TYPE 2 DIABETES REDUCES OVERALL SURVIVAL AND INCREASES THE RISK OF HEPATIC DECOMPENSATION IN COMPENSATED HCV-RELATED LIVER CIRRHOSIS. RESULTS FROM A PROSPECTIVE LONG-TERM STUDY DURING 8 YEARS

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Background and aims

- Glucose metabolism abnormalities such as Type 2 diabetes mellitus (T2DM), pre-diabetes and insulin resistance frequently coexist with liver cirrhosis.
- HCV infection is associated with an increased risk of developing insulin resistance and T2DM. Both conditions may accelerate the fibrosis progression and natural history of CHC.
- Previous studies have reported that IR may increase the risk of developing varices and decompensation in patients with compensated cirrhosis.
- Despite the increasing interest in the role of diabetes and IR as triggers for liver-related complications and mortality, only few prospective studies have focused on this scenario.
- We examined the influence of DM/pre-diabetes/insulin resistance (IR) on overall survival and liver-related complications in compensated HCV-related cirrhotic patients

Study design and participants

- Longitudinal and prospective cohort study during 8 years.
- 440 patients with HCV-related cirrhosis were consecutively evaluated between January 2004 and June 2007 at a tertiary academic centre (Institute of Gastroenterology, Havana).
- 250 patients who fulfilled the following inclusion criteria were enrolled:

- Compensated HCV-related cirrhosis.
- Both sexes and > 18 years old
- Non-responders to, ineligible for or intolerant of peg-interferon plus ribavirin treatment

Exclusion

- Other causes of liver disease.
- Previous diagnosis of type 1 and 2 diabetes.
- Current or past history of hepatic decompensation.
- Concomitant illness with limited life expectancy, drug dependence, or evidence of HCC.
- Prior SVR to antiviral therapy or underwent treatment with peginterferon plus ribavirin.

Clinical and laboratory assessment

- All patients were assessed at baseline and every 8 weeks till the end of the study.
- Liver ultrasonography and serum AFP at baseline and every 24 weeks during the study to screen HCC.
- Fasting glucose, oral glucose tolerance test (OGTT), insulin and HOMA-IR at baseline.
- Diagnosis of glucose abnormalities such as diabetes, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) were established based on American Diabetes Association criteria.

Definition of outcomes

- The **primary outcome** was overall survival or liver transplantation.
- The **secondary outcome** was the development of the first event of clinical hepatic decompensation.
- ✓ Overall clinical outcomes were measured from the study start date until the date of clinical outcome
- ✓ Patients lost to follow-up were censored at the last date they were known to be alive
- ✓ In order to avoid the influence of HCC development on liver-related outcomes, patients with a diagnosis of HCC overtime were censored at the time when diagnosed. During the study period, 13 patients developed HCC. All patients developing HCC were free of complications at the time of diagnosis.

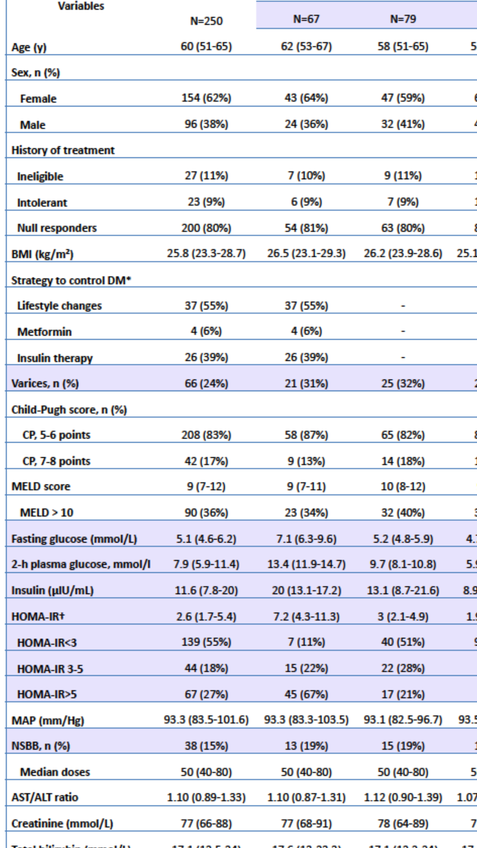
Statistical analysis

The main objective of the study was to explore the potential association of T2DM with the overall survival and the occurrence of a first event of clinical hepatic decompensation, thus, cumulative probabilities for each outcome were analysed by standard Kaplan–Meier methods (including 95% confidence intervals [CI]) and compared by the log-rank test. Additionally, we explored associations between different cut-offs of HOMA-IR, 2-hour plasma glucose concentrations, and fasting insulin levels and outcomes.

