Interferon-based therapy delays but metabolic comorbidity accelerates progression of chronic hepatitis C

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ABSTRACT

Background. We compared mortality and complications of chronic hepatitis C between treated and untreated Mexican patients after long-term follow-up. We used a time-to-event analysis and identified the prognostic factors. **Material and methods.** Seventy-four patients with chronic hepatitis C were studied. They were $\geq$ 18 years of age and had a molecular diagnosis of chronic hepatitis C and $\geq$ 6 months of follow-up. Patients with neoplasia or those infected with human immunodeficiency virus or hepatitis B Virus were excluded. Kaplan-Meier analysis, log-rank test, annualized incidence per 100 person-years, and stepwise discriminant analysis were used to analyse mortality and complications. **Results.** The end-point of annualized incidence was lowest in sustained virological responders, intermediate in non-responders, and highest in untreated patients. The absence of treatment impacted adversely on cirrhosis development and the occurrence of portal hypertension and hepatic decompensation/hepatocellular carcinoma (log-rank, $p < 0.05$). Diabetes impacted adversely on liver-related death/liver transplantation among untreated patients. Stepwise discriminant analysis showed that diabetes, high blood pressure, and no retreatment predicted cirrhosis development (eigenvalue $\geq$ 0.8; $p < 0.05$). A MELD score $\geq$ 18 and age $\geq$ 50 years predicted hepatic decompensation/hepatocellular carcinoma (eigenvalue < 0.8; $p < 0.05$). APRI $\geq$ 1.5 predicted mortality/liver transplantation and liver-related death/liver transplantation (eigenvalue < 0.8; $p < 0.05$). **Conclusions.** This is the first long-term study of chronic hepatitis C among Mexican patients. Treated patients showed less progression of liver disease. Treated patients showed less progression of liver disease; and older patients, those with metabolic comorbidities, with MELD score $\geq$ 18 and APRI $\geq$ 1.5 exhibited adverse effects.

Key words. Hepatic disease. Longitudinal follow-up. Diabetes mellitus. Hepatic decompensation. Hispanics.

INTRODUCTION

Globally, up to 170 million people are estimated to have chronic hepatitis C virus (HCV) infection.[1] Once HCV-related cirrhosis has developed, the annual incidence of clinical decompensation, death or liver transplantation (LT), and hepatocellular carcinoma (HCC) among untreated patients or non-responders (NRs) to antiviral therapy (AT) with chronic hepatitis C (CHC) is ~4%, ~3%, and ~3% per year, respectively.[2-7] A sustained virological response (SVR) is associated with improved overall survival,[2,5] reduced risk of morbidity and liver failure, and improved quality of life.[8] The relationship between AT and long-term viral suppression depends on host, viral, and on-treatment factors.[9]

Intermediate benefits of AT on patient outcomes and the natural history of disease are also present in NRs.[5,10] Any duration of AT for HCV was associated with a lower risk of mortality in a large national sample of HCV-infected people.[10] In Mexico, the CHC incidence is rising,[11] and its prevalence and percentage of patients with genotype (G) 1 are 1.2-1.5%[12] and ~70%,[13] respectively. Hispanic patients are under-represented in longitudinal multinational studies of CHC. There is scarce information on long-

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term follow-up in treated Mexican patients with CHC. The aim of this study was to compare mortality and clinical complications of CHC between treated and untreated Mexican patients. We developed a time-to-event analysis and identified the prognostic factors.

MATERIAL AND METHODS

Study design, participants, and setting

We conducted a dynamic, retrospective, comparative cohort study at the Liver Unit of Dr. José Eleuterio González University Hospital, Universidad Autónoma de Nuevo León (UANL), the main tertiary centre treating patients with liver diseases in north-east Mexico. Medical records of patients with CHC admitted from 1987 onwards were reviewed; 310 of > 500 patients were studied and 134/310 (43%) were eligible. Reasons for the exclusion of the remaining 176 (57%) patients were: < 6 months of follow-up (n = 131, 42%), non-molecular diagnosis of CHC (n = 21, 7%), occurrence of mortality or LT during the first 6 months of follow-up (n= 5, 2%), ALD (n = 5, 2%), neoplasia (n = 5, 2%), HIV (n = 2, 1%), HBV (n = 2, 1%), AIH (n = 4, 1%), <18 years old at baseline (n = 1, 1%). There were two inception cohorts: patients exposed to AT (RxG) (n = 67) and those not exposed to AT (noRxG) (n = 67). Nevertheless, over the 134 eligible patients, cirrhosis and hepatic decompensation were more commonly found among noRxG than RxG patients (57%, 44% vs 40%, 13%, respectively), therefore only 74 patients were included in this study, in order to provide baseline comparability and to avoid membership bias. RxG patients were treated according to the guidelines at the time. Reasons for not fulfilling therapy were too-advanced liver disease (n = 12, 32%), medical contraindications (n = 9, 24%), refusal to receive AT (n = 12, 32%), < 12 weeks of AT because of adverse events (n = 2, 5%), and lack of financial support (n = 2, 5%). Follow-up started when RxG received their first AT and at their first medical interview for noRxG; all variables were concurrent with each start point. Inclusion criteria were aged ≥ 18 years, CHC diagnosis by HCV polymerase chain reaction (PCR) and/or HCV G, and medical management in this unit for ≥ 6 months. The exclusion criteria were coexistent malignant neoplasia, hepatitis B or HIV infection, alcoholic liver disease, autoimmune hepatitis (excluding probable and definite cases according to the revised score of the International Autoimmune Hepatitis

