Effects of Hepatitis C Virus Antibody-Positivity on Cardiac Function and Long-Term Prognosis in Patients With Adult Congenital Heart Disease

Ryo Konno, MD[a], Shunsuke Tatebe, MD, PhD[a,*], Koichiro Sugimura, MD, PhD[a], Kimio Satoh, MD, PhD[a], Tatsuo Aoki, MD, PhD[a], Masanobu Miura, MD, PhD[a], Saori Yamamoto, MD, PhD[a], Haruka Sato, MD, PhD[a], Katsuya Kozu, MD, PhD[a], Yosuke Terui, MD[a], Satoshi Miyata, PhD[b], Osamu Adachi, MD, PhD[c], Masato Kimura, MD, PhD[d], Yoshikatsu Saiki, MD, PhD[c], and Hiroaki Shimokawa, MD, PhD[a,b]

It was reported that hepatitis C virus (HCV) antibody-positivity adversely affects cardiac function. As the screening for HCV began in 1992, we hypothesized that HCV antibody-positive rate would be high in adult congenital heart disease (ACHD) patients who underwent heart surgery before 1992 and adversely affected cardiac function and long-term prognosis. We retrospectively enrolled 243 ACHD patients (mean age 25.9 years) who underwent cardiac surgery before 1992 and visited our hospital from 1995 to 2015. We compared clinical characteristics including cardiac function and long-term prognosis between HCV antibody-positive (n = 48) and antibody-negative (n = 195) patients. The composite end point (CEP) included cardiac death, heart failure hospitalization, lethal ventricular arrhythmias, and cardiac reoperation. The prevalence of reduced systemic ventricular ejection fraction <50% was significantly higher in the HCV antibody-positive group compared with the HCV antibody-negative group (17 vs 5.4%, p = 0.014). During a mean follow-up period of 10.1 years (interquartile range 6 to 14 years), the CEP was noted in 51 patients. Kaplan-Meier analysis showed the HCV antibody-positive group had significantly poor event-free survival than the HCV antibody-negative group (log-rank, p = 0.002). In contrast, HCV ribonucleic acid-positivity was not a significant predictor of the CEP in the HCV antibody-positive group (log-rank, p = 0.442). Furthermore, the HCV antibody-positivity was significantly associated with the CEP in both univariable and multivariable Cox regression models (hazard ratio 2.37, 95% confident interval 1.32 to 4.15, p = 0.005 and 1.96, 1.06 to 3.63, p = 0.032, respectively). In conclusion, these results suggest that more attention should be paid to HCV antibody-positivity in the management of ACHD patients. **(Am J Cardiol 2018;122:1965−1971)**

With the progress of treatment in congenital heart disease (CHD), the number of patients with adult congenital heart disease (ACHD) has been increasing worldwide.[1] Epidemiological evidence showed that these patients are not cured and at high risk of cardiovascular morbidity and mortality.[2−5] However, risk factors are not completely elucidated. Patients with CHD often need blood transfusion when they undergo cardiac surgery, in which hepatitis C virus (HCV) can be transmitted. As the screening for HCV began in 1992, it was reported that ACHD patients who underwent congenital cardiac surgery before 1992 had a fivefold higher prevalence of HCV infection than the age-matched general population.[6] HCV antibody-positivity was also reported to be associated with impaired cardiac function[7,8] and poor survival after heart transplantation.[9] In the present study, we thus tested our hypothesis that HCV antibody-positivity would adversely affect cardiac function and long-term prognosis in ACHD patients who underwent cardiac surgery before 1992, by conducting a retrospective cohort study with our AHCD database in the Tohoku University Hospital.

Methods

The study protocol was in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethics Committee of the Tohoku University Graduate School of Medicine. Informed consent was obtained by the opt-out method.

[a]Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan; [b]Department of Evidence-Based Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan; [c]Department of Cardiovascular Surgery, Tohoku University Graduate School of Medicine, Sendai, Japan; and [d]Department of Pediatrics, Tohoku University Graduate School of Medicine, Sendai, Japan. Manuscript received June 28, 2018; revised manuscript received and accepted August 21, 2018.

This research was supported by the Practical Research Project for Life-Style-related Diseases including Cardiovascular Diseases and Diabetes Mellitus from Japan Agency for Medical Research and development, AMED (JP16ek0210068).

See page 1971 for disclosure information.

*Corresponding author: Tel: +81-22-717-7153; fax: +81-22-717-7156.
E-mail address: shuntatebe@cardio.med.tohoku.ac.jp (S. Tatebe).

