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Impact of Hepatitis C Virus Infection on Patient 12-Year Mortality Rates after Acute Myocardial Infarction

Kuo, Hung: Impact of hepatitis C virus on myocardial infarction

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List of Abbreviations

ACEI, angiotensin-converting enzyme inhibitors; AMI, acute myocardial infarction; ARB, angiotensin receptor blockers; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CI, confidence interval; ESRD, end-stage renal disease; HCV, hepatitis C virus; ICD-9-CM, International Classification of Diseases, 9th edition, Clinical Modification; HR, hazard ratio; LMWH, low molecular weight heparin; NHI, National Health Insurance; NHIRD, National Health Insurance Research Database; PCI, percutaneous coronary intervention; SD, standard deviation

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ABSTRACT

Introduction: The influence of hepatitis C virus (HCV) infection on long-term outcomes of acute myocardial infarction (AMI) patients is unclear. Therefore, this study aimed to analyze the impact of HCV infection on 12-year mortality rates after AMI using Taiwan National Health Insurance Research Database (NHIRD) data.

Methods: NHIRD data for approximately 23,000,000 patients between January 2000 and December 2012 were analyzed. A total of 186,112 cases of first AMI admission were identified. A total of 4,659 HCV-infected patients not receiving interferon therapy were enrolled and divided into those with (n: 107) or without (n: 4,552) cirrhosis. Using one-to-one matching, 4,552 matched controls were included for final analysis.

Results: The 12-year mortality rate was significantly higher in AMI patients with HCV and cirrhosis than HCV but without cirrhosis (P<.0001) or controls (P<.0001). The patients with HCV but without cirrhosis had significantly higher long-term mortality rates than the matched controls (P<.0001). The hazard ratio (HR) for mortality was higher in patients with HCV but without cirrhosis (HR: 1.09; 95% CI: 1.04–1.15) and those with HCV and cirrhosis (HR: 2.23; 95% CI: 1.82–2.73). HCV influenced outcomes among the subgroups of patients who were male (HR: 1.06), were younger (HR: 1.27), had hypertension (HR: 1.10), had dyslipidemia (HR: 1.19), or received percutaneous coronary intervention (HR: 1.20).

Conclusions: HCV infection influenced the 12-year mortality rates of AMI patients, especially those who were male, were younger, had hypertension, had dyslipidemia, and received percutaneous coronary intervention. Cirrhosis further increased long-term mortality rates of AMI patients with HCV.

Keywords: acute myocardial infarction, case control study, hepatitis C, liver cirrhosis, propensity score

Strengths and limitations of this study:

1. Our study present a reliable and clear relationship between HCV infection and its impact on post AMI patient based on NHIRD data(which participated by 93% medical institution of Taiwan and covering 99.9% Taiwan (approximately 23,000,000) patients over the past 12 years, which is representative of the general population in Taiwan).
2. The propensity score–matching technique was applied to minimize confounding factors between the HCV and control groups found in retrospective cohort study.
3. The diagnosis validation of AMI population might by doubtful owing to lacking information on the burden of atherosclerosis assessed, but previous studies confirmed the validity of AMI data in the NHIRD of Taiwan.
4. The HCV infection population might be under estimated based on NHIRD data, which may have minorly impacted the study results.
5. Thought the relationship between HCV infection and post AMI mortality was found, the distinct cause-effect relation is still vague and pending study to clarify.

INTRODUCTION

Acute myocardial infarction (AMI) is one of the leading causes of death among men and women in Taiwan and worldwide, and it is now becoming increasingly more common in developed countries.[1] The coronary arteries of patients with AMI have lipid-rich cores after atherosclerosis plaques rupture that induce the formation of unstable platelet aggregates following an intermittent reduction in coronary flow and distal embolization.[2, 3] Despite advances in revascularization and medications, AMI can still trigger lethal arrhythmia, hemodynamic instability, or death. Therefore, assessing the risk factors of clinical outcomes after AMI remains an important research topic.[4-7] Infection has been hypothesized as a contributing risk factor of coronary artery disease (CAD).[8, 9] Several direct and indirect mechanisms have been proposed to explain the association between infectious agents and coronary heart disease.[9-11]

