ORIGINAL RESEARCH

Risk of New-Onset Atrial Fibrillation Among Asian Chronic Hepatitis C Virus Carriers: A Nationwide Population-Based Cohort Study

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***Background*—**Hepatitis C virus (HCV) infection not only links closely to systemic inflammation but also has numerous extrahepatic manifestations. Chronic inflammation also increases the risk of new-onset atrial fibrillation (AF). However, little is known regarding the clinical association between HCV infection and new-onset AF.

***Methods and Results*—**We conducted a population-based cohort study using Taiwan's National Health Insurance Research Database during 1997 to 2013. A total of 11 771 HCV-infected patients were included in this study, and each of them was matched in a ratio of 1:4. Because of higher mortality among HCV cohorts, we used both Cox proportional hazard regression and competing risk regression models to compute the hazard ratios accompanying 95% CIs after adjustment for relevant confounder. The results demonstrated that the patients with chronic HCV infection had significantly higher incidence rate (332.0 versus 265.8 in 100 000 person-years, $P<0.0001$) of new-onset AF compared with the non-HCV population. The adjusted hazard ratio of HCV for new-onset AF was 1.32 (95% CI, 1.20–1.44; $P<0.0001$) and 1.20 (95% CI, 1.10–1.31; $P=0.0001$) while calculated with Cox proportional hazard regression model and competing risk model, respectively. Intriguingly, we observed that the patients with HCV treated with antiviral agents had significantly lower incidental AF than those without anti-HCV treatment (1.2% versus 6.0%; $P<0.0001$).

***Conclusions*—**Chronic HCV infection was associated with an increased risk of incidental AF probably through sharing common pathology of chronic inflammation. Furthermore, a well-designed study is needed to clarify whether anti-HCV therapy can provide protection against the occurrence of AF. **(*J Am Heart Assoc*. 2019;8:e012914. DOI: 10.1161/JAHA.119.012914.)**

Key Words: atrial fibrillation • chronic hepatitis C • extrahepatic manifestations • inflammation • population-based cohort study

Chronic viral hepatitis is not only a common infectious disease around the world but also causes heavy public health problems and socioeconomic burden.[1,2] Its prevalence is particularly high in Asia Pacific regions.[3] Unlike hepatitis B, which is commonly self-limiting,[4] patients with hepatitis C virus (HCV) infection easily become chronic carriers and even develop liver cirrhosis or cancer several decades later.[5] In addition to hepatic pathologic change, chronic HCV infection has many extrahepatic manifestations, eg, hematological diseases, autoimmune disorders, nephropathy, and dermatological abnormalities.[6,7] Data from recent studies[8,9] have also shown that chronic HCV infection is strongly associated with atherosclerosis, cardiovascular/cerebrovascular events, and relevant mortality. Among them, HCV infection–associated systemic inflammation and consequent vasculitis are thought to be the major disease mediators of atherosclerotic cardiovascular diseases.[10–12]

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An accompanying Table S1 is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012914

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Clinical Perspective

What Is New?

- Chronic infection of hepatitis C virus was associated with an increased risk of incidental atrial fibrillation probably through sharing the common pathological mechanism of chronic inflammation.
- We found that antiviral therapy might reduce the risk of new-onset atrial fibrillation.

What Are the Clinical Implications?

- Regular follow-up of ECGs to identify new-onset atrial fibrillation early in chronic hepatitis C virus carriers is strongly suggested in clinical practice.
- A larger population-based or well-designed prospective study is needed to investigate whether antiviral therapy could decrease and delay the development of new-onset atrial fibrillation.

Atrial fibrillation (AF), the most common cardiac arrhythmia in middle-aged and elderly adults, is positively associated with stroke, heart failure (HF), and cardiac death if not identified early and treated appropriately with antiarrhythmic or anticoagulant agents.[13] The causes of AF are relevant to diverse hereditary and acquired factors.[14,15] Apart from progressive atrial remodeling and fibrosis, which are considered as a primary pathologic change for AF,[16] emerging recent evidence[17] has revealed that genetic factors and inflammation are 2 major contributors for AF development. Furthermore, clinical observation and literature reviews[18,19] have revealed that new-onset AF (NOAF) is frequently observed in the critically ill or patients with sepsis, implicating that acute or chronic inflammation might lead to occurrence and progression of AF. Thus, it is rationale to hypothesize that HCV carriers might have an increased risk for NOAF through sharing common mechanisms of inflammation. Nevertheless, in contrast to cardiovascular/cerebrovascular events, which have been frequently noted in HCV,[11] the clinical evidence for a relationship between AF arrhythmia and HCV remains scarce. In this study, we attempt to investigate the real-world risk of NOAF in patients with chronic HCV infection by employing a nationwide database with a long-term follow-up.