0002-9149/
https://doi.org/10.1016/j.amjcard.2018.08.045

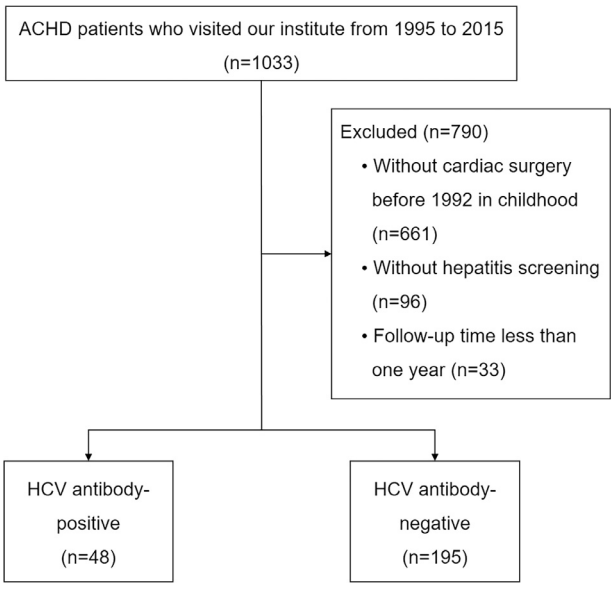

Figure 1. Study population diagram. Of the 1,033 AHCD patients who visited Tohoku University Hospital during 1995 to 2015, 372 patients underwent cardiac surgery in childhood before 1992. After excluding the patients without hepatitis screening or follow-up time of more than 1 year, 243 patients were finally analyzed in the present study. ACHD = adult congenital heart disease; HCV = Hepatitis C virus.

A total of 1,033 ACHD patients aged over 18 years visited our hospital from 1995 to 2015. In them, 372 patients underwent cardiac surgery before 1992. Patients with unknown HCV antibody status (n = 96) or follow-up time of less than 1 year (n = 33) were excluded. Finally, 243 ACHD patients (48% men, mean age 25.9 ± 9.0 years) were enrolled in the present study (Figure 1).

Baseline data were obtained from the patients at the first follow-up visit between 1995 and 2015. We reviewed medical records regarding age, gender, diagnosis of CHD, New York Heart Association (NYHA) functional class, cardiac function, HCV antibody status, HCV ribonucleic acid (RNA) status, liver function, anemia, and other clinical characteristics. Anemia was defined as hemoglobin concentration <13.0 g/dl for men and <12.0 g/dl for women. Dyslipidemia was defined based on the criteria of the Japan Atherosclerosis Society (LDL-C ≥ 140 mg/dl and/or HDL-C <40mg/dl and/or triglycerides ≥ 150 mg/dl).[10] Liver cirrhosis was defined based on clinical, laboratory, and imaging findings. Systemic ventricular ejection fraction (SVEF) and subpulmonary ventricular (SPV) function were evaluated by echocardiography or magnetic resonance imaging. SPV dysfunction was defined as SPV ejection fraction ≤45% or SPV fractional area change ≤35%. Valvular disease was defined as moderate or severe valvular stenosis or regurgitation on echocardiography. Pulmonary hypertension was defined as mean pulmonary artery pressure ≥25 mm Hg on right heart catheterization or estimated SPV systolic pressure ≥40 mm Hg on echocardiography. The complexity of CHD was assigned according to the Bethesda classification.[11]

The composite end point (CEP) included cardiac death, HF hospitalization, lethal ventricular arrhythmias, and cardiac reoperation. Lethal ventricular arrhythmias were defined as composite arrhythmic events, including ventricular fibrillation and sustained ventricular tachycardia. Hospitalization for HF was defined as an unplanned hospitalization due to worsening HF signs and symptoms of NYHA class III/IV. We retrospectively observed the patients until the occurrence of the CEP or the end of 2016.

Continuous variables are expressed as the mean ± standard deviation and were assessed by the Student *t* test or Wilcoxon rank-sum test as appropriate. Categorical variables are expressed as proportions and were analyzed by Fisher exact test. We performed logistic regression analysis for variables associated with SVEF <50%. We also performed multiple logistic regression analysis using a forward stepwise method with variables entered if p value was less than 0.2 on univariable analysis. CEP-free curves were estimated by the Kaplan-Meier method and compared between HCV antibody-positive and -negative groups by using the log-rank test. To assess the association of baseline variables with the CEP, univariable, and multivariable Cox proportional hazards regression analyses were performed. In the multivariable models, we selected the variables by using a forward stepwise method with variables entered if p value was less than 0.2 on univariable analysis. Event rate of the CEP and its each component were compared between HCV antibody-positive and -negative groups using the Wald method. The CART survival analysis was also performed to identify subgroups at risk for CEP. Patients were divided into 3 groups according to their age based on the CART survival analysis; 18 to 26 years, 27 to 40 years, and over 40 years.

Data were considered to be statistically significant at $p < 0.05$. All statistical analyses were performed using JMP Pro 13.0.0 (SAS Institute Inc., Cary, North Carolina) and R version 3.3.2 (The R Project for Statistical Computing; https://www.r-project.org/).

