Impact of sustained virological response to chronic hepatitic C antiviral therapy on new onset diabetes mellitus type 2 after controlling for metabolic syndrome

Prashant Pandya,[1,2] Chaitanya Pant,[2] Ryan Taylor,[2] Olurinde Oni[1]

[1]Kansas City Veterans Affairs Medical Center, Kansas City, Missouri, USA
[2]Division of Gastroenterology, Hepatology and Motility, Department of Internal Medicine, Kansas University Medical Center, Kansas City, Kansas, USA

Correspondence to
Dr Prashant Pandya, Kansas City Veterans Affairs Medical Center, Kansas City, 4801 E Linwood Blvd, MO 64128, USA; ppandya@kumc.edu

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ABSTRACT

The high cost associated with antiviral treatment for chronic hepatitis C virus (HCV) infection mandates further investigation in the context of preventing complications such as type 2 diabetes mellitus (DM2). We determined the cumulative incidence of DM2 in subjects with chronic HCV infection who received concomitant pegylated interferon (Peg-IFN) and ribavirin. We conducted a retrospective analysis of data obtained from Veterans Administrations Informatics and Computing Infrastructure (VINCI) to identify an adult cohort of patients without diabetes with chronic HCV infection who received Peg-IFN-based therapy between October 2001 and December 2011. Patients with history of HIV, hepatitis B infection, hepatocellular cancer (HCC), non-HCC cancers, and history of transplantation were excluded. Sustained virological response (SVR) was defined as negative HCV RNA 3 months after completion of therapy. Using Cox proportional hazards regression for multivariable analysis, we determined that patients who achieved SVR were at a significantly less risk of developing DM2. Adjusted survival rates showed that the responders' group was significantly less likely to develop DM2 over time (HR 0.60, CI 0.48 to 0.74, p<0.001). Peg-IFN-based therapy in chronic HCV patients that resulted in SVR significantly decreased the risk of developing DM2 and independently predicts the development of new onset disease after controlling for correlates of metabolic syndrome.

Significance of this study

What is already known about this subject?

- Chronic hepatitis C virus (HCV) infection is associated with several extrahepatic manifestations.
- Several metabolic factors are known to be associated with chronic HCV infection.
- Relationship between chronic HCV infection and diabetes mellitus type 2 is less clear.

What are the new findings?

- Sustained virological response to chronic HCV therapy is associated with reduced new onset diabetes mellitus type 2 after controlling for correlates of metabolic syndrome.
- Sustained virological response to chronic HCV therapy is associated with reduced risk of new onset diabetes mellitus type 2, independent of race and viral genotype.
- Hepatitis C viral genotype is not independently associated with the risk of new onset diabetes mellitus type 2.

How might these results change the focus of research or clinical practice?

- Our findings provide another compelling argument for aggressive screening and treatment of patients with HCV despite high cost of newer chronic HCV antiviral therapy.

INTRODUCTION

Chronic hepatitis C virus (HCV) infection affects more than 185 million patients worldwide.[1] It is associated with persistent hepatic inflammation and in up to 20% of cases may result in cirrhosis and to a lesser extent, hepatocellular carcinoma (HCC).[2] In concurrence with liver-specific morbidity and mortality, chronic HCV infection is associated with several extrahepatic manifestations that negatively impact the clinical outcomes and economic burden associated with this disease. In this regard, the association of chronic HCV infection and disordered glucose metabolism has been most extensively studied.[3]

Several metabolic factors are known to be associated with chronic HCV infection; these include insulin resistance (IR), type 2 diabetes mellitus (DM2), steatosis, visceral obesity, atherosclerosis, and disordered lipoprotein metabolism.[3] IR is frequently encountered in chronic HCV infection and is believed to play a critical role the development of hepatic steatosis and fibrosis.[4] Significantly, several studies have demonstrated that IR impairs virological response to interferon (IFN)-based regimens in patients with chronic HCV infection.[5] Furthermore, sustained virological response (SVR) following treatment of HCV infection is associated with an improvement in IR.[6]

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The relationship between chronic HCV infection and DM2 is less clear. While multiple studies have demonstrated an association between HCV infection and DM2,[7–16] their results are limited by a selection bias and the failure to adjust for confounding variables such as age, gender, body mass index (BMI), and severity of liver disease.[17] Recently, a US population-based study concluded that chronic HCV infection was not associated with diabetes or with IR in subjects with normal glucose.[18]

The introduction of novel NS3/4A protease inhibitors, NS5A inhibitors, and nucleoside, nucleotide and non-nucleoside polymerase inhibitors heralds an era of significantly increased rates of SVR for a majority of subjects regardless of cirrhosis and genotype.[19] Considering the high cost associated with these novel therapies, it is important to determine if additional downstream savings are possible with highly effective HCV treatment in the context of preventing the future development of extrahepatic manifestations such as DM2. Therefore, we initiated an investigation to determine the cumulative incidence of DM2 with prolonged follow-up in subjects with chronic HCV infection who received concomitant pegylated-IFN (Peg-IFN) and ribavirin.

