AP&T Alimentary Pharmacology and Therapeutics

Associations of chronic hepatitis C with metabolic and cardiac outcomes

Z. M. Younossi*,†, M. Stepanova*, F. Nader*, Z. Younossi† & E. Elsheikh*

*Center for Liver Diseases, Department of Medicine, Inova Fairfax Hospital, Falls Church, VA, USA.
†Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, VA, USA.

Correspondence to:
Dr Z. M. Younossi, Betty and Guy Beatty Center for Integrated Research, Claude Moore Health Education and Research Building, 3300 Gallows Road, Falls Church, VA 22042, USA.
E-mail: zobair.younossi@inova.org

Publication data
Submitted 15 October 2012
First decision 20 November 2012
Resubmitted 7 January 2013
Accepted 14 January 2013
EV Pub Online 5 February 2013

SUMMARY

Background
Chronic hepatitis C virus (CH-C) infection is associated with metabolic conditions such as insulin resistance and type 2 diabetes (DM) and may increase the risk of cardiovascular diseases.

Aim
To assess the association of CH-C with risk factors for cardiovascular diseases using US population data.

Methods
The National Health and Nutrition Examination Surveys (NHANES) collected between 1999 and 2010 were used.

Results
Of 19 741 participants considered eligible for the study, 173 individuals (0.88%) had detectable HCV RNA and were considered to have CH-C. Compared with controls, CH-C patients were predominantly African American (23.5% vs. 10.5%, $P < 0.0001$), men (66.6% vs. 46.1%, $P = 0.0001$), more likely to be between 45 and 55 years of age (41.9% vs. 20.4%, $P = 0.0001$), had higher rate of insulin resistance (44.1% vs. 31.1%, $P = 0.0301$), hypertension (40.1% vs. 28.9%, $P = 0.0201$), and history of smoking (76.2% vs. 29.9%, $P < 0.0001$). In multivariate analysis, in addition to known risk factors for insulin resistance, CH-C was independently associated with the presence of insulin resistance [OR (95% CI) = 2.06 (1.19–3.57)], DM [OR = 2.31 (1.18–4.54)] and hypertension [OR = 2.06 (1.30–3.24)]. Independent predictors of cardiovascular diseases included older age, presence of obesity and smoking. CH-C was independently associated with congestive heart failure subtype of cardiovascular diseases but not ischaemic heart disease and stroke.

Conclusion
Chronic hepatitis C virus infection is independently associated with presence of metabolic conditions (insulin resistance, type 2 diabetes mellitus and hypertension) and congestive heart failure.

Aliment Pharmacol Ther 2013; **37:** 647–652

doi:10.1111/apt.12234

INTRODUCTION

Hepatitis C virus (HCV) is the most common cause of cirrhosis and hepatocellular carcinoma in the United States.[1, 2] In addition, HCV is associated with a number of important extrahepatic manifestations.[3] Of these, there is increasing evidence that HCV infection increases the risk for type 2 diabetes (DM) and insulin resistance (IR). In fact, previous data indicated that in individuals older than 39 years of age, HCV infection increases the risk of DM by almost 4 times.[4] In addition, in longitudinal studies, development of DM has been reported to be 11 times more common in those infected with HCV than those who were not.[5] Although the association of HCV with DM has been confirmed, its underlying mechanism remains unknown. Some of these mechanisms include direct interaction of HCV proteins with the hepatocyte insulin signalling cascade[6–8] or impairment of pancreatic β-cell function.[9] In addition, recent evidence suggests involvement of the striated muscle in the pathogenesis of IR in patients with CH-C.[10]

The consequences of IR and DM in HCV-infected patients can be divided into those that affect liver disease outcomes and those affecting nonliver related outcomes.[11] HCV patients with DM or IR tend to have more advanced hepatic fibrosis, hepatocellular carcinoma and lower efficacy of treatment regimens.[12] In addition to metabolic conditions (DM and IR), HCV has also been associated with arthrosclerosis and coronary artery disease.[13–15] Although HCV and its contribution to DM and IR can explain some of these associations, the exact underlying mechanism of how CH-C can predispose to cardiovascular complications remains unknown. The aim of this study was to assess the independent association of HCV with metabolic conditions (DM, IR, hypertension and hyperlipdaemia) as well as cardiovascular complications using a large population-representative sample.

