-alcoholic fatty liver disease (NAFLD).

## Aims

We sought to determine whether T2DM cirrhotic patients on dual metformin and SGLT2-i therapy had a mortality benefit and reduced hepatic decompensation versus metformin alone.

## Methodology

Retrospective cohort study on T2DM cirrhotic patients, including a NASH subset using TriNetX

Propensity score matched analysis comparing patients on metformin and those on metformin and SGLT2-i

Our primary outcome was all-cause mortality and our secondary outcome composite hepatic decompensation over three years defined as having any diagnosis code for hepatic encephalopathy, ascites, and gastric or esophageal varices.

## T2DM Cirrhosis Characteristics

T2DM Cirrhosis			
Baseline Characteristics After Propensity Score Matching			
Characteristic	Metformin (n = 1,123)	Metformin + SGLT2i (n = 1,123)	P
Age (Mean ± SD)	63.58 ± 13.66	63.28 ± 11.23	0.570
Gender			
Men	649 (57.79)	625 (55.65)	0.307
Women	474 (42.21)	498 (44.35)	0.307
Unknown	0 (0)	0 (0)	NA
Race			
White	785 (69.9)	772 (68.74)	0.552
Black or African American	144 (12.82)	162 (14.43)	0.268
Asian	25 (2.23)	24 (2.14)	0.885
Native Hawaiian or Other Pacific Islander	10 (0.89)	10 (0.89)	1
American Indian or Alaska Native	10 (0.89)	10 (0.89)	1
Unknown	157 (13.98)	155 (13.8)	0.903
Ethnicity			
Hispanic or Latino	117 (10.42)	114 (10.15)	0.835
Not Hispanic or Latino	710 (63.22)	735 (65.45)	0.271
Unknown	296 (26.36)	274 (24.4)	0.286
Comorbidities			
Hypertensive Diseases	878 (78.18)	888 (79.07)	0.607
Overweight, Obesity	854 (76.03)	866 (76.9)	0.613
Heart Failure	330 (29.39)	305 (27.16)	0.241
Metabolic Disorders	838 (74.62)	878 (78.18)	0.047