Results

The most common diagnosis of CHD was tetralogy of Fallot, followed by ventricular septal defect and complete transposition of great arteries (Table 1). HCV antibody-positivity was detected in 48 patients (20%). Of these, HCV

Table 1
Diagnoses of congenital heart disease

Diagnosis	n (%)
Tetralogy of Fallot	74 (30%)
Ventricular septal defect	42 (17%)
Complete transposition of the great arteries	19 (7.8%)
Atrial septal defect	17 (7.0%)
Pulmonary atresia	14 (5.8%)
Aortic coarctation	11 (4.5%)
Atrioventricular septal defect	11 (4.5%)
Tricuspid atresia	8 (3.3%)
Double outlet right ventricle	8 (3.3%)
Congenitally corrected transposition of the great arteries	8 (3.3%)
Single ventricle	6 (2.5%)
Patent ductus arteriosus	3 (1.2%)
Ebstein disease	3 (1.2%)
Valvular disease	6 (2.5%)
Others	13 (5.3%)
All patients	243

Table 2
Baseline characteristics of the study population

Variable	HCV Antibody		p value
	Positive (n = 48)	Negative (n = 195)	
Age (years)	28.5 ± 10.2	25.2 ± 8.6	0.029
18 to 26	25 (52%)	131 (67%)	0.064
27 to 40	14 (29%)	49 (25%)	0.584
≥ 41	9 (19%)	15 (7.7%)	0.030
Men	29 (60%)	88 (45%)	0.076
Congenital heart disease complexity			
Simple	13 (27%)	52 (27%)	1.000
Moderate	23 (48%)	85 (44%)	0.628
Great	12 (25%)	58 (30%)	0.596
New York Heart Association functional class ≥ II	29 (60%)	86 (44%)	0.053
Heart reoperation in adulthood	8 (17%)	21 (11%)	0.318
Systemic right ventricle	5 (10%)	14 (7.2%)	0.547
Fontan circulation	3 (6.3%)	13 (6.7%)	1.000
Eisenmenger syndrome	0 (0%)	2 (1.0%)	1.000
Pacemaker implantation in childhood	2 (4.2%)	11 (5.6%)	1.000
Hypertension	0 (0%)	6 (3.2%)	0.604
Dyslipidemia	2 (4.2%)	2 (1.1%)	0.185
Diabetes mellitus	1 (2.1%)	5 (2.7%)	1.000
Liver cirrhosis	2 (4.2%)	3 (1.5%)	0.257
Serum creatinine >1.0 mg/dL	0/48 (0%)	4/188 (2.1%)	0.585
Total bilirubin >1.0 mg/dL	18/48 (38%)	44/175 (25%)	0.103
γ-glutamyltranspeptidase >50 IU/L	16/47 (34%)	31/176 (18%)	0.025
Aspartate aminotransferase >40 IU/L	13/48 (27%)	8/177 (4.5%)	<0.001
Alanine aminotransferase >40 IU/L	14/48 (29%)	11/179 (6.2%)	<0.001
Anemia	6/48 (13%)	27/179 (15%)	0.820
Serum albumin <3.5 g/dL	3/48 (6.3%)	9/177 (5.1%)	0.722
Platelet count <150,000/μL	16/48 (33%)	24/179 (13%)	0.003
Echocardiography			
Systemic ventricular ejection fraction	65.8 ± 13.6	68.8 ± 11.9	0.123
<50%	8/47 (17%)	10/184 (5.4%)	0.014
<40%	1/47 (2.1%)	6/184 (3.3%)	1.000
Subpulmonary ventricular dysfunction	3/41 (7.3%)	15/164 (9.2%)	1.000
Valvular disease	17/47 (36%)	54/182 (30%)	0.383
Pulmonary hypertension	8/46 (17%)	25/181 (14%)	0.639

Continuous variables and categorical variables are expressed as mean ± SD and number (percentage), respectively.

RNA-positivity was detected in 26 patients and was unknown in 5 patients. HCV genotype was determined in 20 patients, including genotype 1 in 16 and genotype 2 in 4. Baseline characteristics were shown in Table 2. Compared with the HCV antibody-negative group, the HCV antibody-positive group had significantly higher age and higher prevalence of SVEF<50% (Table 2). The prevalence of advanced NYHA functional class (≥ II) tended to be higher in the HCV antibody-positive group. The HCV antibody-positive group also had significantly higher prevalence of increased aspartate aminotransferase, alanine aminotransferase, and γ-glutamyl transpeptidase, and decreased platelet count (Table 2). There were no significant differences in the severity of CHD, the prevalence of heart reoperation in adulthood, Fontan patients, systemic right ventricle, pacemaker implantation (PMI) in childhood, anemia, renal dysfunction, SPV dysfunction, valvular disease or pulmonary hypertension between the 2 groups (Table 2). In both groups, few patients had liver cirrhosis or metabolic disorders including hypertension, dyslipidemia, and diabetes.