METHODS

Study sample

Our study uses the data derived from the National Health and Nutrition Examination Survey (NHANES), a nationwide survey that represents the health and nutritional status of the of the non-institutionalised civilian US population. The data were collected by the US National Center for Health Statistics (NCHS) with the Centers for Disease Control and Prevention (CDC), and it is currently publicly available. Detailed description of NHANES study design and methods are available elsewhere.[16] For the purpose of the study, we used six cycles of continuous NHANES collected between 1999 and 2010. These surveys were based on similar questionnaires and similar methods for serum and blood assays.

The NHANES participants were included in the study if they were age of 18 years or older, had complete demographic and relevant clinical data including HCV serologic tests and completed questionnaires with history of cardiovascular diseases. Additional data used in the study included body mass index (BMI), waist circumference and blood pressure which were measured at the time of examination by the NHANES representatives for all eligible participants. The data from a number of questionnaires and laboratory tests were also used for our study, namely, alcohol consumption and smoking history, fasting serum glucose and insulin, HDL cholesterol, LDL cholesterol and total cholesterol, AST, ALT, transferrin saturation and serologic tests for HBV (hepatitis B surface antigen, or HBsAg) and HCV (anti-HCV by ELISA followed by HCV RNA by PCR for HCV positive or indeterminate samples). Participants with insufficient data for ruling in HCV infection or ruling out chronic liver disease were excluded from the study.

Study definitions

Definitions for metabolic conditions used in the study have been previously described.[17] Briefly, insulin resistance was defined as HOMA score greater than 3.0, type II diabetes was defined as fasting blood glucose of greater than 125 mg/dL or the use of hypoglycaemic agents, and hypertension was defined as blood pressure (average of four readings) of greater than 140/90 mmHg or the use of antihypertensive medications. Furthermore, obesity (BMI $\geq$ 30.0) and visceral obesity (waist circumference greater than 102 cm in men or 88 cm in women) were also evaluated for all eligible participants.

The history of cardiovascular disease was established using a medical conditions questionnaire where NHANES participants were asked about a number of chronic conditions and if they were ever diagnosed by a healthcare provider. For the purpose of the study, ischaemic heart disease (IHD) was defined as self-reported history of coronary artery disease or heart attack. Furthermore, the history of stroke and congestive heart failure was also collected for eligible participants, and these two conditions together with IHD, as defined above, were used to establish the diagnosis of cardiovascular diseases (CVD).

Smoking was defined as ongoing smoking (a question SMQ040 'Do you now smoke cigarettes?' answered either 'Every day' or 'Some days') and given a total number of cigarettes smoked in life exceeds one hundred. The data

Aliment Pharmacol Ther 2013; 37: 647-652

were collected from the Smoking and Tobacco Use questionnaire during NHANES data collection.

Chronic HCV infection

All sera from NHANES participants were tested for antibody to hepatitis C virus (anti-HCV). Sera testing positive for anti-HCV were tested further for HCV RNA. Participants with positive HCV RNA were considered to have chronic hepatitis C (CH-C). On the other hand, individuals without any evidence of chronic liver disease such as excessive alcohol consumption (defined as self-reported consumption of >20 g/day for at least a year for men, and >10 g/day for women), elevated aminotransferases (ALT > 40 U/L or AST > 37 U/L for men, AST and ALT > 31 U/L for women), elevated transferrin saturation (>50%), HBV infection (positive HBsAg) were presumed not to have chronic liver disease and were further used as controls. Patients with presumed non-alcoholic fatty liver disease (elevated liver enzymes with no evidence of other liver diseases or excessive alcohol consumption), were also excluded. Participants with data insufficient to rule-in HCV infection or rule-out CLD were excluded from the study.

