Original Article

Protective Effect of Interferon-based Antiviral Therapy on Risk of Bipolar Disorder in Patients with Hepatitis C Virus Infection: A Nationwide Longitudinal Study

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Abstract

Background: A recent study has shown the beneficial effects of interferon (IFN)-based antiviral therapy (AVT) in reducing the risk of newly diagnosed depression among patients with hepatitis C virus (HCV) infection. But whether IFN-based AVT reduces the risk of bipolar disorder remains unknown. **Methods:** This is a retrospective study based on the Taiwan National Health Insurance Research Database. From enrollment to the end of 2013, 24,240 patients with HCV infection (4473 treated with IFN-based AVT and 19,767 without such treatment) as well as 96,960 age- and sex-matched controls were included in this study. Time-dependent Cox regression models were used to study the differences in risk of newly-diagnosed bipolar disorder between patients being treated with and without IFN-based AVT and the control participants. **Results:** Patients with HCV infection who had not yet received IFN-based AVT (hazard ratio = 4.86, 95% confidence interval = 1.87–12.66, $p = 0.001$), but not those who were receiving IFN-based AVT (1.69, 0.94 - 30.50, nonsignificance) and those who completed the IFN-based AVT (1.77, 0.69 - 4.54, nonsignificance), were significantly more to be diagnosed with bipolar disorder compared with the control group. **Conclusion:** Our study supports the temporal association between HCV infection and subsequent bipolar disorder, further suggesting that the optimal AVT to eradicate HCV may be associated with a reduced risk of incident bipolar disorder later in life.

Key words: depression, inflammation, temporal association, the Taiwan National Health Insurance Research Database
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Introduction

Hepatitis C virus (HCV) is a hepatotropic RNA virus that causes progressive liver damage and infects more than 170 million individuals worldwide [1, 2]. Patients with chronic HCV infection are at high risk of developing life-threatening complications. For example, cirrhosis occurs in 20% of cases and hepatocellular carcinoma has an incidence of 4%–5% per year in patients with cirrhosis [2]. In addition to the hepatic complications, HCV infection is also associated with extrahepatic complications, such as insulin resistance, type 2 diabetes mellitus, neurodegenerative disorders, and depression [2-4].

Increasing evidence suggests a relationship between HCV infection and bipolar disorder, which is a recurrent, chronic, and severe affective disorder that manifests as alternating episodes of mania or hypomania and depression [5-7]. In one study, the investigators assessed the prevalence of HCV infection among 931 patients with severe mental disorders (schizophrenia and bipolar disorder) and found that up to 20% of patients are infected with HCV, which is about 11 times the overall estimated rate among the population [7]. Chong et al.

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showed that patients with HCV infection only (hazard ratio [HR] = 1.93, 95% confidence interval [CI] = 1.07–3.48) or with HCV and HIV coinfection (HR = 3.22, 95% CI = 1.64–6.32) are more likely to develop the bipolar disorder during follow-up than those without diagnoses of viral hepatitis and HIV infection [8]. A meta-analysis of 28 studies on 14,888 patients with severe mental disorders for HCV showed a prevalence of 17.4% in North America and 4.4% in Asia, being higher than the 1% prevalence seen in the general population [2]. However, most previous studies are cross-sectional, thus confounding the investigation of the temporal association between HCV infection and bipolar disorder.

In current clinical practice, interferon (IFN)-based antiviral treatment (AVT) is a standard treatment for HCV infection, being able to reduce HCV-related intra- and extrahepatic complications, including stroke and Parkinson's disease [9-11]. Hsu et al. compared the risk of ischemic stroke between patients with HCV being treated with and without IFN-based AVT and found that AVT is associated with a lower risk of ischemic stroke (HR = 0.62; 95% CI = 0.46 - 0.83) [9]. Lin et al. demonstrated that among patients with HCV infection, IFN-based AVT reduced the risk (HR = 0.75; 95% CI = 0.59 - 0.96) for Parkinson's disease at the 5-year follow-up [11]. However, IFN-related treatment can be a double-edged sword with having benefits and risks for mood disorders [12, 13]. Assessing 200 HCV-infected patients starting IFN-based AVT for 24 weeks, Su et al. found that 59 (30%) patients have developed IFN-α-induced depression during the IFN-based AVT [12]. They further found that IFN-α-induced depression is associated with more somatic symptoms and fewer symptoms of mood, anxiety, and negative cognition [12]. A murine BV-2 microglia cell line study showed that IFN-α induces nitric oxide synthase expression and haem oxygenase-1 down-regulation, which may play a crucial rôle on the development of IFN-α-induced depression [14]. On the contrary, Sun et al. revealed that the HR for incident depressive disorder is 0.79 (95% CI = 0.72 - 0.87) for patients with HCV treated with IFN-based AVT compared with untreated patients [10]. But whether IFN-based AVT reduces the risk of bipolar disorder among patients with HCV infection remains unknown.

