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Clinical outcomes in chronic hepatitis C long-term responders to pre-direct antiviral agents: a single center retrospective study

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Summary

Background. Obesity, type 2 diabetes (T2D), dyslipidemia, arterial hypertension as well as hepatic steatosis (HS) are common conditions that can affect clinical outcomes of patients with chronic hepatitis C (CHC) who achieved sustained virological response (SVR). The aim of this study was to assess the impact of metabolic cofactors on the occurrence of clinical events during follow-up (FU) in a group of CHC long term responders (LTRs) to interferon (IFN) -based therapy.

Methods. A total of 5172 medical records of CHC patients enrolled from 1990 to 2011 were examined. 1034/5172 (20%) patients were treated with IFN-based therapy and 382/1034 (37%) of them achieved SVR. A total of 188 (49%) LTRs performed liver biopsy before antiviral treatment. Data on liver and cardiometabolic events such as cirrhosis and its complications, hepatocellular carcinoma, coronary artery disease, arterial hypertension, impaired fasting glucose (IFG)/type 2 diabetes (T2D) and dyslipidemia, were collected over time.

Results. The mean age of the whole cohort was 46 ± 12 years and 114/188 (61%) patients were males. HS was found in 82/188 (43.6%) patients and most of them were infected by HCV genotype 3a. The prevalence of obesity, IFG/T2D, dyslipidemia and arterial hypertension was 4.3%, 6.9%, 37.2% and 5.9%, and was similarly distributed among patients with and without HS. Cirrhosis was histologically diagnosed in 18/188 (9.6%) patients. After a median follow-up of 11 years (range 3-21), the cumulative incidence of cardiovascular events, IFG/T2D and dyslipidemia was higher in CHC-LTRs who had HS at baseline compared to those without HS (1.2%, 2.3% and 3.0% *vs* 0.4%; 0.8% and 2.5%, respectively). At multivariable Cox regression analysis, HS was significantly associated to the development of cardiovascular events and IFG/T2D (HR=5.2, 95%CI=1.3-20.7, p=0.019 and HR=2.6, 95%CI=1.1-6.2, p=0.027, respectively).

Conclusions. In CHC-LTRs, HS at baseline may predispose to the development of cardiovascular events and T2D during follow-up emphasizing the importance of an accurate counseling in order to prevent extra-hepatic complications.

Introduction

For nearly 30 years, interferon (IFN) alone or in combination with ribavirin (RBV), has been the gold standard for the treatment of hepatitis C virus (HCV) infection. The rate of treatment success is closely linked to viral and host factors such as HCV-genotype, patient age, sex, genetic factors, stage of liver fibrosis and the presence of other comorbidities.[1-2] Sustained virological response (SVR), defined as undetectable HCV-RNA 24 weeks after the end of therapy, was achievable in 75% of patients infected with genotypes 2 and 3 and only in 40–50% of patients infected with genotype 1. [3-5] It is well known that viral eradication improves liver histology, quality of life and reduces the risk to develop cirrhosis and hepatocellular carcinoma (HCC).[6-7] Metabolic cofactors such as obesity, insulin resistance (IR), type 2 diabetes (T2D) and dyslipidemia may impact on the morbidity and mortality of chronic hepatitis C (CHC) accelerating the progression of liver fibrosis, increasing the risk of developing HCC and reducing the response to antiviral therapy.[8-9] From a metabolic point of view, HCV infection resembles non-alcoholic steatohepatitis (NASH) for the impairment of glucose metabolism even if the signaling pathways involved are different. The prevalence of hepatic steatosis (HS) in the setting of CHC is around 40% [10] while the risk to develop T2D is higher compared to the other chronic liver diseases suggesting a potential diabetogenic effect of the virus.[10] Specifically, HCV core protein impairs insulin pathway increasing the phosphorylation of insulin receptor substrate-1 (IRS-1) through the up-regulation of the suppressor of cytokine signaling (SOCS) that in turn impairs insulin signaling. In HCV genotype 3 patients, the up-regulation of SOCS leads to a down-regulation of the peroxisome proliferator-activated receptor-g (PPARg) promoting HS thus IR.[11-12] Conversely, in patients with non-3 HCV genotypes, HS is associated with body mass index (BMI) and IR and may persist even if the viral infection is resolved.[10,13]