Methods

Taiwan's National Health Insurance Research Database

Because of the Computer-Processed Personal Data Protection Law and relevant regulations in Taiwan, the data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. The program of Taiwan's National Health Insurance Research Database (NHIRD) provides health care to 99% of the 23.74 million residents and links to >95% of individual background and medical information (http://nhird.nhri.org.tw/en/).[20] The databank contains substantial amounts of information regarding personal medical records, medical facilities, details of inpatient and outpatient orders, dental services, prescription of drugs, examinations, procedures, subsequent patient care, and other paramedical registration files, eg, payment, regions, and catastrophic illness, except for laboratory data and description of reports. Diagnoses are entered into computers based on *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes. The study was performed by using the Longitudinal Health Insurance Database 2000 of NHIRD, which randomly sampled 1 million patients from the 2010 registry for beneficiaries of the NHIRD and contained the entire original claim data from 1997 to 2013. The study design and protocol were approved by the ethics institutional review board of Kaohsiung Chang Gung Memorial Hospital (No. 201900269B0). The requirement of informed consent from each study participant was waived as a result of deidentification of NHIRD.

Study Population and Allocation

This was a retrospective population-based cohort study. Patients with chronic HCV infection (*ICD-9-CM* codes: 070.7, 070.41, 070.44, 070.51, 070.54, V02.62) were selected from 1 million individuals in Taiwan's NHIRD between January 1997 and December 2013. After excluding: (1) participants with follow-up duration <1 year; (2) missing relevant baseline data; (3) age younger than 18 years; (4) diagnoses of AF (427.31) or atrial flutter (427.32) in the beginning of enrollment; and (5) hepatitis B viral infection (070.2, 070.3, V02.61), a total of 11 771 eligible patients were assigned to the HCV group. Participants without HCV infection were selected and 4:1 matched with study group by age, sex, income, and urbanization. Finally, there were 47 084 patients without HCV assigned as a comparison group (Figure 1). The urbanization level was categorized into 4 grades from levels 1 to 4.[21] Level 1 corresponded to patients who resided in the most urban areas (cities), to level 4, indicating the most rural areas (villages). Insurance taxable income was stratified into 4 levels based on monthly insurance payment of individual insured enrollee, ie, level 1: none, level 2: 1 to 15 840, level 3: 15 841 to 25 000, and level 4: >25 000 New Taiwan dollars per month. These 2 background parameters were matched between groups at baseline to eliminate the differences in patients' lifestyle and socioeconomic status.