An estimated 2–3% of the global population is infected with the hepatitis C virus (HCV).[12] HCV infection was proposed to be associated with endothelial dysfunction,[13] atherosclerosis,[10, 14-16] CAD,[17-19] carotid disease,[20] and stroke.[21, 22] However, the association between HCV infection and CAD remains controversial.[23-27] Previous studies showed an association between the HCV core protein and carotid atherosclerosis[18] as well as between HCV seropositivity and CAD.[10, 28, 29] However, in a study of active-duty military personnel in whom the prevalence of HCV infection was high, no association was found between HCV seropositivity and AMI.[9] Additionally, other studies concluded that there was no association between HCV infection and CAD,[30] carotid plaque,[31] or the risk of incident myocardial infarction.[32, 33] A recent study showed that patients with HCV infection had less obstructive CAD on coronary angiography.[34]

Furthermore, the influence of HCV infection on the long-term outcomes of patients after AMI is unclear.

The present study aimed to analyze the impact of HCV infection on 12-year mortality after AMI using data from the Taiwan National Health Insurance Research Database (NHIRD).

MATERIAL AND METHODS

The National Health Insurance (NHI) program in Taiwan has financed the healthcare of more than 99% of its residents since 1995. The NHIRD includes detailed information from the medical records of patients admitted to hospitals, including their age, sex, diagnosis, prescriptions, interventions, and relevant survival data. This study was approved by the Human Research Committee of Kaohsiung Veterans General Hospital, Taiwan.

All patients who were admitted to hospitals with the main diagnosis of AMI (International Classification of Diseases, 9th edition, Clinical Modification [ICD-9-CM] codes 410–410.92) between January 2000 and December 2012 were identified from the NHIRD, which includes data for approximately 23,000,000 patients. Among these patients, those with a history of admission for AMI, whose sex was undetermined, or who were <18 years of age were excluded, and a total of 186,112 unique cases of AMI were identified.

Of the 186,112 patients, 4,666 with HCV infection (ICD-9-CM codes V02.62, 070.51, and 070.54) were identified. Among the remaining 181,446 patients, those with a history of hepatitis (ICD-9-CM codes V02.61, 070.30, 070.32, and 571.1) or other liver-associated diseases (ICD-9-CM codes 155, 070, 570, 571, 572, 573, 197.7, 230.8, 235.3, 789.1, and V02.6) were excluded, leaving 112,896 AMI controls.

Of the 4,666 AMI patients with HCV infection, those who had ever received interferon

therapy were excluded to minimize the variables. Therefore, a total of 4,659 patients with HCV were enrolled and further divided into those with liver cirrhosis (n=107) and those without liver cirrhosis (n=4,552). To minimize baseline differences between the AMI cohort with HCV infection but without liver cirrhosis and the control group, a propensity score–matching technique was used. One-to-one matching was performed using the following variables: sex, age, hypertension (IDC-9-CM codes 401–405), dyslipidemia (IDC-9-CM code 272), peripheral vascular disease (ICD-9-CM codes 443.9, 441, 441.9, 785.4, and V43.4 or procedure code 38.48), diabetes mellitus (ICD-9-CM code 250), heart failure (ICD-9-CM code 428), previous stroke (ICD-9-CM codes 430–437 and A290–A294), end-stage renal disease (ESRD; ICD-9-CM code 585), chronic obstructive pulmonary disease (ICD-9-CM codes 491, 492, and 496), and percutaneous coronary intervention (PCI, CD-9-CM procedure codes 36.0, 36.01, 36.02, 36.05, 36.06, and 36.09). The data from 4,552 AMI patients with HCV infection but without liver cirrhosis and 4,552 matched controls were included in our final analysis.

For the outcome analysis, survival was defined as the time interval from the hospital admission date to the NHI coverage end date. Since the NHI premium is paid on a monthly basis, coverage can easily be discontinued at the time of death. Thus, the end date of NHI coverage is a valid proxy for mortality, which had a maximum error of 1 month.[35-39]

Statistical analysis

SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA) was used to extract and analyze the data. Descriptive statistics were calculated for all variables, with categorical data reported as percentile values and continuous data reported as mean and standard deviation. The paired *t*-test was used to compare continuous variables and the chi-squared test was used to compare

categorical variables among the different groups. Hazard ratios (HRs), confidence intervals (CIs), and *P* values from Cox proportional hazards regression models are presented. Kaplan-Meier cumulative survival curves were constructed to compare survival among the groups. *P* values <.05 were considered statistically significant.

