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MAJOR ARTICLE

Successful Antiviral Therapy Reduces Risk of Schizophrenia Among Chronic Hepatitis C Patients: A Nationwide Real-World Taiwanese Cohort (T-COACH)

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Background. Chronic hepatitis C (CHC) has been associated with major psychoses, and interferon (IFN)-based therapy may cause psychiatric sequelae. We aimed to evaluate the effects of sustained virological response (SVR) on the incidence of major psychoses in a nationwide Taiwanese CHC cohort.

Methods. Fifteen thousand eight hundred thirty-six CHC Taiwanese who received IFN-based therapy were enrolled between 2003 and 2015. Of those, 12 723 patients were linked to the National Health Insurance Research Databases for the incidence of major psychoses. Death before major psychoses was considered a competing risk.

Results. Twenty-four patients developed new-onset major psychoses during 67 554 person-years (3.6 per 10 000 person-years), including 16 affective psychoses, 7 schizophrenia, and 1 organic psychotic condition. The incidence of major psychoses and affective psychoses did not differ between the SVR and non-SVR groups. The 10-year cumulative incidence of schizophrenia were significantly higher in the non-SVR than in SVR patients (0.14% vs 0.04%, $P = .036$). Cox subdistribution hazards showed that SVR and older age were associated with a significantly lower risk of schizophrenia (hazard ratio = 0.18 and 0.17). Sustained virological response was associated with decreased incidence of schizophrenia and majorly observed among patients with age <45 ($P = .02$).

Conclusions. Successful IFN-based therapy might reduce the incidence of schizophrenia among CHC patients, especially among younger patients.

Keywords. competing risk; HCV; psychiatric disorders; schizophrenia; sustained virological response.

Chronic hepatitis C virus (HCV) infections can lead to end-stage liver diseases and several extrahepatic manifestations [1], such as glucose dysregulation [2], renal function impairment [3], and central nervous system dysfunction [4]. Hepatitis C virus has been associated with neuropsychiatric symptoms for years. Emerging evidence from active HCV replication in cerebrospinal fluid suggested that HCV may cross the blood-brain barrier, leading to neuroinvasion and neuroinflammation [5–7]. Patients with chronic hepatitis C (CHC) had higher risks

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of fatigue and cognitive impairment, primarily in attention, concentration, psychomotor speed, and higher executive function [8, 9], which might be related to the alternation of serotonergic and dopaminergic neurotransmission [10]. Patients with chronic HCV infections were also at higher risk of psychiatric disorders [11]. Tension, depression, and confusion were significantly more severe in patients with end-stage liver disease due to HCV infection than in other liver transplant candidates. One Swedish study found that patients with severe mental illness were associated with a 6-fold increase in risk for HCV infection [12].

Successful antiviral therapy with pegylated-interferon (IFN) plus ribavirin has been associated with long-term benefits for patients with HCV, in terms of risk reduction in liver-related as well as extrahepatic complications, including hepatocellular carcinoma, liver failure, cardiovascular events, diabetes, and end-stage renal diseases [13–17]. This therapy, through the achievement of sustained virological response (SVR), could improve attentional and neurocognitive functions [18, 19]. However, the therapy did not affect the short-term frequency of depressive disorders [19]. Another recent study demonstrated that achieving SVR did not matter for the frequency of psychiatric disorders among patients coinfected with human immunodeficiency virus (HIV)/HCV [20]. Whether HCV eradication may reduce the risk of major psychiatric disorders remains unclear. In addition, IFN-based therapy itself may result in psychiatric sequelae, including depression, anxiety, irritability, and mood swings [21]. Therefore, the long-term risk for major psychiatric disorders after anti-HCV treatment for patients with CHC patients needs to be clarified.

In the current study, we aimed to evaluate the long-term outcome of successful antiviral therapy on the new-onset of major psychiatric disorders, including *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes 290–297, among patients with CHC by recruiting a large, real-world cohort. The study had well defined baseline demographics, laboratory and virological data, and treatment responses to IFN-based therapy. In addition, the study was linked to the National Health Insurance Research Databases (NHIRD) of Taiwan for data collection of consequent development of major psychiatric disorders during antiviral treatment and the posttreatment follow-up period.