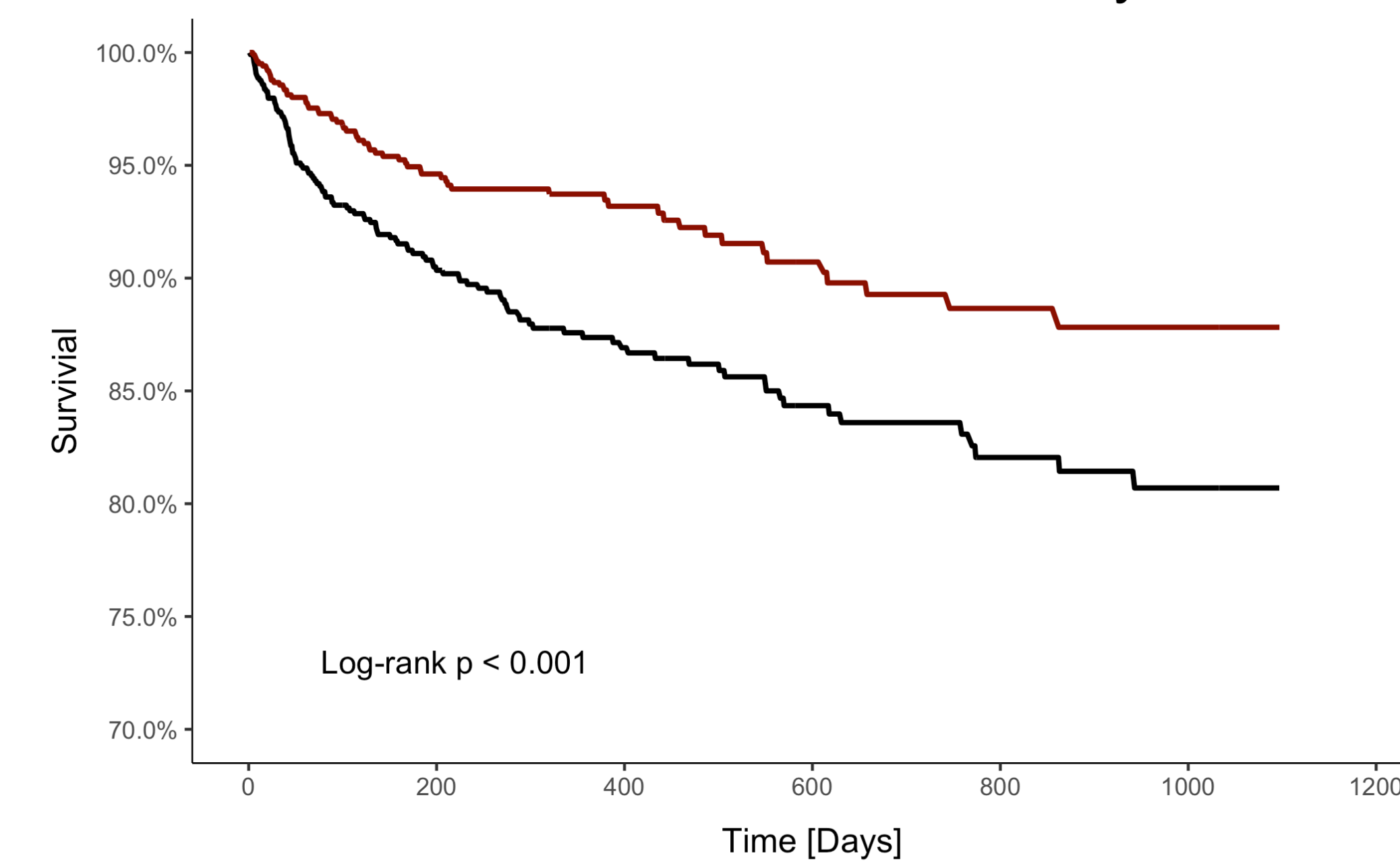
Values are n (%) or Mean ± SD. Abbreviations: T2DM: Type 2 Diabetes Mellitus; SGLT2i: Sodium Glucose Co-transporter 2 Inhibitor. Age is defined as age of patient when treated with Metformin or Metformin and SGLT2i. Comorbidities are defined as having a diagnostic code in the EMR anytime before starting Metformin or Metformin and SGLT2i treatment

## Primary Outcome

Mortality	After Propensity Score Matching			
	Metformin	Metformin + SGLT2i	RR (95% CI)	P
All	1123	1123	1.91 (1.42-2.56)	< 0.001
Demographic Subgroup †				
Men	627	627	1.55 (1.07-2.25)	0.020
Men Age 60-79	397	397	2.2 (1.34-3.62)	< 0.01
Men Age 40-59	191	191	1.01 (0.53-1.91)	0.987
Women	492	492	2.4 (1.46-3.93)	< 0.001
Women Age 60-79	288	288	1.86 (0.99-3.5)	0.048
Women Age 40-59	142	142	1 (0.43-2.33)	1.000
White	768	768	1.59 (1.1-2.29)	0.013
Non-White	185	185	1.11 (0.48-2.54)	0.812
NASH ‡	152	152	1 (0.43-2.33)	1

Abbreviations: SGLT2i: Sodium Glucose Co-transporter 2 Inhibitor  
P values indicate significance between patients treated with Metformin monotherapy and patients with Metformin and SGLT2i dual therapy

## 3 Year All-Cause Mortality



— T2DM Cirrhotic Patients on Metformin  
— T2DM Cirrhotic Patients on Metformin + SGLT2i

