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Original article

Risk of cardiac arrhythmias in patients with chronic hepatitis B and C infections – A 13-year nationwide population-based study

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ABSTRACT

Background: Chronic hepatitis C virus (HCV) infection is associated with higher risk of cardiovascular events than chronic hepatitis B virus (HBV). We aimed to investigate whether there is higher risk of arrhythmia in HCV infection.
Methods: Electronic medical records from National Health Institute Research Database during 2000–2012 were retrieved for patients with HBV or HCV. Patients with missing information, aged <18 years, diagnosed with HBV or HCV before year 2000, concomitant HBV and HCV, coagulopathy or organ transplant, history of arrhythmia, device implantation, congenital heart disease, rheumatic heart disease, hypertrophic cardiomyopathy, thyroid disease, alcohol or drug abuse, valvular heart disease, or follow-up <6 months were excluded. Primary outcomes were cardiac arrhythmias and all-cause mortality.
Results: After 1:1 propensity score matching, 5480 patients with HBV and 5480 patients with HCV were included for study. During a mean follow-up of 6.5 years, the risk of all-cause mortality was higher in the HCV patients than in HBV patients [hazard ratio (HR) 1.35, 95% confidence interval (CI) 1.16–1.58]. There was also a trend toward higher incidence of atrial fibrillation (HR 1.25, 95% 0.98–1.59, $p = 0.070$) and a significantly higher incidence of sick sinus syndrome (HR 1.77, 95% CI 1.07–2.91) in HCV patients. In addition, among patients with all-cause mortality, arrhythmia death was significantly higher with chronic HCV infection.
Conclusions: In patients with chronic viral hepatitis, patients with HCV were associated with significantly increased risks of sick sinus syndrome, and all-cause mortality compared to patients with HBV.

Introduction

Infectious disease has long been considered to be capable of causing heart disease and cardiac arrhythmias [1,2]. A wide variety of viral infections have been linked to the development of arrhythmias, such as coxsachievirus, respiratory syncytial virus, herpes simplex virus, influenza virus, hepatitis virus, and human immunodeficiency virus [3–8]. Both atrial and ventricular arrhythmias have been described to be caused by viral infections where no other apparent triggers could be found [9,10]. Coxsachievirus-adenovirus receptor (CAR), a transmembrance protein that functions in the tight junction and is responsible for virus uptake, has been shown that its loss of function is associated with impaired electrical conduction between the atrium and ventricle

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[11–14]. In addition to the conduction defect in the atrioventricular node, CAR knockout mice also exhibited sinus node tachycardia and bradycardia, indicating an additional effect on sinoatrial node (SAN) function [14].

Hepatitis infection has been shown to be associated with cardiovascular events with worse outcome observed in hepatitis C virus (HCV) infection than hepatitis B virus (HBV) infection [15]. A previous study has shown that HCV infection was associated with ventricular dilatation, cardiac dysfunction, and myocardial fibrosis leading to dilated cardiomyopathy, heart failure, and arrhythmia [16]. In this study, we aimed to investigate chronic HBV and HCV infections on risks of development of cardiac arrhythmia in these patients.

Methods

Data source

The National Health Institute (NHI) Program in Taiwan was established in 1995 and provides greater than 99% coverage for the 23 million local residents. The NHI Research Database (NHIRD) provides all dates of inpatient, outpatient, and emergency services. In addition, all records of diagnosis, prescriptions, examinations, operations, and expenditures are updated biannually. With over 95% of Taiwan's population consisting of Han Chinese, our study is considered of homogenous ethnic background. This study was conducted using a subset database of the NHIRD. We used the Longitudinal Health Insurance Database 2000 (LHID 2000) which includes the claims data of 1,000,000 individuals randomly sampled from all population of the NHI program (a total of 23.75 million persons). The Institutional Review Board of Chang Gung Memorial Hospital Linkou Branch approved this study (IRB No. 201800177B1).