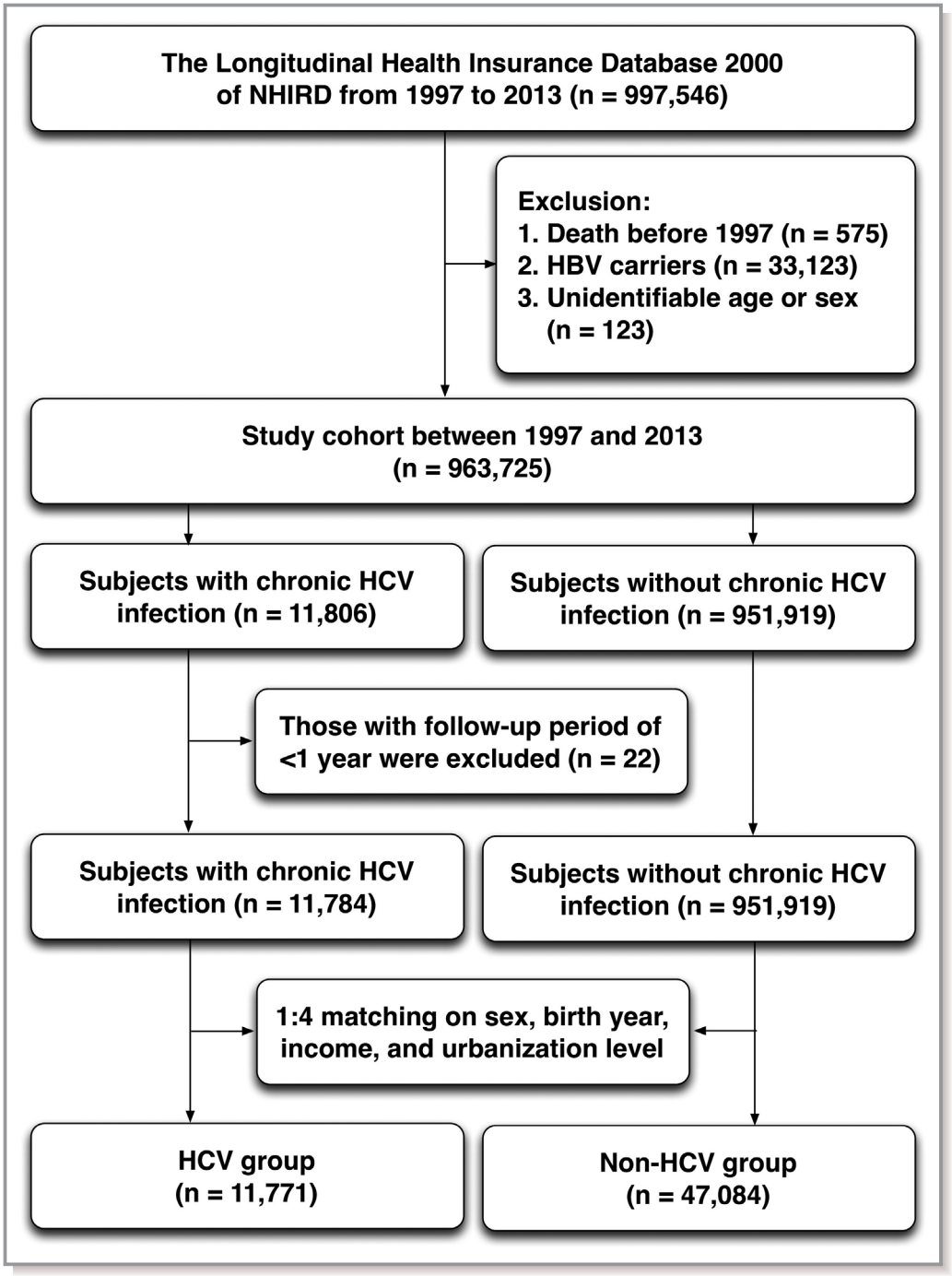

Figure 1. Flow diagram of patient selection and allocation into the hepatitis C virus (HCV) and matched non-HCV groups. The non-HCV group was selected by matching the HCV group with age, sex, and socioeconomic status in a 4:1 ratio after excluding patients who died before 1997, hepatitis B virus (HBV) carriers, and incomplete or missing detailed information. NHIRD indicates National Health Insurance Research Database.

Definition of Chronic HCV Infection, Incidental AF, and Antiviral Agents

Chronic HCV infection was defined as an *ICD-9-CM* diagnosis of hepatitis C entered for at least 3 months with corresponding abdomen/liver ultrasound study at hospitalization or outpatient clinic. In addition, diagnosis of incidental or NOAF (427.31) was confirmed by a record of at least 3 consecutive outpatient visits within 1 year or based on a diagnosis of AF at an emergency department or hospitalization during study period. CHA_2DS_2-VASc score was calculated at baseline (ie, at the beginning of patient allocation into the 2 groups) and after

AF diagnosis for assessment of disease severity (ie, extent of comorbidities) and risk of ischemic stroke, respectively.[22,23] Data regarding exposure to anti-HCV treatment regardless of therapeutic course were acquired from NHIRD according to World Health Organization Anatomical Therapeutic Chemical classification system codes, namely L03AB for interferons and J05AP01 for ribavirin. In contrast, patients without prescription for antiviral agents were defined as "no treatment."

Comorbidities and Outcomes

During the 17-year data set period, a total of 11 764 patients with HCV and 47 084 matched counterparts without HCV were identified to be eligible in this study. The date of January 1, 1997, was defined as the index date. We evaluated the comorbidities including traditional atherosclerotic risk factors, relevant cardiovascular, noncardiovascular, or cerebrovascular diseases, or other systemic diseases for each participant. Data were retrieved and diagnoses were confirmed by 3 consecutively identical *ICD-9-CM* codes, such as hypertension (401–405), diabetes mellitus (250), dyslipidemia (272), cerebrovascular accident (430–436), acute coronary syndrome (410, A270, 411.1), chronic ischemic heart disease (412–414, 429.2), peripheral vascular disease (440, 443.9, 444–445, 447.8, 447.9), valvular heart disease (394–396), ventricular arrhythmia (427.1, 427.4, 427.6), heart failure (428), chronic obstructive pulmonary disease (491, 492, 493.2), obstructive sleep apnea (780.51, 780.53, 780.57), and chronic kidney disease (585) or end-stage renal disease (V451, 549.8). We further investigated the prevalence of the above comorbidities between the 2 groups during the whole study period. Regarding the outcomes, the first day of event occurrence was defined as event date. Therefore, the incidences of NOAF and all-cause mortality were further studied. The patients in both groups who experienced the first attack of AF or death before AF were identified as event occurrence. Otherwise, those patients without events were censored at the end of the study.

Statistical Analysis

After matching on age, sex, and socioeconomic background, the demographic data including prevalence rate of comorbidities and incidence rate of outcomes between the HCV and matched non-HCV cohorts were compared with the independent *t* and chi-square tests, as appropriate. The incidence rate and 95% CIs of NOAF were calculated between groups during the entire follow-up period. Additionally, we used the Kaplan-Meier method to estimate cumulative incidences and performed the log-rank test to examine differences between disease and nondisease groups. By using Cox proportional hazard regression model, we analyzed the hazard ratio (HR) concomitant with 95% CI of each parameter to identify the risk factors of NOAF. Mortality rate was found to be relatively higher than the rate of NOAF in both groups. Considering that all-cause mortality might be a competing factor for NOAF, a competing risk regression model with case-specific hazard approach was utilized to calculate and verify the individual HR for incidental AF.[24,25] Further, sensitivity analysis was performed to examine the risk consistency of HCV infection for NOAF after adjustment for each of the covariates in addition to the main model, including age, sex, and baseline socioeconomic status. Finally, to further understand the impact of anti-HCV treatment on incidental AF in the patients with HCV, we performed independent *t* test for the rate of NOAF between the treatment and no-treatment groups. Two-tailed $P<0.05$ was considered statistically significant. All analyses were conducted using SAS statistical software (version 9.4, SAS Institute).