Cox regression models were used to identify predictors of overall survival and a first event of hepatic decompensation. All confidence intervals, significance tests, and resulting *P* values were two-sided, with an α = 0.05.

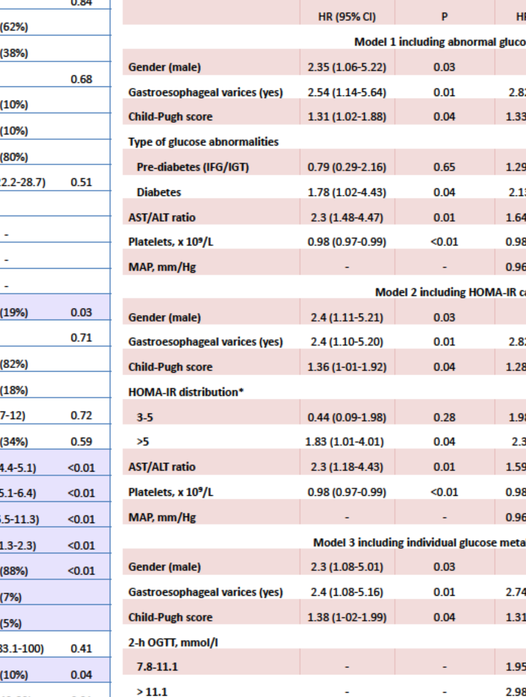
Results

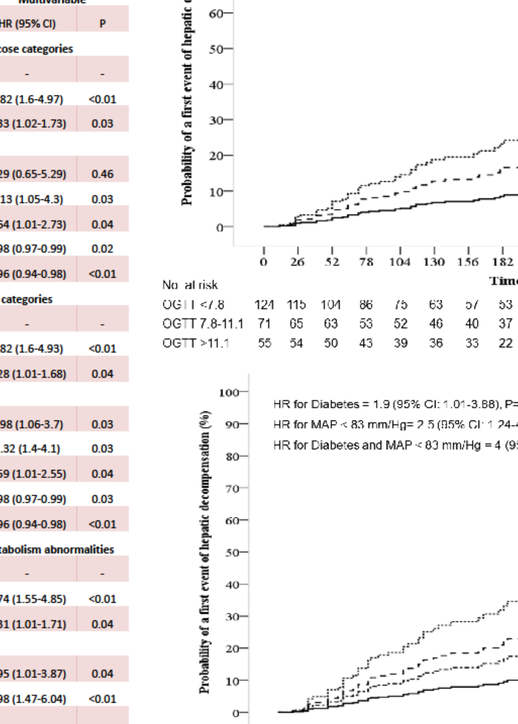
Flow of patients through the study



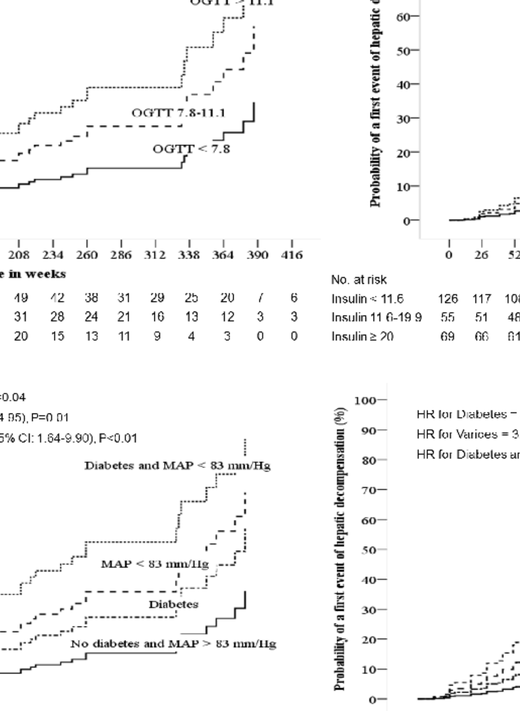
Probability of outcomes adjusting by covariates