Study patients

By searching electronic medical records from the LHID 2000 between January 1, 2000 and December 31, 2012, we retrieved patients with diagnosis of HBV or HCV. The date of diagnosis was defined as the index date. Patients who had missing information, aged less than 18 years old, diagnosed with HBV or HCV before year 2000, had concomitant HBV and HCV, had coagulopathy, or organ transplant were excluded. In addition, patients who had history of arrhythmia (or prescribed with anti-arrhythmia agents), device implantation, congenital heart disease, rheumatic heart disease, hypertrophic cardiomyopathy, thyroid disease, alcohol or drug abuse, valvular heart disease, or follow up less than 180 days were excluded (Fig. 1). The diagnosis of HBV or HCV was based on hepatitis B surface antigen (HBsAg) or serum hepatitis C antibody (anti-HCV) and hepatitis C virus nucleic acid (HCV-RNA) test.

Covariate and study outcomes

Disease was detected using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes. Covariates included gender, age, and clinical medical history of diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease (CAD), chronic kidney disease, stroke, malignancy, heart failure, chronic obstructive pulmonary disease, Charlson comorbidity score, and medications at baseline. The comorbidity was defined as having two outpatient diagnoses or one inpatient diagnosis in the previous year. Most diagnostic codes of these comorbidities have been validated in previous NHIRD studies. Usage of medication was retrieved based on claim data in the previous year.

Outcomes of primary interest included all-cause mortality, supraventricular tachycardia, atrial flutter, atrial fibrillation (AF), ventricular tachycardia, ventricular fibrillation, sick sinus syndrome (SSS), and heart block. All-cause mortality was defined by a withdrawal from the national health insurance. All-cause mortality was checked for the underlying cause whether it was related to cardiac arrhythmia by the diagnosis at outpatient clinic, emergency room, or admission 7 days at or before the date of death. Each patient was followed until the day of outcome occurrence, date of death, or December 31, 2012, whichever came first. The ICD-9-CM disease codes are provided in Supplementary Table 1.

Statistical analysis

There were substantial differences in the clinical characteristics between the HBV and HCV cohorts (left panel in Table 1) and this might induce bias with low comparability when comparing the two groups. To reduce the bias, we performed a propensity score matching to make two groups be comparable. Each patient in the HCV group was matched with a counterpart in the HBV group. The

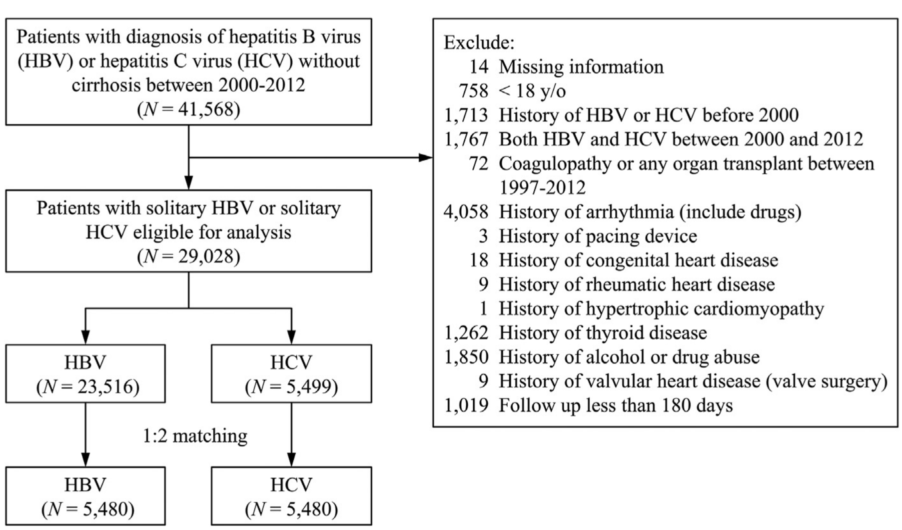

Fig. 1. Study design and screening criteria flow chart for the inclusion of patients with hepatitis B virus (HBV) and hepatitis C virus (HCV) infections.