Group [R-IAIHG]), or drug-induced liver disease. Table 1 summarizes the baseline characteristics of the two groups. The protocol was approved by the UANL Medical School Institutional Review Board, and was complied with the Helsinki Declaration.

Clinical and laboratory assessment

The baseline variables recorded were: demographics; AT type; comorbidities (diabetes mellitus [DM], dyslipidaemia, liver steatosis [LS]); alcohol abuse history; liver-related complications (cirrhosis, portal hypertension [PH]; gastro-oesophageal varices [GEV]; a history of ascites or gastro-intestinal bleeding secondary to PH [GIBsPH] and/or encephalopathy); body mass index (BMI); biochemical, haematological, and serological tests; α-fetoprotein (AFP) level; imaging study results; endoscopic features; and fibrosis stage (liver biopsy, non-invasive methods). In eight patients, the G was not available. Viral load (VL) values not expressed in IU/mL were converted using the conversion factor of Pawlosky, *et al.*[14] Liver enzyme levels were expressed in IU/L and AFP in ng/mL. RxG on-treatment follow-up was performed in weeks 4, 12, 24, and 48, and then 24 weeks after AT (24postAT). Imaging studies were performed and AFP level was measured every 6 months in cirrhotic patients. AT adverse events were recorded in a predefined fashion. Follow-up times were computed as the difference in months between the cirrhosis diagnosis date and the date of attrition, end of follow-up (21 April, 2013), and/or each end-point occurrence date. For mortality/LT, liver-related death (LRD)/LT, and cirrhosis, the time-to-event analysis considered the date of occurrence minus each cohort's follow-up starting point. Whenever a non-cirrhotic patient developed cirrhosis, a clock-reset approach was used; the follow-up was censored for non-cirrhotic status when cirrhosis was diagnosed, the follow-up of the cirrhotic patient was reset to zero, and the case was restarted as a new case. The same assessment features recorded at baseline were recorded during the last visit for a medical consultation.

Definition of end-points and baseline features

End-points were primary outcomes: mortality/LT and LRD/LT, and secondary outcomes: occurrence of cirrhosis, PH, HCC and the composite event of clinical decompensation defined as D'Amico, García-Tsao stage progression (DAGTP)[15] and HCC, (DAGTP/HCC).

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Fibrosis stage was defined by METAVIR whenever a liver biopsy was available (n = 53) and by non-invasive tests (FibroTest, FibroScan or aspartate transaminase-to-platelet ratio index [APRI] results

n = 11), and/or clinical criteria (fibrosis stage F4) (n = 10). International definitions to classify PH,[16] HCC,[17] ascites, HRS, SBP,[18] GEV, GIBsPH,[19] and encephalopathy[20] were used. DAGTP from stage 1-2

Table 1. Baseline features of the cohort.