Based on the evidence of an association between HCV infection and bipolar disorder as well as the potential neuroprotective effect of IFN-based AVT, we used the Taiwan National Health Insurance Research Database (NHIRD) with a large sample size and a longitudinal study design and intended to study the risk of newly diagnosed bipolar disorder after HCV infection. We also intended to clarify whether IFN-based AVT reduces this risk. We hypothesized that HCV infection would be related to an elevated likelihood of subsequent bipolar disorder and that this risk could be reduced through the administration of the optimal IFN-based AVT.

Methods

Data source for study patients

In the current study, we analyzed the data from the Taiwan National Health Insurance Research Database (NHIRD), i.e., the Longitudinal Health Insurance Database. Established for research purposes and audited by the Ministry of Health and Welfare and the Bureau of the NHI program, the NHIRD contains comprehensive medical information between 1996 and 2013 about the insured patients, including demographics (birthdate, sex, residential location, and income status), clinical visits (dates and diagnoses), medical assessment (laboratory examination), and interventions (prescriptions). Each patient is assigned a unique and anonymous identifier upon enrollment by the NHI, which allows researchers to follow their diseases and outcomes. Claims data of subjects included in the NHIRD are anonymous to protect individual privacy. Diagnoses were captured using *the International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*). The NHIRD has been used extensively for epidemiologic studies [15-18]. The study protocol was approved by the Taipei Veterans General Hospital institutional review board (IRB protocol number = 2018-07-016AC and date of approval = July 23, 2021) with the waiver of the requirement for any informed consents.

Inclusion criteria for patients with hepatitis C virus

We included adolescent patients aged between 10 and 19 years and adult patients ≥ 20 years who were diagnosed with HCV (*ICD-9-CM* codes: 070.41, 070.44, 070.51, 070.54, V02.62) given by board-certified physicians after the real-time PCR HCV genotyping test between January 1, 1997, and December 31, 2012, and those without any history of major psychiatric disorder (*ICD-9-CM* codes: 295 for schizophrenia, 296 for affective disorder) before their HCV diagnoses in this HCV cohort. Excluded from this study cohort were patients with a diagnosis of hepatitis B virus (HBV) infection (*ICD-9-CM*: 070.2, 070.3, V02.61), human immunodeficiency virus (HIV) infection (*ICD-9-CM*: 042–044, V08).

Interferon-based antiviral therapy

The regimen of IFN-based AVT is a combination of pegylated IFN α-2b and ribavirin [11, 19]. The adequate IFN-based AVT was defined as receiving at least a 16-week course AVT in this study. The duration of IFN-based AVT ranged from 16 to 48 weeks. In clinical practice, the duration of IFN-based AVT mainly depends on the serum virologic response and the adverse effects of treatment. Less than 16 weeks of an IFN-based AVT has been suggested as inadequate and premature termination of therapy [11, 19].

Selection of matched controls

Exact matching was used to match this cohort in a 1:4 fashion to controls without diagnoses of neither HCV, HBV, and HIV nor major psychiatric disorder before the enrollment on the bases of age (±1 year), sex, enrollment time, medical comorbidities, income level, and urbanization level of residence (levels 1-5, most to least urbanized), a proxy for health-care availability in Taiwan [20]. Medical comorbidities, such as hypertension, dyslipidemia, diabetes mellitus, obesity, smoking, alcohol use disorder, substance use disorder, and cerebrovascular diseases, were assessed

[21-24]. In addition, Charlson Comorbidity Index (CCI) and all-cause clinical visits were provided for the HCV and the matched-control cohorts. CCI consisting of 22 physical conditions was also assessed to determine the systemic health conditions of all enrolled subjects [25]. All-cause clinical visits (the numbers of clinical visits per year) for the HCV cohort and the matched-controls cohort were included to account for potential detection bias.