Table 1
Characteristics of the study patients.

Variable	Before matching			After matching		
	Hepatitis B (n = 23,516)	Hepatitis C (n = 5499)	ASMD	Hepatitis B (n = 5480)	Hepatitis C (n = 5480)	ASMD
Characteristic						
Male	13,888 (59.1)	2715 (49.4)	0.195	2743 (50.1)	2711 (49.5)	0.012
Age (years)	41.2 ± 13.5	52.8 ± 15.1	0.811	52.5 ± 14.5	52.7 ± 15.1	0.015
Age > 65 years	1297 (5.5)	1241 (22.6)	0.506	1141 (20.8)	1224 (22.3)	0.045
Medical history						
Diabetes mellitus	1404 (6.0)	845 (15.4)	0.308	811 (14.8)	835 (15.2)	0.014
Hypertension	2541 (10.8)	1408 (25.6)	0.391	1342 (24.5)	1395 (25.5)	0.026
Hyperlipidemia	1555 (6.6)	545 (9.9)	0.120	548 (10.0)	544 (9.9)	0.003
Coronary artery disease	579 (2.5)	355 (6.5)	0.194	316 (5.8)	348 (6.4)	0.028
Chronic kidney disease	504 (2.1)	362 (6.6)	0.219	304 (5.5)	355 (6.5)	0.046
Stroke	233 (1.0)	199 (3.6)	0.176	151 (2.8)	196 (3.6)	0.055
Malignancy	554 (2.4)	173 (3.1)	0.048	181 (3.3)	173 (3.2)	0.009
Heart failure	45 (0.2)	63 (1.1)	0.117	35 (0.6)	61 (1.1)	0.058
Chronic obstructive pulmonary disease	421 (1.8)	285 (5.2)	0.186	236 (4.3)	280 (5.1)	0.044
Charlson comorbidity score	0.7 ± 1.2	1.4 ± 1.6	0.474	1.3 ± 1.8	1.3 ± 1.6	0.039
Medication at baseline						
ACEi/ARB	1414 (6.0)	751 (13.7)	0.259	719 (13.1)	747 (13.6)	0.017
Beta blockers	1216 (5.2)	608 (11.1)	0.217	597 (10.9)	602 (11.0)	0.003
Dihydropyridine CCB	1470 (6.3)	892 (16.2)	0.320	818 (14.9)	883 (16.1)	0.038
Statins	626 (2.7)	269 (4.9)	0.117	263 (4.8)	267 (4.9)	0.004
Diuretics	396 (1.7)	259 (4.7)	0.173	232 (4.2)	252 (4.6)	0.021
Oral hypoglycemic agent	1081 (4.6)	635 (11.5)	0.257	605 (11.0)	628 (11.5)	0.016
Follow-up (years)	7.1 ± 3.5	6.7 ± 3.6	0.093	6.3 ± 3.5	6.7 ± 3.6	0.113

ASMD, absolute standardized mean difference; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

propensity score was the predicted probability to be HCV group derived from logistic regression given the values of covariates. The covariates were demographics (sex and age), 9 comorbidities and CCI score, 6 medications at baseline (listed in Table 1), and the index date. The matching was processed using a greedy nearest neighbor algorithm with a caliper of 0.2 times of the standard deviation of the logit of propensity score. The quality of matching was assessed using the absolute standardized mean difference (ASMD) between the 2 groups after matching where a value less than 0.1 was considered to have negligible difference.