	Total (%)	RxG (%)	noRxG (%)	p
n	74 (100)	37 (100)	37 (100)	-
Age ± SD	49 ± 12	46 ± 10	51 ± 14	0.025
Gender				
F/M	44/30 (60/40)	24/13 (65/35)	20/17 (54/46)	0.593
Fibrosis stage				
F0-F2	25 (34)	11 (30)	14 (38)	0.595
F3	11 (15)	7 (19)	4 (11)	0.172
F4	38 (51)	19 (51)	19 (51)	0.592
D'amico, García-Tsao in cirrhotics				
Stages 1 & 2	23 (61)	12 (63)	11 (58)	0.500
Stage 3 & 4	15 (39)	7 (37)	8 (42)	
BMI + SD	28 ± 9	27 ± 8	28 ± 10	0.926
> 30 kg/m^2	19 (28)	10 (29)	9 (27)	0.618
HCV RNA (UI/mL) ± SD	842,629 ± 1,432,718	938,938 ± 1,879,569	743,310 ± 781,117	0.740
HCV RNA (log/mL) ± SD	5.9 ± 6.1[a]	6 ± 6.2 [e, b]	5.9 ± 5.9 [c, d, e]	
HCV RNA > 600,000 UI/mL	25 (36)	11 (31)	14 (41)	0.592
HCV genotype				
G1	50 (68)	22 (59)	28 (76)	0.007
G 2, 3, 4	16 (22)	14 (38)	2 (5)	
Non available	8 (10)	1 (3)	7 (19)	
Child-Pugh in cirrhotics				
A/B/C	26/11/0(68/29/0)[f]	14/4/0 (74/21/0)[f]	12/7/0 (63/37/0)	0.050
MELD > 18 in cirrhotics	2 (5)	2 (11)	0	0.247
High blood pressure	14 (19)	4 (11)	10 (27)	0.117
Diebetes mellitus	14 (19)	4 (11)	10 (27)	0.117
Dyslipidemia	7 (10)	3 (8)	4 (11)	0.500
Liver steatosis	17 (23)[f]	11 (31)[f]	6 (16)	0.270
History of alcohol abuse	9 (12)	5 (14)	4 (11)	0.375
Blood transfusion before 1992/IV drugs/tattoos/other	51/6/4/26 (69/8/5/35)	22/2/3/13 (59/5/8/35)	29/4/1/13 (78/11/3/5)	0.300
ALT (UI/L)	116 ± 92[g]	125 ± 104[f]	107 ± 79[f]	0.665
AST (UI/L)	113 ± 75[g]	116 ± 73[g]	109 ± 77	0.884
Platelet count, x 10^9/L in cirrhotics	150 ± 83	154 ± 63	146 ± 106	0.045
APRI ≥ 1.5 in cirrhotics	24 (63)	11 (58)	13 (68)	0.297
Interferon α standard alone	6 (8)	6 (16)	-	-
Interferon α standard or natural Interferon + ribavirin	11 (15)	11 (30)	-	-
PegInterferon α 2a/b + ribavirin	20 (27)	20 (54)	-	-

[a] 5, [b] 2, and [c] 3, patients had qualitative rather than quantitative HCV PCR, respectively. [d] 2 patients had VL below LLOQ (range 1,000-1,800 UI/mL) but either had HCV genotype and/or qualitative HCV PCR (+). [e] One patient had HCV viral load above upper limit of quantification. [f] 1 and [g] 2, patients did not have that feature available for study.

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to 3-4 was assessed by the date of onset of the pertinent secondary outcomes and/or jaundice (direct bilirubin ≥ 2.50 mg/dL). Patients were not censored according to previous secondary outcomes. Patients were censored if they were lost to follow-up and if they received LT before developing any end-point.

The baseline features studied included history of alcohol abuse defined as an alcohol consumption of > 60 g/day in men and > 40 g/day in women (no patient had alcohol abuse at the baseline), DM, high blood pressure (HBP), and dyslipidaemia as defined by expert committee criteria[21] or mention of their diagnosis and current treatment in the patient's history. SVR was defined as the absence of VL at 24postAT[9] according to the lower limit of quantification (LLOQ) or lower limit of detection available at that time. LS was identified according to the criteria of Chalasani, *et al.*[22] Any event that happened within the first 6 months of follow-up was framed as a baseline feature.
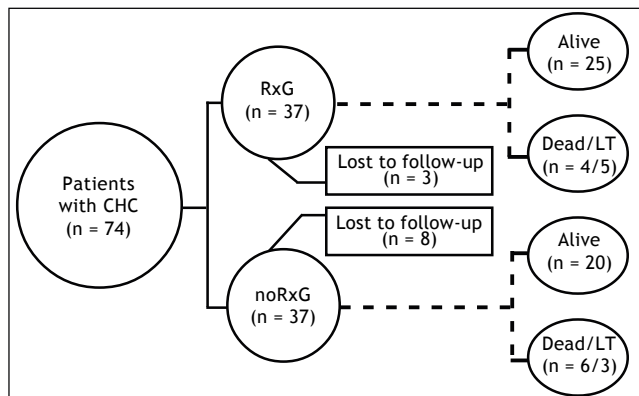

Figure 1. Patient follow-up. CHC: chronic hepatitis C. RxG: exposed to antiviral therapy. noRxG: unexposed to antiviral treatment. LT: liver transplantation.