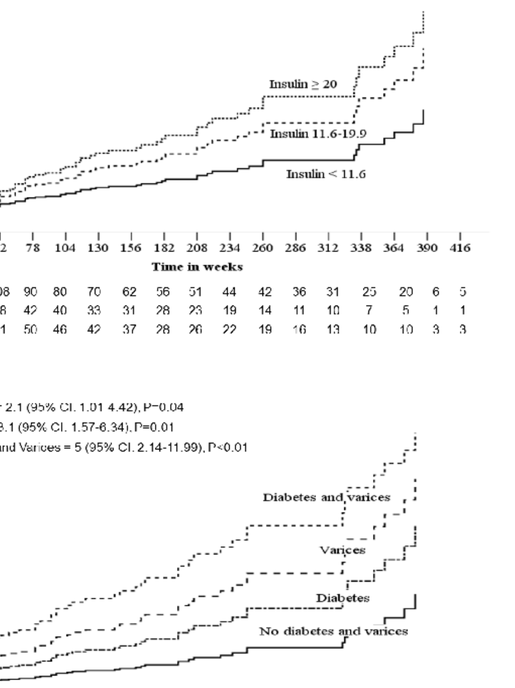
Overall survival





Hepatic decompensation





Hepatic decompensation

Baseline characteristics of the participants.

Variables	Overall N=250	Diabetic N=67	Pre-diabetic N=79	Non diabetic N=104	P Value
Age (y)	60 (51-65)	62 (53-67)	58 (51-65)	58 (50-64)	0.21
Sex, n (%)					0.84
Female	154 (62%)	43 (64%)	47 (59%)	64 (62%)	
Male	96 (38%)	24 (36%)	32 (41%)	40 (38%)	
History of treatment					0.68
Ineligible	27 (11%)	7 (10%)	9 (11%)	11 (10%)	
Intolerant	23 (9%)	6 (9%)	7 (9%)	10 (10%)	
Null responders	200 (80%)	54 (81%)	63 (80%)	83 (80%)	
BMI (kg/m²)	25.8 (23.3-28.7)	26.5 (23.1-29.3)	26.2 (23.9-28.6)	25.1 (22.2-28.7)	0.51
Strategy to control DM*					
Lifestyle changes	37 (55%)	37 (55%)	-	-	
Metformin	4 (6%)	4 (6%)	-	-	
Insulin therapy	26 (39%)	26 (39%)	-	-	
Varices, n (%)	66 (24%)	21 (31%)	25 (32%)	20 (19%)	0.03
Child-Pugh score, n (%)					0.71
CP, 5-6 points	208 (83%)	58 (87%)	65 (82%)	85 (82%)	
CP, 7-8 points	42 (17%)	9 (13%)	14 (18%)	19 (18%)	
MELD score	9 (7-12)	9 (7-11)	10 (8-12)	9 (7-12)	0.72
MELD > 10	90 (36%)	23 (34%)	32 (40%)	35 (34%)	0.59
Fasting glucose (mmol/L)	5.1 (4.6-6.2)	7.1 (6.3-9.6)	5.2 (4.8-5.9)	4.7 (4.4-5.1)	<0.01
2-h plasma glucose, mmol/l	7.9 (5.9-11.4)	13.4 (11.9-14.7)	9.7 (8.1-10.8)	5.9 (5.1-6.4)	<0.01
Insulin (µIU/mL)	11.6 (7.8-20)	20 (13.1-17.2)	13.1 (8.7-21.6)	8.9 (6.5-11.3)	<0.01
HOMA-IR†	2.6 (1.7-5.4)	7.2 (4.3-11.3)	3 (2.1-4.9)	1.9 (1.3-2.3)	<0.01
HOMA-IR<3	139 (55%)	7 (11%)	40 (51%)	92 (88%)	<0.01
HOMA-IR 3-5	44 (18%)	15 (22%)	22 (28%)	7 (7%)	
HOMA-IR>5	67 (27%)	45 (67%)	17 (21%)	5 (5%)	
MAP (mm/Hg)	93.3 (83.5-101.6)	93.3 (83.3-103.5)	93.1 (82.5-96.7)	93.5 (83.1-100)	0.41
NSBB, n (%)	38 (15%)	13 (19%)	15 (19%)	10 (10%)	0.04
Median doses	50 (40-80)	50 (40-80)	50 (40-80)	50 (40-80)	0.91
AST/ALT ratio	1.10 (0.89-1.33)	1.10 (0.87-1.31)	1.12 (0.90-1.39)	1.07 (0.88-1.27)	0.37
Creatinine (mmol/L)	77 (66-88)	77 (68-91)	78 (64-89)	77 (66-88)	0.62
Total bilirubin (mmol/L)	17.1 (12.5-24)	17.6 (13-23.3)	17.1 (12.2-24)	17 (12.7-21.5)	0.40
Albumin (g/L)	40 (37-43)	39.8 (37.7-42.1)	40 (36.7-44)	40.2 (36.5-43)	0.93
INR	1.17 (1.09-1.43)	1.18 (1-1.4)	1.19 (1.09-1.41)	1.16 (1.01-1.33)	0.36
Sodium, mEq/L	143 (141-146)	142 (138-144)	142 (138-145)	143 (137-145)	0.96
Platelets (x 10⁹/L)	145 (112-175)	132 (110-174)	134 (102-161)	154 (117-190)	0.04
α-fetoprotein (ng/ml)	12 (7-19)	13 (8-21)	12 (8-20)	11 (7-19)	0.88

* Strategy applied to control hyperglycaemia in diabetic patients during the follow-up.