We compared the risk of all-cause mortality between the 2 groups using Cox proportional hazard model. The risk of non-fatal outcomes (arrhythmia events listed in Table 2) between the 2 groups was compared using the Fine and Gray's subdistribution hazard model which considered death during the follow up as a competing risk. The study group (HCV vs. HBV) was the only explanatory variable in both Cox and Fine and Gray's models. We generated the plot of cumulative incidence rates using subdistribution hazard function for non-fatal outcomes. As to all-cause mortality, we plotted unadjusted event rates. A two-sided p-value <0.05 was considered to be statistically significant. No adjustment of multiple testing (multiplicity) was made in this study. All statistical analyses were performed using commercial software (SAS 9.4, SAS Institute, Cary, NC, USA), including procedure of '*psmatch*' for propensity score matching, '*phreg*' for survival analysis, and the macro of '*%cif*' for cumulative incidence function.

Results

Study population

There were 41,568 patients with the diagnosis of HBV or HCV and without cirrhosis during 2000 and 2012 identified in the LHID 2000. After excluding patients <18 years old and aforementioned clinical criteria, there were 29,028 patients with HBV or HCV. The cohort comprised 23,516 (80.6%) solitary HBV patients and 5499 (19.4%) solitary HCV patients. After 1:1 propensity score matching, remaining 5480 patients with HBV and 5480 patients with HCV were included for study (Fig. 1). Before matching, HBV patients were male predominant, younger, had lower prevalence of all comorbidities except malignancy, and were less likely to be prescribed with medications (all ASMD ≥ 0.1). After matching, the distribution of baseline characteristics, medical history, and medications was well-balanced between the HBV and HCV groups (all ASMD < 0.1, as right panel in Table 1).

Table 2
Mortality and arrhythmia events during the follow up.

Outcome	Number of events (%)		Hepatitis C vs. Hepatitis B	
	Hepatitis B (n = 5480)	Hepatitis C (n = 5480)	HR (95% CI)[a]	p-Value
All-cause mortality	446 (8.1)	631 (11.5)	1.35 (1.16–1.58)	<0.001
Supraventricular tachycardia	44 (0.80)	40 (0.73)	0.83 (0.56–1.22)	0.334
Atrial flutter	5 (0.09)	7 (0.13)	0.50 (0.14–1.77)	0.283
Atrial fibrillation	94 (1.72)	123 (2.24)	1.25 (0.98–1.59)	0.070
Ventricular tachycardia	11 (0.20)	14 (0.26)	1.33 (0.63–2.84)	0.456
Ventricular fibrillation	6 (0.11)	4 (0.07)	0.50 (0.14–1.77)	0.283
Sick sinus syndrome	17 (0.31)	33 (0.60)	1.77 (1.07–2.91)	0.025
Heart block	33 (0.60)	42 (0.77)	1.17 (0.79–1.72)	0.435

CI, confidence interval; HR, hazard ratio.
[a] Estimated using Fine and Gray's subdistribution hazard model which considered all-cause mortality as a competing risk.

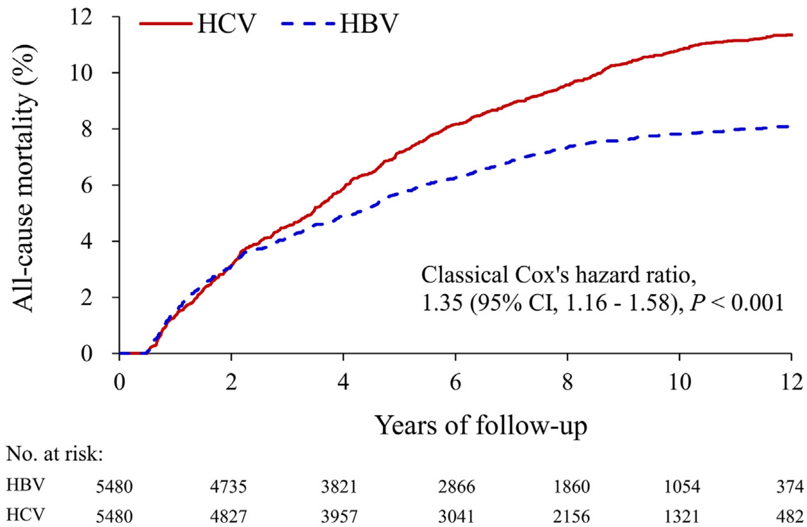

Fig. 2. All-cause mortality in patients with chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. Using Cox proportional hazard model, the patients with HCV showed a significantly higher risk compared to patients with HBV ($p < 0.001$).