In univariable logistic regression analysis, factors correlating with SVEF <50% were HCV antibody positivity, age group of over 40 years, and PMI in childhood (Table 3A). Multivariable analysis revealed that HCV antibody-positivity, age group of over 40 years, and PMI in childhood were independent predictors for SVEF <50% (Table 3B). In contrast, regarding HCV RNA positivity, there were no significant differences in SVEF or SPV function between the HCV RNA-positive and the HCV RNA-negative group (Table 4). No significant differences were also noted in the prevalence of SVEF <50% (13% vs 50%, p = 0.178) and SPV dysfunction (0% vs 25%, p = 0.267) between the genotype 1 and genotype 2 groups.

During the mean follow-up period of 10.1 ± 5.4 years (interquartile range 6 to 14 years), CEP was noted in 51 (21%) patients, including cardiac reoperation in 25, HF hospitalization in 18, cardiovascular death in 4, and lethal ventricular arrhythmias in 4. The incidence rate of the CEP was significantly higher in the HCV antibody-positive group compared with the HCV antibody-negative group (3.9 vs 1.6%/year, p = 0.002; Figure 2). The incidence rate

Table 3
Results of logistic regression analysis for variables associated with systemic ventricular ejection fraction <50%

A. Univariable analysis

Variable	OR (95% CI)	p value
Hepatitis C virus antibody-positivity	3.57 (1.32−9.63)	0.012
Age (years)		
18 to 26	Ref	
27 to 40	0.50 (0.11−2.40)	0.390
≥41	6.22 (2.05−18.9)	0.001
Congenital heart disease complexity		
Simple	Ref	
Moderate	0.80 (0.22−2.97)	0.744
Great	1.74 (0.50−6.10)	0.378
Heart reoperations in adulthood	1.44 (0.39−5.31)	0.585
Systemic right ventricle	0.64 (0.08−5.07)	0.670
Fontan circulation	1.92 (0.40−9.27)	0.415
Pacemaker implantation in childhood	4.06 (1.01−16.3)	0.049

B. Multivariable analysis

Variable	OR (95% CI)	p value
Hepatitis C virus antibody-positivity	3.09 (1.06−9.04)	0.040
Age ≥41 years	8.09 (2.54−25.8)	<0.001
Pacemaker implantation in childhood	7.70 (1.71−34.8)	0.008

Association of systemic ventricular ejection fraction and Hepatitis C virus positivity, adjusted for age and pacemaker implantation in childhood (model p <0.001).

CI = confidence interval; OR = odds ratio; Ref = reference.

of each component of the CEP between the 2 groups was also analyzed. A cardiac reoperation occurred more frequently in the HCV antibody-positive group compared with the HCV antibody-negative group (2.2 vs 0.7%/year, p = 0.003; Figure 2). In contrast, there were no significant differences in cardiac death (0.20 vs 0.15%/year), HF hospitalization (1.2 vs 0.6%/year), and lethal ventricular arrhythmias (0.20 vs 0.15%/year).

Kaplan-Meier survival curve analysis for the CEP is shown in Figure 3. The HCV antibody-positive group had significantly poor event-free survival compared with the HCV antibody-negative group (log-rank, p = 0.002). The overall estimated 5 and 10-year event-free survival rates were 78% and 74% for the HCV antibody-positive group, and 92% and 85% for the HCV antibody-negative group, respectively (Figure 3). Interestingly, HCV RNA-positivity was not a significant predictor of the CEP in the HCV antibody-positive group (log-rank, p = 0.442; Figure 3). The CEP-free survival was also comparable between the genotype 1 and genotype 2 groups (log-rank, p = 0.358).

Univariable Cox proportional hazard analysis revealed that 9 risk factors were significantly associated with the CEP, including HCV positivity, age group of 27 to 40 years, age group of over 40 years, NYHA functional class ≥II, a history of heart reoperation in adulthood, SVEF <50%, SPV dysfunction, valvular disease, and pulmonary hypertension (Table 5A). Multivariable Cox analysis demonstrated that HCV antibody-positivity was an independent predictor of the CEP even after adjustment of age, group of 27 to 40 years, age group of over 40 years, NYHA functional class ≥II, and pulmonary hypertension (Table 5B).

Table 4
Comparison of cardiac function between Hepatitis C virus ribonucleic acid positive and negative patients

Variable	HCV RNA		p value
	Positive (n = 26)	Negative (n = 17)	
Systemic ventricular ejection fraction			
Mean	66.0 ± 13.8	65.9 ± 12.8	0.929
<50%	4/25 (16%)	3/17 (18%)	1.000
Subpulmonary ventricular dysfunction	1/21 (4.8%)	2/15 (13%)	0.559

Continuous variables and categorical variables are expressed as mean ± SD and number (percentage), respectively.

HCV = Hepatitis C virus; RNA = ribonucleic acid.