Statistical analysis

Sample size was determined in a non-probabilistic fashion. Baseline features were compared using the χ^2 test (categorical) or Student's t test (continuous). Incidence rates per 100 person-years (p100py) of primary and secondary outcomes were calculated along with 95% confidence intervals (CIs).[23] Kaplan-Meier cumulative incidence analysis, grouped by end-point status (1 = present; 2 = absent), and log-rank post hoc testing were applied for the time-to-event analysis. Stepwise discriminant analysis (SDA) was performed to predict the profile and number of patients presenting with each of the 13 end-points at the end of follow-up: end-point present or end-point absent.[24,25] Variables were selected for this analysis because they are alleged predictors of a favourable or unfavourable outcome of CHC. They were entered as binary predictor variables, with values corresponding to those registered at the end of follow-up. Statistical tests were done using SPSS v.19 and online resources.[23]

RESULTS

The median follow-up was 83 (6-195) months: 82 (6-178) and 84 (10-195) months in RxG and noRxG, respectively. In RxG, AT reached 48 weeks (n = 26 G1) and 24 weeks (n = 13 non-G1). AT was not completed because of treatment failure (n = 6) and stroke at week 43 of AT (n = 1, G1). One G1 patient who completed 48 weeks of AT did not achieve 24postAT because of LT. SVR was achieved by 13 (35%). Despite retreatment, no treatment-experienced patient (n = 6) became HCV RNA negative. Around 15% of all patients were lost to follow-up: RxG, n = 3 (8%) and noRxG, n = 8 (21%) (Figure 1).

Table 2. End-point annualized incidence according to antiviral treatment status.

End-points[a]	Overall patients	RxG		noRxG
		SVR	NR	
	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)
Mortality/LT	6.4 (3.9-9.9)	0.7 (0.03-3.5)	5.5 (2.5-10.4)	3.4 (1.7-6.1)
Non-LRD	0.7 (0.1-2.3)	–	0.6 (0.03-3.1)	0.3 (0.02-1.7)
LRD/LT	5.7 (3.3-9.1)	0.7 (0.03-3.5)	4.8 (2.1-9.5)	3.1 (1.5-5.6)
DAGTP/HCC	4.2 (2.3-7.2)	–	5.2 (1.6-12.4)	11.1 (5.1-21.1)
Cirrhosis	4.2 (1.8-8.4)	1.34 (0.06-6.6)	3.3 (0.16-16.4)	11.1 (4.1-24.6)
PH[b]	9.2 (5.6-16.4)	11.0 (1.9-38.9)	11.0 (3.4-25.7)	46.2 (18.7-96)
HCC	3.6 (1.5-7.1)	–	3.0 (0.5-10.0)	4.2 (1.5-9.3)

[a] All complications except cirrhosis, mortality/LT, and LRD/LT were studied from the time of cirrhosis diagnosis onwards. [b] Portal hypertension was diagnosed as splenomegaly (n = 7), ascites (n = 3), and gastro-oesophageal varices (n = 1).