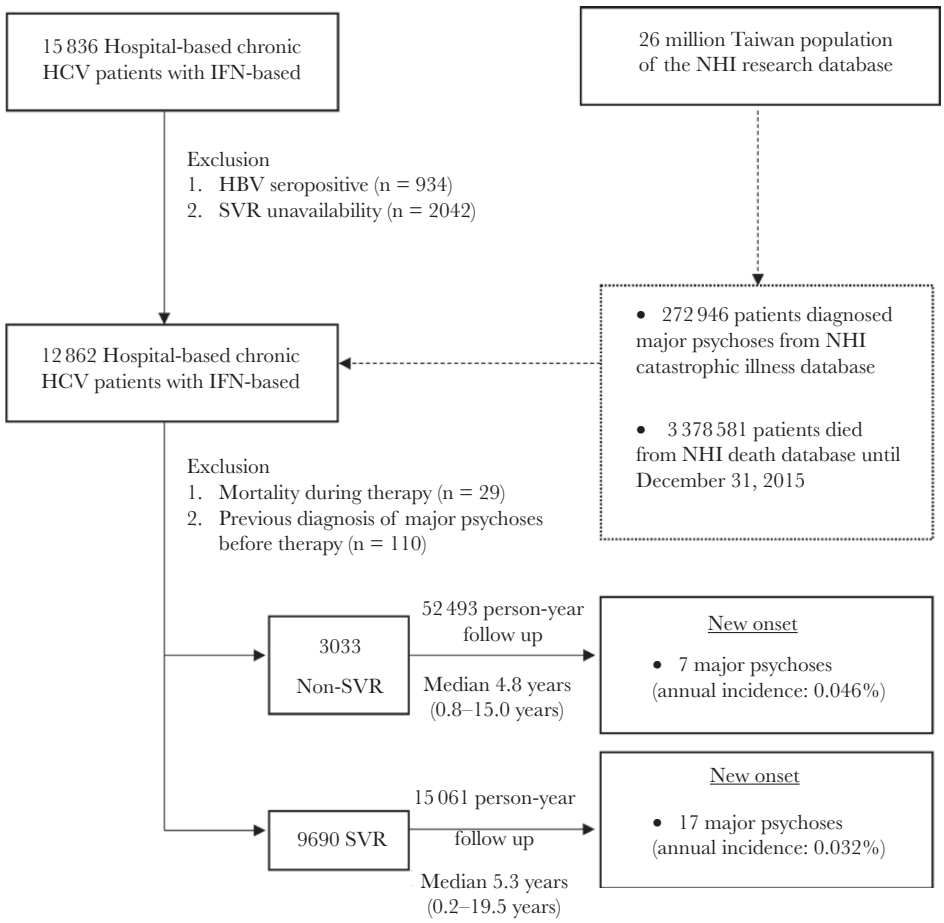


Figure 1. Patient flow chart from Taiwanese Chronic Hepatitis C Cohort (T-COACH) and linkage to Taiwan National Health Insurance Research Databases. HBV, hepatitis B virus; HCV, hepatitis C virus; IFN, interferon; NHI, National Health Insurance; SVR, sustained virological response.

MATERIALS AND METHODS

Study Cohort

The Taiwanese Chronic Hepatitis C Cohort (T-COACH) is a nationwide HCV registry cohort in Taiwan, which consists of 15 836 patients with CHC from 23 regional hospitals and medical centers enrolled between 1993 and 2015. The majority of patients enrolled between 2003 and 2015. The key eligible criteria for patients included in this study are as follows: they are over 20 years old; CHC was diagnosed using liver histology, or patients were seropositive for anti-HCV for >6 months; patients were seropositive for HCV RNA; and patients had received IFN-based therapy for at least 4 weeks. Patients coinfected with HIV were excluded. The Taiwan Health Insurance administration began to reimburse anti-HCV agents for patients with CHC in 2003. A total of 75 431 patients with CHC were reimbursed with IFN-based therapy since 2003 (https://data.nhi.gov.tw/). The T-COACH cohort included approximately 21% of the CHC-treated population in Taiwan during this 13-year period.

Patient demographic characteristics, medical history, clinical features, and laboratory data were collected from participating sites, including host profiles (age, sex, biochemistry, complete blood count, renal function, liver fibrosis) and virological characteristics (HCV genotype, HCV ribonucleic acid [RNA] level, and the virological responses after anti-HCV treatment). Sustained virological response was defined as HCV RNA seronegativity at 24 weeks after the end of antiviral therapy. Advanced fibrosis was defined as a noninvasive, fibrosis-4 index (FIB-4) [22] >3.25. Liver cirrhosis was defined as any of the following: liver histology [23], transient elastography (FibroScan; Echosens, Paris, France) >12 kPa [24], acoustic radiation force impulse >1.98 m/s [25], FIB-4 >6.5 [26], or the presence of clinical, radiological, endoscopic, or laboratory evidence of cirrhosis and/or portal hypertension.

Table 1. Baseline Patients Demographic Characteristics and Virological Features

Variables	N	Mean ± SD or n (%)
Age	12 723	54.65 ± 11.35
>45 years		10 391 (81.7)
Female	12 723	6766 (53.2)
BMI (kg/m^2)	12 723	25.01 ± 3.50
Diabetes history	6950	1261 (18.1)
Hypertension history	6950	1411 (20.3)
Dyslipidemia history	6950	628 (9.0)
HCV genotype 1	11 815	6028 (51.0)
HCV RNA (log IU/mL)	11 167	5.68 ± 0.99
>400 000 IU/mL		6799 (60.9)
AST (IU/L)	12 723	91.10 ± 64.48
ALT (IU/L)	12 723	137.49 ± 110.27
FIB-4	12 723	2.94 ± 2.52
≥3.25 (advance fibrosis)		3694 (29.0)
Liver cirrhosis	12 723	1960 (15.4)
eGFR (mL/min/1.73 m^2)	12 723	99.55 ± 34.96
Follow-up duration (years)	12 723	5.31 ± 2.94
Follow-up person-years	67 554	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis-4 index; HCV, hepatitis C virus; N, case number; RNA, ribonucleic acid; SD, standard deviation.