Discussion

In the present study, we demonstrated that ACHD patients who underwent cardiac surgery before 1992 had higher HCV antibody-positive rate and that HCV antibody-positivity was significantly associated with both SV dysfunction and poor long-term prognosis. To the best of our knowledge, this is the first report that identifies HCV antibody-positivity as a novel risk factor for SV dysfunction and long-term prognosis in ACHD patients.

The previous studies reported a high prevalence of HCV antibody-positivity in patients who had a history of cardiac surgery for CHD before blood screening (8.6% to 14.6%).[6,12] Our findings are consistent with these reports and demonstrate that HCV antibody-positive rate was as high as 20% (48/243 patients). Thus, all ACHD patients who underwent cardiac surgery before 1992 are at high risk for HCV infection and recommended to have HCV screening.[13]

The prevalence of patients with SVEF <50% was higher in the HCV antibody-positive group (Table 2). Matsumori et al reported that the presence of HCV antibody was significantly higher in patients with dilated cardiomyopathy than in those with ischemic heart disease (16.7 vs 2.5%, respectively).[14] El-Waseef et al reported that HCV antibody-positive group had significantly impaired left ventricular systolic function compared with HCV antibody-negative group in multitransfused children.[15] HCV positivity was also reported to be associated with left ventricular diastolic dysfunction,[16] increased NT-pro-BNP,[17] and HF development.[18] The relation between HCV infection and several cardiovascular diseases, such as carotid atherosclerosis, coronary artery disease, myocarditis, idiopathic dilated cardiomyopathy, and hypertrophic cardiomyopathy were reported.[19] Taken together, our findings suggest that HCV antibody-positivity has an additional role in the progression of SV dysfunction in ACHD patients, although major contributing factors for cardiac function after repair of CHD are underlying diagnosis, myocardial injury during cardiac surgery, and residuals and sequelae after surgery.[20,21] Possible contributing mechanisms for myocardial injury of HCV infection include metabolic and atherogenic alteration, chronic inflammation, endothelial dysfunction, direct

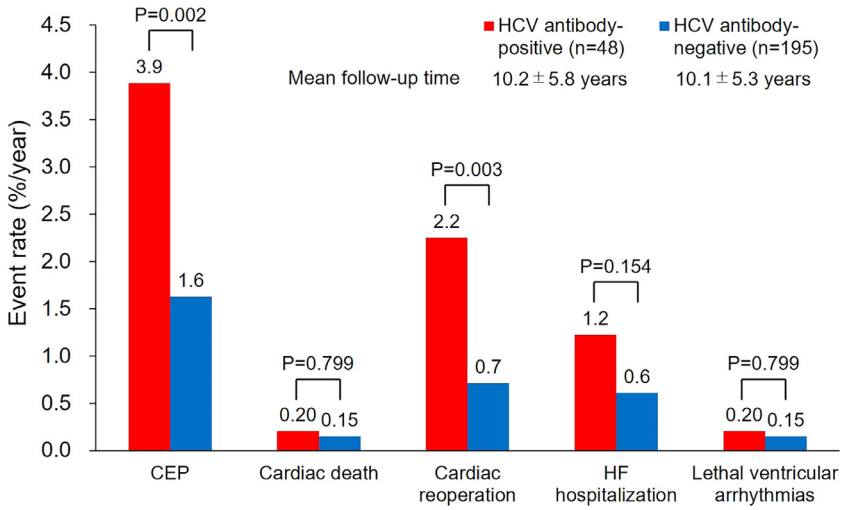

Figure 2. Comparison of event rate between the HCV antibody-positive and -negative groups. During the mean follow-up time of 10.1 (5.4) years, the CEP was noted in 51 (21%) patients. The incidence rate of the CEP was significantly higher in the HCV antibody-positive group compared with the HCV antibody-negative group (3.9 vs 1.6%/year, p = 0.002). A cardiac reoperation was performed more frequently in the HCV antibody-positive group than in the HCV antibody-negative group (2.2 vs 0.7%/year, p = 0.003). CEP = composite end point; HCV = hepatitis C virus; HF = heart failure.

viral infection of the arterial wall, and genetic and/or environmental factors.[22]

The prevalence rate of HCV RNA-positivity in our study was similar to that reported by Vogt et al (both 55%).[12] Unlike HCV antibody-positivity, HCV RNA-positivity was not a determinant factor for SV dysfunction or poor long-term survival (Figure. 3, Table 4). Interestingly, the previous study showed that HCV RNA was detected in the myocardial tissue of hypertrophic cardiomyopathy patients but not in their serum.[23] HCV RNA was found in serum in 3 out of 7 patients with ischemic heart disease, who had HCV RNA-positive carotid plaque.[24] These findings may support the notion that HCV replicates in myocardial tissue and cause an active local infection of the heart, which exerts SV dysfunction. Thus, serum HCV RNA status alone may not be a risk marker for SV dysfunction or poor long-term survival. HCV RNA test should be performed in all ACHD patients with HCV antibody-positivity because HCV treatment may have a beneficial impact on the clinical outcome in HCV RNA-positive patients.