Similarly, HCV can affect lipid metabolism through its interaction with very low density lipoproteins (VLDL) and low density lipoproteins (LDL). The association of HCV with host lipoproteins facilitates its entry into the hepatocytes favoring the development of chronic liver disease.[14] The association between HCV infection and metabolic alterations may predispose to the development of clinical events over time notwithstanding viral eradication, accelerating liver fibrosis. In CHC patients who achieved SVR after IFN+RBV therapy, the assessment of metabolic derangement is crucial for their management to prevent the occurrence of hepatic and cardio-metabolic events over time. Furthermore, this strategy remains important also in the era of the new drugs named direct antiviral agents (DAAs) characterized by a high HCV eradication rate.[15] In this context, the aim of this study was to define the main baseline metabolic predictors of clinical outcomes in a monocentric cohort of CHC-LTRs who underwent liver biopsy at the time of HCV antiviral therapy.

Materials and Methods

Patients

From 1990 to 2011, a total of 5172 patients were approached at the Division of Gastroenterology and Hepatology, Città della Salute e della Scienza University Hospital, Turin. All the available medical records were retrospectively examined. Patients included in the study were infected with HCV, underwent IFN-based therapy (IFN mono-therapy or pegylated IFN plus RBV) and achieved a SVR (Figure 1). Patients with HCV/HBV coinfection (N=12), with a follow-up period less than 3 years (N=35) and without liver biopsy prior to treatment (N=147) were excluded from the analysis (Figure 1).

Antiviral therapy duration was 48 weeks or less according to specific guidelines.[5] The beginning of follow-up for each patient started at the initiation of antiviral therapy while the end coincided with the last medical examination available (at least three years after the end of treatment). Long-term

response was defined as the maintenance of SVR throughout follow-up which had an average of 10 years (range 3-21 years). Liver enzymes (AST, ALT, GGT) and metabolic parameters (total-cholesterol, triglycerides, glucose), BMI and instrumental examination (abdominal ultrasound [US]) were collected from medical records prior to treatment initiation and at the last available follow-up visit. Liver biopsies were analyzed at baseline by an expert pathologist. Hepatic fibrosis and inflammation were scored according to Ishak classification.[16] Steatosis was defined as absent or significant if the percentage of fat into the hepatocytes was less than 5% or ≥ 5%, respectively. All patients gave their consent for including their personal data in the database. The study was approved by the ethics committee of the University Hospital Città della Salute e della Scienza of Turin and was in accordance with the Helsinki Declaration.

Metabolic cofactors definition

Metabolic cofactors considered in this study were: overweight/obesity (BMI ≥ 24.9 kg/m^2/BMI ≥ 29.9 kg/m^2), impaired fasting glucose (IFG)/T2D (fasting glucose levels ≥ 110 mg/dl), dyslipidemia (total cholesterol ≥ 200 mg/dl, triglycerides ≥ 150 mg/dl), arterial hypertension (≥ 130/85 mm/Hg) and HS at biopsy (≥ 5%).

Follow up and clinical outcomes

All the patients were followed-up for at least 3 years (median FU period 10 years): every 6 months after the end of antiviral treatment for the first 2 years and every 24 months, subsequently. Cirrhotic patients were examined every 6 months. The liver-related events occurred during FU and considered for the analysis were collected from the outpatients' registries and were: the development of cirrhosis and its complications (ascites, bleeding varices, hepatic encephalopathy and HCC). The diagnosis of HCC was done using imaging techniques. The cardiovascular events considered in the analysis included acute myocardial infarction and stroke.