Patient Consent Statement

This study was approved by the Institutional Review Board (IRB) at each participating hospital (IRB number KMUHIRB-EXEMPT(I)-20170040). All patients provided written informed consents. All patient identifiers were removed or transcoding from these databases before analysis to protect personal privacy.

Study Endpoints and Linked Databases

The primary endpoint of the current study was the development of newly diagnosed major psychiatric disorders reportable to NHIRD. The secondary endpoints were the development of sequela such as dementias, subacute delirium, schizophrenia, affective psychoses, paranoia, and other organic psychotic disorders.

Approximately 23 million (99.7%) of the Taiwanese have been covered under the Taiwan National Health Insurance (NHI) since 1995, which has provided many comprehensive research databases. The registry of patients with catastrophic illness patients and the death registry were 2 widely used databases. The disease diagnoses were coded to identify diseases according to ICD-9-CM. A Taiwanese registry of the catastrophic illness included major illnesses such as carcinoma, renal failure, chronic mental disorders, congenital diseases, and rare diseases. The chronic psychiatric disorders in the catastrophic registration include ICD-9-CM codes 290 to 299. The codes for major psychoses assessed in this study were coded 290-dementias, 293.1-subacute delirium, 294-other organic psychotic conditions, 295-schizophrenia, 296-affective psychoses, and 297-paranoid. Code 299-psychiatric disorders with origin specific from childhood were excluded,

After excluding 934 patients seropositive for hepatitis B surface antigen and 2042 without posttreatment virological data available, a total of 12 862 patients with CHC were linked to NHI catastrophic illness and death databases. After receiving data from the catastrophic illness registry, 110 patients were excluded for having a previous diagnosis of major psychiatric disorders, and, according to the death registry, 29 died during or within 6 months of antiviral therapy and were excluded from the results. Data from the last course of antiviral therapy were retrieved if patients experienced more than 1 course of IFN-based therapy. New onset of major psychiatric disorders was calculated after the beginning of antiviral therapy. The final analysis consisted of 12 723 patients (Figure 1).

Statistical Analysis

Continuous variables were expressed as the mean ± standard deviation or median/range. Category variables were expressed as number (percentage). Differences between groups were

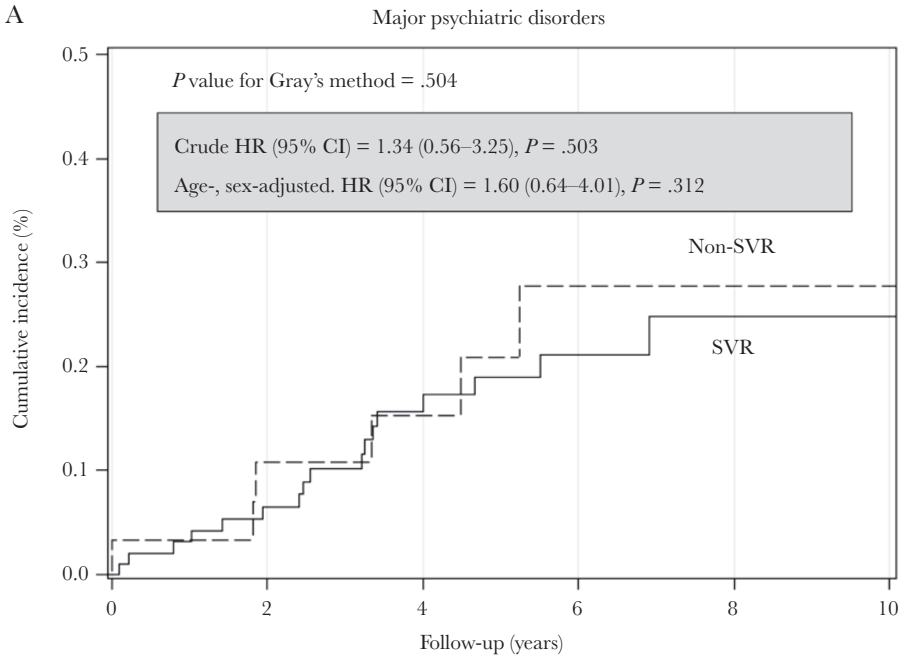
Table 2. Relationship Between Anti-HCV Responses and Incidence of Major Psychiatric Disorders, Affective Psychoses, and Schizophrenia

Variables	Total (n = 12 723)	SVR (n = 9690)	Non-SVR (n = 3033)	*P* Value
Follow-up duration (years)	5.31 ± 2.94	5.42 ± 2.97	4.97 ± 2.78	<.0001
Median (range)	5.16 (0.22–19.49)	5.27 (0.23–19.49)	4.76 (0.82–15.04)	
Follow-up person-years	67 554	52 493	15 061	
Events		n (annual incidence per 10 000 person-year)		
Major psychoses	24 (3.6)	17 (3.2)	7 (4.6)	.540
Affective psychoses	16 (2.4)	13 (2.5)	3 (2.0)	.776
Schizophrenia	7 (1.0)	3 (0.6)	4 (2.6)	.060
Others[a]	1 (0.2)	1 (0.2)	0 (0.0)	NA

Abbreviations: HCV, hepatitis C virus; NA, not applicable; SVR, sustained virological response.