RESULTS

Characteristics of the study group

The characteristics of the 4,552 patients with HCV but without cirrhosis and the 4,552 patients in the control group are presented in Table 1. The primary demographic variables of age, male:female distribution, and comorbidities were comparable among the groups. Additionally, the medications used were comparable between the groups except for antiplatelet medications (*P*=.0005) and statins (*P*=.0323), which were used more often in the control group than in the HCV-infected group (Table 1). The proportion of patients who underwent PCI was comparable between the liver cirrhosis group (43.23%) and the control group (42.95%; *P*=.7832), independent of sex or age subgroup (Table 1).

Table 1. Characteristics of overall patients with first hospitalized AMI with and without HCV infection in this propensity score–matched case control study

Characteristics	AMI cohort without HCV n = 4552 Group 1	AMI cohort with HCV but not liver cirrhosis n = 4552 Group 2	AMI cohort with HCV and liver cirrhosis n = 107 Group 3	P value Group 1 vs group 2	P value Group 3 vs group 2	P value Group 3 vs group 1
Age <65 years	1538(33.79%)	1574(34.58%)	41(38.32%)	0.4264	0.4217	0.3278
Male ratio	2812(61.78%)	2826(62.08%)	55(51.4%)	0.7625	0.0246	0.0293
Comorbidity						
Hypertension	3214(70.61%)	3197(70.23%)	66(61.68%)	0.6963	0.0563	0.0456
Dyslipidemia	1680(36.91%)	1703(37.41%)	20(18.69%)	0.6179	<.0001	0.0001
Diabetes mellitus	2217(48.7%)	2163(47.52%)	70(65.42%)	0.2573	0.0002	0.0006
Peripheral vascular disease	220(4.83%)	246(5.4%)	3(2.8%)	0.2163	0.2371	0.3311

Heart failure	1305(28.67%)	1339(29.42%)	31(28.97%)	0.7325	0.9207	0.9453
End-stage renal disease	681(14.96%)	697(15.31%)	13(12.15%)	0.6399	0.3683	0.4195
Previous stroke	1219(26.78%)	1226(26.93%)	25(23.36%)	0.3685	0.4103	0.4300
Chronic obstructive pulmonary disease	745(16.37%)	777(17.07%)	14(13.08%)	0.3688	0.2778	0.3635
Medication						
Any antiplatelet	3821(83.94%)	3695(81.17%)	68(63.55%)	0.0005	<.0001	<.0001
ACEI or ARB	2571(56.48%)	2523(55.43%)	32(29.91%)	0.3109	<.0001	<.0001
Statin	1288(28.3%)	1197(26.3%)	13(12.15%)	0.0323	0.0010	0.0002
Beta blocker	2191(48.13%)	2156(47.36%)	36(33.64%)	0.1627	0.0049	0.003
Calcium channel blocker	1615(35.48%)	1631(35.83%)	26(24.3%)	0.7263	0.0138	0.0167
Heparin	2579(56.66%)	2548(55.98%)	40(37.38%)	0.5124	0.0001	<.0001
Low molecular weight heparin	1173(25.77%)	1151(25.29%)	20(18.69%)	0.3969	0.1201	0.0973
Dopamine	824(18.1%)	762(16.74%)	29(27.1%)	0.1867	0.0048	0.0173
Epinephrine	227(4.99%)	224(4.92%)	8(7.48%)	0.3848	0.2296	0.2447
Norepinephrine	601(13.2%)	596(13.09%)	19(17.76%)	0.2768	0.1589	0.1704
Atropine	161(3.54%)	146(3.21%)	5(4.67%)	0.3838	0.3975	0.4328

Nitrate	3509(77.09%)	3508(77.07%)	72(67.29%)	0.9801	0.0178	0.0175
Nicorandil	381(8.37%)	434(9.53%)	9(8.41%)	0.0517	0.6955	0.9878
PCI	1968(43.23%)	1955(42.95%)	25(23.36%)	0.7832	<.0001	<.0001
PCI ratio in male patients	1377(48.97%)	1372(48.55%)	15(27.27%)	0.7527	0.0018	0.0014
PCI ratio in female patients	591(33.97%)	583(33.78%)	10(19.23%)	0.9069	0.0284	0.0266
PCI ratio in patients aged <65 years	840(54.62%)	842(53.49%)	11(26.83%)	0.5300	0.0007	0.0004
PCI ratio, age ≥ 65 years	1128(37.43%)	1113(37.37%)	14(21.21%)	0.9673	0.0072	0.007

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention

Compared to group 1 (matched control group) and group 2 (AMI patients without cirrhosis group), the 107 AMI patients with HCV and liver cirrhosis had a lower male ratio, higher prevalence of dyslipidemia, and higher prevalence of diabetes mellitus. Additionally, the medications used were significantly lower in group 3 than the other two groups, including antiplatelet, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, statins, beta blockers, calcium channel blockers, heparin, and nitrate. The proportion of patients who underwent PCI was lower in the liver cirrhosis group than in groups 1 and 2.