Statistical analysis

Data are reported as mean and standard deviation (SD) for continuous normally distributed variables, as median and interquartile range (25°-75° percentiles) for continuous non-normally distributed variables and as number and frequency (%) for categorical variables. Data normality was checked by D'Agostino-Pearson test. Comparisons between groups were performed using the two-tailed Student's t-test, for normal continuous variables, and the Kruskal-Wallis non-parametric test, for non-normal continuous variables. For categorical data, the Fisher exact test or the Chi-square test were used as appropriate. To assess the occurrence of liver/cardio-metabolic events over time, according to the presence of baseline metabolic cofactors, the Kaplan-Meier survival analysis was performed and differences between the curves were determined by the Logrank test. To evaluate the risk to develop clinical events in the FU, univariate and multivariable Cox regression analysis adjusted for age, sex and BMI were performed. All the analysis were performed with MedCalc software version 12.7.

Results

Clinical features of the study population at baseline

A total of 188 CHC patients (114 male, 61%) were followed-up for 3 to 21 years (mean 11 years). Most of the patients (93%) were treated with the combination of pegylated IFN and RBV while the others received the IFN monotherapy. Baseline clinical, biochemical and histological characteristics of the study cohort, according to the presence or absence of HS, are reported in Table 1. HS was found at liver biopsy in 82 CHC patients with a prevalence of 43.6%. Patients with HS were older and showed a higher BMI compared to those without HS. Overall, 33 patients (17.6%) were infected by HCV genotype 3a and most of them (22 out of 33, 67%) had HS. Overall, the prevalence of obesity, IFG/T2D, dyslipidemia and arterial hypertension was 4.3%, 6.9%, 37.2% and

5.9%, respectively, and was not different in the two groups. Older age, HCV genotype 3a, and dyslipidemia were significantly associated to the presence of baseline HS at univariate logistic regression analysis but, after multivariable regression analysis, the only factor significantly associated to HS was HCV-genotype 3a (odds ratio [OR]=8.4; 95% confidence interval [CI] 2.7-26.0, p<0.001) (Supplementary Table 1).

Follow-up analysis

After 20 years of follow-up, one CHC patient had a recurrence of HCV infection. Of the 6 deaths occurred, 2 LTRs died for liver-related events, 3 for cardiovascular events and 1 for colorectal cancer (Table 2). The cumulative incidence of mortality was similar in LTRs who had HS at biopsy compared to those who did not have HS (Table 2).

Liver-related morbidity

Liver-related events occurred in 5 LTRs with a cumulative incidence of 0.3%. One subject developed cirrhosis, 1 with pre-existent cirrhosis at baseline developed its complications (hepatic decompensation), 3 subjects developed HCC (2 on cirrhotic liver and 1 on non-cirrhotic liver with steatosis). Baseline HS did not impact on the development of liver-related events during follow-up (Table 2). Conversely, CHC-LTRs who had severe fibrosis at baseline showed a higher cumulative incidence of liver related outcomes compared to those with mild/moderate fibrosis (0.9% vs 0.1%, p<0.001) (Supplementary Table 2). After multivariable Cox regression analysis adjusted for age, sex, BMI and HCV genotypes, severe fibrosis was the only baseline predictor of liver-related outcomes with a hazard ratio (HR) of 11 (95% CI=1.5-87.9, p=0.025, data not shown).

Cardiometabolic-related morbidity

Overall, cardiovascular events occurred in 14 LTRs and the cumulative incidence was significantly higher in those who had HS at liver biopsy compared to those without HS (1.2% vs 0.4%, p=0.011) (Table 2). At univariate Cox regression analysis, IFG/T2D, dyslipidemia and HS showed a higher probability to develop cardiovascular events (Figure 2 A-C). After multivariable Cox regression analysis, the only metabolic cofactor significantly associated to a higher risk of developing cardiovascular events was IFG/T2D (HR=5.2, 95% CI=1.3-20.7, p=0.019) (Table 3).

Arterial hypertension occurred in 24 LTRs with a similar cumulative incidence in both patients with and without HS at liver biopsy (1.4% vs 1.3%, p=0.610) (Figure 2D). At univariate Cox regression analysis, no metabolic cofactors were significantly associated to the development of arterial hypertension over time, and multivariable analysis confirmed this result.