## T2DM NASH Cirrhosis Characteristics

T2DM NASH Cirrhosis			
Baseline Characteristics After Propensity Score Matching			
Characteristic	Metformin (n = 152)	Metformin + GLP1-RA (n = 152)	P
Age (Mean ± SD)	57.58 ± 15.45	59.57 ± 11.52	0.203
Gender			
Men	71 (46.71)	70 (46.05)	0.908
Women	81 (53.29)	82 (53.95)	0.908
Unknown	0 (0)	0 (0)	NA
Race			
White	117 (76.97)	118 (77.63)	0.891
Black or African American	15 (9.87)	11 (7.24)	0.412
Asian	10 (6.58)	10 (6.58)	1.000
Native Hawaiian or Other Pacific Islander	0 (0)	0 (0)	NA
American Indian or Alaska Native	10 (6.58)	10 (6.58)	1.000
Unknown	16 (10.53)	20 (13.16)	0.478
Ethnicity			
Hispanic or Latino	16 (10.53)	14 (9.21)	0.701
Not Hispanic or Latino	102 (67.11)	105 (69.08)	0.712
Unknown	34 (22.37)	33 (21.71)	0.890
Comorbidities			
Hypertensive Diseases	115 (75.66)	118 (77.63)	0.684
Overweight, Obesity	101 (66.45)	97 (63.82)	0.630
Heart Failure	35 (23.03)	28 (18.42)	0.322
Metabolic Disorders	115 (75.66)	117 (76.97)	0.787

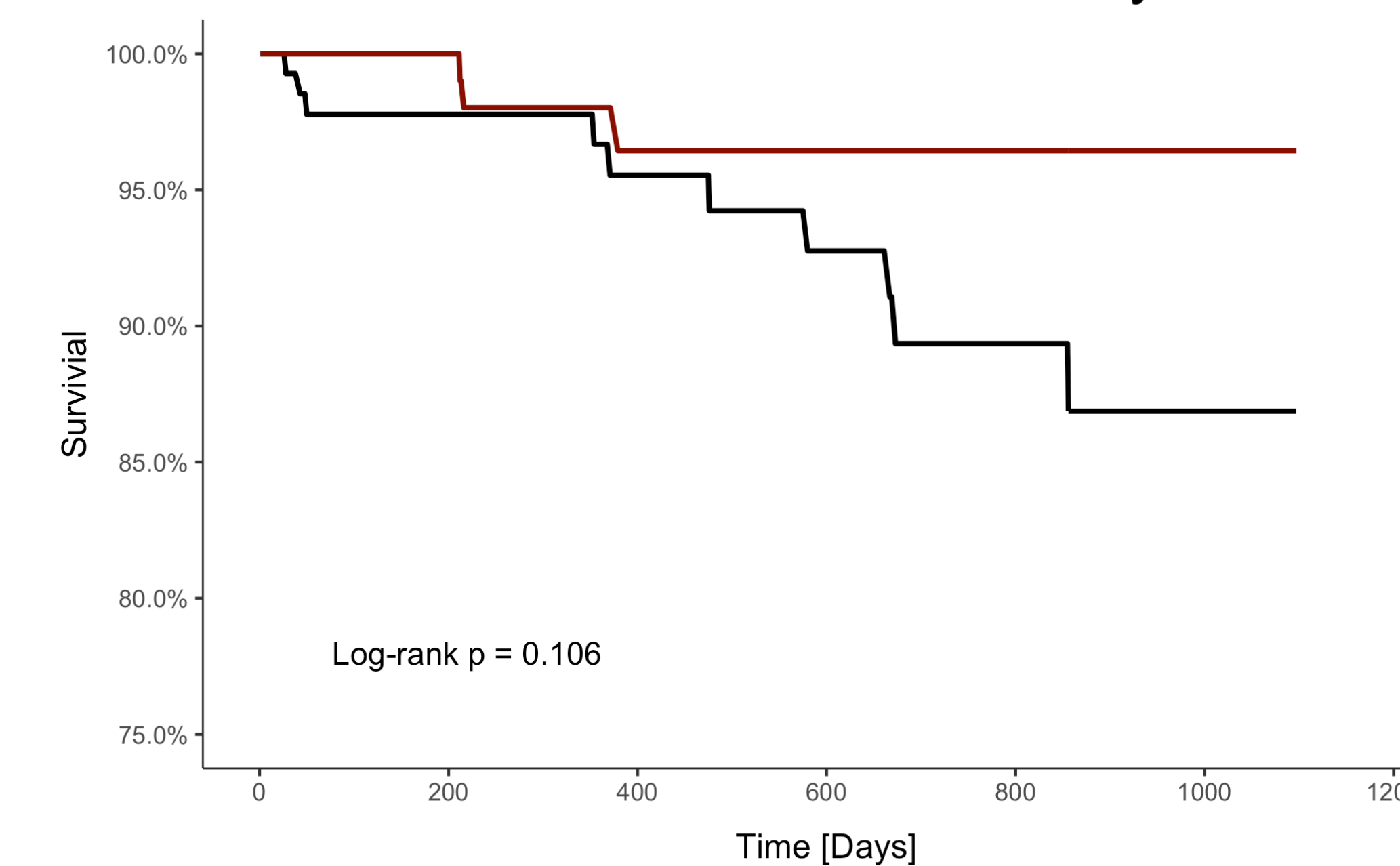
Values are n (%) or Mean ± SD. Abbreviations: T2DM: Type 2 Diabetes Mellitus; NASH: Non-Alcoholic Steatohepatitis; SGLT2i: Sodium Glucose Co-transporter 2 Inhibitor. Age is defined as age of patient when treated with Metformin or Metformin and SGLT2i. Comorbidities are defined as having a diagnostic code in the EMR anytime before starting Metformin or Metformin and SGLT2i treatment