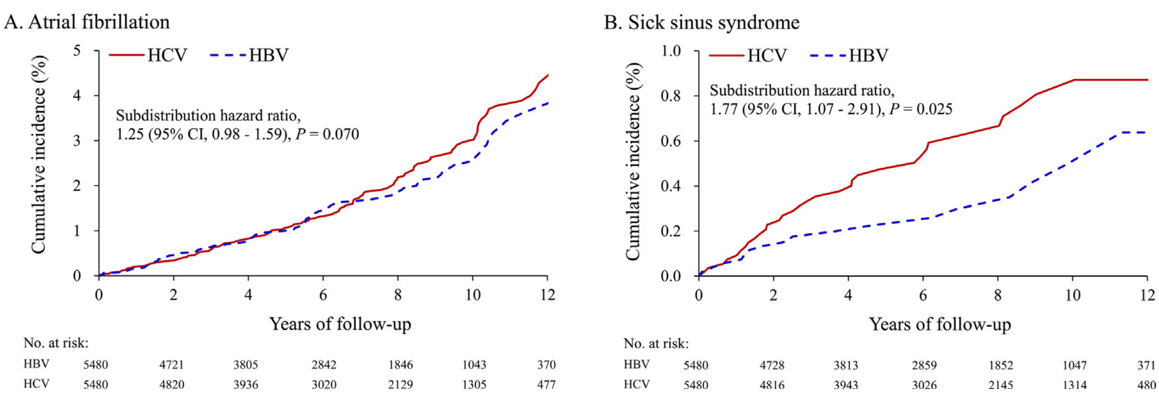

Fig. 3. Cumulative incidence function of atrial fibrillation (A) and sick sinus syndrome (B) in patients with chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. The incidence of sick sinus syndrome was higher in patients with chronic HCV infections than patients with chronic HBV infections.

Mortality and arrhythmia events during follow up

As shown in Table 2, higher risks of all-cause mortality were observed in the HCV patients than in the HBV patients [hazard ratio (HR) 1.35, 95% confidence interval (CI) 1.16–1.58] (Fig. 2). There was no difference in supraventricular tachycardia, atrial flutter, ventricular tachycardia, ventricular fibrillation, and heart blocks between the two groups. There was however, a trend toward higher incidence of atrial fibrillation (HR 1.25, 95% 0.98–1.59, $p = 0.070$) in patients with HCV (Fig. 3A). In addition, the HCV patients had significantly higher incidence of sick sinus syndrome (HR 1.77, 95% CI 1.07–2.91) (Fig. 3B) with higher tendency of implantation of pacemaker (HR 1.83, 95% CI 0.88–3.82) (Supplementary Table 2). All-cause mortality was checked for association with cardiac arrhythmia and chronic HCV infection had significantly higher arrhythmia death compared to chronic HBV infection (Table 3).

Subgroup analysis of primary outcomes

The subgroup analysis of cardiac arrhythmia-related outcomes included atrial fibrillation (Fig. 4A) and SSS (Fig. 4B). The observed increased risks of HCV infection (compared to HBV infection) on atrial fibrillation or SSS were not significantly different across levels of gender, age, comorbidities of diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, chronic kidney disease, stroke, and chronic obstructive pulmonary disease.

Table 3
All-cause mortality secondary to cardiac arrhythmia.

Outcome	Number of events (%)		Hepatitis C vs. Hepatitis B	
	Hepatitis B ($n = 5480$)	Hepatitis C ($n = 5480$)	HR (95% CI)	*p*-Value
Arrhythmia death[a]	29 (0.53)	48 (0.88)	1.93 (1.01–3.68)	0.046

[a] Arrhythmia death diagnosed at outpatient clinic, emergency room, or admission; CI, confidence interval; HR, hazard ratio.