[a]Two hundred ninty-four organic psychotic conditions.

evaluated using a χ^2 test (or Fisher's exact test when n < 5) for categorical data and Student's *t* test (or analysis of variance) for continuous data. The FIB-4 score for liver fibrosis was calculated as follows: FIB-4 $= \frac{\text{AST}}{\text{upper limit of normal}} \times 100$ The estimated glomerular filtration rate (eGFR) for renal function was calculated as follows [27]: eGFR = $186 \times \text{Cr}^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if female). Person-years were calculated from the date of the start of therapy to the date of the first diagnosis of any major



	Years	1	3	5	8	10
SVR	No. at risk	9172	7548	5219	1876	922
	Cumulative Incidence (%)	0.03	0.10	0.19	0.25	0.25
Non-SVR	No. at risk	2854	2282	1427	432	197
	Cumulative Incidence (%)	0.03	0.11	0.21	0.28	0.28

Figure 2. Incidence of (*A*) major psychiatric disorders, (*B*) affective psychoses and (*C*) schizophrenia between sustained virological response (SVR) and non-SVR patients after antihepatitis C virus therapy with death as competing risk. CI, confidence interval; HR, hazard ratio; SVR, sustained virological response.

psychoses, death, or December 31, 2015, whichever occurred first. Annual incidences of any major psychoses were calculated as new-onset events divided by the person-years. The missing value was interpolated using the mean of the continuous variables.

Death before any major psychiatric disorders was considered a competing risk event. Therefore, we modified the Kaplan-Meier method according to Gray's cumulative incidence method [28] and compared the incidence of newly diagnosed major psychiatric disorders between patients who achieved an SVR and those who did not achieve an SVR. Cox subdistribution hazards models with univariate and age- and sex-adjusted multivariate were performed accordingly [29]. Subgroups analysis were focused on special patients to understand the effects of successful antiviral therapy on new-onset major psychiatric disorders. Statistical analyses were performed using the SAS Enterprise Guide (SAS Institute Inc., Cary, NC), and $P < .05$ with a 2-tailed test was considered to be statistically significant.

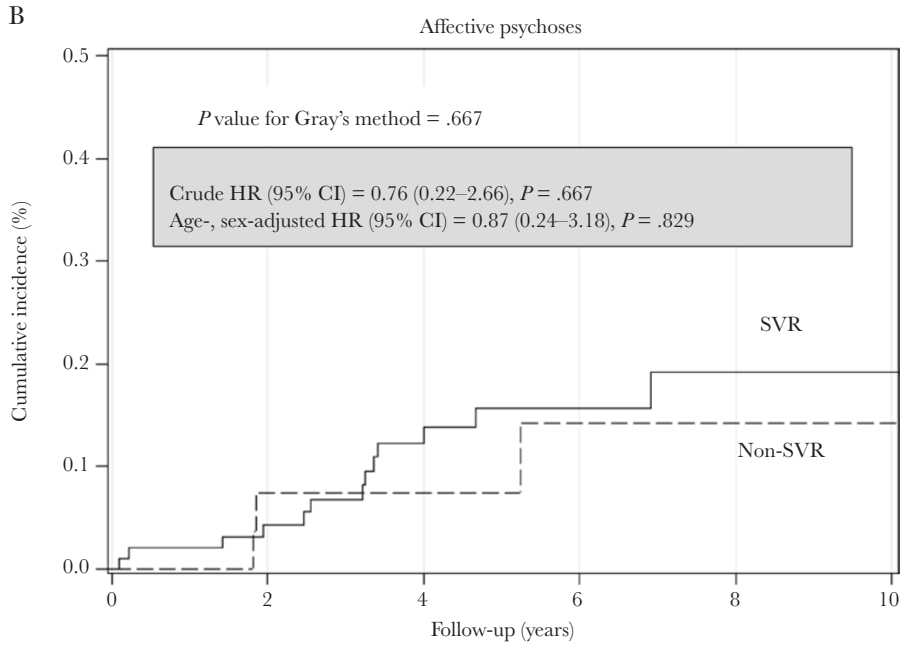
RESULTS

Patients Characteristics

A total of 12 723 patients with CHC, including 9690 SVR and 3033 non-SVR patients, were enrolled in the final analysis with a mean follow-up period of 5.3 ± 2.9 years (range, 0.2–19.5). The baseline demographic profile of these patients is shown in Table 1. The mean age was 54.7 years and women accounted for 53.2% of the participants. The mean baseline HCV viral loads were 5.68 log IU/mL, 51.0% were infected with HCV genotype 1, 29.0% had advanced fibrosis, and 15.4% had liver cirrhosis. Factors associated with non-SVR were older age, men, higher BMI, diabetes, HCV genotype 1, higher viral load, and advance fibrosis or cirrhosis (see Supplementary Table S1).