Cirrhosis development

During follow-up, in the non-cirrhotic patients at baseline, 2/18 (11%) in RxG and 5/18 (28%) in noRxG developed cirrhosis. Annual incidence p100py was 3.3 times greater in noRxG than in NRs and 8.2 times greater in noRxG than in those with SVR (Table 2). Kaplan–Meier cumulative incidence of cirrhosis in years 6, 8, 10, and 13 remained at 13% in RxG, but increased from 25% to 75% to 100% in years 6, 8, and 11 in noRxG (log-rank p = 0.036) (Figure 2A).
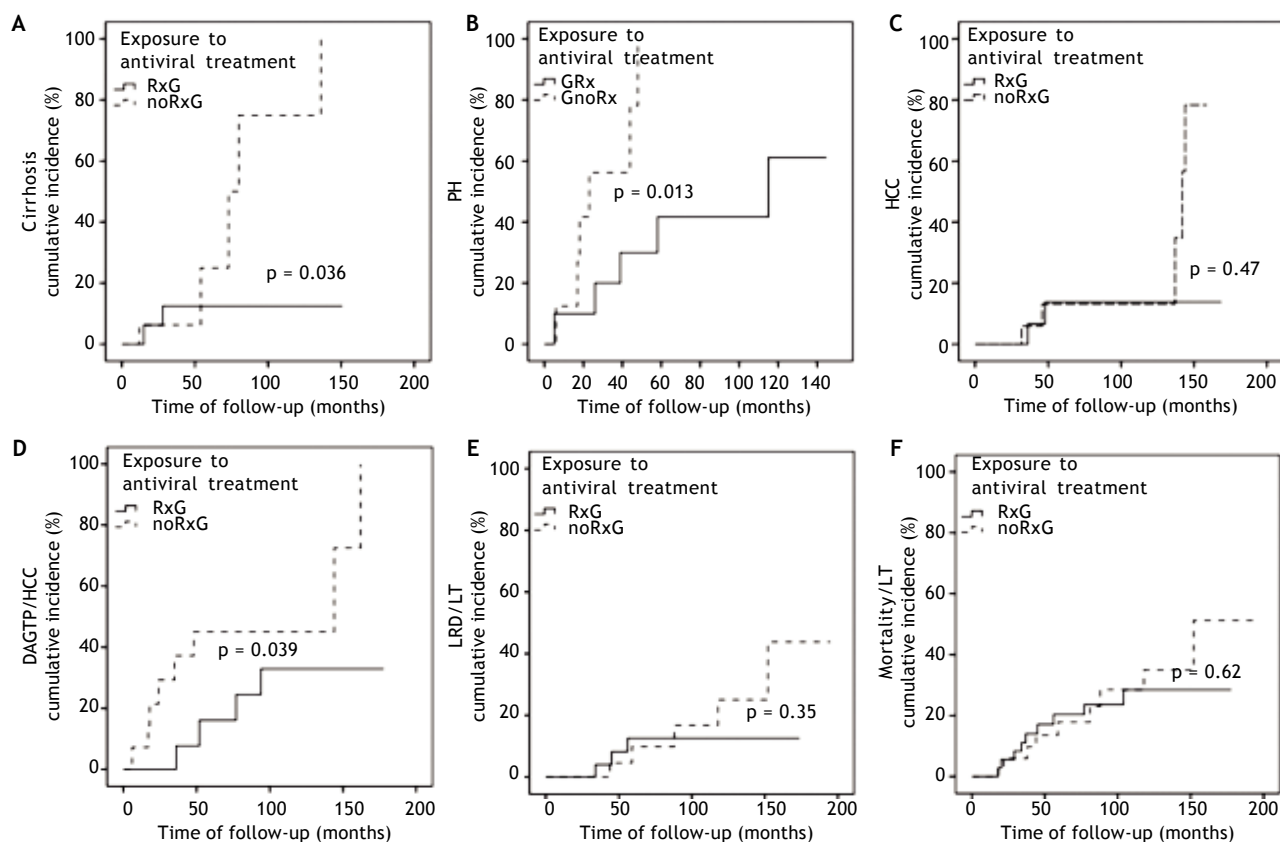

Figure 2. *Comparison by log-rank test between RxG and noRxG: **A**. Cirrhosis. **B**. Portal hypertension (PH). **C**. Hepatocellular carcinoma (HCC). **D**. D'Amico, García-Tsao progression/hepatocellular carcinoma (DAGTP/HCC). **E**. Liver-related death (LRD)/Liver transplantation (LT). **F**. Mortality/LT.*

Table 3. Endpoint occurrences at the end of follow-up.

	Total, n (%)	RxG, n (%)	noRxG, n (%)
Portal hypertension	11/19 (58)	5/10 (50)	6/9 (67)
D'Amico, García-Tsao progression	8/38 (21)	3/14 (21)	5/14 (36)
D'Amico, García-Tsao progression/Hepatocellular carcinoma[a]	12/28 (43)	4/14 (21)	8/14 (57)
Ascites	9/33 (28)	4/17 (24)	5/16 (31)
Gastro-intestinal bleeding secondary to portal hypertension	5/41 (12)	3/20 (15)	2/21 (10)
Encephalopathy	10/43 (23)	5/21 (24)	5/22 (23)
Hepatorenal syndrome	3/45 (7)	1/21 (5)	2/24 (4)
Spontaneous bacterial peritonitis	2/45 (4)	1/21 (5)	1/24 (4)
Hepatocellular carcinoma	7/45 (16)	2/21 (10)	5/24 (21)
Death/liver transplantation [b]	18/74 (24)	9/37 (24)	9/37 (24)

[a] Appeared as ascites (n = 2), GIBsPH (n = 1), and HCC (n = 1) in the RxG and as ascites (n = 4), jaundice (n = 1), and HCC n = 3) in the noRxG. [b] Causes of liver-related death were encephalopathy (n = 2), HRS (n = 2), HCC (n = 1), GIBsPH (n = 3), LT (n = 8), non-liver related (n = 2), heart disease (n = 1) and DM (n = 1).