Discussion

Previous studies

The occurrence of cardiac arrhythmia secondary to viral infections was not infrequently observed. Cardiac manifestation of HCV infection was localized myocardial lesion with thickening

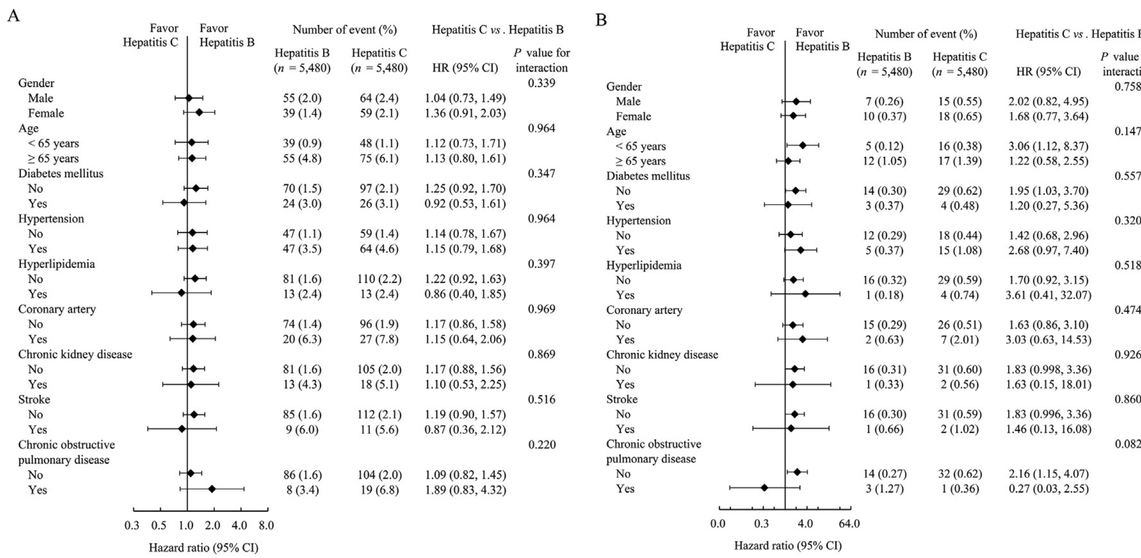

Fig. 4. Subgroup analysis of atrial fibrillation (A) and sick sinus syndrome (B) in patients with chronic hepatitis B virus and hepatitis C virus infections.

or thinning of ventricular wall, leading to development of hypertrophic cardiomyopathy or dilated cardiomyopathy [7]. In a Japanese study, an initial analysis of 31 patients with cardiomyopathy and myocarditis reported 6 patients had HCV RNA found by polymerase chain reaction in the heart of 6 patients (19.4%) [17]. Over a 10-year study period, 19 among 191 patients with dilated cardiomyopathy had evidence of HCV infection (9.9%) with initial presentation of heart failure and arrhythmia [7]. In a recent US report of a case–control study using administration data from Veterans Health Administration, an increased risk of incident AF was found in patients with HCV compared to controls, and the hazard ratio of newly diagnosed AF was 1.42 times higher in patients with HCV [18]. In addition, the presentations of hypotension, bradycardia, and sinus arrest during the acute phase of viral hepatitis have been documented, and may require the implantation of a pacemaker for treatment [19].

Sinus node dysfunction (SND) and atrial arrhythmias were frequently found to associate with each other and thereby coexist, interact, initiate, and perpetuate each other [20]. Atrial arrhythmias are present in 40–70% patients with SND and high frequency of atrial depolarizations may in turn exacerbate SND [20]. The time course of SND progression is accompanied by bradycardia, sinoatrial block, or sinus arrest extending over years, with the development of supraventricular arrhythmias of which AF is the most common. In patients who underwent catheter ablation for symptomatic paroxysmal AF, regional atrial remodeling near sinus node area of right atrium was associated with SND [20]. The mechanisms thought to be involved in the pathophysiology common to AF and SND were atrial myopathy, atrial stretch, atrial remodeling, and atrial inflammation [20].