Statistical analysis

The prevalence of various clinical parameters, including CVD, its subtypes and metabolic conditions, was compared between those with and without HCV infection using the stratum-specific chi-squared test for independence. Furthermore, logistic regression was used to identify independent predictors of CVD and its risk factor while adjusting for potential clinical and demographic confounders. P value <0.05 was selected to identify potentially statistically significant associations.

For the purpose of the study, all sampling errors were calculated by Taylor linearisation. Sampling weights calculated for each NHANES participant were used to account for nonresponse and unequal selection probabilities, so, after weighing, the study cohort is designed to be representative of the US population. Furthermore, stratification and sampling units that describe the design stages of the NHANES data collection were used to account for the complex, multi-stage probability sample design of these data. According to the NHANES Analytic and Reporting Guidelines,[16] when merging several analytic cycles, adjustment coefficients were applied to all sampling weights. All analyses were run using standalone SUDAAN 10.0 (SAS Institute Inc., Cary, NC, USA). The study was granted an exemption from full review by Inova Institutional Review Board (VA, USA).

RESULTS

From NHANES 1999–2010, 19 741 individuals were considered eligible for the study. Of the study cohort, 173 (0.88%) individuals tested positive for HCV RNA and were presumed to have CH-C, and 19 568 had no evidence of chronic liver disease and, therefore, were used as controls.

The results of pairwise comparison of the CH-C cohort to controls without liver disease are summarised in Table 1. Expectedly, individuals with hepatitis C were less likely to be Caucasian (62.0% vs. 72.5%, $P = 0.0202$) and more likely to be African American (23.5% vs. 10.5%, $P < 0.0001$), predominantly men (66.6% vs. 46.1%, $P = 0.0001$), more likely to be between 45 and 55 years of age (41.9% vs. 20.4%, $P = 0.0001$) and less likely to be older than 65 (3.70% vs. 14.5%, $P < 0.0001$). Of the metabolic conditions known to be associated with increased cardiac risks, insulin resistance and hypertension were observed significantly more frequently in those with CH-C (44.1% vs. 31.1%, $P = 0.0301$ and 40.1% vs. 28.9%, $P = 0.0201$ respectively) (Table 1). The rate of smoking in the CH-C cohort was also significantly higher (76.2% vs. 29.8%, $P < 0.0001$).

Older age is known to be a major contributor to the risk of cardiovascular disease. At the same time, the CH-C cohort was found to be significantly younger than average for the population: only 3.70% of those actively infected with HCV were 65 years old or older, compared to 14.46% in controls ($P < 0.0001$). To better separate the

Table 1 | Comparison of CH-C cohort and controls without chronic liver disease

	CH-C	Controls	P
Caucasian, %	62.04 ± 4.91	72.55 ± 1.59	0.0202
African American, %	23.51 ± 3.66	10.50 ± 0.86	<0.0001
Non-Mexican Hispanic, %	4.78 ± 1.98	4.96 ± 0.67	0.9192
Mexican American, %	6.66 ± 1.85	7.01 ± 0.73	0.8472
Male, %	66.58 ± 4.56	46.06 ± 0.37	0.0001
Age <45, %	43.72 ± 5.68	51.91 ± 0.76	0.1408
Age 45–55, %	41.89 ± 5.42	20.40 ± 0.51	0.0001
Age 55–65, %	10.70 ± 2.13	13.23 ± 0.42	0.2582
Age >65, %	3.70 ± 1.61	14.46 ± 0.43	<0.0001
Obesity, %	22.95 ± 4.20	29.97 ± 0.62	0.1147
Visceral obesity, %	47.11 ± 4.88	48.53 ± 0.73	0.7788
Insulin resistance, %	44.10 ± 5.87	31.13 ± 0.86	0.0301
Type II diabetes, %	12.66 ± 3.50	7.36 ± 0.26	0.1354
Hypercholesterolaemia, %	58.08 ± 5.20	66.96 ± 0.59	0.1079
Hypertension, %	40.09 ± 4.76	28.91 ± 0.60	0.0201
Excessive alcohol, %	6.50 ± 2.49	8.38 ± 0.32	0.4465
Smoking, %	76.23 ± 4.92	29.85 ± 0.80	<0.0001