Cirrhosis-related secondary outcomes

The time-to-event sub-analysis stratified several factors related to AT as shown in table 3 and figures 2B-2F. Only PH and DAGTP/HCC in RxG vs noRxG were significant by the log-rank test (p < 0.05).

The rates of PH, DAGTP/HCC, and HCC annual incidences p100py were 4.2, 1.7, and 1.4 times higher, respectively, in noRxG than in NRs (Table 2). No patients with SVR experienced any of these, except for PH (11 p100py) (Table 2).

Mortality, LRD, and LT

Mortality/LT reached 18/74 (24%) at the end of follow-up and was 9/37 (24%) in both groups. LRD occurred in 3/37 patients (8%) in RxG and in 5/37 patients (14%) in noRxG. Mortality/LT and LRD/LT Annual incidences p100py were more common in RxG than noRxG (Table 2). Kaplan-Meier cumulative incidence estimates were not significant for mortality/LT (p = 0.62) or LRD/LT (p = 0.35) in the RxG and noRxG (Figures 2E and 2F).

Discriminant analysis

PH and DAGTP sub-analyses did not qualify for SDA (F value to enter < 3.84 or overfitting). Six variables separated the two subgroups according to their end-point occurrence (present/absent) (p < 0.05). Mortality/LT and LRD/LT were predicted by APRI ≥ 1.5; cirrhosis by DM, HBP, and no retreatment; DAGTP/HCC was predicted by model of end-stage liver disease (MELD) ≥ 18 and age ≥ 50 years (Table 4). Predictor subsets with the highest power to predict prognosis had eigenvalues > 0.8. These subsets included retreatment (Wilks' λ = 0.534; p < 0.001); HBP (Wilks' λ = 0.643; p = 0.001); and DM (Wilks' λ = 0.754; p = 0.002) in the cirrhosis model. Age ≥ 50 years (Wilks' λ = 0.670; p = 0.001) and MELD ≥ 18 (Wilks' λ = 0.839; p = 0.001) were significant in the DAGTP/HCC model. Despite a high positive predictive value (PPV) of > 80%, only the cirrhosis model had high sensitivity (> 85%) and predicted membership with classification accuracy > 25% compared with classification by chance. All other models had p < 0.05 and PPV > 80% but lower sensitivity, classification accuracy < 25%, eigenvalues < 0.80, and high variability of their predictors (Wilks' λ > 0.2).

Comparison of end-points in patients with and without DM

DM was present in 14/74 patients at baseline: RxG n = 4, noRxG n = 10. At end of follow-up, two non-diabetics (n = 1/25 [4%] NR, n = 1/28 [3.6%] noRxG) developed DM. The clock-reset approach introduced 16 newly diagnosed patients into the time-to-event analysis. The median follow-up for diabetics and non-diabetics was 52 (17-167) and 88 (6-195) months, respectively. The percentage of patients

Table 4. Discriminant models for the presence/absence of each end-point according to concurrent predictors present at the end of the follow-up.

End-point occurrence	Discriminant analysis								
End-point^	Predictor	Wilks' λ	F	Discriminant function	Eigen value	Misclassified cases			CCC (%)
						Sen (%)	PPV (%)	MPP (%)	
Cirrhosis development	Retreatment **	0.534	6.5	-0.721	0.872	86	86	68	94.4
	HBP **	0.643	11.5	0.911					
	DM **	0.754	17.2	0.948					
DAGTP/HCC[a]	Age ≥50 years**,[b]	0.670	5.5	0.644	0.823	42	100	51	75.0
	MELD ≥ 18 **,[c]	0.839	13.2	0.890					
LRD/LT	APRI ≥ 1.5 **,[d]	0.819	12.8	1	0.221	25	40	76	85.9
Mortality/LT	APRI ≥ 1.5 **,[d]	0.888	9.0	1	0.126	30	60	76	86.5

Sen: sensitivity. MPP: membership prior probability. CCC: correctly classified cases. [a] Child-Pugh score ≥ 6 was not included in SDA because encephalopathy and ascites as end-points were included in the predictor score. [b] 8/12 were ≥ 50 years old when experiencing DAGTP/HCC. [c] 2 and [d] 4 patients did not have this finding available. ** p ≤ 0.001. ^ End-points at the end of follow-up.
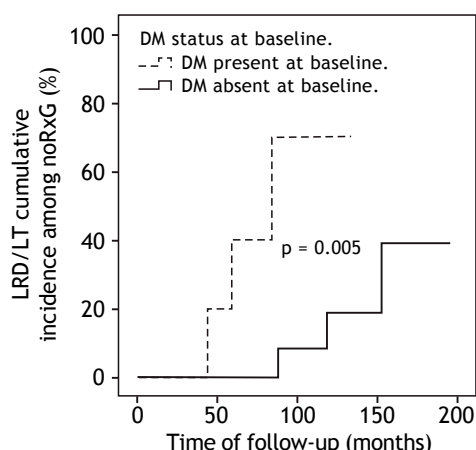
Figure 3. *Kaplan-Meier analysis of the cumulative inciden-ce of liver-related death (LRD)/liver transplantation (LT) ac-cording to the presence of diabetes mellitus at baseline (DM) in noRxG.*