METHODS AND STATISTICAL ANALYSIS

This study was conducted using data obtained from Veterans Administrations Informatics and Computing Infrastructure (VINCI) which comprises of data extracted from the Veterans Administrations Corporate Data Warehouse (CDW)—a national repository of data from several Veterans Health Administration (VHA); and Statistical Analysis System (SAS) datasets extracted from the National Subject Care Database (NPCD) maintained by the VHA Office of Information at the Austin Information Technology Center (AITC).

The study comprised of individuals who received concomitant Peg-IFN and ribavirin for treatment of chronic HCV infection. The start date for treatment was defined as the first date of dispensing Peg-IFN and the last date of treatment was the last date covered by the cumulative Peg-IFN prescription. Subjects who received treatment for 4 weeks or less were excluded from the analysis. A subject was defined as diabetic if he/she met three predefined criteria: (1) an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for diabetes (250×), (2) blood glucose >200 mg on two different occasions, and (3) use of oral hypoglycemic drugs or insulin. We excluded those who were diabetic before the start of HCV antiviral therapy from this study. End of follow-up was when a subject became diabetic or their last day to access healthcare in the Veterans Administration.

SVR was defined in our study as undetectable HCV RNA by PCR, that is, negative qualitative or quantitative PCR with any viral load below 50 copies/mL, in all follow-up HCV RNA tests after the end of treatment including at least one test more than 12 weeks after treatment end date. Subjects who had an undetectable HCV RNA test after the treatment end date but did not have HCV RNA result after at least 12 weeks from that day were excluded from the cohort. Subjects were stratified into those that achieved SVR (responders) and those that did not (non-responders).

Comorbidities were defined based on ICD-9-CM codes. Race and ethnicity groups were recorded in accordance to VHA directive 2003–027 on mandatory revision of reporting standards. Extent of liver fibrosis before start of antiviral therapy was determined using the Fibrosis-4 (FIB4)-index,[20] a model using platelet count, aspartate transaminase (AST), alanine transaminase (ALT) calculated as:

$$\text{FIB4 - Index} = \text{Age (years)} \times \text{AST (U/L)}/(\text{platelets}\,(10^9/\text{L}) \times \text{ALT}^{1/2}(\text{U/L}))$$

BMI was computed as (weight (lbs)×703)/height (in)^2. Other covariates included in the analysis were the standard definition parameters for metabolic syndrome including blood glucose, triglycerides, hypertension, change in weight during the post-treatment time frame and BMI, high-density lipoprotein (HDL) and ALT. All the parameters were obtained from the last documented values prior to start of anti-HCV therapy.

Subjects with pretreatment diagnosis of hepatitis B surface antigen positivity, HIV infection (ICD-9-CM code 042-4), HCC (ICD9 code 1550-2), and other cancers, or a history of transplant (as defined by use of immunosuppressant drugs as specific transplant history data was not accessible) were excluded. All subjects with missing data on the main study exposure (virological response), outcome including new onset diabetes mellitus (NDM) and other study covariates were excluded from the analysis. Figure 1 shows the process for sample selection.

The primary outcome for this study was the development of NDM as defined above. Descriptive statistics were presented using proportions and means. The χ^2 tests were performed for categorical variables. Univariable Cox proportional hazards analysis was used to identify factors independently associated with incidence of diabetes. The proportionality of hazard assumption was confirmed by creating time-dependent variables for all independent variables and using the test statement to identify the time-dependent covariates simultaneously. In order to generate log-rank p value for univariate comparison of time to NDM between groups, we performed Kaplan-Meier survival analysis (graph not shown) to estimate NDM probabilities. Multivariable Cox proportional hazard model was constructed to compare time to NDM between responders and non-responders and to control for baseline covariates (age, gender, race, ethnicity, blood glucose, triglycerides, hypertension, HDL, ALT, FIB4-index, HCV genotype, change in weight during the post-treatment time frame and BMI). Table 1 shows the distribution of these variables in the overall study population and in SVR and non-SVR groups. We used multivariable analysis to control for some differences between the groups with respect to the confounding variables. From the Cox proportional hazards analyses, survival rates were calculated using corrected group prognosis method and the graph with unadjusted and adjusted survival curves by group was generated.[21] All of the performed statistical tests were two-tailed, and a p value <0.05 was considered to be statistically significant. Analyses were carried out using the SAS Enterprise Guide (SAS EG) V.5.1.