Events and Incidence of Major Psychiatric Disorders

During the follow-up period, 662 patients died without newly diagnosed major psychiatric disorders. Twenty-four patients developed new-onset major psychiatric disorders in 67 554 person-years of follow-up with an annual incidence of 3.6 per



	Years					
SVR	No. at risk	9173	7551	5222	1877	922
	Cumulative Incidence (%)	0.02	0.07	0.16	0.19	0.19
Non-SVR	No. at risk	2855	2283	1428	432	306
	Cumulative Incidence (%)	0	0.07	0.07	0.14	0.14

Figure 2. Continued.

10 000 person-years. Among 24 patients with new-onset major psychoses, 16 were affective psychoses, 7 cases were schizophrenia, and 1 was an organic psychotic condition. No patients developed dementias, paranoid, or subacute delirium. The annual incidence per 10 000 person-years was 2.4 for affective psychoses, 1.0 for schizophrenia, and 0.2 for the organic psychotic condition, respectively (Table 2).

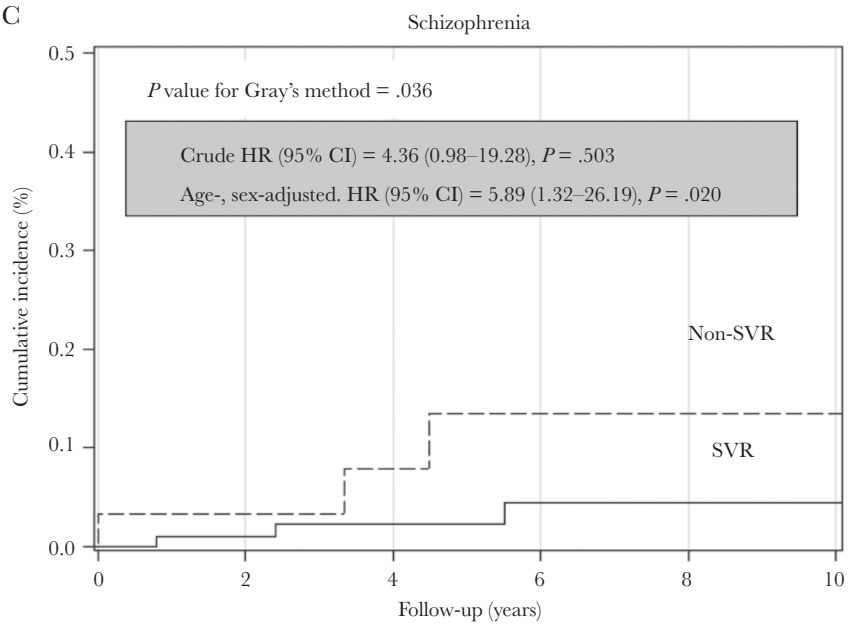
Impact of Successful Antihepatitis C Virus Therapy on Risk for Major Psychiatric Disorders

The annual incidence of major psychiatric disorders did not differ between the SVR and non-SVR groups (3.2 vs 4.6 per 10 000 person-years, respectively). The 1-, 3-, 5-, 8-, and 10-year cumulative incidence rates of major psychiatric disorders were 0.03%, 0.11%, 0.21%, 0.28%, and 0.28% for non-SVR patients compared with 0.03%, 0.10%, 0.19%, 0.25%, and 0.25% for SVR patients, respectively (crude hazard ratio [HR]/confidence interval [CI], 1.34/0.56–3.25, $P = .503$; adjusted HR/CI, 1.60/0.64–4.01, $P = .312$ for the CHS method and $P = .504$ for Gray's method, respectively) (Figure 2A). The annual incidence of affective psychoses was not statistically different between the SVR and non-SVR groups (2.5 vs 2.0 per 10 000 person-years, respectively). The 1-, 3-, 5-, 8-, and 10-year cumulative incidence rates of major psychiatric disorders were 0%, 0.07%, 0.07%, 0.14%, and 0.14% for non-SVR patients compared with 0.02%, 0.07%, 0.16%, 0.19%, and 0.19% for SVR patients, respectively (crude HR/CI, 0.76/0.22–2.66, $P = .667$, adjusted HR/CI, 0.87/0.24–3.18, $P = .829$ for the CHS method and $P = .667$ for Gray's method, respectively) (Figure 2B).

By contrast, the annual incidence of schizophrenia was substantially lower in the SVR compared with the non-SVR groups with a borderline significant (0.6 vs 2.6 per 10 000 person-years, $P = .060$). The 1-, 3-, 5-, 8-, and 10-year cumulative incidence rates of schizophrenia were 0.03%, 0.03%, 0.14%, 0.14%, and 0.14% for non-SVR patients, which were significantly higher than those of SVR patients (0.01%, 0.02%, 0.02%, 0.04%, and 0.04%, respectively, crude HR/CI, 4.36/0.98–19.28, $P = .053$ for the CHS method and 0.036 for Gray's method, respectively). After adjustment for age and sex, non-SVR patients had a significant 5.9-fold increased risk of schizophrenia compared with SVR patients (adjusted HR/CI, 5.89/1.32–26.19, $P = .020$) (Figure 2C).