Results

Demographic Data in Patients With and Without Chronic HCV Infection

As shown in Table 1, one half of patients were men and only one fifth were older than 65 years in both HCV and non-HCV groups. More than half of the patients lived in or near cities with acceptable economic conditions. Except for ventricular arrhythmia, which was similar between groups, the frequencies of traditional atherosclerotic risk factors and cardiovascular, cerebrovascular, lung, and kidney diseases were significantly higher in the HCV than non-HCV group. The prevalence rates of hypertension, diabetes mellitus, and dyslipidemia in the patients with HCV were >30%. Among the HCV group, about 20% had heart failure. Additionally, the frequencies of ischemic heart disease and chronic obstructive pulmonary disease were close to 30%. Furthermore, patients with HCV had significantly higher baseline CHA_2DS_2-VASc score, which was calculated before diagnosis of AF. The aforementioned findings implied that the HCV carriers not only were sicker but also had more extrahepatic manifestations and higher disease severity (ie, more relevant comorbidities) as compared with their non-HCV counterparts. As a result, all-cause mortality in the HCV group was up to 20% and significantly higher than that in the non-HCV group.

Comparison of Disease Severity, Mortality, and NOAF Between the HCV and Non-HCV Groups

At the end of follow-up, the incidence of NOAF was significantly higher in the HCV than non-HCV group (5.15% versus 4.34%, $P=0.0002$). The incidence rate was 332 and 265.8 per 100 000 person-years in the HCV and non-HCV

Table 1. Patient Characteristics and NOAF Between the HCV and Non-HCV Groups

Variables	HCV Group (n=11 771)		Non-HCV Group* (n=47 084)		*P* Value
	No.	%	No.	%	
Sex					
Male	6060	51.48	24 240	51.48	1.0000
Female	5711	48.52	22 844	48.52	
Age, y					
18 to 65	9344	79.38	37 376	79.38	1.0000
>65	2427	20.62	9708	20.62	
Mean±SD	51.61±15.55		51.61±15.55		1.0000
Urbanization level					
1 (City)	2524	21.44	10 096	21.44	1.0000
2	5136	43.63	20 544	43.63	
3	2604	22.12	10 416	22.12	
4 (Village)	1507	12.80	6028	12.80	
Income level					
1 (Lowest)	2014	17.11	8056	17.11	1.0000
2	1784	15.16	7136	15.16	
3	6218	52.82	24 872	52.82	
4 (Highest)	1755	14.91	7020	14.91	
Comorbidities					
Hypertension	6618	56.22	22 076	46.89	<0.0001
Diabetes mellitus	4010	34.07	11 037	23.44	<0.0001
Dyslipidemia	3794	32.23	14 350	30.48	0.0002
Cerebrovascular accident	2796	23.75	9230	19.60	<0.0001
Acute coronary syndrome	783	6.65	2543	5.40	<0.0001
Ischemic heart disease	3511	29.83	11 323	24.05	<0.0001
Peripheral vascular disease	725	6.16	2377	5.05	<0.0001
Valvular heart disease	256	2.17	786	1.67	0.0002
Ventricular arrhythmia	109	0.93	357	0.76	0.0662
Heart failure	2305	19.58	6897	14.65	<0.0001
COPD	3417	29.03	10 142	21.54	<0.0001
Obstructive sleep apnea	116	0.99	369	0.78	0.0303
CKD or ESRD	1168	9.92	2279	4.84	<0.0001
CHA_2DS_2-VASc score† (baseline)	2.67±2.06		2.27±2.05		<0.0001
Death from any cause	2428	20.63	3227	6.85	<0.0001
Outcomes					
NOAF	606	5.15	2045	4.34	0.0002
Total follow-up person-y	182,534.5		769,360.8		
Incidence rate‡ (95% CI)	332.0 (306.6–359.5)		265.8 (254.5–277.6)		
CHA_2DS_2-VASc score (AF)	3.91±1.98		4.01±2.07		0.2838

AF indicates atrial fibrillation; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; ESRD, end-stage renal disease; NOAF, new-onset atrial fibrillation.
*Non–hepatitis C virus (HCV) group was matched by age, sex, income, and urbanization level.
†CHA_2DS_2-VASc score was calculated by summation of point for congestive heart failure (C=1), hypertension (H=1), age (A, age of 65–74 years=1, ≥75 years=2), diabetes mellitus (D=1), stroke/transient ischemic attack/embolic event (S=2), vascular disease (V=1), and sex category (Sc=1 if female) according to baseline characteristics and comorbidities.
‡The unit of incidence rate was 100 000 person-years.

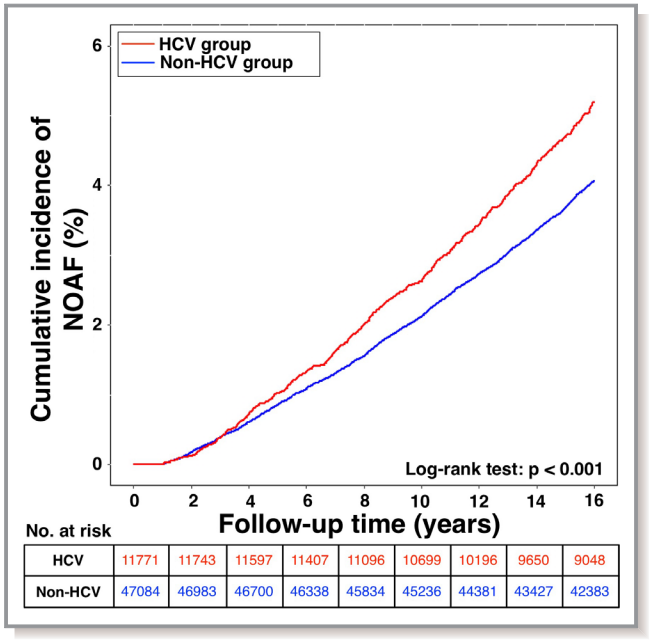

Figure 2. Cumulative incidence of new-onset atrial fibrillation (NOAF) in patients with and without chronic hepatitis C virus (HCV) infection.