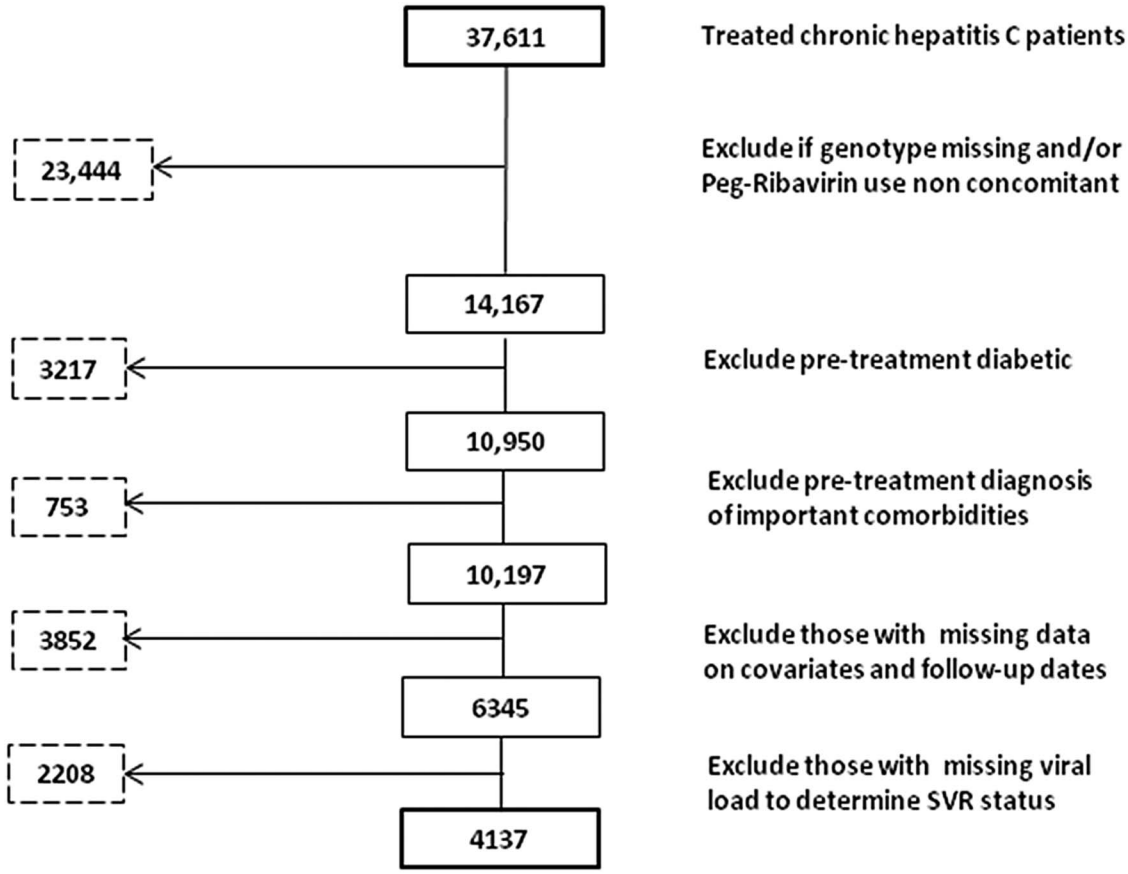

Figure 1 Patients selection process. SVR, sustained virological response.

RESULTS

Overall, we identified 37,611 patients who received Peg-IFN and ribavirin for the treatment of chronic HCV infection from October 2001 to December 2011. From this initial cohort, some patients were excluded because they did not satisfy inclusion criteria for the study. Specifically, in 23,444 (62.3%) patients we could not determine virus genotype and/or concomitant use of Peg-IFN and ribavirin. In total, 3852 (10.3%) patients lacked data pertaining to model covariates or follow-up. In total, 3217 (8.6%) patients carried a pretreatment diagnosis of diabetes. In 2208 (5.8%) patients, there were missing data detailing post-treatment viral loads. Finally, 753 (2.0%) patients were excluded due to a pretreatment diagnosis of previously stated comorbidities.