impact of age to the risk of CVD from that of CH-C, we evaluated the association of CH-C and CVD in different age groups separately (Table 2). A significantly higher rate of congestive heart failure (CHF) in HCV-infected individuals was found for those of 64 years of age or younger: 3.84 ± 1.50% vs. 0.89 ± 0.08% in controls of the same age, $P = 0.0467$. Other cardiovascular diseases were not different between those with and without HCV in all studied age groups (data not shown). Furthermore, since the rate of smoking, was found to be significantly higher in those with CH-C, we also studied smoking and nonsmoking CH-C cohorts separately. In these two separate rounds of analysis, no association of CH-C with CVD or its subtypes was found as well (all $P > 0.05$, data not shown).

Independent predictors of metabolic conditions and cardiovascular diseases

In multivariate analysis, after adjustment for other major contributors metabolic conditions such as older age, obesity and non-Caucasian race or ethnicity, CH-C was found to be independently associated with type II diabetes [OR (95% CI) = 2.90 (1.35–6.19)], hypertension [OR = 2.01 (1.18–3.41)] and insulin resistance [OR = 2.20 (1.16–4.17)] (Table 3), and similar associations were observed when smoking and nonsmoking cohorts were studied separately (data not shown).

In multivariate analysis, CH-C was also independently associated with congestive heart failure [OR (95% CI) = 2.49 (1.04–5.96)] after controlling for age, obesity and smoking. No other independent association between CH-C and overall CVD diagnosis or other subtypes of CVD (IHD and Stroke) could be established (Table 4).

Table 2 | Cardiovascular diseases and CH-C according to age groups (<65 and >65)

	CH-C	Controls	*P*
Age group <65			
Cardiovascular diseases	6.01 ± 1.87	3.96 ± 0.20	0.2622
Congestive heart failure	3.84 ± 1.50	0.89 ± 0.08	0.0467
Ischaemic heart disease	1.97 ± 1.04	2.89 ± 0.17	0.3889
Stroke	1.51 ± 0.68	1.14 ± 0.11	0.5913
Age group ≥65			
Cardiovascular diseases	17.54 ± 12.34	24.27 ± 0.90	0.6236
Congestive heart failure	1.18 ± 1.22	6.40 ± 0.45	0.0735
Ischaemic heart disease	15.18 ± 12.01	17.82 ± 0.80	0.8322
Stroke	1.19 ± 1.28	7.14 ± 0.50	0.0720

DISCUSSION

This study assesses the association of CH-C with metabolic conditions and cardiovascular diseases using a general population database. Our study shows that CH-C is independently associated with three important metabolic conditions: IR, DM and hypertension. Although the association of HCV with IR and DM has been previously reported,[18–24] the association of HCV with hypertension is a novel finding.[3, 4] In fact, in one of our previous population-based studies,[21] we reported that the association of HCV with IR and DM might have been attenuated in the last decade by the epidemics of obesity. In this study, having a larger sample from additional NHANES cycles, we confirm that the association between HCV and IR/DM, in fact, remains significant and strong at the population level.