group, respectively, and therefore the patients with HCV had an incidence rate ratio of 1.27 for development of NOAF compared with the control group ($P<0.0001$). The patients with NOAF had relatively high CHA_2DS_2-VASc score (AF), but the score did not differ between the HCV and non-HCV groups (Table 1). Furthermore, among the HCV carriers, the mortality rate in the patients with NOAF was 38.3% as compared with 20.6% in patients without NOAF, suggesting that the patients with chronic HCV infection had multiple comorbidities and high mortality regardless of NOAF (Table S1).

Regarding occurrence of AF in relation to time period since diagnosis of HCV infection, results from the Kaplan-Meier curve in Figure 2 demonstrate that the HCV group had significantly higher cumulative incidence of NOAF than the non-HCV group during a mean follow-up period of 15 years ($P<0.001$ with log-rank test). Of note, unadjusted data on Table 2 shows that the patients with HCV treated with antiviral agents had a significantly lower incidence of NOAF compared with those without anti-HCV treatment ($P<0.0001$).

Identification of the Independent Risk Factors for NOAF

As shown in Table 3, the results of Cox regression analysis revealed that chronic HCV infection was significantly associated with NOAF, even after adjustment with the competing risk model for death from any cause. As expected, advanced age, hypertension, ischemic and valvular heart diseases, ventricular arrhythmia, and heart failure were still considered major risk factors for development of NOAF. Our study indicated that the patients with HCV had an ≈1.2-fold increased risk of incidental AF as compared with those without HCV infection. Importantly, the risk of HCV for NOAF remained significant after being adjusted with different models of Cox regression analysis and with competing risk regression model. Furthermore, the influence of HCV on NOAF was highly consistent after being examined with sensitivity analysis in Table 4, suggesting that chronic HCV infection per se, at least in the Asian population, could be identified as an independent risk factor for NOAF.

Table 2. Comparison of NOAF Between Patients With HCV With and Without Antiviral Treatment

Variables	NOAF* (n=606)		No NOAF (n=11 165)		*P* Value*
	No.	%	No.	%	
Anti-HCV treatment (n=2038)	24	1.2	2014	98.8	
No treatment (n=9733)	582	6.0	9151	94.0	<0.0001

**P* value was calculated by comparison of new-onset atrial fibrillation (NOAF) (percentage) between anti–hepatitis C virus (HCV) treatment and no treatment.

Discussion

By using Taiwan's NHIRD to investigate the association between HCV and NOAF, the present study yielded several novel clinical findings. First, chronic HCV infection not only was concomitant with many extrahepatic manifestations but also had a substantially higher incidence and a 1.2 times increased risk of NOAF. Second, CHA_2DS_2-VASc score, which was used for evaluation of disease severity and all-cause mortality, was significantly higher in the HCV than non-HCV group. Finally, we observed that the patients with HCV receiving antiviral therapy had notably lower incident AF compared with those without anti-HCV treatment, suggesting that anti-HCV agents may reduce NOAF in the HCV population through direct antiviral or indirect anti-inflammatory effect.

The most common extrahepatic problems induced by hepatitis C are mixed cryoglobulinemia, an inflammation of small and medium blood vessels[26,27] and atherosclerotic plague formation.[11] In addition, a previous study revealed that these extrahepatic manifestations of hepatitis C appear to be directly related to HCV.[5] The strong association between vascular inflammation and subsequent atherosclerosis, further leading to major adverse cerebrovascular or cardiovascular events and mortality, has been well documented in numerous clinical investigations.[28–31] The present study

Table 3. Utilization of Cox Proportional Hazard Regression and Competing Risk Regression Models to Calculate Risk Factors of NOAF