The final cohort who met eligibility criteria for this study was comprised of 4137 patients (11.0%, figure 1). Demographic characteristics revealed patients were predominantly male (96.0%) and white (67.9%). The mean age was 52.9 years (SD 6.0) and the mean BMI was 28.7 kg/m^2 (SD 5.0). Patients were predominantly infected with HCV genotype 1 (75.4%). These data are consistent with previously reported patient demographics in chronic hepatitis studies that used the VHA national database.[22 23]

In our study cohort, the rate of SVR was 31.3% (1296/4137). Furthermore, the incidence of diabetes was 13.1% (542/4137) and was significantly higher among patients who were non-responders (15.0% vs 9.0%, p<0.0001, table 1). The median follow-up time was 3.2 (IQR 1.5–5.5) years for the entire cohort; 2.7 (IQR 1.4–4.5) years for responders and 3.3 (IQR 1.6–5.6) for non-responders.

Univariate analysis revealed that an increase in patient age (>50 years), BMI (≥30 kg/m^2), glucose (≥100 mg/dL), triglyceride level (≥150 mg/dL), and the fibrosis score (>3.25) were all associated with and increased risk of NDM. The presence of hypertension also increased the risk of NDM, while SVR and high HDL (≥40 mg/dL) appeared to be protective.

Using Cox proportional hazards regression for multivariable analysis, we determined that patients who achieved SVR were at a significantly less risk of developing NDM (HR 0.60, CI 0.48 to 0.74, p<0.001). The final model was adjusted for age, gender, race, ethnicity, change in weight during the post-treatment time frame, BMI, baseline glucose, HDL, ALT, triglyceride, FIB4-score, genotype, and hypertension (yes/no; table 2).

Unadjusted and adjusted curves generated from the Cox proportional hazards analyses were presented in figure 2. The responders' group had significantly lower probability of developing NDM over time.

DISCUSSION

In the present study, we have reported on the risk of developing NDM following treatment with Peg-IFN and ribavirin in a large patient cohort comprised of US veterans with chronic HCV infection. Our results demonstrate that

Table 1 Baseline characteristics of study population (N=4137)

	N (%)	SVR	NSVR
Age (years)			
≤50	1318 (31.9)	444 (34.3)	874 (30.8)
>50	2819 (68.1)	852 (65.7)	1967 (69.2)
Gender			
Male	3972 (96.0)	1233 (95.1)	2739 (96.4)
Female	165 (4.0)	63 (4.9)	102 (3.6)
Race			
African-American	798 (19.3)	144 (11.1)	654 (23.0)
Caucasian	2808 (67.9)	985 (76.0)	1823 (64.2)
Others	531 (12.8)	167 (12.9)	364 (12.8)
Ethnicity			
Hispanic/Latino	452 (10.9)	124 (9.6)	328 (11.5)
Not Hispanic/Latino	3685 (89.1)	1172 (90.4)	2513 (88.5)
Body mass index (kg/m^2)			
<30	2674 (64.6)	864 (66.8)	1810 (63.7)
≥30	1463 (35.4)	432 (33.2)	1031 (36.3)
ALT (IU/L)			
≤40	907 (21.9)	320 (24.7)	587 (20.7)
>40	3230 (78.1)	976 (75.3)	2254 (79.3)
Glucose (mg/dL)			
<100	2269 (54.9)	747 (57.6)	1522 (53.6)
≥100	1868 (45.1)	549 (42.4)	1319 (46.4)
HDL (mg/dL)			
<40	1997 (48.3)	665 (51.3)	1332 (46.8)
≥40	2140 (51.7)	631 (48.7)	1509 (53.2)
Triglyceride (mg/dL)			
<150	2897 (70.0)	948 (73.2)	1949 (68.6)
≥150	1240 (30.0)	348 (26.8)	892 (31.4)
Hypertension			
Yes	1043 (25.2)	288 (22.2)	755 (26.6)
No	3094 (74.8)	1008 (77.8)	2086 (73.4)
FIB4-score			
≤3.25	3361 (81.2)	1118 (86.3)	2243 (79.0)
>3.25	776 (18.8)	178 (13.7)	598 (21.0)
Genotype			
1	3120 (75.4)	704 (54.3)	2416 (85.0)
2	655 (15.8)	391 (30.2)	264 (9.3)
3	362 (8.8)	201 (15.5)	161 (5.7)

ALT, alanine transaminase; HDL, high-density lipoprotein; NSVR, non-SVR; SVR, sustained virological response.