Outcome assessment

Diagnosis of bipolar disorder (*ICD-9-CM* codes: 296 except 296.2x, 296.3x, 296.9x, and 296.82) was given by board-certified psychiatrists at least twice during the follow-up period (from enrollment to December 31, 2013, or until death).

Statistical analysis

For between-group comparisons, the F-test was used for continuous variables and Pearson's chi-square test for nominal variables**.** Stratified Cox-regression analyses on each matched-pair (the patient and their four matched controls in a 1:4 ratio) with adjustment for age, CCI score, and all-cause clinical visits were applied to investigate the bipolar disorder risk between HCV and control groups. In order to avoid the immortal time bias, IFN-based AVT was treated as a time-dependent variable in the regression models: before or never IFN-based AVT, during IFN-based AVT, and after IFN-based AVT. In addition, the sex effect was also clarified in our study.

Data processing and statistical analyses were done with Statistical Analysis System (version 9.1, SAS Institute, Cary, North Carolina, USA). Statistical significance was set at two-tailed $p \leq 0.05$.

Results

We included 24,240 patients with HCV infection and 96,960 demographic characteristics- and comorbidities-matched controls in the current study, with a mean age of 55 years and equal sex distribution (Table 1). Among patients with HCV infection, 4,473 (18.5%) were ever treated with IFN-based AVT and 19,767 (81.5%) were not (Table 1). Compared with the

Table 1. Demographic data and incidence of bipolar disorder among patients with hepatitis C virus and control group

	Patients with HCV (n=24,240), n (%)	Controls (n=96,960), n (%)
Age at enrollment, years, mean ± SD	55.51 ± 15.10	55.42 ± 15.15
Sex		
Male	12,031 (49.6)	48,124 (49.6)
Female	12,209 (50.4)	48,836 (50.4)
IFN-based AVT		
Yes	4,473 (18.5)	
No	19,767 (81.5)	
Medical and psychiatric comorbidities		
Hypertension	11,801 (48.7)	47,204 (48.7)
Dyslipidemia	6,280 (25.9)	25,120 (25.9)
Diabetes mellitus	6,935 (28.6)	27,740 (28.6)
Cerebrovascular diseases	3,578 (14.8)	14,312 (14.8)
Obesity	460 (1.9)	1,840 (1.9)
Smoking	815 (3.4)	3,260 (3.4)
Substance use disorder	1,085 (4.5)	4,340 (4.5)
Alcohol use disorder	2,251 (9.3)	9,004 (9.3)
CCI score, mean ± SD	3.82 ± 2.60***	2.36 ± 2.29
Level of urbanization		
1 (most urbanized)	2,860 (11.8)	11,440 (11.8)
2	4,855 (20.0)	19,420 (20.0)
3	2,211 (9.1)	8,844 (9.1)
4	2,780 (11.5)	11,120 (11.5)
5 (most rural)	11,534 (47.6)	46,136 (47.6)
Income-related insured amount		
≤ 15,840 NTD/month	8485 (35.0)	33940 (35.0)
15,841–25,000NTD/month	11319 (46.7)	45276 (46.7)
≥ 25,001 NTD/month	4436 (18.3)	17744 (18.3)
Numbers of newly diagnosed bipolar disorder	102 (0.42)***	37 (0.04)
Age at diagnosis of bipolar disorder, years, mean ± SD	50.41 ± 14.22	48.39 ± 17.60
Duration between enrollment and bipolar disorder, years, mean ± SD	4.48 ± 3.20**	6.37 ± 4.32
All-cause clinical visits, times per year, mean ± SD	23.68 ± 19.35***	15.75 ± 14.75

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

US dollar is roughly equal to 30 NTDs.