Model 1*	Univariate Analysis			Competing Risk Model†		
Variables	cHR	95% CI	*P* Value	cHR	95% CI	*P* Value
HCV	1.27	1.16 to 1.39	<0.0001	1.19	1.09 to 1.30	0.0002
Sex						
Female	1.00	Reference		1.00	Reference	
Male	1.08	1.00 to 1.16	0.063	1.06	0.99 to 1.15	0.1176
Age, y						
18 to 65	1.00	Reference		1.00	Reference	
>65	4.91	4.55 to 5.30	<0.0001	4.51	4.18 to 4.87	<0.0001
Comorbidities						
Hypertension	3.09	2.83 to 3.37	<0.0001	3.01	2.76 to 3.28	<0.0001
Diabetes mellitus	1.41	1.30 to 1.53	<0.0001	1.37	1.26 to 1.48	<0.0001
Dyslipidemia	1.00	0.92 to 1.09	0.9566	1.01	0.93 to 1.10	0.7475
Cerebrovascular accident	2.10	1.94 to 2.28	<0.0001	2.03	1.87 to 2.20	<0.0001
Acute coronary syndrome	2.67	2.38 to 2.99	<0.0001	2.56	2.29 to 2.87	<0.0001
Ischemic heart disease	3.97	3.68 to 4.28	<0.0001	3.86	3.57 to 4.16	<0.0001
Peripheral vascular disease	1.61	1.40 to 1.85	<0.0001	1.58	1.38 to 1.82	<0.0001
Valvular heart disease	5.38	4.67 to 6.19	<0.0001	5.23	4.54 to 6.02	<0.0001
Ventricular arrhythmia	3.40	2.66 to 4.35	<0.0001	3.31	2.59 to 4.23	<0.0001
Heart failure	5.34	4.95 to 5.76	<0.0001	5.08	4.71 to 5.49	<0.0001
COPD	2.34	2.16 to 2.53	<0.0001	2.25	2.08 to 2.43	<0.0001
Obstructive sleep apnea	1.08	0.73 to 1.62	0.6984	1.09	0.73 to 1.63	0.6624
CKD or ESRD	1.61	1.40 to 1.85	<0.0001	1.49	1.30 to 1.71	<0.0001
CHA_2DS_2-VASc score (baseline)	1.40	1.38 to 1.43	<0.0001	1.39	1.37 to 1.40	<0.0001
Model 2‡	Multivariate Analysis			Competing Risk Model		
Variables	aHR	95% CI	*P* Value	aHR	95% CI	*P* Value
HCV	1.20	1.09 to 1.31	<0.0001	1.10	1.00 to 1.20	0.0485

aHR indicates adjusted hazard ratio; cHR, crude hazard ratio; CKD, chronic kidney disease; ESRD, end-stage renal disease; HCV, hepatitis C virus

*Model 1 used univariate analysis without adjustment for potential confounder.

†A competing risk model was used to analyze the risk of 2 event types: new-onset atrial fibrillation (NOAF) or death without atrial fibrillation.

‡Model 2 used multivariate analysis by adjusting for age, sex, urbanization, income level, hypertension, diabetes mellitus, dyslipidemia, and chronic obstructive pulmonary disease (COPD).

found not only that the prevalence of atherosclerotic risk factors and concomitant extrahepatic diseases but also that the frequency of major adverse cerebrovascular or cardiovascular events and mortality were significantly higher in the HCV group than in the normal population. Thus, our findings were compatible with previous study results in terms of the atherogenic characteristics of HCV infection. The supposed pathological mechanisms in response to our present observational findings are shown in Figure 3.[32,33]

In this study, we calculated CHA_2DS_2-VASc scores before and after NOAF, mainly according to recent studies showing that CHA_2DS_2-VASc score is not only a risk score to estimate risk of ischemic stroke in an AF population but also could be used to assess severity of arterial and venous thromboembolic events such as myocardial infarction or pulmonary embolism.[34–36] In addition, this scoring system could also be applied reversely to predict NOAF in special populations.[22] Higher prevalence of comorbid diseases in the HCV group resulted in higher baseline CHA_2DS_2-VASc score and subsequently more incidental AF. To clarify the impact of HCV on NOAF, we performed sensitivity analysis by using the main model with additional adjustment for each of the covariates and baseline CHA_2DS_2-VASc score to test whether the risk of HCV infection for NOAF varied with every relevant comorbidity. We found that the results were highly consistent by utilizing either multivariate analysis or competing risk

Table 4. Sensitivity Analysis to Test Risk Consistency of HCV Infection for NOAF With Cox Proportional Hazard Model and Competing Risk Regression Model

	Cox Proportional Hazard Model			Competing Risk Regression Model*		
HCV	aHR	95% CI	*P* Value	aHR	95% CI	*P* Value
Main model†	1.32	1.20 to 1.44	<0.0001	1.20	1.10 to 1.31	0.0001
Additional covariates‡						
Main model+hypertension	1.24	1.13 to 1.36	<0.0001	1.14	1.04 to 1.25	0.0055
Main model+diabetes mellitus	1.31	1.20 to 1.43	<0.0001	1.19	1.09 to 1.31	0.0001
Main model+dyslipidemia	1.32	1.20 to 1.44	<0.0001	1.20	1.10 to 1.31	<0.0001
Main model+cerebrovascular accident	1.30	1.19 to 1.43	<0.0001	1.19	1.09 to 1.30	0.0002
Main model+acute coronary syndrome	1.31	1.20 to 1.43	<0.0001	1.19	1.09 to 1.31	0.0002
Main model+ischemic heart disease	1.22	1.12 to 1.34	<0.0001	1.12	1.03 to 1.23	0.0119
Main model+peripheral vascular disease	1.32	1.20 to 1.44	<0.0001	1.20	1.09 to 1.31	<0.0001
Main model+valvular heart disease	1.29	1.18 to 1.41	<0.0001	1.18	1.08 to 1.29	0.0004
Main model+ventricular arrhythmia	1.31	1.20 to 1.44	<0.0001	1.20	1.09 to 1.31	0.0001
Main model+heart failure	1.21	1.10 to 1.32	<0.0001	1.11	1.01 to 1.21	0.0283
Main model+COPD	1.28	1.17 to 1.40	<0.0001	1.17	1.07 to 1.28	0.0006
Main model+obstructive sleep apnea	1.32	1.20 to 1.44	<0.0001	1.20	1.10 to 1.31	<0.0001
Main model+CKD or ESRD	1.31	1.20 to 1.43	<0.0001	1.20	1.09 to 1.31	<0.0001
Main model+CHA_2DS_2-VASc score	1.19	1.09 to 1.30	0.0002	1.09	1.00 to 1.20	0.0608
Main model+anti-HCV treatment	1.45	1.32 to 1.59	<0.0001	1.30	1.18 to 1.42	<0.0001