The prevalence of SPV dysfunction was comparable between the HCV antibody-positive and negative groups (Table 2). This finding is in contrast with the previous report that HCV antibody positivity was associated with SPV dysfunction in patients without CHD.[8] A possible explanation of this discrepancy might be the differences in the definition of SPV dysfunction and study population.

The previous report suggested that cardiovascular mortality increased in patients with HCV.[25] The present study demonstrates that HCV antibody-positivity was a significant predictor of the CEP in ACHD patients who underwent heart surgery before 1992 (Figure 3, Table 5A, B). This was

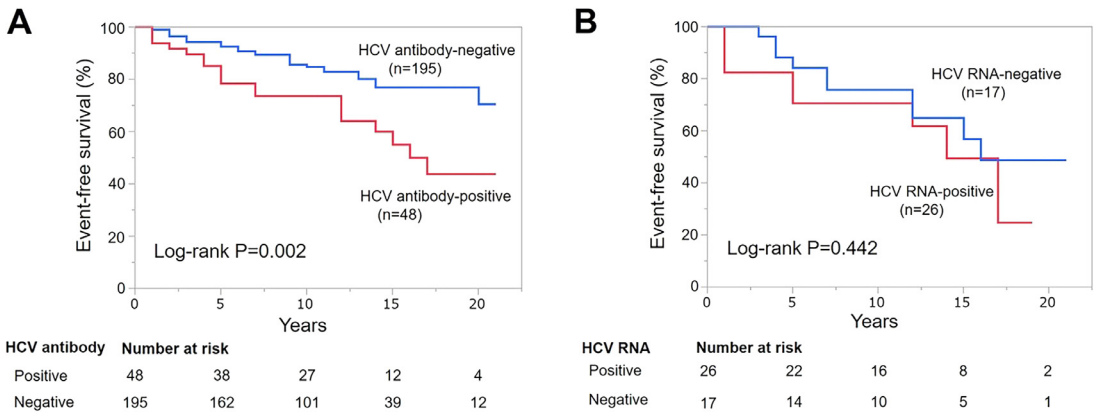

Figure 3. Kaplan-Meier analysis of freedom from the composite end point. (*A*) Kaplan-Meier curves for all ACHD patients (n = 243) according to HCV antibody status. The HCV antibody-positive group showed significantly poor event-free survival compared with the HCV antibody-negative group (log-rank, p = 0.002). (*B*) Kaplan-Meier curves for a subgroup of HCV antibody-positive ACHD patients who had HCV RNA test (n = 43) stratified by HCV RNA status. Event-free survival was not significantly different between the HCV RNA-positive and -negative groups (log-rank, p = 0.442). ACHD = adult congenital heart disease; HCV = hepatitis C virus; RNA = ribonucleic acid.

Table 5
Univariable and multivariable Cox proportional hazards regression analysis for prediction of the composite end point

A. Univariable analysis

Variable	HR (95% CI)	p value
Hepatitis C virus antibody-positivity	2.37 (1.32−4.15)	0.005
Age (years)		
18 to 26	Ref	
27 to 40	3.48 (1.90−6.47)	<0.001
≥41	3.99 (1.72−8.60)	0.002
Congenital heart disease complexity		
Simple	Ref	
Moderate	1.33 (0.66−2.91)	0.441
Great	1.19 (0.54−2.74)	0.675
New York Heart Association functional class ≥ II	3.06 (1.69−5.85)	<0.001
Heart reoperations in adulthood	2.43 (1.22−4.50)	0.014
Systemic right ventricle	0.99 (0.34−2.27)	0.987
Fontan circulation	1.15 (0.35−2.83)	0.792
Pacemaker implantation in childhood	0.93 (0.23−2.54)	0.904
Serum creatinine >1.0 mg/dL	4.60 (0.74−15.2)	0.089
Anemia	0.84 (0.32−1.82)	0.678
Serum albumin <3.5 g/dl	1.14 (0.28−3.11)	0.828
Echocardiography		
Systemic ventricular ejection fraction <50%	8.36 (4.05−16.3)	<0.001
Subpulmonary ventricular dysfunction	2.81 (1.22−5.73)	0.018
Valvular disease	2.23 (1.28−3.86)	0.005
Pulmonary hypertension	2.10 (1.05−3.89)	0.037

B. Multivariable analysis

Variable	HR (95% CI)	P Value
Hepatitis C virus antibody-positivity	1.95 (1.05−3.61)	0.034
Age (years)		
27 to 40	3.03 (1.58−5.80)	<0.001
≥41	2.63 (1.11−6.26)	0.028
New York Heart Association functional class ≥ II	2.46 (1.24−4.90)	0.010
Heart reoperations in adulthood	1.93 (0.96−3.91)	0.067
Pulmonary hypertension	2.11 (1.06−4.18)	0.033

Association of the composite endpoint and Hepatitis C virus antibody-positivity, adjusted for age, New York Heart Association functional class, a history of heart reoperation in adulthood, and pulmonary hypertension (model p <0.001).