Current study

In this study, there was an increased all-cause mortality risk in chronic HCV infection compared to chronic HBV infection, which has also been reported in a previous study [15]. Regarding inflammation of the vascular system secondary to chronic hepatitis infection, it has been reported that the increased atherosclerosis lead to increased composite outcomes of acute coronary syndrome, acute ischemic stroke, and peripheral artery disease events [15]. And in this current investigation, we specifically examined whether the inflammation of the cardiovascular system caused by chronic HBV and HCV infections would also affect the heart itself demonstrated by cardiac arrhythmias.

Concerning atrial and ventricular arrhythmia including SND and heart blocks, our results showed significantly higher risks of SSS in patients with chronic HCV infection compared with patients with chronic HBV infection. In addition, there was a higher tendency of implantation of pacemaker in patients with chronic HCV infection, although this did not reach statistical significance. Risk of developing AF was higher in patients with HCV compared with patients with HBV, although not significantly. Our subgroup analyses showed that there was no difference across gender, age, and comorbidities for which chronic HCV infection carried higher risks of atrial fibrillation and SSS than chronic HBV infection. These results could be attributed to higher inflammatory activity level caused by chronic HCV infection, compared with chronic HBV infection.

The relationship between SND and AF has been validated previously with detailed electrophysiological mapping performed in patients with SND showing a diffuse atrial myopathy predates the development of clinical AF [20]. In addition, bradycardia or low heart rate itself may also facilitate the development of AF through increased likelihood of atrial ectopy. On the other hand, it is well-documented that rapid atrial pacing or atrial arrhythmia results in SND. In human studies, even short duration of pacing or paroxysmal episodes of AF is associated with sinus node remodeling, reduced sinus node reserve, or SND [20]. Our study showed higher number of diagnosed AF and SSS in patients with chronic HCV infection compared to patients with chronic HBV infection, although only SSS reached statistical difference. Exactly how SND occurred before AF or if AF caused SND could be difficult to discern, although it could be suggested the larger number of AF may predate and triggered SND in chronic hepatitis infection. In addition, the chronic viral hepatitis-related inflammatory activity could be affecting the whole heart where SND or ventricular standstill could result. In our study, there were significantly higher risks of all-cause death secondary to arrhythmia death in patients with chronic HCV infections compared to patients with chronic HBV infection.

In summary, this is the first study to report the type of cardiac arrhythmias that developed in patients with chronic HBV and HCV infections. Compared to patients with chronic HBV infection, patients with chronic HCV infection were associated with a trend toward higher AF, and significantly increased risks of SSS and all-cause mortality.

Limitations

There are several limitations in epidemiologic data from NHIRD. First, using ICD-9-CM codes for patient screening and enrollment may miss some cases for which conditions were coded incorrectly. Second, the exact sequence of AF and SSS could not be determined in this insurance-based national cohort study. Third, the claim-based National Health Institute Research Database (NHIRD) has data whether aspartate transaminase (AST) or alanine transaminase (ALT) was checked for particular patients but does not have the data of level of AST/ALT. Fourth, one of the major outcomes, arrhythmia death, was not widely reported and validated in previous studies. Last, since our study consisted of nearly homogenous racial background, application of the results to other populations requires further studies.

Conclusion

In patients with chronic viral hepatitis, patients with HCV infection were associated with significantly increased risks of SSS and all-cause mortality compared to patients with HBV infection.

Funding

None.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2019.03.009.