aHR indicates adjusted hazard ratio; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; HCV, hepatitis C virus.
*A competing risk model was used to analyze the risk of 2 event types: new-onset atrial fibrillation (NOAF) or death without atrial fibrillation.
†Main model was adjusted for age, sex, urbanization, and income level.
‡The models were adjusted for covariates in the main model as well as each additional listed covariate.

model, confirming that the disease process of HCV or hepatitis virus per se could be associated with an increased risk of NOAF. Furthermore, the present study implied that the patients with chronic HCV infection had more concomitant extrahepatic diseases, linked to high CHA_2DS_2-VASc score (around 2.5 at baseline and 4.0 at the diagnosis of AF), which led to a high rate of stroke or systemic embolic events and consequently resulted in a high all-cause mortality rate. The strong association between HCV and AF reminded clinicians of the importance of routine follow-up of ECG to identify NOAF early for HCV carriers who always express higher disease severity and mortality risk.

In order to broadly discuss the incidence of NOAF in the HCV population and reflect the clinical reality, we did not exclude transient perioperative AF, valvular AF, and hyperthyroidism-related AF in our study. Several studies have demonstrated the relationship of chronic HCV infection with thyroid dysfunction[37,38] and valvular heart disease[32,39] are strong namely based on chronic inflammation and systemic involvement of HCV. In addition, the patients with HCV might receive more medical or surgical intervention,[39,40] because they have more comorbidities and higher mortality rates compared with the general population. To further clarify the risk of NOAF in such a relatively high-risk HCV group, we adopted multivariate regression analysis and sensitivity test to verify the impact of HCV on NOAF. Moreover, CHA_2DS_2-VASc scores before and after diagnosis of NOAF were also used to explore the impact of disease severity on the occurrence of AF.

There were only <20% of patients with HCV who received partial or complete anti-HCV treatment in the current Asian population-based database. However, after antiviral therapy, the incidence rate of NOAF was dramatically reduced from 6% to 1.2%. This interesting observation suggests that the treatment for HCV might be negatively associated with the risk of NOAF. Although the causal relationship between anti-HCV treatment and risk reduction of NOAF cannot be answered in the present study, at least in part, it is rational to treat HCV and control relevant comorbidities as possible. In addition, anti-HCV agents were available in Taiwan since 2004 with self-payment and started to be fully paid by the Health Insurance Bureau since 2016 for the indicated high-risk HCV population. Thus, the number of patients with HCV receiving complete anti-HCV treatment is limited and this phenomenon also causes overestimation of effectiveness of antiviral