CI = confidence interval; HR = hazard ratio; Ref = reference.

mainly due to a higher incidence of cardiac reoperation in the HCV antibody-positive group (Figure 2). Considering the association between HCV antibody-positivity and SV dysfunction, we assume that HCV infection was involved in the development of adverse events late after repair of CHD through SV dysfunction. Thus, more attention should be paid to HCV antibody-positivity in the follow-up management of ACHD patients.

The HCV antibody-positive group had significantly higher liver enzymes and lower platelet count compared with the HCV antibody-negative group (Table 2). This indicates that liver injury was more common in HCV antibody-positive patients. However, the prevalence of severe liver injury and cirrhosis were low in both groups. Thus, we consider that liver injury was not directly involved in the pathogenesis of SV dysfunction or poor prognosis of our patients.

Several limitations should be mentioned for the present study. First, the present study was a single-center retrospective study and included selected ACHD patients who underwent repair of CHD before 1992 and visited our institute from 1995 to 2000. The number of patients analyzed was relatively small and the cohort consisted of patients with a wide variety of CHD. Thus, the present results may not be generalized to all ACHD populations. Second, there were missing data because of retrospective nature of chart review. In the majority of cases, we were unable to obtain detailed information about risks of HCV infection, not only blood transfusion but also risks regarding occupation, comorbidities, and lifestyle. Thus, the exact time of HCV infection was unknown for most patients. However, we consider that the likelihood of HCV infection unrelated to blood transfusion was very low in the present population. Third, we did not evaluate BNP levels or diastolic function in the present study. Finally, the lack of endomyocardial biopsy makes it impossible to verify HCV RNA in the myocardium as the chronic HCV infection and the cause for SV dysfunction in our patients. Further studies are needed to clarify whether newer HCV treatments can prevent SV dysfunction and improve long-term outcomes in ACHD patients with HCV RNA-positivity.

In conclusion, we were able to demonstrate that HCV antibody-positive rate was very high in ACHD patients

who underwent cardiac surgery before 1992 and that HCV antibody-positivity was significantly associated with both SV dysfunction and poor prognosis in those patients. These results indicate that screening for HCV should be performed in all ACHD patients with a history of heart surgery before 1992. Further, cardiac functions should be monitored more frequently to detect SV dysfunction earlier in case of a positive result. These management strategies may have a beneficial impact on the long-term prognosis of in this population.

Disclosures

The authors have no conflicts of interest to disclose.

Acknowledgment

The authors would like to thank the staff of the Departments of Cardiovascular Medicine, Cardiovascular Surgery, and Pediatrics at the Tohoku University Hospital for their valuable contributions.