Overall, the cumulative incidence of overweight/obesity, IFG/T2D and dyslipidemia was 1.2%, 1.5% and 2.8%, respectively (Table 2). Specifically, the cumulative incidence of IFG/T2D and dyslipidemia was significantly higher in LTRs who had HS at liver biopsy compared to those who did not have HS (2.3% *vs* 0.8%, p=0.005 and 3.0% *vs* 2.5%, p=0.010, respectively), while the cumulative incidence of overweight/obesity was similar among the two groups.

At univariate Cox regression analysis, older age, dyslipidemia and HS were significantly associated to the development of IFG/T2D. After multivariable analysis, the only baseline metabolic cofactor associated to the development of IFG/T2D was HS (HR=2.6, 95% CI=1.1-6.2, p=0.027) (Table 4).

Concerning the other metabolic outcomes, older age increased the risk of developing dyslipidemia during follow-up (HR=1.0, 95% CI=1.0-1.1, p=0.005) (Supplementary Table 3) while no baseline cofactors increased the risk of overweight/obesity over time.

Discussion

In this study, on 188 CHC LTRs to IFN and RBV therapy, we assessed the impact of metabolic cofactors (HS, overweight/obesity, T2D, dyslipidemia and arterial hypertension) on the

development of clinical events (both hepatic and cardio-metabolic) during a long follow-up. Particularly, it is well known that HS may be considered as a marker of metabolic dysfunction predisposing to the development of clinical events even after a long time from HCV eradication. On the other side, CHC infection has been associated with a poor prognosis affecting both liver- and cardio-metabolic-related outcomes.[17]

The median duration of FU was 11 years (range 3-21), one of the longer. Concerning virological and histological characteristics, our population slightly differs from another cohort of 150 Italian CHC-LTRs. In fact, in the former, the prevalence of HCV genotype 3a was higher compared to that reported by Morisco (17.6% vs 3.3%). Similarly the prevalence of cirrhosis was higher in our cohort compared to that reported in the other cohort (9.6% vs 1.3%).[18]

At the time of baseline screening for antiviral therapy, HS was found at liver biopsy in 82 LTRs with a prevalence of 43.6%. This data was in agreement with several studies indicating that, in the setting of HCV infection, the prevalence of HS may range from 42% to 73%.[19-20] It is well known that HS can be induced directly by HCV genotype 3a (viral steatosis) or indirectly, through the development of IR, by HCV-genotype 1 (metabolic steatosis).[21-26] Particularly, HCV genotypes 1 and 4 infection is associated to the development of IR regardless of the presence of steatosis.[23, 27-28] Recently, Lerat et al. demonstrated that in HCV transgenic mice, the development of IR and glucose intolerance are supported by HCV *per se* through the expression of viral proteins in the hepatocytes which negatively act on the glucose uptake by the liver through the down-regulation of Glut2 and IRS-2 expression via SOCS3-dependent mechanisms.[28] Unfortunately, in our population we did not have data on homeostasis model of assessment (HOMA)-IR, but we showed that in HCV patients infected with HCV genotype non-3, baseline BMI was significantly higher compared to those infected with HCV genotype 3a indicating that in the first group, steatosis was mainly driven by metabolic rather than viral derangements. Conversely, 67% of HCV genotype 3a infected patients had HS at biopsy, probably driven by viral infection.

Overall, our population of LTRs had a good prognosis with a mortality rate of 0.3%, similar to that reported by Morisco et al. (0.7%) and by George et al. (0.6%) in two independent studies.[18,29] The cumulative incidence of IGF/T2D in our population is 1.5%, the same reported by Giordanino et al.[30] In their study, the authors stated that HCV eradication did not significantly reduce the risk of IFG/T2D during 8 years FU and that the incidence of T2D was similar in LTRs compared to non-responders at IFN or PegIFN plus RBV treatment.[30] In another study, Metha et al. demonstrated that among 1084 non-diabetic subjects at baseline, HCV infection was associated with an elevated risk of T2D development over 9 years FU.[31]