These associations have been shown to be related both to the host factors as well as viral factors. In fact, HCV has been shown to affect glucose-insulin homeostasis as well as lipid metabolism and lipid synthesis.[7–12, 18] In addition, viral factors such as HCV genotypes and HCV core protein can have a direct impact on these interactions.[12] These are significant evidence to support the notion that HCV predisposes patients to insulin resistance and possibly other metabolic abnormalities with their potential consequences such as cardiovascular diseases.[22]

In addition to an increased risk for metabolic conditions, our data show that CH-C is also independently associated with an important subtype of cardiovascular disease, congestive heart failure. This association was present after controlling for important confounders

Predictor	Type II diabetes	Insulin resistance	Hypertension
CH-C	2.31 (1.18–4.54)	2.06 (1.19–3.57)	2.06 (1.30–3.24)
Caucasian race	0.46 (0.39–0.53)	0.62 (0.54–0.72)	Not significant
African American race	Not significant	Not significant	2.33 (2.04–2.65)
Age, per year	1.06 (1.05–1.06)	1.01 (1.01–1.02)	1.09 (1.09–1.09)
Obesity	3.52 (3.00–4.12)	6.64 (5.80–7.60)	2.62 (2.36–2.92)
Hypercholesterolaemia	1.20 (1.01–1.44)	1.88 (1.64–2.15)	1.32 (1.16–1.51)
Excessive alcohol	0.60 (0.42–0.85)	0.62 (0.48–0.79)	1.41 (1.18–1.68)

Table 3 | Independent predictors of insulin resistance, type II diabetes and hypertension in the US population without chronic liver disease other than CH-C [OR (95% CI)]

Aliment Pharmacol Ther 2013; 37: 647-652

Table 4 | Independent predictors of cardiovascular disease in the US population without chronic liver disease other than CH-C [OR (95% CI)]

Predictor	CVD	CHF	IHD	Stroke
CH-C	0.93 (0.47–1.81)	2.49 (1.04–5.96)*	0.53 (0.20–1.40)	0.58 (0.16–2.02)
Age, per year	1.08 (1.08–1.09)*	1.08 (1.07–1.09)*	1.08 (1.08–1.09)*	1.07 (1.06–1.08)*
Obesity	1.64 (1.37–1.96)*	1.86 (1.39–2.50)*	1.40 (1.11–1.77)*	1.88 (1.40–2.51)*
Smoking	2.31 (1.85–2.90)*	1.92 (1.34–2.77)*	2.48 (1.93–3.18)*	2.16 (1.58–2.94)*

* $P < 0.05$.

associated with both metabolic conditions as well as cardiovascular diseases, namely, age, smoking and obesity. Although previous studies have suggested an increased risk of carotid atherosclerosis in patients with CH-C,[22–25] the most important association between HCV and coronary artery disease (CAD) has been reported in the HIV/HCV co-infected cohort.[26] In fact, another study reported that the risk of acute myocardial infarction in patients with CH-C was not increased.[27] However, other recent studies have suggested evidence for myocardial injury and left ventricular systolic and diastolic dysfunction in patients with CH-C.[28–30]

Our findings may have important clinical and public health implications. It is estimated that about 4 million people are infected with CH-C in the United States and over 130 million people are infected worldwide. The vast majority of CH-C patients have not yet been diagnosed and remain untreated. In the United States, the highest prevalence of HCV infection is in the so called 'Baby Boomers'.[31] As this group gets older, the burden of HCV-related complications is expected to increase tremendously.[1] In addition, we believe that the metabolic and cardiovascular complications of HCV can add to this tremendous clinical and economic burden, potentially making CH-C one of the most important chronic diseases for the next few decades.

The main weakness of our study is the lack of follow-up for the target cohort. Since the majority of HCV-infected individuals are still younger than 65 years and therefore are relatively healthy, we may not be able to explicitly appreciate the association of metabolic and cardiovascular conditions with HCV given the low overall rate of these conditions in the predominantly middle-aged CH-C population. However, we believe that with ageing of the target CH-C population, it may become possible to highlight the impact of HCV infection to the natural history of CVD with higher significance and impact. Furthermore, we used self-reports which may have led to underestimation of the true rate of CVD in patients with CH-C and controls. However, the systematic data collection for both CH-C and the controls was the same which should minimise any real bias towards one group. Also, the study is based on a large sample representative of the non-institutionalised US population which contains extensive clinical and laboratory data collected and presented in a standardised form. Finally, our study definition may have underestimated the true prevalence of NAFLD. Despite these limitations, the study uses a very systematic approach at the population level to assess these potential associations.