References

[1] Abelmann WH. Virus and the heart. Circulation 1971;44:950–6.
[2] Salerno F, Girerd N, Chalabreysse L, Billaud G, Lina B, Chevalier P. Myocarditis and cardiac channelopathies: a deadly association? Int J Cardiol 2011;147:468–70.
[3] Stinke K, Sachse F, Ettischer N, Strutz-Seebohm N, Henrion U, Rohrbeck M, et al. Coxsachievirus B3 modulates cardiac ion channels. FASEB J 2013;27:4108–21.
[4] Ivey KS, Edwards KM, Talbot HK. Respiratory syncytial virus and associations with cardiovascular disease in adults. J Am Coll Cardiol 2018;71:1574–83.
[5] Chiang CH, Huang CC, Chan WL, Huang PH, Chen YC, Chen TJ, et al. Herpes simplex virus infection and risk of atrial fibrillation: a nationwide study. Int J Cardiol 2013;164:201–4.
[6] Chang TY, Chao TF, Liu CJ, Chen SJ, Chung FP, Liao JN, et al. The association between influenza infection, vaccination, and atrial fibrillation: a nationwide case–control study. Heart Rhythm 2016;13:1189–94.
[7] Matsumori A. Hepatitis C virus infection and cardiomyopathies. Circ Res 2005;96:144–7.
[8] Hsu JC, Li Y, Marcus GM, Hsue PY, Scherzer R, Grunfeld C, et al. Atrial fibrillation and atrial flutter in human immunodeficiency virus-infected persons: incidence, risk factors, and association with markers of HIV disease severity. J Am Coll Cardiol 2013;61:2288–95.
[9] Sanders JM, Steverson AB, Pawlowski AE, Schneider D, Achenbach CJ, Lloyd-Jones DM, et al. Atrial arrhythmia prevalence and characteristics for human immunodeficiency virus-infected persons and matched uninfected controls. PLoS ONE 2018;13:e0194754.
[10] Huang M, Bigos D, Levine M. Ventricular arrhythmia associated with respiratory syncytial viral infection. Pediatr Cardiol 1998;19:498–500.
[11] Cohen CJ, Shieh JT, Pickles RJ, Okegawa T, Hsieh JT, Bergelson JM. The coxsackievirus and adenovirus receptor is a transmembrane component of the tight junction. Proc Natl Acad Sci U S A 2001;98:15191–96.
[12] Bergelson JM, Cunningham JA, Droguett G, Kurt-Jones EA, Krithivas A, Hong JS, et al. Isolation of a common receptor for coxsackie B viruses and adenoviruses 2 and 5. Science 1997;275:1320–3.
[13] Tomko RP, Xu R, Philipson L. HCAR and MCAR: the human and mouse cellular receptors for subgroup C adenoviruses and group B coxsackieviruses. Proc Natl Acad Sci U S A 1997;94:3352–6.
[14] Lisewski U, Shi Y, Wrackmeyer U, Fischer R, Chen C, Schirdewan A, et al. The tight junction protein CAR regulates cardiac conduction and cell–cell communication. J Exp Med 2008;205:2369–79.
[15] Wu VC, Chen TH, Wu M, Chen SW, Chang CW, Chen CC, et al. Comparison of cardiovascular outcomes and all-cause mortality in patients with chronic hepatitis B and C: a 13-year nationwide population-based study in Asia. Atherosclerosis 2018;269:178–84.
[16] Omura T, Yoshiyama M, Hayashi T, Nishiguchi S, Kaito M, Horiike S, et al. Core protein of hepatitis C virus induces cardiomyopathy. Circ Res 2005;96:148–50.
[17] Matsumori A, Mabota Y, Sasayama S. Dilated cardiomyopathy associated with hepatitis C virus infection. Circulation 1995;92:2519–25.
[18] Bhave P, Kabra R, Sarrazin MV. Association of hepatitis C infection and incident atrial fibrillation. Circulation 2016;134:A11217.
[19] Gordon SC, Patel AS, Veneri RJ, Keskey KA, Korotkin SM. Acute type A hepatitis presenting with hypotension, bradycardia, and sinus arrest. J Med Virol 1989;28:219–22.
[20] John RM, Kumar S. Sinus node and atrial arrhythmias. Circulation 2016;133:1892–900.