The incidence of cardiovascular events was 3-fold higher in CHC-LTRs who had HS at baseline compared to those without HS, and this data is comparable to that reported in the Italian population.[32] The link between HCV infection and CAD is supported by the fact that HCV is able to interfere with both glucose and lipid metabolism, leading to the development of IR, HS and T2D, which are directly associated to atherosclerosis development.[33] Furthermore, HCV increases cardiovascular risk by inducing a systemic inflammatory status and oxidative stress.[33] Specifically, HCV infection promotes inflammation increasing pro-inflammatory cytokines levels such as interleukin (IL)-6, tumor necrosis factor alpha (TNF-a), C-reactive protein (CRP) and fibrinogen which in turn are associated with increased risk of CAD.[34-35]

According to previous data, we confirm that hepatic fibrosis is the main risk factor for the development of hepatic complications.[36-37] The incidence of HCC in our population was very low (0.2%) and similar between CHC-LTRs who had HS at baseline and those who did not have HS. The association between HS and fibrosis in the setting of HCV infection is controversial: while in the majority of the studies a robust association has been reported,[38-40] some authors did not find any relationship.[41]

Our study has some limitations. The first is the lack of a second liver biopsy making difficult the longitudinal comparison of the degree of hepatic fibrosis and steatosis. Nevertheless, from an

ethical point of view, in the clinical setting, it would be difficult to perform a second liver biopsy for histological revaluation. The second limitation is the retrospective design of the study making difficult to find clinical data from old medical records. Furthermore, during the last 30 years, all consultations has been recorded in both a paper archive and a digital databank. However, the potential heterogeneity arising from this, is limited by the fact that in our unit all authors followed international guidelines. Finally, we are aware that the lack of data on alcohol consumption in our cohort may represent another important limitation. However, all patients stopped drinking at the time of HCV diagnosis and during antiviral treatment.

In conclusion, this study indicates that in a population of CHC-LTRs to IFN-based therapies, SVR is associated with a good prognosis. Notwithstanding this, the presence of HS at baseline may predispose to the development of cardiovascular events and T2D during follow-up emphasizing the importance of an accurate counseling in order to prevent extra-hepatic complications.

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Tables

Table 1. Baseline clinical, biochemical and histological characteristics of CHC infected patients in the whole cohort and according to the presence histological steatosis.

Variables	All (N=188)	CHC (N=106)	HS-CHC (N=82)	*P* value
Age (years)	46 ± 12	45 ± 12	48 ± 11	0.043
M/F, n	114/74 (61/39)	58/48 (55/45)	56/26 (68/32)	0.082
BMI (kg/m^2)	24.3 ± 3.2	23.7 ± 3.0	25.1 ± 3.4	0.007
HCV genotype, n (%)				0.019
1a/1b	111 (59.0)	67 (63.2)	44 (53.7)	
2a/2c	41 (21.8)	27 (25.5)	14 (17.1)	
3a	33 (17.6)	11 (10.4)	22 (26.8)	
4	3 (1.6)	1 (0.9)	2 (2.4)	
AST (U/L)	57 (55-67)	59 (52-72)	56 (55-67)	0.658
ALT (U/L)	82 (78-93)	85 (76-97)	82 (77-104)	0.605
gGT (U/L)	45 (37-52)	40 (34-45)	50 (34-67)	0.149
Hb (g/dL)	14.6 ± 1.4	14.5 ± 1.3	14.7 ± 1.5	0.551
Platelets (x10^9)	211 (201-220)	210 (206-232)	203 (187-220)	0.176
Total cholesterol (mg/dL)	175 (168-182)	173 (160-179)	183 (168-193)	0.166
Triglycerides (mg/dL)	101 (90-110)	98 (88-112)	102 (89-116)	0.253
Glucose (mg/dL)	88 (84-91)	85 (83-88)	92 (88-95)	0.097
Log_{10} HCV-RNA	5.86 ± 0.69	5.82 ± 0.62	5.91 ± 0.78	0.456
Follow-up (years)	11 ± 4	12 ± 5	11 ± 4	0.412
Histology				
Fibrosis mstage, n (%)				0.585
F1	23 (12.2)	16 (15.1)	7 (8.5)	
F2	54 (28.7)	28 (26.4)	26 (31.7)	
F3	63 (33.5)	36 (34.1)	27 (32.9)	
F4	16 (8.5)	8 (7.5)	8)9.8)	
F5	14 (7.4)	8 (7.5)	6 (7.3)	
F6	18 (9.6)	10 (9.4)	8 (9.8)	
Inflammation grading	4.8 ± 2.1	4.6 ± 1.9	5.1 ± 2.2	0.139