SVR is associated with a significantly reduced risk of developing NDM, independent of race and viral genotype. In patients who achieved SVR, the reduced risk was sustained even when other risk factors for developing DM2 (change in weight during the post-treatment time frame, advanced age, metabolic syndrome and liver cirrhosis) were concurrently present. Finally, our results demonstrate that in addition to virological persistence, the presence of advanced age, metabolic syndrome and liver cirrhosis increased the risk of developing NDM.

Our results are supported by previous studies that have analyzed the association between chronic HCV infection and DM2. In 1994, Allison *et al*[7] performed a retrospective review of 100 consecutive adult patients with cirrhosis undergoing assessment for liver transplantation. They demonstrated that of the 34 patients with HCV-related cirrhosis, 17 (50%) had DM. Conversely, only 6 (9%) of the 66 patients with cirrhosis unrelated to HCV had DM ($p<0.0001$). Since this time, several large epidemiological studies have demonstrated an increased prevalence of NDM in patients chronically infected with HCV. A Taiwanese community-based population-based study reported a positive association between anti-HCV-positive persons and NDM.[24] Additionally, a retrospective cohort study of 2482 Japanese patients with chronic HCV infection and treated with IFN-based therapy demonstrated that achieving SVR was associated with a two-thirds reduction in the risk of DM2 development.[25] Furthermore, two meta-analyses have also supported this association albeit with significant heterogeneity of results between the studies.[26 27]

Although the exact mechanisms by which HCV leads to DM2 are not clear, it is hypothesized that the virus may induce a T helper 1 lymphocyte immune-mediated

Table 2 Univariable and multivariable hazards of incident diabetes

	Univariable analysis			Multivariable analysis		
	HR	95% CI	p Value	HR	95% CI	p Value
SVR (Ref—no)						
Yes	0.56	0.45 to 0.68	<0.001	0.60	0.48 to 0.74	<0.001
Age (years) (Ref—≤50)						
>50	1.35	1.13 to 1.62	0.001	1.24	1.03 to 1.49	0.02
Gender (Ref—female)						
Male	1.19	0.75 to 1.88	0.46	0.89	0.55 to 1.42	0.61
Race (Ref—Caucasian)						
African-American	1.23	1.00 to 1.51	0.06	1.19	0.95 to 1.48	0.13
Others	1.04	0.80 to 1.35	0.78	1.09	0.84 to 1.42	0.53
Ethnicity (ref—NH/L)						
Hispanic/Latino	1.00	0.78 to 1.31	0.96	1.01	0.77 to 1.32	0.96
Body mass index (Ref—<30)						
≥30 kg/m^2	1.90	1.60 to 2.24	<0.001	1.71	1.44 to 2.03	<0.001
ALT (Ref—≤40)						
>40 IU/L	1.15	0.93 to 1.42	0.21	1.03	0.83 to 1.28	0.82
Glucose (Ref—<100)						
≥100 mg/dL	2.38	2.00 to 2.84	<0.001	2.13	1.78 to 2.54	<0.001
HDL (Ref—<40)						
≥40 mg/dL	0.74	0.63 to 0.88	<0.001	0.87	0.72 to 1.04	0.12
Triglyceride (Ref—<150)						
≥150 mg/dL	1.47	1.24 to 1.75	<0.001	1.33	1.12 to 1.60	<0.01
Hypertension (Ref—no)						
Yes	1.47	1.22 to 1.76	<0.001	1.28	1.07 to 1.54	<0.01
FIB4-score (Ref—≤3.25)						
>3.25	1.65	1.35 to 2.01	<0.01	1.49	1.21 to 1.83	<0.001
Genotype (Ref—1)						
2	0.81	0.63 to 1.05	0.11	1.06	0.81 to 1.39	0.68
3	0.73	0.51 to 1.05	0.09	0.94	0.65 to 1.37	0.75

ALT, alanine transaminase; HDL, high-density lipoprotein; NH/L, non-Hispanic/Latino; SVR, sustained virological response.