In summary, our study confirms an association between HCV and DM and IR. In addition, it shows an association between HCV and hypertension. Furthermore, our study suggests that HCV patients are at increased risk for congestive heart failure. All of these findings emphasise the importance of assessing the true impact of HCV not only for its hepatic complications but also for its extra-hepatic manifestations.

AUTHORSHIP

Guarantor of the article: Dr Zobair Younossi.

Author contributions: All authors contributed to the design of the study, data interpretation, manuscript review, editing and approved the final version of the manuscript.

ACKNOWLEDGEMENT

Declaration of personal and funding interests: None.

REFERENCES

1. Davis GL, Alter M, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. *Gastroenterology* 2010; **138**: 513–21.
2. Alter MJ. Epidemiology of hepatitis C infection. *World J Gastroenterol* 2010; **13**: 2436–41.

3. Jacobson IM, Cacoub P, Dal ML, Harrison SA, Younossi ZM. Manifestations of chronic hepatitis C virus infection beyond the liver. *Clin Gastroenterol Hepatol* 2010; **8**: 1017–29.
4. Mehta SH, Brancati FL, Sulkowski MS, Strathdee SA, Szklo M, Thomas DL. Prevalence of type 2 diabetes mellitus among persons with hepatitis C virus infection in the United States. *Ann Intern Med* 2000; **133**: 592–9.
5. Mehta SH, Brancati FL, Strathdee SA, *et al.* Hepatitis C virus infection and incident type 2 diabetes. *Hepatology* 2003; **38**: 50–6.
6. Aytug S, Reich D, Sapiro LE, Bernstein D, Begum N. Impaired IRS-1/PI3-kinase signaling in patients with HCV: a mechanism for increased prevalence of type 2 diabetes. *Hepatology* 2003; **38**: 1384–92.
7. Kawaguchi T, Yoshida T, Harada M, *et al.* Hepatitis C virus down-regulates insulin receptor substrates 1 and 2 through up-regulation of suppressor of cytokine signaling 3. *Am J Pathol* 2004; **165**: 1499–508.
8. Pazienza V, Clément S, Pugnale P, *et al.* The hepatitis C virus core protein of genotypes 3a and 1b downregulates insulin receptor substrate 1 through genotype-specific mechanisms. *Hepatology* 2007; **45**: 1164–71.
9. Kawaguchi T, Ide T, Taniguchi E, *et al.* Clearance of HCV improves insulin resistance, beta-cell function, and hepatic expression of insulin receptor substrate 1 and 2. *Am J Gastroenterol* 2007; **102**: 570–6.
10. Vanni E, Abate ML, Gentilcore E, *et al.* Sites and mechanisms of insulin resistance in nonobese, nondiabetic patients with chronic hepatitis C. *Hepatology* 2009; **50**: 697–706.
11. Milner KL, van dPD, Trenell M, *et al.* Chronic hepatitis C is associated with peripheral rather than hepatic insulin resistance. *Gastroenterology* 2010; **138**: 932–41, e931–3.
12. Younossi ZM, McCullough AJ. Metabolic syndrome, non-alcoholic fatty liver disease and hepatitis C virus: impact on disease progression and treatment response. *Liver Int* 2009; **29** (Suppl. 2): 3–12.
13. Romero-Gómez M, Del Mar Viloria M, Andrade RJ, *et al.* Insulin resistance impairs sustained response rate to peginterferon plus ribavirin in chronic hepatitis C patients. *Gastroenterology* 2005; **128**: 636–41.
14. Butt AA, Xiaoqiang W, Budoff M, Leaf D, Kuller LH, Justice AC. Hepatitis C virus infection and the risk of coronary disease. *Clin Infect Dis* 2009; **49**: 225–32.