1. Mulder BJM. Epidemiology of adult congenital heart disease: demographic variations worldwide. *Neth Heart J* 2012;20:505–508.
2. Verheugt CL, Uiterwaal CS, van der Velde ET, Meijboom FJ, Pieper PG, van Dijk AP, Vliegen HW, Grobbee DE, Mulder BJ. Mortality in adult congenital heart disease. *Eur Heart J* 2010;31: 1220–1229.
3. Diller GP, Kempny A, Alonso-Gonzalez R, Swan L, Uebing A, Li W, Babu-Narayan S, Wort SJ, Dimopoulos K, Gatzoulis MA. Survival prospects and circumstances of death in contemporary adult congenital heart disease patients under follow-up at a large tertiary centre. *Circulation* 2015;132:2118–2125.
4. Engelings CC, Helm PC, Abdul-Khaliq H, Asfour B, Bauer UMM, Baumgartner H, Kececioglu D, Körten M-A, Diller G-P, Tutarel O. Cause of death in adults with congenital heart disease—an analysis of the German National Register for congenital heart defects. *Int J Cardiol* 2016;211:31–36.
5. Naidu P, Grigg L, Zentner D. Mortality in adults with congenital heart disease. *Int J Cardiol* 2017;245:125–130.
6. Wang A, Book WM, McConnell M, Lyle T, Rodby K, Mahle WT. Prevalence of hepatitis C infection in adult patients who underwent congenital heart surgery prior to screening in 1992. *Am J Cardiol* 2007;100:1307–1309.
7. Demir M, Demir C. Effect of hepatitis C virus infection on the left ventricular systolic and diastolic functions. *South Med J* 2011;104: 543–546.
8. Demir C, Demir M. Effect of hepatitis C virus infection on the right ventricular functions, pulmonary arterypressure and pulmonary vascular resistance. *Int J Clin Exp Med* 2014;7:2314–2318.
9. Kumar S, Deo SV, Altarabsheh SE, Dunlay SM, Sarabu N, Sareyyupoglu B, Elgudin Y, Medalion B, ElAmm C, Ginwalla M, Zacharias M, Benatti R, Oliveira GH, Kilic A, Fonarow GC, Park SJ. Effect of hepatitis C positivity on survival in adult patients undergoing heart transplantation (from the United Network for Organ Sharing Database). *Am J Cardiol* 2016;118:132–137.
10. Teramoto T, Sasaki J, Ishibashi S, Birou S, Daida H, Dohi S, Egusa G, Hiro T, Hirobe K, Iida M, Kihara S, Kinoshita M, Maruyama C, Ohta T, Okamura T, Yamashita S, Yokode M, Yokote K. Diagnostic criteria for dyslipidemia. *J Atheroscler Thromb* 2013;20:655–660.
11. Warnes CA, Liberthson R, Danielson GK, Dore A, Harris L, Hoffman JI, Somerville J, Williams RG, Webb GD. Task force 1: the changing profile of congenital heart disease in adult life. *J Am Coll Cardiol* 2001;37:1170–1175.
12. Vogt M, Lang T, Frosner G, Klingler C, Sendl AF, Zeller A, Wiebecke B, Langer B, Meisner H, Hess J. Prevalence and clinical outcome of hepatitis C infection in children who underwent cardiac surgery before the implementation of blood-donor screening. *N Engl J Med* 1999;341:866–870.
13. Bhatt AB, Foster E, Kuehl K, Alpert J, Brabeck S, Crumb S, Davidson WR Jr., Earing MG, Ghoshhajra BB, Karamlou T, Mital S, Ting J, Tseng ZH. American Heart Association Council on Clinical C. Congenital heart disease in the older adult: a scientific statement from the American Heart Association. *Circulation* 2015;131:1884–1931.
14. Matsumori A, Matoba Y, Sasayama S. Dilated cardiomyopathy associated with hepatitis C virus infection. *Circulation* 1995;92:2519–2525.
15. El-Waseef MM, Taha S, Elgindi H. Left ventricular diastolic abnormalities and the impact of hepatitis C virus infection in multitransfused Egyptian children. *Arch Med Sci* 2010;6:96–99.
16. Che W, Liu W, Wei Y, Xu Y, Hou L, Matsumori A, Hu D. Increased serum N-terminal pro-B-type natriuretic peptide and left ventricle diastolic dysfunction in patients with hepatitis C virus infection. *J Viral Hepat* 2012;19:327–331.
17. Antonelli A, Ferri C, Ferrari SM, Marchi S, De Bortoli N, Sansonno D, Chiavacci C, Ferrannini E, Fallahi P. N-terminal pro-brain natriuretic peptide and tumor necrosis factor-alpha both are increased in patients with Hepatitis C. *J Interferon Cytokine Res* 2010;30:359–363.
18. Tsui JI, Whooley MA, Monto A, Seal K, Tien PC, Shlipak M. Association of hepatitis C virus seropositivity with inflammatory markers and heart failure in persons with coronary heart disease: data from the Heart and Soul study. *J Card Fail* 2009;15:451–456.
19. Petta S. Hepatitis C virus and cardiovascular: a review. *J Adv Res* 2017;8:161–168.
20. Budts W, Roos-Hesselink J, Rädle-Hurst T, Eicken A, McDonagh TA, Lambrinou E, Crespo-Leiro MG, Walker F, Frogoudaki AA. Treatment of heart failure in adult congenital heart disease: a position paper of the Working Group of Grown-Up Congenital Heart Disease and the Heart Failure Association of the European Society of Cardiology. *Eur Heart J* 2016;37:1419–1427.
21. Warnes CA. The adult with congenital heart disease: born to be bad. *J Am Coll Cardiol* 2005;46:1–8.
22. Negro F. Facts and fictions of HCV and comorbidities: steatosis, diabetes mellitus, and cardiovascular diseases. *J Hepatol* 2014;61: S69–S78.
23. Matsumori A, Matoba Y, Nishio R, Shioi T, Ono K, Sasayama S. Detection of hepatitis C virus RNA from the heart of patients with hypertrophic cardiomyopathy. *Biochem Biophys Res Commun* 1996;222:678–682.
24. Boddi M, Abbate R, Chellini B, Giusti B, Giannini C, Pratesi G, Rossi L, Pratesi C, Gensini GF, Paperetti L, Zignego AL. Hepatitis C virus RNA localization in human carotid plaques. *J Clin Virol* 2010;47:72–75.
25. Petta S, Maida M, Macaluso FS, Barbara M, Licata A, Craxi A, Camma C. Hepatitis C virus infection is associated with increased cardiovascular mortality: a meta-analysis of observational studies. *Gastroenterology* 2016;150:145–155.