## Secondary Outcome

Combined Hepatic Decompensation †	After Propensity Score Matching			
	Metformin	Metformin + SGLT2i	RR (95% CI)	P
All	1123	1123	1.25 (0.93-1.67)	0.131
Demographic Subgroup †				
Men	627	627	1.21 (0.82-1.8)	0.341
Men Age 60-79	397	397	0.97 (0.59-1.6)	0.902
Men Age 40-59	191	191	0.9 (0.39-2.08)	0.804
Women	492	492	1.29 (0.84-1.96)	0.242
Women Age 60-79	288	288	1.12 (0.66-1.89)	0.683
Women Age 40-59	142	142	0.99 (0.43-2.29)	0.983
White	768	768	1.31 (0.91-1.88)	0.141
Non-White	185	185	1.01 (0.43-2.34)	0.987
NASH ‡	152	152	1.17 (0.55-2.51)	0.683

Abbreviations: SGLT2i: Sodium Glucose Co-transporter 2 Inhibitor P values indicate significance between patients treated with Metformin monotherapy and patients with Metformin and SGLT2i dual therapy † Combined Hepatic Decompensation are defined as having any EMR diagnosis codes for following: ascites, hepatic encephalopathy, and gastric or esophageal varices

## 3 Year All-Cause Mortality



— T2DM NASH Cirrhotic Patients on Metformin  
— T2DM NASH Cirrhotic Patients on Metformin + SGLT2i

## Results

T2DM cirrhotics on mono metformin therapy had higher mortality risk (RR 1.91, 95%CI 1.42-2.56, p<0.001) and lower survival (80.7% vs. 87.8%, p<0.001) compared to those on dual metformin and SGLT2i therapy.

T2DM NASH cirrhotics on mono metformin therapy had equivalent mortality risk (RR 1.0, 95%CI 0.43-2.33, p=1), compared to those on dual therapy.

Dual metformin and SGLT2i therapy was not associated with lower risk for becoming decompensated across sex, Whites, Non- Whites and in our NASH subset.

## Discussion

Improved mortality seen in T2DM cirrhotics on dual metformin and SGLT2i therapy maybe be due to beneficial effects of SGLT2Is on patient comorbidities rather than their liver issues.

There may be underreporting of NASH patients in the database since our analysis relied in part on patients' having ICD-10 codes (K76.0, K75.8). Further prospective studies in patients with biopsy-confirmed NASH and from underrepresented populations are needed to investigate our outcomes.

## Conclusion

We found a potential mortality benefit in T2DM cirrhotic patients on dual metformin and SGLT2-i therapy versus metformin alone.

There was no clear effect on the risk of hepatic decompensation.