with SVR was lower in diabetics (20%) than in non-diabetics (36%). Because of the low DM prevalence, only the LRD/LT comparison in noRxG with and without DM is presented here (p < 0.05) (Figure 3).

DISCUSSION

This is the first study of Mexican patients with CHC to evaluate the effects of AT given before the protease-inhibitor era and assessed after long-term follow-up. As expected, the end-point annual inci-dence was lowest among those with SVR (4.4 to 11.1 times less than in the noRxG), intermediate in NRs (1.3 to 4.2 times less) and highest among the noRxG (0.3-46.2 p100py). The prognostic factors identified by SDA showed that MELD ≥ 18 and age ≥ 50 years predicted DAGTP/HCC and that APRI ≥ 1.5 predicted mortality/LT and LRD/LT. The log-rank test showed that the absence of AT impacted adversely on cirrho-sis, PH, and DAGTP/HCC cumulative incidences in noRxG vs RxG even after > 10 years of follow-up.

Our comparison of the AT effect vs the noRxG agrees with that in a previous report showing that the rates of hepatic decompensation/HCC and mor-tality were higher in untreated *vs.* treated patients[26] during a similar follow-up (50 *vs.* 13% and 45 *vs.* 13%, respectively). A higher percentage of noRxG had G1, Child-Pugh score ≥ 6, and thrombocytope-nia than RxG (p < 0.05), although mortality/LT did not differ significantly between these groups. The higher mortality/LT ratio among the noRxG (6/3) *vs.* the RxG (4/5) group, alongside the non-probabil-istic nature of the present sample-size and the high proportion of patients with advanced liver disease at baseline, could have overcome the benefit among the RxG that the improvement in fibrosis progression and cirrhosis complications should have had on their mortality/LT. When SVR is reached, DM may not have a negative impact on LRD/LT.[2] There were few RxG diabetics in this cohort, and any adverse influence of DM on LRD/LT was confirmed only in the noRxG (p < 0.05).

The treated CHC patients had increased end-points of cumulative incidences for mortality/LT at 6 and 10 years compared with Italian[27] and US[26] co-horts, and for HCC compared with Taiwanese[3] and Italian-Argentine[28] cohorts. The cumulative inci-dence of DAGTP/HCC was also higher here than in US patients[26] during a similar follow-up. The lower cumulative incidence in non-Latino cohorts could reflect different AT schemes or G distribution, lower percentage of patients with cirrhosis (≤ 36% in other studies, ≥ 51% in our study), and higher percentage of an SVR (67% in Taiwanese patients,[3] 36% in our study). Studies from other countries have demon-strated diverse CHC complication burdens in treated and untreated patients; notably, the baseline distri-bution of features and cohort data collection designs were not uniform.[3-7,26,28-33]

Mortality/LT cumulative incidence among noRxG CHC patients here and in a Japanese cohort[6] were similar after 6 years of follow-up and lower than in the US (26) (~18%, ~20%, and ~28%, respectively). However, the cumulative incidence in both stud-ies[6,26] increased steadily thereafter, as opposed to the value in these Mexican patients, which re-mained lower at 10 years (~35%, ~45%, and ~50%, respectively). The HCC cumulative incidence here is similar to that in Italian-Argentine patients[28] (~16% at 6 years and ~36% at 10 years) but is low-er than that reported in two large Japanese cohorts (≥ 28% at 6 years and ≥ 55% at 10 years).[6,33] Mortal-ity here and in the Japanese study[6] was mostly liver related, whereas ~50% of mortality in the US pa-tients was not.[26] Older age and male sex were prog-nostic factors for mortality/LT and HCC by multivariate analysis in noRxG CHC co-horts.[6,26,28,33] History of alcohol abuse was also a significant factor for HCC in US[26] and Japanese[6] pa-tients.