15. Lee MH, Yang HI, Wang CH, *et al.* Hepatitis C virus infection and increased risk of cerebrovascular disease. *Stroke* 2010; **41**: 2894–900.
16. Available at: http://www.cdc.gov/nchs/nhanes/nhanes2003-2004/analytical_guidelines.htm. Accessed August 18, 2012.
17. Stepanova M, Rafiq N, Younossi ZM. Components of metabolic syndrome are independent predictors of mortality in patients with chronic liver disease: a population-based study. *Gut* 2010; **59**: 1410–5.
18. Ratziu V, Heurtier A, Bonyhay L, Poynard T, Giral P. Review article: an unexpected virus-host interaction–the hepatitis C virus-diabetes link. *Aliment Pharmacol Ther* 2005; **22**(Suppl. 2): 56–60.
19. Petta S, Camma C, DI Marco V, *et al.* Insulin resistance is a major determinant of liver stiffness in nondiabetic patients with HCV genotype 1 chronic hepatitis. *Aliment Pharmacol Ther* 2009; **30**: 603–13.
20. Eslam M, Aparcero R, Kawaguchi T, *et al.* Meta-analysis: insulin resistance and sustained virological response in hepatitis C. *Aliment Pharmacol Ther* 2011; **34**: 297–305.
21. Stepanova M, Lam B, Younossi Y, Srishord MK, Younossi ZM. Association of hepatitis C with insulin resistance and type 2 diabetes in US general population: the impact of the epidemic of obesity. *J Viral Hepat* 2012; **19**: 341–5.
22. Adinolfi LE, Restivo L, Zampino R, *et al.* Chronic HCV infection is a risk of atherosclerosis. Role of HCV and HCV-related steatosis. *Atherosclerosis* 2012; **221**: 496–502.
23. Alyan O, Kacmaz F, Ozdemir O, *et al.* Hepatitis C infection is associated with increased coronary artery atherosclerosis defined by modified Reardon severity score system. *Circ J* 2008; **72**: 1960–5.
24. Sosner P, Wangermez M, Chagneau-Derrode C, Le MG, Silvain C. Atherosclerosis risk in HIV-infected patients: the influence of hepatitis C virus co-infection. *Atherosclerosis* 2012; **222**: 274–7.
25. Forde KA, Haynes K, Troxel AB, *et al.* Risk of myocardial infarction associated with chronic hepatitis C virus infection: a population-based cohort study. *J Viral Hepat* 2012; **19**: 271–7.
26. Freiberg MS, Chang CC, Skanderson M, *et al.*; Veterans Aging Cohort Study. The risk of incident coronary heart disease among veterans with and without HIV and hepatitis C. *Circ Cardiovasc Qual Outcomes* 2011; **4**: 425–32.
27. Forde KA, Haynes K, Troxel AB, *et al.* Risk of myocardial infarction associated with chronic hepatitis C virus infection: a population-based cohort study. *South Med J* 2011; **104**: 543–6.
28. Maruyama S, Koda M, Oyake N, *et al.* Myocardial injury in patients with chronic hepatitis C infection. *J Viral Hepat* 2012; **19**: 271–7.
29. Demir M, Demir C. Effect of hepatitis C virus infection on the left ventricular systolic and diastolic functions. *South Med J* 2011; **4**: 425–32.
30. Younossi ZM, Braun WE, Protiva DA, Gifford RW Jr, Straffon RA. Chronic viral hepatitis in renal transplant recipients with allografts functioning for more than 20 years. *Transplantation* 1999; **67**: 272–5.
31. McGarry LJ, Pawar VS, Panchmatia HR, *et al.* Economic model of a birth cohort screening program for hepatitis C virus. *Hepatology* 2012; **55**: 1344–55.