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INCIDENCE OF ANTIVIRAL THERAPY IN AMELIORATING HEPATITIS C ASSOCIATED COMORBIDITIES IN TAIWAN: A 7 YEAR FOLLOW UP NATIONWIDE POPULATION-BASED STUDY

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ABSTRACT

Objectives: Hepatic C Virus (HCV) infection is associated with development of type 2 diabetes (T2D). This population-based study was designed to assess whether anti-viral therapy following HCV-infected hepatitis may reduce the incidence rates of T2D and hazard ratios for associated cormobidities. **Methods**: A total of 13,025 subjects were retrieved from the NHIRD cohort from 2000 to 2003. Among them, 2641 (20%) were diagnosed with HCV-infected hepatitis, and 10,564 HCV negative subjects served as control group. Among the 2,641 HCV-infected subjects, 139 (5.3%) subjects received IFN/RBV therapy.The other 2,502 hepatitis C patients not receiving IFN/RBV therapy served as comparison group. **Results**: Among the 10,564 HCV sero-negative control subjects, 920 subjects (8.7%) developed T2D in 7 years. On the other hand, there were 444 (16.8%) HCV-infected subjects developed T2D in 7 years. HCV-hepatitis patients were more likely to develop T2D (hazard ratio 2.097, 95% CI 1.872–2.348; p <0.001). Among the 2502 HCV patients not receiving IBT therapy, 434 patients (17.3%) developed T2D in 7 years. In contrast, only 10 (7.2%) in 139 HCV-infected subjects who received IBT therapy developed T2D in 7 years. The adjusted hazard ratio was 0.341 (95% CI 0.182–0.639; p<0.001).The hepatitis C patients have a higher incidence of T2D, hepatic steatosis, cardiovascular disorders and hepatocellular carcinoma (HCC). After interferon-base therapy intervention T2D significantly reduce its incidence. **Conclusions**: Our data suggest that HCV infection was associated with increased risk of T2D, and anti-viral therapy may be reduce the incidence of T2D.

KEYWORDS: Hepatitis C virus (HCV), Type 2 diabetes (T2D), Epidemiology, Incidence, Hazard ratios.

INTRODUCTION

It has been estimated that about 2.8% of world population, corresponding to 185,000,000 persons were infected with hepatitis C virus (HCV).[1, 2] In Taiwan, the prevalence rate of HCV infection (4.4%) is relatively higher than other countries.[3] Nosocomial infection, blood transfusion and injection were considered as major risk factors.[4] Today, there is no prophylactic vaccine available against HCV. HCV infection causes numerous comorbidities, including chronic hepatitis, which may lead to cirrhosis and hepatocellular carcinoma (HCC).[5-7] The incidence of insulin resistance(IR) or type 2 diabetes (T2D) in patients infected with HCV has been shown to be high. A study assessing an outpatient clinic of a university hospital estimated that more than 30% of HCV subjects had glucose abnormalities.[8] Patients infected with HCV have higher incidence of developing T2D[9,10], which may accompany with HCV infection is deemed to carry an increased cardiovascular disorders risk[11] and hepatic steatosis.[12,13] HCV infection suppresses insulin signal transduction pathway by decreasing insulin-receptor substrate-1 (IRS-1) tyrosine phosphorylation, and impaired IRS-1/ phosphatidylinositol 3-kinase/Akt association and activation in the liver.[14,15] These defects may contribute to insulin resistance and thus increased the incidence of T2D in hepatitis C patients.