response, leading to activation of the tumor necrosis factor—a system and an increase in interleukin-6 levels. This ultimately leads to IR by perturbing the tyrosine phosphorylation of insulin receptor substrate-1, therefore resulting in impaired insulin action in peripheral tissues and hepatic glucose uptake.[28] More non-specific actions of the virus lead to liver steatosis, liver fibrosis, increased oxidative stress, and increased peroxidation. All of these trigger a systemic inflammatory response, which also contributes to the development of IR.[28–30]

However, other researchers have refuted the association between chronic HCV infection and DM2. They have instead attributed this purported relationship to a non-specific increase in liver enzymes observed in patients with HCV. This is a major potential confounder, since advanced liver disease from any cause may be associated with diabetes.[31 32] For example, in an Italian cohort study, chronic HCV infection was associated with DM2 only in subjects with elevated ALT (OR 1.47, 95% CI 1 to 2.16) after controlling for age, gender and BMI.[17] Most recently, Ruhl and colleagues have reported population-based data from the US National Health and Nutrition Examination Survey from 15,128 patients from 1999 to 2010. In multivariate-adjusted analysis, diabetes remained unassociated with anti-HCV (OR=1.0, 95% CI 0.6 to 1.7) or with HCV RNA (OR=1.1, 95% CI 0.6 to 1.9). However, elevated alanine aminotransferase and γ-glutamyltransferase activities were associated with diabetes regardless of HCV status.[18]

The strengths of our study included a large number of subjects drawn from a high-risk demographic pool for HCV with a reasonably long follow-up time as well as the use of standardized diabetes criteria to exclude patients with pre-existing diabetes or prediabetes. We were able to meticulously control for several potential confounding variables in our study including the presence of elevated liver enzymes. We were also able to control for any weight gain experienced by patients post-treatment. This is an especially important consideration when viewed in the context of the risk of these patients to develop non-alcoholic fatty liver disease.

A chief limitation of our results is an overwhelming number of male veterans in our study demographic which is typical of the US veteran population. Additionally, we were forced to exclude a large number of patients due to missing or incomplete data. Like every retrospective study, unmeasured confounding or hidden biases might be present. Another limitation of our study is the patients were not randomly allocated into the groups. This could partly explain the discrepancies with respect to the

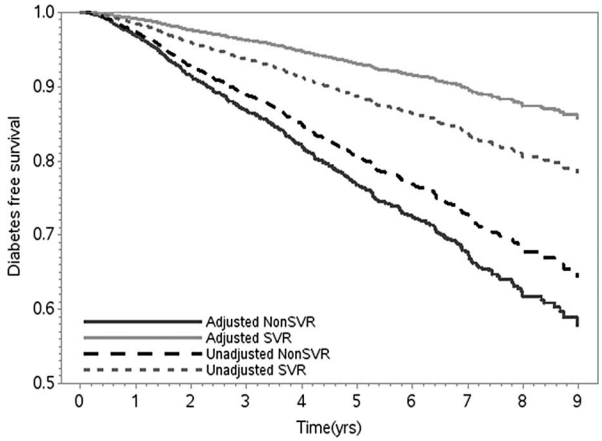

Figure 2 Unadjusted and adjusted Kaplan-Meier curves showing higher diabetes-free survival rates in the unadjusted and adjusted SVR, compared with unadjusted and adjusted non-responders (non-SVR), respectively. SVR, sustained virological responders.

confounding variables presented in table 1. However, we anticipate that the use of multivariable analysis has controlled for this imbalance.

The natural history of chronic HCV infection has been considered by several authorities to not impact the life of the large majority of those infected with the recommendation that treatment be reserved for those patients that demonstrate evidence of advanced liver disease with increased risk of liver decompensation and HCC. In this background, the importance of our results may be viewed in two related, but different contexts. First, in patients with HCV infection, DM2 is an independent predictor of a more rapid progression of liver fibrosis and impaired response to antiviral treatment. Identification of these chronically infected HCV patients with DM2 is critical given a higher risk of developing hepatic encephalopathy and HCC.[33]

Second, over 25% of the US population age 65 and older has diabetes; DM2 is the most common form.[34] Diabetes is associated with microvascular and macrovascular complications, hypoglycemic episodes and infections, all of which lead to substantial medical costs as well as unmeasured patient suffering.[35] Given the promise of current and future pan-genotypic direct-acting HCV antiviral agents leading to high rates of SVR, our results are another compelling argument for aggressive screening and treatment of patients with HCV.

Contributors All the authors contributed to the conception, design, writing and critical analysis of this manuscript. PP and OO contributed to the statistical analysis of the data.

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