Cirrhosis annual incidence among our NR CHC non-cirrhotic patients (3.5 p100py) was lower than that in a US cohort (9.9 p100py),[32] although the US cohort had a higher incidence of BMI ≥ 30, G1 (100%), and DM (26%), possibly accounting for these differences.[32] Longer follow-up of noRxG and the baseline occurrence of DM (27%), overweight

(BMI = 28), hepatic decompensation (22%), and G1 (74%) may explain the higher frequency of cirrhosis and HCC annual incidence compared with Asian[3,31] populations.

End-point annual incidence values among NR CHC compensated cirrhotic patients were similar to those reported for Canadian-European[2] patients for DAGTP and LRD/LT, and higher than in North American,[2] European,[2,5] and/or Taiwanese[3] cohorts for HCC. However, the HCC annual incidence is lower here than in Japanese patients.[33]

The annual incidence in SVR compensated CHC cirrhotic patients here was nil for DAGTP suggesting that a favourable response to treatment affected the CHC natural history. This was reported in similar cohorts from North America,[2] South America,[30] and Europe,[2,5] although the annual incidence of HCC among Canadian-European,[2] Italian,[5] and Japanese[33] patients was slightly higher than in our patients with SVR (0.55, 0.66, 0.49, and 0 p100py, respectively).

In our non-cirrhotic CHC cohort, the cirrhosis annual incidence was 4.2 p100py, whereas fibrosis/year progression was 0.04-0.12 METAVIR units in an Argentinean retrospective study.[7] DM, HBP, and no retreatment were negative prognostic factors in our patients, whereas in the Argentinean study[7] alcohol abuse predicted fibrosis/year progression. Annual incidence values for HCC and mortality/LT in compensated CHC cirrhotics were higher here than those reported in other Latin-American populations (3.4 and 6.4 *vs.* ≤ 3.0 and ≤ 3.5 p100py, respectively).[4,29] Annual incidence for hepatic decompensation in Cubans[4] was double that in our patients, possibly because of higher G1 and NR/noRxG prevalence in the Cubans (96 and 92% *vs.* 68 and 82%, respectively). The reasons for these differences between ethnic groups are unclear.

This study has some limitations. It was a retrospective study of a sample of the Mexican population. Because of the non-probabilistic sample size, log-rank differences and SDA findings were not evident for all end-points. Fifteen per cent of the overall cohort abandoned the follow-up, and noRxG may have been susceptible to attrition bias (21%). We tried to reduce potential bias by studying secondary outcomes only among cirrhotic patients fulfilling similar inclusion/exclusion criteria.

CONCLUSION

We found that interferon-based therapy beneficially affected HCV-related complications among Mexican patients with CHC after a long-term follow-up. The prognostic factors were metabolic comorbidities and no retreatment for cirrhosis development; APRI ≥ 1.5 for mortality/LT and LRD/LT; and older age and MELD ≥ 18 for DAGTP/HCC. DM was confirmed to impact adversely on LRD/LT in noRxG. Noteworthy, the high proportion of patients with advanced liver disease at baseline in this study could have overcome the benefit among the RxG that the improvement in fibrosis progression and cirrhosis complications should have had on their mortality/LT.

ABBREVIATIONS

- **24postAT**: 24 weeks after antiviral therapy.
- **AFP:** α-fetoprotein.
- **APRI:** aspartate transaminase-to-platelet ratio index.
- **AT:** antiviral therapy.
- **BMI:** body mass index.
- **CHC:** chronic hepatitis C.
- **CI:** confidence interval.
- **DAGTP:** D'Amico, García-Tsao progression.
- **DM:** diabetes mellitus.
- **G:** genotype.
- **GEV:** gastroesophageal varices.
- **GIBsPH:** gastro-intestinal bleeding secondary to portal hypertension.
- **HBP:** high blood pressure.
- **HCC:** hepatocellular carcinoma.
- **HCV:** hepatitis C virus.
- **HRS:** hepatorenal syndrome.
- **LLOQ:** lower limit of quantification.
- **LRD:** liver-related death.
- **LS:** liver steatosis.
- **LT:** liver transplantation.
- **MELD:** model of end-stage liver disease.
- **noRxG:** group of patients not exposed to antiviral therapy.
- **NR:** non-responder to antiviral therapy.
- **p100py:** per 100 person-years.
- **PCR:** polymerase chain reaction.
- **PH:** portal hypertension.
- **PPV:** positive predictive value.
- **RxG:** group of patients exposed to antiviral therapy.
- **SBP:** spontaneous bacterial peritonitis.
- **SDA:** stepwise discriminant analysis.
- **SVR:** sustained virological response.
- **VL:** viral load.

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FINANCIAL DISCLOSURES

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