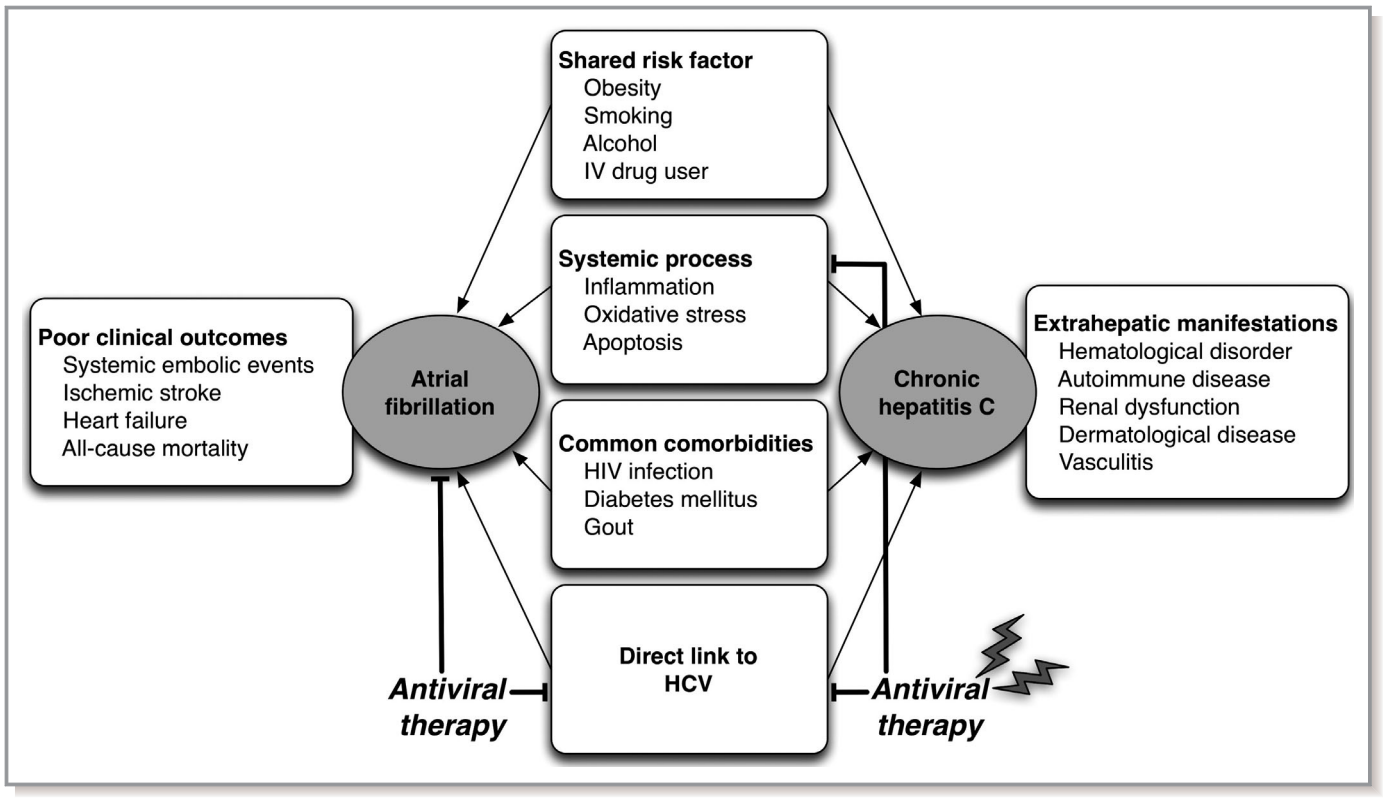

Figure 3. Schematic diagram of the conjectured common pathological mechanisms between atrial fibrillation (AF) and chronic hepatitis C virus (HCV) infection, as well as their relevant comorbidities and clinical presentations. The conceptual illustration is based on present findings and literature reviews.[32,33] IV indicates intravenous.

therapy on prevention of NOAF. Currently, majority of HCV carriers in Taiwan could receive complete antiviral therapeutic course due to popularity and cost-down of anti-HCV drugs. However, we still need more evidence to answer the question regarding whether treatment of HCV can effectively reduce the risk of NOAF. Also, how to lower the risk of cardiovascular comorbidities in chronic HCV infection by using other antiviral, anti-inflammatory, or immunomodulatory drugs deserves further study.

The treatment of AF includes rate/rhythm control, stroke prevention, and management of predisposing factors and underlying diseases.[16] Early identification and appropriate treatment of AF are strongly recommended to further prevent cardioembolic stroke, heart failure, and mortality.[41] Regrettably, many potential agents to treat or control AF, eg, amiodarone, β-blockers, and anticoagulants, are relatively contraindicated in patients with HCV who develop cirrhosis or malignancy[42,43] because many antiarrhythmic and anticoagulant drugs used for AF are metabolized by the cytochrome P450 pathway.[44] Once liver inflammation or dysfunction occurs, the drug's effectiveness is unpredictable with potentially increased adverse effects. The above clinical issue highlights the importance of understanding increased AF risk in the HCV population. Hence, our findings encourage physicians to not only recognize NOAF and treat AF or its associated comorbidities in the early phase but also administer antiviral therapy to reduce the risk of NOAF in the future.

Study Strengths

This is the largest-scale population-based cohort study, to our knowledge, to identify the association between HCV and NOAF in the Asian population. We found that HCV and relevant comorbidities did increase the risk of NOAF and subsequent mortality. In contrast, the risk could be reduced via anti-HCV treatment. Therefore, our study provides useful and practical insights regarding the importance of early identification and timely treatment of NOAF in patients with chronic HCV infection.

Study Limitations

There are several limitations in the cohort study. First, the data were retrospectively analyzed so that we were unable to adjudicate and define some clinical events by reviewing medical charts. Second, detailed personal history and lifestyle information, eg, alcohol consumption and physical activity, are

not provided by Taiwan's NHIRD. Third, all data in the current study have been registered with *ICD-9-CM* codes, and therefore further classification of disease status was impracticable. Fourth, laboratory data are not available in NHIRD. Fifth, we excluded patients with hepatitis B virus infection, so the differences in incidental AF among HCV, hepatitis B virus, and normal populations were not compared. Finally, we did not obtain and analyze medications other than anti-HCV agents from NHIRD that might affect AF-associated outcomes. Over-the-counter and traditional medicines, which are not covered by health insurance, were also unavailable.

Conclusions

The results of this population-based study demonstrated that patients with chronic HCV infection had significantly higher incidental AF and consequently higher mortality than the general population. Regular follow-up of ECG to identify NOAF early in HCV at the clinic is suggested. Furthermore, a well-designed study to clarify the influence of anti-HCV treatment on NOAF is also warranted.

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Disclosures

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SUPPLEMENTAL MATERIAL

Table S1. Sub-analysis for mortality according to NOAF or not between HCV and non-HCV groups.

	HCV group (N=11771)	Non-HCV group (N=47084)
All death	2660 (22.6%)	3689 (7.8%)
Death without NOAF	2428 (20.6%)	3227 (6.9%)
Death with NOAF	232 (2.0%)	462 (1.0%)
NOAF	606 (5.1%)	2045 (4.3%)
Mortality (%) in NOAF	38.3%	22.6%

HCV = hepatitis C virus; NOAF = new-onset atrial fibrillation