Variables found as significant predictors of overall mortality and hepatic decompensation.

Variable	Overall mortality n=28 Multivariable HR (95% CI)	P	Hepatic decompensation n=55 Multivariable HR (95% CI)	P
Model 1 including abnormal glucose categories				
Gender (male)	2.35 (1.06-5.22)	0.03	-	-
Gastroesophageal varices (yes)	2.54 (1.14-5.64)	0.01	2.82 (1.6-4.97)	<0.01
Child-Pugh score	1.31 (1.02-1.88)	0.04	1.33 (1.02-1.73)	0.03
Type of glucose abnormalities				
Pre-diabetes (IFG/IGT)	0.79 (0.29-2.16)	0.65	1.29 (0.65-5.29)	0.46
Diabetes	1.78 (1.02-4.43)	0.04	2.13 (1.05-4.3)	0.03
AST/ALT ratio	2.3 (1.48-4.47)	0.01	1.64 (1.01-2.73)	0.04
Platelets, x 10⁹/L	0.98 (0.97-0.99)	<0.01	0.98 (0.97-0.99)	0.02
MAP, mm/Hg	-	-	0.96 (0.94-0.98)	<0.01
Model 2 including HOMA-IR categories				
Gender (male)	2.4 (1.11-5.21)	0.03	-	-
Gastroesophageal varices (yes)	2.4 (1.10-5.20)	0.01	2.82 (1.6-4.93)	<0.01
Child-Pugh score	1.36 (1-01-1.92)	0.04	1.28 (1.01-1.68)	0.04
HOMA-IR distribution*				
3-5	0.44 (0.09-1.98)	0.28	1.98 (1.06-3.7)	0.03
>5	1.83 (1.01-4.01)	0.04	2.32 (1.4-4.1)	0.03
AST/ALT ratio	2.3 (1.18-4.43)	0.01	1.59 (1.01-2.55)	0.04
Platelets, x 10⁹/L	0.98 (0.97-0.99)	<0.01	0.98 (0.97-0.99)	0.03
MAP, mm/Hg	-	-	0.96 (0.94-0.98)	<0.01
Model 3 including individual glucose metabolism abnormalities				
Gender (male)	2.3 (1.08-5.01)	0.03	-	-
Gastroesophageal varices (yes)	2.4 (1.08-5.16)	0.01	2.74 (1.55-4.85)	<0.01
Child-Pugh score	1.38 (1-02-1.99)	0.04	1.31 (1.01-1.71)	0.04
2-h OGTT, mmol/l				
7.8-11.1	-	-	1.95 (1.01-3.87)	0.04
> 11.1	-	-	2.98 (1.47-6.04)	<0.01
Fasting insulin, uIU/mL‡				
11.6-19.9	-	-	1.83 (0.90-3.63)	0.09
≥ 20	-	-	2.48 (1.34-4.62)	<0.01
AST/ALT ratio	2.32 (1.19-4.46)	0.01	1.61 (1.01-2.89)	0.04
Platelets, x 10⁹/L	0.98 (0.97-0.99)	<0.01	0.98 (0.97-0.99)	0.03
MAP, mm/Hg	-	-	0.96 (0.94-0.98)	<0.01

* HOMA-IR <3, between 3 and 5 and >5 correspond with 50th, between 50-75th and more than 75th percentile, respectively.
† Nonselective beta-blockers as primary prophylaxis for variceal bleeding
‡ Fasting insulin plasma concentrations were categorized according to <50th (<11.6 uIU/mL), between 50th and 75th (11.6-19.9 uIU/mL) and ≥ 75th (≥20 uIU/mL) percentile.

In conclusion, our study revealed close relationship between diabetes, IR, fasting insulin and 2-hour plasma glucose levels and the progression of chronic liver disease. The presence of T2DM or a marked IR significantly reduce overall survival and increase cirrhosis progression in accelerating the occurrence of hepatic decompensation. Moreover, higher levels of 2-hour plasma glucose or fasting plasma insulin are associated with increased occurrence of decompensation.