Pegylated interferon-α(PEG-IFN-α) is a recombinant interferon with additional molecule of polyethylene glycol, which improves antiviral efficiency and its half life.[16] The rate increased 10% to 50% of viral response from combining pegylated interferon-α and ribavirin.[16] In 7.8% of the patients with hepatitis C, Pegylated interferon-α reduced 5-year cumulative incidence of HCC.[5] Antiviral treatment with pegylated interferon-α

and ribavirin may reduce the risk of incident T2D in hepatitis C patients[17], and improved renal and cardiovascular outcomes in T2D patients.[18,19]

Although HCV infection is known to associate with abnormal carbohydrate metabolism and increased the risk of developing T2D, effects of IFN/RBV therapy on the outcomes of hepatitis C associated comorbidities is not completely clear. A population-based, longitudinal survey is required to assess this issue. Taiwan's National Health Insurance Research Database (NHIRD) was longer in the system of Taiwan National Health Insurance (NHI) program which was maintained by the Taiwan National Health Research Institute. This study sought to determine the incidence of therapeutic efficacy among hepatitis C patients receiving interferon/ribavirin therapy using the NHIRD.

MATERIALS AND METHODS

Data Sources

This population-based study used the Taiwan National Research Database (NHIRD), which is provided by the Taiwanese National Health Insurance Bureau (NHIB). NHIB is a single-player compulsory program that covers all forms of healthcare for residents in Taiwan. NHIB assembles data from the National Health Insurance program arranges it into data files every year which includes registration files and original claim data for reimbursement. Longitudinal Health Insurance Database 2000 was used. These electronic data consists the data of health services received, the clinic or hospital code, the claim data of patients' gender, birthday, the classification code of the diseases diagnosed, and the clinic or hospital code.

In the NHI program in 2008 which covered 22.89 million of the country's 22.96 million people (amounting to 99.7% of the island's population).[20, 21] Data used in this study were retrieved from the representative NHIRD cohorts from January 2000 to December 2003 were used for this longitudinal study. Individuals with duplicate files, incomplete information were excluded from the data analyses.

Identification and definition of cohorts

From the year 2000 to 2003, Cases of hepatitis C were identified from the NHIRD, using the 9th revision of the International Classification of Diseases, Clinical Modification (ICD-9-CM). The hepatitis C was characterized as patients diagnosed with either ICD-9-CM code between 070.41, 070.44, 070.51, 070.54, 070.70 and V02.62. The follow-up ambulatory care visits or hospitalization confirmed 7,286 HCV-infected patients for hepatitis C from the 2000-2003 reimbursement claims data of the NHIRD.

Erroneous birthday or gender code, Previously diagnosis with T2D, hepatitis C, renal transplantation, cirrhosis of liver, hypertension or hyperlipidemia before code date were excluded. A total of 2,641 HCV-infected patients without comorbidities were recruited and tracked for 7 years from date of T2D (see Fig.1 for the flow diagram of the enrollment process). Hepatitis C patients treated with interferon (ATC No: L03AB01, L03A10, L032A11, L032A12, L032A60 and L032A61) and/or ribavirin (ATC No: J50AB04) were defined as hepatitis C patients receiving anti-viral therapy. Among HCV-infected subjects, those who received IBT therapy (n=139) between January 2000 to December 2003 were grouped into the IBT cohort. Those who did not receive IBT therapy (n=2,502) were grouped into non-IBT cohort. Non-HCV cohort was matched by age and sex and exclude comorbidities was randomly selected from NHIRD at a ratio of 1:4 (n=10,564) (Fig.1).

The incidence rate of T2D (ICD-9-CM code 250.0 or A code: A181), steatosis (ICD-9-CM code 571.8), cardiovascular disorders (ICD-9-CM code 414.00-414.05430-432.9 or 433-434, 430-432.9 or 433-434) and hepatocellular carcinoma(HCC) (ICD-9-CM code 155.0) were also compared in this study.