Outcome analysis

The 12-year survival rate was significantly lower in AMI patients with HCV and liver cirrhosis than in those with HCV but without liver cirrhosis (log rank, $P<.0001$) and control group (log rank, $P<.0001$). Furthermore, AMI patients with HCV but without liver cirrhosis had significantly lower long-term survival rates than the matched AMI controls (log rank, $P<.0001$).

In the subgroup analysis, the AMI patients with liver cirrhosis had lower long-term survival rates than the control group and the patients without cirrhosis regardless of sex, age, or PCI status (Figures 1). Among the male patients, the mortality rate was lower among the matched controls than among the patients without cirrhosis (log rank, $P<.0001$; Figure 1), those with younger age (log rank, $P<.0001$; Figure 1), those who underwent PCI (log rank, $P<.0001$; Figure 1), and those who did not undergo PCI (log rank, $P=.0003$; Figure 1). However, the 12-year survival rate was comparable between the HCV group without cirrhosis and the AMI control group among female (log rank, $P=.1049$; Figure 1) and elderly patients (log rank, $P=.4145$; Figure 1).

A Cox proportional hazard regression analysis was performed to evaluate the impact of

different factors including sex, age, comorbidities, PCI, and HCV on the survival of patients admitted for a first AMI (Table 2). Overall, the HR for mortality was high for patients aged ≥ 65 years (HR, 2.21; 95% CI, 2.07–2.36) as well as those with diabetes (HR, 1.30; 95% CI, 1.23–1.38), peripheral vascular disease (HR, 1.31; 95% CI,1.18–1.46), heart failure (HR, 1.25; 95% CI, 1.18–1.33), ESRD (HR, 1.77.10; 95% CI, 1.65–1.90), previous stroke (HR, 1.37; 95% CI, 1.30–1.46), or chronic obstructive pulmonary disease (HR, 1.27; 95% CI, 1.19–1.36). Conversely, the HR was low for patients who underwent PCI (HR, 0.44; 95% CI, 0.41–0.47). Overall, HCV infection (HR, 1.09; 95% CI, 1.04–1.15) or liver cirrhosis (HR, 2.23; 95% CI, 1.82 – 2.73) increase the mortality rate. In further sex subgroup analyses, the findings were similar to those of the overall group except for HCV in female patients (HR, 1.06.23; 95% CI, 0.97 – 1.15), which suggested that HCV infection did not influence the outcomes of female patients (Table 2).

Table 2. Cox proportional hazard regression in patients with first hospitalized AMI with versus without HCV infection

Variable	All (n = 9211)		Male (n = 5693)		Female (n = 3518)	
	Hazard ratio	(95% CI)	Hazard ratio	(95% CI)	Hazard ratio	(95% CI)
Sex (male vs female)	1.00	(0.95-1.06)	-	-	-	-
Age (≥65 vs <65 years)	2.21	(2.07-2.36)*	2.37	(2.18-2.58)*	1.96	(1.75-2.19)*
Hypertension (yes vs no)	0.97	(0.91-1.03)	1.00	(0.92-1.08)	0.90	(0.82-1.00)
Dyslipidemia (yes vs no)	0.69	(0.65-0.74)*	0.70	(0.65-0.76)*	0.69	(0.63-0.76)*
Diabetes mellitus (yes vs no)	1.30	(1.23-1.38)*	1.35	(1.25-1.45)*	1.25	(1.14-1.36)*
Peripheral vascular disease (yes vs no)	1.31	(1.18-1.46)*	1.43	(1.25-1.65)*	1.20	(1.01-1.42)*
Heart failure (yes vs no)	1.25	(1.18-1.33)*	1.30	(1.20-1.40)*	1.20	(1.10-1.30)*
End stage renal disease (yes vs no)	1.77	(1.65-1.90)*	1.93	(1.75-2.13)*	1.63	(1.46-1.81)*
Previous stroke (yes vs no)	1.37	(1.30-1.46)*	1.40	(1.30-1.52)*	1.34	(1.23-1.47)*
Chronic obstructive pulmonary disease (yes vs no)	1.27	(1.19-1.36)*	1.29	(1.19-1.41)*	1.24	(1.10-1.40)*
Percutaneous coronary intervention (yes vs no)	0.44	(0.41-0.47)*	0.42	(0.39-0.46)*	0.47	(0.43-0.52)*
Hepatitis C (yes vs no)	1.09	(1.04-1.15)*	1.12	(1.04-1.20)*	1.06	(0.97-1.15)
Liver cirrhosis (yes vs no)	2.23	(1.82-2.73)*	2.71	(2.05-3.59)*	1.89	(1.42-2.53)*