Data are reported as mean ± standard deviation or as median (95% confidence interval for the median). ALT, alanine aminotransferases; AST, aspartate aminotransferases; BMI, body mass index; CHC, chronic hepatitis

C; F, female; gGT, glutamyl-aminotransferases; Hb, hemoglobin; HS, hepatic steatosis; M, male; SD, standard deviation.

T**able 2.** Liver-related and cardio-metabolic-related mortality/morbidity according to the presence of hepatic steatosis.

Events (N) and cumulative incidence (%)	**All (N=188)**	**No HS (N=106)**	**HS (N=82)**	**P**
Mortality				
All causes	6 (0.3)	2 (0.2)	4 (0.5)	0.144
Liver-related	2 (0.1)	-	2 (0.2)	0.081
Cardiovascular-related	3 (0.2)	1 (0.09)	2 (0.2)	0.342
Other causes	1 (0.05)	1 (0.09)	-	0.527
Liver-related events				
Liver-related events	5 (0.3)	3 (0.3)	2 (0.2)	0.978
Cirrhosis and complications	2 (0.1)	1 (0.1)	1 (0.1)	0.423
HCC	3 (0.2)	2 (0.2)	1 (0.1)	0.848
Cardiovascular events				
CAD	14 (0.7)	4 (0.4)	10 (1.2)	**0.011**
Arterial hypertension	24 (1.3)	13 (1.2)	11 (1.3)	0.610
Metabolic-related outcomes				
Ow/Ob	22 (1.2)	10 (0.9)	12 (1.5)	0.073
IFG/T2D	28 (1.5)	9 (0.8)	19 (2.3)	**0.005**
Dyslipidemia	52 (2.8)	27 (2.5)	25 (3.0)	**0.010**

The cumulative incidence rate per 100 person-year was derived by the ratio of the number of events to the patient-years per 100. Group 1, long-term steatosis; group 2, incident steatosis; group 3, improved steatosis; group 4, no history of steatosis.

The p value has been derived from the Logrank test and is referred to the comparison of survival curves.

CAD, cardiovascular diseases; HCC, hepatocellular carcinoma; IFG, impaired fasting glucose; Ob, obese; Ow, overweight; T2D, type 2 diabetes mellitus.

T**able 3.** Univariate and multivariable Cox regression analysis of viral and metabolic cofactors associated to the development of cardiovascular events during follow-up.

	Univariate analysis		Multivariable analysis	
Variables	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Age	1.0 (0.9-1.1)	0.078	-	-
Sex (male)	2.0 (0.6-7.4)	0.281	-	-
BMI ≥ 24.9 kg/m^2	1.7 (0.6-4.9)	0.838	-	-
HCV genotype 3a	0.4 (0.1-3.4)	0.430	-	-
HCV genotype 1a/b	0.9 (0.3-3.1)	0.999	-	-
IFG/T2D	7.7 (2.4-24.3)	<0.001	5.2 (1.3-20.7)	0.019
Dyslipidemia	3.5 (1.1-10.8)	0.028	-	-
Arterial hypertension	2.9 (0.6-13.0)	0.171	-	-
Hepatic steatosis	3.3 (1.0-10.7)	0.046	-	-

BMI, body mass index; CI, confidence interval; HCV, hepatitis C virus; IFG, impaired fasting glucose; OR, odd ratio; T2D, type 2 diabetes.

T**able 4.** Univariate and multivariable Cox regression analysis of viral and metabolic cofactors associated to the development of glucose intolerance or type 2 diabetes during follow-up.