We identified 7,286 HCV-infected patients from the 2000-2003 reimbursement claims data of the NHIRD.After exclusion, 2,641 adults newly diagnosed with hepatitis C infection without comorbidities were used as HCV-infected sample subjects. There were10,564 adults consisted in the comparison group who were without hepatitis C infection. They were randomly selected from the same data seta, also the frequency matched by age and gender. Hepatitis C's Events were confirmed by medical claims (International Classification of Diseases, Ninth Revision, Clinical Modification, ICD-9-CM, codes).95% confidence intervals (CIs) and Multivariate adjusted hazard ratios (HRs) were measured potential associated factors along with HCV infection, stratified age group, and gender. This study protocol was approved by the institutional review board of China Medical University Hospital (CMUH103-REC1-088).

Statistics

For the study group (hepatitis C treated with IBT therapy) to the reference group (hepatitis C not treated with IBT therapy) risk ratios presented as hazard ratios (HRs) and 95% confidence interval (CI). The annual incidence of T2D was calculated to obtain the HRs and 95% CI, The multivariate-adjusted Cox proportional hazard model was used. Data analysis further compared the adjusted age-specific incidences between the two groups in the seven year.

RESULTS

Table 1 shows the distributions of demographic characteristics. The 2,641 sampled subjects 1433 (54.3%) were male. Age with an average age of 41.5±11.9 years and most patients 2260(85.6%) were currently employed. Non-HCV cohort matched by age and sex and exclude

comorbidities was randomly selected from NHIRD at a ratio of 1:4 (n=10,564) (Fig. 1).

Each subject of the two cohorts (HCV-infected and non-HCV infected) were tracked for 7 years from the index date. Among the 2,641 HCV-infected subjects, 444 patients (16.8%) developed T2D in the 7 year follow-up period. On the other hand, 8.7% or 920 out of 10,564 non-HCV infected subjects developed T2D in the 7 year follow-up period (Table 2).The incidence rate for HCV-infected subjects was 26.6 per 1000 person-years compared to 12.9 for the non-HCV group. The adjusted hazard ratio for developing T2D in the HCV-infected subjects was 2.097(95%CI, 1.872-2.348, p<0.001).