Factors Associated With New Onset of Major Psychiatric Disorders, Affective, Psychoses, and Schizophrenia Among Patients With Chronic Hepatitis C Who Received Antiviral Therapy

In univariate analysis, older age (>45 years) and advanced hepatic fibrosis (FIB-4 ≥3.25) were significantly associated with a



	Years	1	3	5	8	10
SVR	No. at risk	9174	7554	5229	1882	925
	Cumulative Incidence (%)	0.01	0.02	0.02	0.04	0.04
Non-SVR	No. at risk	2854	2284	1429	432	197
	Cumulative Incidence (%)	0.03	0.03	0.14	0.14	0.14

Figure 2. Continued.

lower risk of new-onset major psychiatric disorders (Table 3). After adjustment for age and sex, older age (>45 years) and advanced hepatic fibrosis (FIB-4 ≥3.25) remained associated with lower risk of new-onset major psychiatric disorders (adjusted HR/CI, 0.42/0.18–1.00 and 0.23/0.05–1.01, respectively, both $P = .051$, borderline significance). Female patients with CHC patients had a significantly higher risk of new-onset major psychiatric disorders after anti-HCV therapy when compared with male patients (adjusted HR/CI, 2.42/1.07–5.48, $P = .034$). Similar results also were observed on affective psychoses. Being a woman was the only factor predictive of affective psychoses after adjustment for age (HR/CI, 4.27/1.31–13.89, $P = .016$) (data not shown).

Table 4 shows the factors associated with the risk of schizophrenia among patients with CHC after anti-HCV therapy. After adjustment for age and sex, SVR and older age (>45 years) were significantly associated with a lower risk of developing schizophrenia (HR/CI, 0.18/0.04–0.90, $P = .037$; HR/CI, .17/.04–.71, $P = .015$).

We further analyzed the impact of successful anti-HCV therapy on the risk of major psychiatric disorders, stratified by age and sex. Among patients with age <45, non-SVR patients had a 3.95-fold and 14.78-fold increased risk of major psychiatric disorders ($P = .04$) and schizophrenia ($P = .02$), respectively, when compared with patients with SVR (Figure 3A). The risk of affective psychoses was similar between SVR and non-SVR patients among the younger patient population. There was no difference between SVR and non-SVR groups in terms of major psychiatric disorders, schizophrenia, and affective psychoses among the older patient population (>45 years) (Figure 3A). The risks of major psychiatric disorders, schizophrenia, and affective psychoses were also similar between SVR and non-SVR patients in both male and female subpopulations (Figure 3B).

DISCUSSION

In the current nationwide cohort study with a total of 67 554 person-years follow-up, the annual incidence of major psychiatric disorders, affective psychoses, schizophrenia, and organic psychotic condition per 10 000 person-years was 3.6, 2.4, 1.0, and 0.2, respectively, among patients with CHC after IFN-based therapy. The risk of major psychiatric disorders and affective psychoses did not differ between patients who did and did not achieve an SVR. However, there was an 83% risk reduction of

Table 3. Cox Subdistribution Hazards Model for Risk Factors of Major Psychiatric Disorders Among Patients With CHC Who Achieved Antiviral Therapy

Variables		Cumulative Incidence (%)	Crude HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Age (years)	<45	0.39	1		1	
	≥45	0.14	0.39 (0.17–0.88)	.024	0.42 (0.18–1.00)	.051
Sex	Male	0.13	1		1	
	Female	0.25	1.89 (0.83–4.29)	.127	2.42 (1.07–5.48)	.034
BMI (kg/m^2)	<24	0.25	1			
	≥24	0.16	0.63 (0.28–1.40)	.256		
Diabetes	No	0.19	1			
	Yes	0.4	2.09 (0.72–6.08)	.177		
Hypertension	No	0.25	1			
	Yes	0.14	0.55 (0.13–2.40)	.426		
Dyslipidemia	No	0.24	1			
	Yes	0.16	0.73 (0.10–5.54)	.764		
HCV Genotype	G1	0.18	1			
	G2	0.19	0.63 (0.22–1.80)	.39		
HCV RNA (IU/mL)	≤400 000	0.14	1			
	>400 000	0.16	1.28 (0.47–3.50)	.634		
AST (IU/L)	<80	0.21				
	≥80	0.16	0.67 (0.29–1.56)	.358		
ALT (IU/L)	<80	0.21	1			
	≥80	0.18	0.70 (0.30–1.61)	.397		
FIB-4	<3.25	0.24	1		1	
	≥3.25	0.05	0.21 (0.05–0.91)	.037	0.23 (0.05–1.01)	.051
Liver Cirrhosis	No	0.23	1			
	Yes	0.05	0.22 (0.03–1.67)	.145		
eGFR (mL/min/1.73 m^2)	≥60	0.17	1			
	<60	0.53	3.13 (0.94–10.50)	.064		
Viral Response	SVR	0.18	1		1	
	Non-SVR	0.23	1.34 (0.56–3.25)	.503	1.56 (0.62–3.95)	.349

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CHC, chronic hepatitis C; CI, confidence interval; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis-4 index; HCV, hepatitis C virus; HR, hazard ratio; RNA, ribonucleic acid; SVR, sustained virological response.