*P<0.05

As shown in Figure 2, HCV infection was found to influence the outcomes in the subgroups of patients who were male, were younger, had hypertension, had dyslipidemia, underwent PCI, or had a history of previous stroke or chronic obstructive pulmonary disease.

DISCUSSION

The present study found that HCV infection influences the 12-year outcome of patients with AMI. To our knowledge, no previous study examined the impact of HCV infection on long-term outcomes after AMI. This study also found that the survival rate was lower among the AMI patients with HCV infection and liver cirrhosis. Furthermore, HCV infection was found to influence long-term mortality among the subgroups of patients who were male, were younger, had hypertension, had dyslipidemia, and underwent PCI.

Some studies did not identify an association between HCV seropositivity and myocardial infarction.[9, 32] However, the previous study population[9] included young healthy men (age <50 years) from the US military, which limited the interpretation and generalizability of the results. Another study reported that HCV infection did not increase the risk of incident myocardial infarction among a large sample of patients from the United Kingdom.[32] The results of the present study are consistent with those of previous studies that linked HCV seropositivity with carotid[10, 40] or coronary atherosclerosis.[18] Our study included data from the NHIRD and only evaluated patients with first AMI. Additionally, the percentage of elderly patients was comparable between the HCV group (65.42%) and the control group (66.21%). Previous studies mainly investigated the prevalence of coronary events in patients with hepatitis.[9, 32] However, our study investigated whether HCV infection influences the outcomes of patients after AMI, which makes it unique.

Tsai et al.[19] recently showed that the risk of developing acute coronary syndrome was greater in patients with HCV than in those without HCV and that the risk was the highest in middle-aged patients. This previous study focused on the influence of HCV infection on the development of acute coronary syndrome, while our study focused on the influence of HCV infection on the outcomes of patients after AMI. Furthermore, the study by Tsai et al.[19] showed that comorbidities such as hypertension, diabetes, and dyslipidemia were more likely to be present in patients with HCV than in those without HCV, which might be attributed to the higher acute coronary syndrome risk in these patients. However, these authors only matched age and sex. Using a propensity score–matching technique, our analyses controlled for a number of established cardiovascular risk factors and other important confounding variables that might influence patient outcomes after AMI, including sex, age, hypertension, dyslipidemia, peripheral vascular disease, diabetes mellitus, heart failure, previous stroke, ESRD, chronic obstructive pulmonary disease, and PCI. Therefore, our study ensured similar baseline characteristics between the groups. Our exclusion criteria were also very strict. Patients with hepatitis, liver cirrhosis, or other liver diseases were excluded from the HCV infection without cirrhosis and control groups. These exclusions were not mentioned in the study by Tsai et al.[19] Considering these factors, our study could accurately analyze the influence of HCV infection on patient outcomes after AMI.

A previous study analyzed data from acute care hospitals across the United States in 1999 and 2009 and showed higher in-hospital mortality rates in ST elevation myocardial infarction patients with cirrhosis compared to patients without cirrhosis.[41] Our study also showed that HCV patients with cirrhosis had significant higher mortality rates than those without cirrhosis, which was consistent with the study in the United States.[41] Unlike those studies, our study

focused on HCV-related cirrhosis and further showed the impact of cirrhosis on long-term (12-year) outcomes. The reasons for the higher mortality rates in cirrhosis patients in this study might contribute to more cases of diabetes mellitus, lower PCI rates, and less use of medications, including antiplatelets, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, statins, and beta blockers. However, after the adjustment for several confounding factors in the Cox proportional hazard regression analysis, liver cirrhosis (HR, 2.23; 95% CI, 1.82–2.73; Table 2) still played a critical role in the long-term mortality of AMI patients.