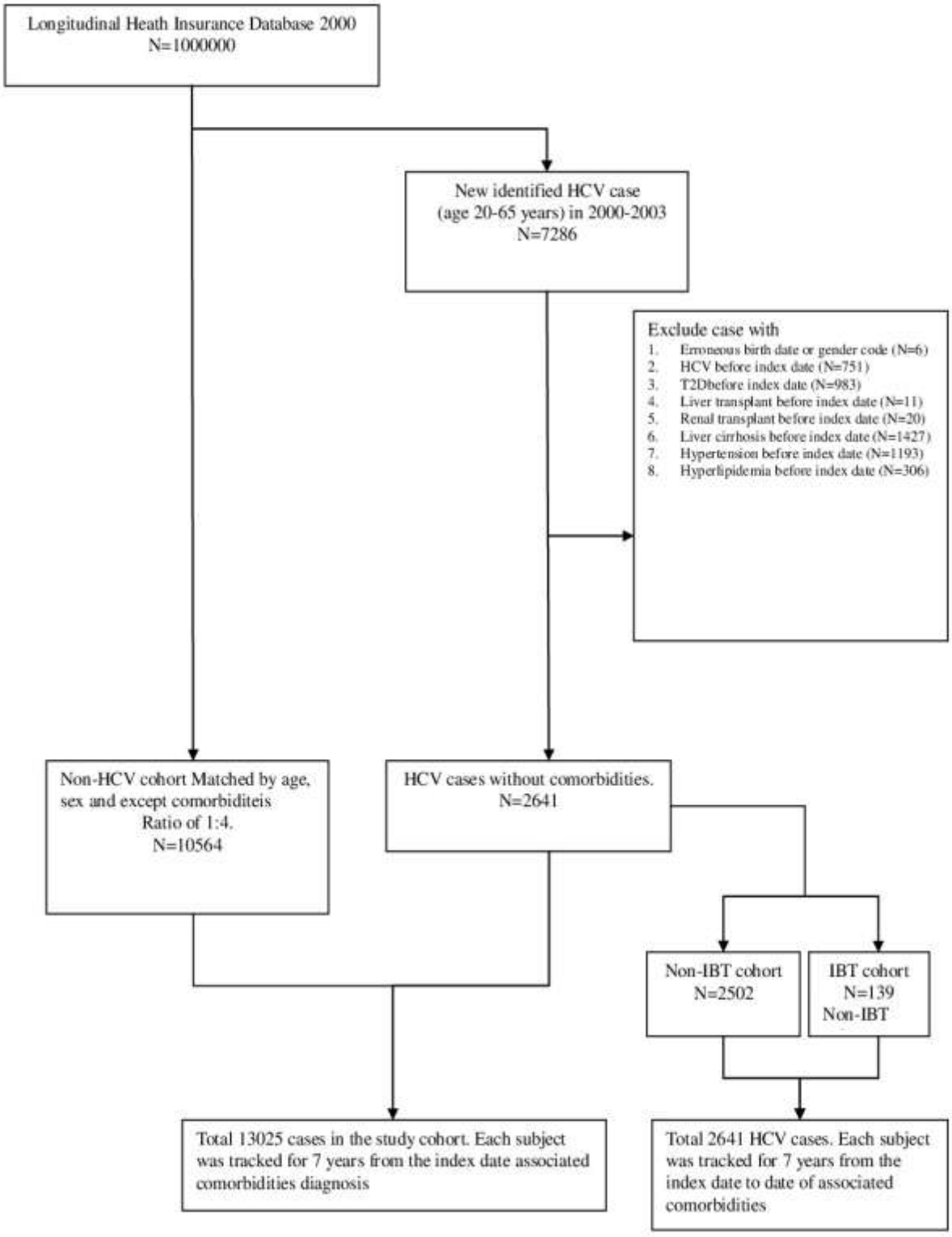

Figure 1: Characteristics of the study population.

Table 1: Sociodemographic characteristics and comorbidities of HCV-infected and HCV-uninfected control groups in Taiwan, 2000-2003(n=13,205).

	HCV-infected group n=2641 n (%)	Control group n=10564 n (%)	*p* value
Gender			0.91
Male	1433(54.3)	5745(54.4)	
Female	1208(45.7)	4819(45.6)	
Age(year)			1.00
20-29	501(19.0)	2005(19.0)	
30-39	658(24.9)	2630(24.9)	
40-49	768(29.1)	3073(29.1)	
50-59	502(19.0)	1998(18.9)	
≧60	212(8.0)	858(8.1)	
Occupation			0.052
Employed	2260(85.6)	8724(82.58)	
Unemployed	264(10.0)	1172(11.09)	
Unknown	117(4.4)	668(6.32)	

Because hepatitis C patients had a higher incidence rate of steatotic hepatitis, we compared the incidence of non-alcoholic steatotic hepatitis among 2 cohorts (HCV-infected and non-HCV infected). Table 2 shows that patients infected with HCV had a higher incidence of non-alcoholic steatotic hepatitis patients (10.4 vs. 2.1 per 1000 person-years). The hazard ratio was 4.837 (95% confidence interval 3.908–5.986; p<0.001). In the HCV-infected subjects, 136 patients (5.1%) developed cardiovascular disorders in the 7 year follow-up period. On the other hand, 3.7% or 392 out of 10,564 non-HCV infected subjects developed cardiovascular disorders in the 7 year follow-up period (Table 2). The incidence rate for HCV-infected subjects was 7.51 per 1000 person-years compared to 5.37 for the non-HCV group. The adjusted hazard ratios for developing cardiovascular disorders in the HCV-infected subjects was 1.402(95% CI, 1.152-1.706, p<0.001).Among the 2,641 HCV-infected subjects, 152 patients (5.8%) developed HCC in the 7 year follow-up period. On the other hand, 0.4% or 45 out of 10,564 non-HCV infected subjects developed HCC in the 7 year follow-up period (Table 2).The incidence rate for HCV-infected subjects was 8.5 per 1000 person-years compared to 0.61 for the non-HCV group. The adjusted hazard ratios for developing HCC in the HCV-infected subjects was 14.148(95% CI, 10.144-19.732, p<0.001) (Table 2).