	Univariate analysis		Multivariable analysis	
Variables	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Age	1.1 (1.0-1.1)	0.001	1.1 (1.0-1.1)	0.008
Sex (male)	0.8 (0.4-1.7)	0.570	-	-
BMI ≥ 24.9 kg/m^2	1.7 (0.8-3.6)	0.171	-	-
HCV genotype 3a	0.7 (0.2-2.3)	0.541	-	-
HCV genotype 1a/b	0.6 (0.3-1.3)	0.224	-	-
Dyslipidemia	3.7 (1.6-8.4)	0.002	-	-
Arterial hypertension	0.8 (0.2-3.6)	0.779	-	-
Hepatic steatosis	3.1 (1.4-6.9)	0.005	2.6 (1.1-6.2)	0.027

BMI, body mass index; CI, confidence interval; HCV, hepatitis C virus; IFG, impaired fasting glucose; OR, odd ratio; T2D, type 2 diabetes.

Figures legend

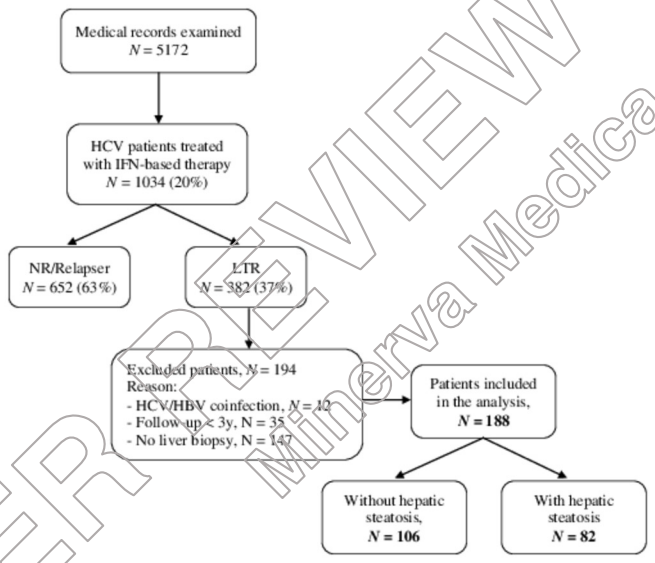
Figure 1. Flow-chart of the study.

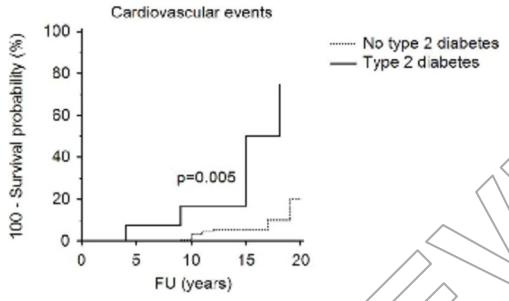
HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; IFN, interferon; LTRs, long term responders; NR, non-responders.

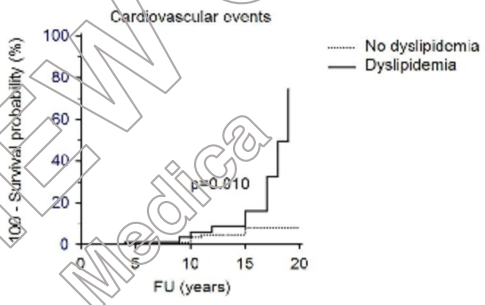
Figure 2. Kaplan-Meier survival curves showing the probability to develop cardiovascular events according to the presence of impaired fasting glucose/type 2 diabetes (A), dyslipidemia (B) and hepatic steatosis (C) at baseline.

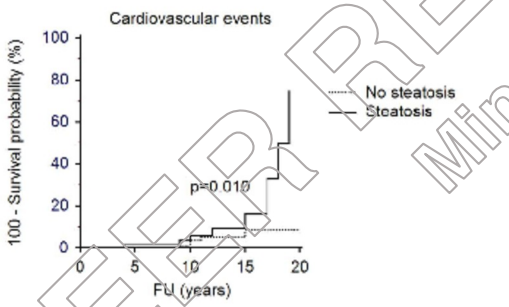
Differences between the curves were determined by the Logrank test.

FU, Follow-up; IFG, impaired fasting glucose; T2D, type 2 diabetes.









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