Table 4. Cox Subdistribution Hazards Model of the Risk Factors of Schizophrenia Among Patients With CHC Who Achieved Antiviral Therapy

Variables		Schizophrenia				
		Cumulative Incidence (%)	Crude HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Age (years)	<45	0.17	1		1	
	≥45	0.03	0.19 (0.04–0.81)	0.025	0.17 (0.04–0.71)	.015
Sex	Male	0.07	1		1	
	Female	0.03	0.46 (0.09–2.36)	0.355	0.60 (0.14–2.59)	.492
BMI (kg/m^2)	<24	0.07	1			
	≥24	0.05	0.72 (0.16–3.28)	0.673		
Diabetes	No	0.05	1			
	Yes	0.16	3.19 (0.50–20.35)	0.219		
Hypertension	No	0.07	1			
	Yes	0.07	0.96 (0.11–8.46)	0.972		
Dyslipidemia	No	0.08	1			
	Yes	0	NA	NA		
HCV genotype	G1	0.07	1			
	G2	0	NA	NA		
HCV RNA (IU/mL)	≤400 000	0.05	1			
	>400 000	0.04	1.01 (0.17–5.98)	0.99		
AST (IU/L)	<80	0.08	1			
	≥80	0.02	0.18 (0.02–1.58)	0.122		
ALT (IU/L)	<80	0.07	1			
	≥80	0.05	0.54 (0.12–2.34)	0.407		
FIB-4	<3.25	0.08	1			
	≥3.25	0	NA	NA		
Liver Cirrhosis	No	0.07	1			
	Yes	0	NA	NA		
eGFR (mL/min/1.73 m^2)	≥60	0.05	1			
	<60	0.18	3.61 (0.43–30.15)	0.236		
Viral Response	SVR	0.03	1		1	
	Non-SVR	0.13	4.36 (0.98–19.28)	0.053	5.41 (1.11–26.44)	.037

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CHC, chronic hepatitis C; CI, confidence interval; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis-4 index; HCV, hepatitis C virus; HR, hazard ratio; NA, not applicable; RNA, ribonucleic acid; SVR, sustained virological response.

schizophrenia for patients with CHC who achieved an SVR compared with those who did not. The benefits of successful antiviral therapy in reducing the risk of schizophrenia among patients with CHC were majorly observed among the population younger than 45 years.

Little published data on the incidence of major psychiatric disorders, affective psychoses, and schizophrenia of comparison the general population and patients with viral hepatitis in Taiwan were available. One population-based cohort from Taiwan NHIRD reported that the incidence rate of bipolar disorders was significantly higher among hepatitis B virus (HBV)/HCV-coinfected patients, but not in HBV-monoinfected or HCV-monoinfected patients, when compared with general controls (3.62, 1.79, 2.23, and 1.14 per 10 000 person-years, respectively) [30]. Likewise, they observed that antiviral therapy for HBV or HCV had no impact on the incidence rate of bipolar disorders [30]. In the present study, we reported that treatment responses to anti-HCV therapy did not influence the incidence of major psychiatric disorders and affective disorders.

In a large-scale, Dutch cohort study of more than 350 000 subjects, the annual incidence rate of schizophrenia was 1.2 per 10 000 person-years in the general population during a 10-year follow-up [31]. A systematic review reported the incidence rate of schizophrenia was approximately 1.2 to 1.5 per 10 000 person-years and much variance around the world [32, 33]. The peak incidence for males and females is in the decade 15–24 [34]. In the present study, we found that the incidence rate of schizophrenia was 2.6 per 10 000 person-years in HCV non-SVR patients and only 0.6 per 10 000 person-years in HCV SVR patients. A gender-specific difference in the incidence of schizophrenia was observed in the younger population of this cohort. Men had a significantly higher incidence rate of schizophrenia spectrum disorders and schizophrenia with a 1.6- and 2.0-fold risk, respectively, when compared with women for subjects <35 years old, but not in those with age ≥35 years old [31]. However, we did not observe a gender effect on the risk of schizophrenia in this HCV cohort due to few patients with age <35 years old. By contrast, compared with SVR patients, non-SVR patients had a 5.9-fold risk of developing schizophrenia in the general CHC population. This increased to 14.8-fold risk among the CHC population younger than 45 years. Our results suggested that continuous CHC infections might be associated