Table 2: Incidence rates and hazard ratios for associated comorbidities in the HCV-infected and HCV-uninfected control groups during the 7-year follow-up period (n=13,205)

	HCV-infected group n=2641 n (%)	Control group n=10564 n (%)	*p* value
T2D (Type 2 diabetes)			
No. of DM	444(16.8)	920(8.7)	<0.001
Incidence rate*	26.65	12.93	
Mean time to DM	2.89	3.95	<0.001
Crude HR(95%CI)	2.062(1.842-2.310)	1(reference)	<0.001
Adjusted HR(95%CI)**	2.097(1.872-2.348)	1(reference)	<0.001
Hepatic steatosis			
No. of HS	183(6.9)	157(1.5)	<0.001
Incidence rate*	10.38	2.14	
Mean time to HS	2.29	3.62	<0.001
Crude HR(95%CI)	4.826(3.900-5.973)	1(reference)	<0.001
Adjusted HR(95%CI)**	4.837(3.908-5.986)	1(reference)	<0.001
CVA(Cerebrovascular Accident)			
No. of CVA	136(5.1)	392(3.7)	0.001
Incidence rate*	7.51	5.37	
Mean time to CVA	4.16	4.25	0.054
Crude HR(95%CI)	1.406(1.155-1.711)	1(reference)	0.001
Adjusted HR(95%CI)**	1.402(1.152-1.706)	1(reference)	0.001
HCC(Hepatocellular carcinoma)			
No. of Hepatoma	152(5.8)	45(0.4)	<0.001
Incidence rate*	8.5	0.61	
Mean time to Hepatoma	2.75	3.55	0.39
Crude HR(95%CI)	13.887(9.958-19.368)	1(reference)	<0.001
Adjusted HR(95%CI)**	14.148(10.144-19.732)	1(reference)	<0.001

Abbreviations: HR: hazard ratio; HCC: hepatocellular carcinoma; T2D: type 2 diabetes.

* Per 1000 person-years

** Adjusted for age, gender

The hepatitis C patients have a higher incidence of T2D, hepatic steatosis, cardiovascular disorders and HCC. After interferon-base therapy intervention T2D significantly reduce its incidence. Incidence rate and hazard ratios for associated comorbidities in the interferon-base therapy (IBT) and non-IBT of HCV-infected groups during the 7-year follow-up show in Table 3. The incidence rate for HCV-infected subjects was 10.7 per 1000 person-years compared to 27.6 for the non-HCV group. The adjusted hazard ratio for developing T2D in the HCV-infected subjects was 0.341(95% CI, 0.182-0.639, p<0.001).The patients with IBT were signification more likely to have lower non-IBT in incidence rate and hazard ratios than comparison patients for associated T2D.

Table 3: Incidence rate and hazard ratios for associated comorbidities in the interferon-base therapy (IBT) and non-IBT of HCV-infected groups during the 7-year follow-up.