HCV, hepatitis C virus; IFN-based AVT, interferon-based antiviral therapy; SD, standard deviation; NTD, new Taiwan dollar; CCI, Charlson Comorbidity Index

Table 2. Risk of developing bipolar disorder among patients with hepatitis C virus and controls

	Bipolar disorder risk, HR (95% CI)		
	Male sample	Female sample	Total sample
HCV patients			
Before/never IFN-based AVT	3.90 (1.17–13.01)*	8.09 (1.53–42.94)*	4.86 (1.87–12.66)**
During IFN-based AVT	1.58 (0.09–29.54)	NA	1.69 (0.94–30.50)
After IFN-based AVT	1.81 (0.55–5.99)	1.39 (0.29–6.73)	1.77 (0.69–4.54)
Non-HCV controls	1 (reference)	1 (reference)	1 (reference)

*$p < 0.05$; **$p < 0.01$

HCV, hepatitis C virus; IFN-based AVT, interferon-based antiviral therapies; HR, hazard ratio; CI, confidence interval; NA, not available

control group, patients with HCV infection significantly had a higher incidence of subsequent newly diagnosed bipolar disorder (0.42% vs. 0.04%, $p < 0.001$), higher CCI scores (3.82 ± 2.60 vs. 2.36 ± 2.29, $p < 0.001$), and greater numbers of all-cause clinical visits (23.68 ± 19.35 vs. 15.75 ± 14.75, $p < 0.001$) (Table 1).

Stratified Cox-regression analyses with adjustment of age, CCI score, and all-cause clinical visits and with IFN-based AVT as time-dependent variable showed that only patients with HCV infection who have not yet received IFN-based AVT (HR = 4.86, 95% CI = 1.87-12.66) were significantly more been diagnosed with bipolar disorder compared with the control group (Table 2). Patients with HCV infection who were receiving IFN-based AVT (HR =1.69, 95% CI = 0.94-30.50) and those who completed the IFN-based AVT (1.77, 0.69-4.54) were not associated with the risk of newly-diagnosed bipolar disorder (Table 2). Findings of an association between before/never IFN-based AVT and bipolar disorder risk were consistent in HCV-infected men (HR = 3.90, 95% CI = 1.17-13.01) and women (HR = 8.09, 95% CI = 1.53- 42.94) (Table 2).

Discussion

Our findings support the study hypotheses that patients with HCV infection are more likely to develop the newly-diagnosed bipolar disorder later in life than are the control group (Table 1). This increased risk of bipolar disorder may be neutralized through the administration of the optimal IFN-based AVT (Table 2).

The prevalence of HCV infection and comorbid severe mental disorders, such as schizophrenia and bipolar disorder, is high (up to 20%) [5-7]. A recent study examined 34,459 patients with HBV infection, 9,893 patients with HCV infection and 3,863 patients with HBV/HCV coinfection and determined that patients with HBV/HCV coinfection had the highest risk (HR = 3.22, 95% CI = 1.64–6.32) of incident bipolar disorder, patients with HCV infection had the second highest risk (HR = 1.93, 95% CI = 1.07–3.48), and those with HBV infection had the lowest risk (HR = 1.95, 95% CI = 1.09 - 2.25) compared with non-HBV/HCV comparison group [8]. Our findings corroborate the findings of Chong et al. [8] and support the relationship between HCV infection with an increased risk of incident bipolar disorder. Neuroimaging studies of patients with HCV infection may have found a partial explanation of the temporal association between HCV infection and subsequent development of bipolar disorder [26, 27]. McCready et al. used functional magnetic resonance imaging (fMRI) and evaluated reward-related functioning, which is commonly impaired in bipolar disorder, to investigate brain activation; the delay discounting task (DDT) was done by patients with HCV infection, and in fMRI, those with HCV infection exhibited less activation in the superior frontal cortex and precuneus than did the controls [26]. Moreover, patients with HCV with high viral loads were more impulsive in the DDT than those with low viral loads, which indicated that HCV-related impulsivity was negatively related to activation in brain regions important for cognitive control, such as the frontal cortex [26]. Hjerrild et al. compared the cortical thickness of 43 patients with HCV but without liver fibrosis, substance abuse, or comorbid HIV or HBV infection and 43 controls; they reported that areas of reduced cortical thickness have particularly been found in the left frontal lobe [27]. A perfusion-weighted MRI study has further confirmed the neurotoxicity of HCV toward the frontal cortex; patients with HCV infection have shown significantly lower relative cerebral blood volume values within the frontal cortex [28]. The frontal cortex, which works as a modulator of affective and cognitive functioning, has been regarded as the core region involved in the neuropathophysiology of bipolar disorder [29, 30]. We suggest that HCV infection takes time to impair the specific brain function and neural circuitry involved in emotional regulation and cognition, especially in the frontal cortex, which may explain the sequential phenomenon of HCV infection being followed by bipolar disorder.