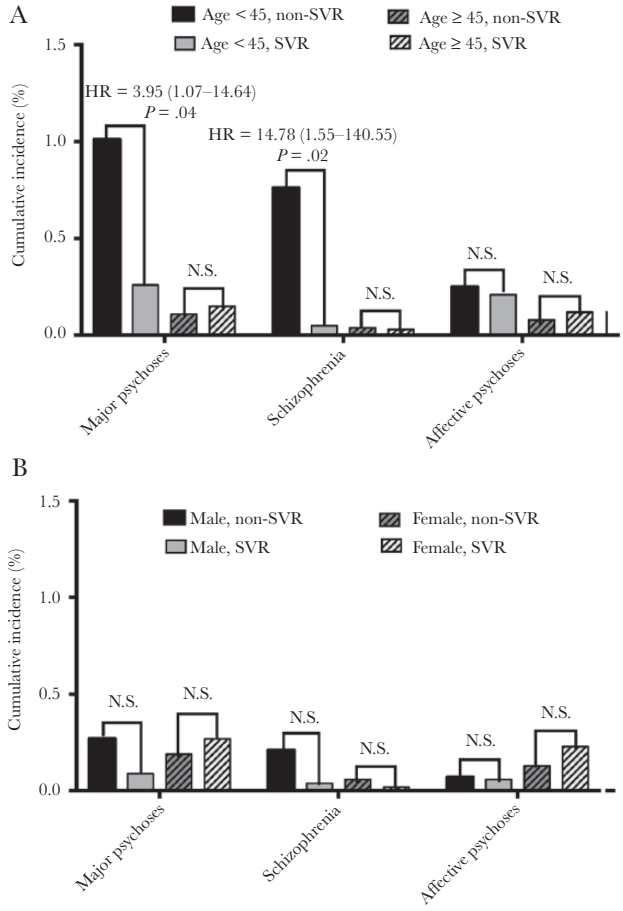


Figure 3. Ten-year cumulative incidence and Cox subdistribution hazards model of major psychoses, schizophrenia, and affective psychoses between sustained virological response (SVR) and non-SVR hepatitis C virus patients among subgroups of age (A) and gender (B) with death as competing risk. HR, hazard ratio; N.S., not significant; SVR, sustained virological response.

with a higher risk of schizophrenia, especially among younger patients. Remarkably, we observed that the mean age of the 7 patients with CHC who presented with newly diagnosed schizophrenia was 42.7 years, which was older than the usual onset age of schizophrenia in the early 30s [34]. Whether the late-onset of schizophrenia is related to HCV exposure needs further study.

Hepatitis C virus infection as a brain fog affects attention, concentration, memory, and mood, which further impairs health-related quality of life (HRQOL) and work productivity [35, 36]. These disturbances might be reduced after HCV is eradicated. Several proteins might play essential roles in the association between HCV and psychiatric disorders. Another review has shown that 4 proteins (DISC1, neuregulin, the D_2 dopamine receptor, and transcription factor 4) that cause schizophrenia susceptibility were homologous with that of HCV [37]. Hepatitis C virus infection as a risk-promoting factor may promote schizophrenia if the human genes encode for the homologous product. Therefore, schizophrenia is perhaps preventable by the homologous pathogen elimination. By contrast, IFN-based treatment may also often lead to psychiatric adverse effects or mental disorders in a subset of patients with CHC [38]. Microarray analysis showed the link between IFN-stimulated-exonuclease-gene 20 kDa (ISG20), IFN-related neuropsychiatric toxicity, and the response to IFN-based treatment for patients coinfected with HIV/HCV [39].

Recent advances in the development of new anti-HCV regimens with IFN-free directly-acting antivirals (DAAs) have not only greatly improved the treatment efficacy but also largely decreased the frequency and magnitude of adverse events [40, 41]. More than 98% of patients with CHC achieved an SVR, and HRQOL has been shown to improve as early as 4 weeks into the treatment, through the end of treatment, and 4 weeks posttreatment in an Asian study [42]. The change in cytokines (interleukin-8 and interleukin-10) and neurotransmitters (dopamine and tryptophan) among patients with CHC who receive IFN-free DAA therapy might influence patients mental and emotional health before, during, and after antiviral therapy [43]. The long-term impact of SVR by using IFN-free DAA regimens on the incidence of major psychiatric disorders remains to be studied.

The limitation of the current study is that only major and defined diagnosis mental illness were enrolled at the registry database for patients with catastrophic illnesses. The limited index cases would also restrict the interpretation of the study outcome. In addition, the rare incidence of major psychiatric disorders in the study, as well as in the general population, makes it challenging to obtain a substantial number of patients with significant events for such studies. Finally, the database lacks detailed classification information (eg, ICD-9-CM: 291 alcohol-induced psychosis disorders) and etiology codes (the 4th code of ICD-9-CM). A longer follow-up period and more patients with CHC who receive DAA are needed for further verification.

CONCLUSIONS

In conclusion, successful IFN-based anti-HCV therapy might reduce the incidence rate of schizophrenia, especially among the younger subpopulation, indicating the urgency in treating patients with CHC as young as possible. Further study with a large cohort of IFN-free DAA-treated patients and a longer follow-up period is warranted.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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