	interferon-base therapy (IBT, n=139) n (%)	**Non-interferon-base therapy (Non-IBT, n=2502) n (%)**	***p* value**
T2D (Type 2 diabetes)			
No. of DM	10(7.2)	434(17.3)	0.01
Incidence rate*	10.7	27.6	
Mean time to DM	3.55	2.87	0.275
Crude HR(95%CI)	0.389(0.208-0.728)	1(reference)	0.003
Adjusted HR(95%CI)**	0.341(0.182-0.639)	1(reference)	0.001
Hepatic steatosis			
No. of hepatic steatosis	19(13.7)	164(6.6)	0.03
Incidence rate*	21.4	9.80	
Mean time to HS	2.61	2.25	0.584
Crude HR(95%CI)	2.149(1.337-3.456)	1(reference)	0.002
Adjusted HR(95%CI)**	2.015(1.248-3.252)	1(reference)	0.004
CVA(Cerebrovascular Accident)			
No. of CVAs	11(7.9)	66(2.6)	0.099
Incidence rate*	11.68	3.8	
Mean time to CVA	4.18	4.54	0.975
Crude HR(95%CI)	1.733(0.934-3.215)	1(reference)	0.082
Adjusted HR(95%CI)**	1.401(0.754-2.605)	1(reference)	0.286
HCC(Hepatocellular carcinoma)			
No. of hepatoma	18(12.9)	134(5.4)	0.001
Incidence rate*	19.8	7.9	
Mean time to hepatoma	3.50	2.66	0.204
Crude HR(95%CI)	2.476(1.514-4.050)	1(reference)	<0.001
Adjusted HR(95%CI)**	1.950(1.190-3.195)	1(reference)	0.008

*Per 1000 person-years
**Adjusted for age, gender

DISCUSSION

The C hepatitis patients with the evaluation of the effectiveness of interferon therapy will help for C treatment and prevention of hepatitis related to T2D. Patients with hepatitis C virus (HCV) infection have increased incidence of developing T2D.[9-11] However, the efficacy of anti-viral therapy in reducing the incidence rates of T2D (10.7/ 1000). In the study, the incidence of T2D after the termination of antiviral therapy in HCV positive patients treated with IBT therapy showed that T2D has been reported in less than 0.08% - 1.0% of patients treated with IBT therapy.[17]

This study is that all subjects were tracked for 7 years for the incidence of T2D. The NHRI collects data from the NHIRD, which consist of records for 96% population of Taiwan. Consequently, based data sources currently available, the NHRID is one of the largest and most comprehensive nationwide population.[20,21] The randomly selected references in this study make the measurement of incidence reliable which is similar to us the whole population as the denominator. Thus, selection bias was significantly lessened. As far as we know, no past studies have used national-wide insurance health data to investigate the efficacy of antiviral therapy in reducing T2D for hepatitis C patients in a population-based cohort. Our findings are consistent with the findings that hepatitis C patients are particularly high risk in developing T2D. Indeed, the present study support the notion that hepatitis C is associated with increased cumulative risk in developing T2D after a 7 year follow-up periods. Antiviral treatment with IBT therapy for hepatitis C virus infection have been shown to reduce the incidence rate of T2D.[17] In the era of IBT therapy, insulin resistance(IR) seemed associated with lower sustained virological response (SVR) on rates,

regardless of viral genotype.[22] In agreement, we showed that antiviral treatment with IBT therapy for hepatitis C greatly reduced the incidence rate of developing T2D.

In this study, the hepatitis C patients have a higher incidence of hepatic steatosis, cardiovascular disorders and HCC,but Antiviral therapy is not significantly reduce incidence of hepatic steatosis, cardiovascular disorders and HCC.[6,11,23] This study suffered some several potential limitations. First, though it is greatly supported that the vast majority of hepatitis C cases were genotype 1, the identification of viral genotype was not included in the population-based dataset also could not be included in this study. The 2000 Longitudinal Health Insurance Database lack of describe liver fibrosis stage reported. Second, there are many novel anti-HCV agents. However, these novel anti-viral agents (such as direct-acting antiviral agent, DAA) were approved for use in Taiwan in 2014. In 2017, the National Health Insurance Administration of Ministry of Health and Welfare provider will only pay for the DAA treatment drug. Third, 139 HCV-infected patients receiving IBT therapy sample is too small.

In conclusion, this study demonstrates that hepatitis C patients receiving IBT therapy have lower incidence rate of developing T2D when compare with hepatitis C patients not receiving IBT therapy. Our findings suggest that antiviral therapy following HCV infection may have beneficial effects in ameliorating the HCV-associated T2D.

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