Our study (Table 2) is the first to suggest a beneficial effect of IFN-based AVT on the risk of newly-diagnosed bipolar disorder among patients with HCV infection. Furthermore, our study results indicate that HCV patients being treated with IFN-based AVT exhibit a similar likelihood of newly-diagnosed bipolar disorder during follow-up as the control group. By assessing the neurocognitive and neurostructural changes among patients with HCV infection before and after IFN-based AVT, Kuhn et al. found that patients with HCV infection experience improvements in cognitive functioning following eradication of HCV, which is related to positive changes in white matter integrity of the superior longitudinal fasciculus [31]. Bladowska et al. further indicated that AVT improves the integrity of bilateral inferior fronto-occipital fascicles and increases the cerebral perfusion in bilateral

basal ganglions among patients with HCV infection, which may explain the improved functioning of frontostriatal regions after AVT [32]. In addition to the normalization of neurofunctioning in the frontal cortex and basal ganglion region after HCV eradication therapy, IFN-based AVT may neutralize the pro-inflammatory cytokine storm caused by HCV infection, which is also commonly observed in major depressive disorder and bipolar disorder [33-35]. Our pro-inflammatory cytokine study of 130 patients with bipolar disorder, 149 patients with unipolar depression, and 130 healthy comparison controls revealed that both patients with bipolar disorder and those with unipolar depression had higher levels of pro-inflammatory cytokines, such as C-reactive protein, soluble interleukin-6 receptor, and soluble tumor necrosis factor (TNF) receptor type 1, compared with the control group, and further suggested a more severe inflammatory dysregulation in bipolar disorder than in unipolar depression [36]. Huang et al. reported that high-sensitivity C-reactive protein serum levels were significantly decreased in patients with HCV after IFN-based AVT, particularly among those achieving a sustained virological response [33]. Torre et al. found that early reduction of soluble TNF-α receptor levels on the 3rd after IFN-based AVT is related to virus decay on day 30 [34]. A decrease in TNF-α level after 12 weeks of HCV eradication therapy has been observed by Esquivel et al. [35]. Based on these studies, we hypothesized that the positive synergic effect of IFN-based AVT in the neurofunctioning of the frontal cortex and in anti-inflammatory modulation could neutralize the risk of newly diagnosed bipolar disorder among patients with HCV infection. However, the pathophysiology of HCV infection and bipolar disorder and the exact underlying mechanisms of how IFN-based AVT reduces the risk of bipolar disorder among patients with HCV infection need further investigation.

Study limitations

- Study limitations reflect those shared by other registry-based analyses.
- The incidence of bipolar disorder may be underestimated because only those who sought medical help and consultation were identified in the database. But the diagnosis of bipolar disorder was made by board-certified psychiatrists, improving the diagnostic validity.
- The NHIRD does not provide some information, such as psychosocial stresses, family history, personal lifestyle, and environmental factors. Without this information, we were unable to examine their influence.

Summary

Patients with HCV infection, particularly those who had not yet received IFN-based AVT, were prone to developing newly-diagnosed bipolar disorder later in life compared with the control participants. IFN-based AVT may neutralize the risk of newly-diagnosed bipolar disorder among patients with HCV infection. The mental health of patients with HCV infection should be closely monitored in regular clinical practice. In addition, the optimal treatment for HCV infection can be beneficial for the long-term mental health among patients with HCV infection.

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Conflicts of Interest

All authors have no financial relationships relevant to this article to disclose.

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