Several studies have discussed the correlation between sex and outcomes in patients with liver disease. In a southern Sweden 10-year population-based study, female patients with liver cirrhosis were shown to have better prognosis than male patients with liver cirrhosis.[42] In a Centers for Disease Control 2013 surveillance, the HCV-related mortality rate for male patients was shown to be approximately 2.6 times that for female patients.[43] However, no previous studies showed the impact of sex on AMI patients with HCV. Our study was the first to show that HCV infection was found to influence long-term mortality in male but not female patients. Previous studies showed that spontaneous resolvers were more common in female patients with HCV,[44, 45] which might be part of reason for the difference.

Interestingly, our study found that antiplatelets and statins were less frequently used in the HCV group than in the control group, which is consistent with the findings of a recent study.[34] The low use of antiplatelet medications and statins in patients with HCV could be secondary to physician concerns regarding liver disease and bleeding risk in these patients.[33, 34] Furthermore, several studies reported that patients with HCV tended to have low cholesterol and low-density lipoprotein levels.[17, 29, 32, 33, 46-48]

The present study has some limitations. First, it was retrospective in design. Therefore, to

minimize confounding factors between the HCV and control groups, we used a propensity score–matching technique, and the characteristics of the controls and the patients with HCV but without cirrhosis did not differ. Matching of the groups further supports the results. Second, we did not confirm the presence of HCV infection, which may have minorly impacted the study results. However, the major strength of this study is that the data were obtained from the NHIRD, which includes data for approximately 23,000,000 patients over the past 12 years and is representative of the general population in Taiwan. Third, the database used here does not include data on family history, body weight, body height, smoking history, and lipid and glucose levels, which are potential confounding factors. Fourth, there was no information on the burden of atherosclerosis assessed using coronary angiography or intracoronary ultrasonography. However, previous studies validated the AMI data in the NHIRD of Taiwan and confirmed the validity of its use for cardiovascular diseases.[35, 39]

CONCLUSION

HCV infection was demonstrated to influence the 12-year mortality of patients after AMI in this study. Additionally, the mortality rate was higher among the patients with HCV and liver cirrhosis. Furthermore, HCV infection was found to influence long-term outcomes in patients after AMI among the subgroups of male patients; younger patients; those with hypertension; those with dyslipidemia; and those who underwent PCI. Therefore, physicians should be aware of the impact of HCV infection in patients with AMI when choosing treatment strategies.

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REFERENCES

1 C.P.Wong, S.Y. Loh, K.K. Loh, et al. Acute myocardial infarction: Clinical features and outcomes in young adults in Singapore, World J. Cardiol. 4 (2012) 206–210.

2 H.D. White, D.P. Chew, Acute myocardial infarction, Lancet. 372 (2008) 570–584.

3 J. Silvain, J.P. Collet, C. Nagaswami, et al. Composition of coronary thrombus in acute myocardial infarction, J. Am. Coll. Cardiol. 57 (2011) 1359–1367.

4 W.C. Huang, K.R. Chiou, C.P. Liu, et al. Multidetector row computed tomography can identify and characterize the occlusive culprit lesions in patients early (within 24 hours) after acute myocardial infarction, Am. Heart J. 154 (2007) 914–922.

5 C.P. Liu, Y.H. Lin, M.S. Lin, et al. Evaluation of myocardial infarction patients after coronary revasculation by dual-phase multi-detector computed tomography: Now and in future, World J. Cardiol. 5 (2013) 115–118.

6 W.C. Huang, C.P. Liu, M.T. Wu, et al. Comparing culprit lesions in ST-segment elevation and non-ST-segment elevation acute coronary syndrome with 64-slice multidetector computed tomography, Eur. J. Radiol. 73 (2010) 74–81.

7 W.C. Huang, M.T. Wu, K.R. Chiou, et al. Assessing culprit lesions and active complex lesions in patients with early acute myocardial infarction by multidetector computed tomography, Circ. J. 72 (2008) 1806–1813.

8 F.J. Nieto, Infections and atherosclerosis: new clues from an old hypothesis? Am. J. Epidemiol. 148 (1998) 937–948.

9 C.M. Arcari, K.E. Nelson, D.M. Netski, et al. No association between hepatitis C virus seropositivity and acute myocardial infarction, Clin. Infect. Dis. 43 (2006) e53–56.

10 N. Ishizaka, Y. Ishizaka, E. Takahashi, et al. Association between hepatitis C virus seropositivity, carotid-artery plaque, and intima-media thickening, Lancet. 359 (2002)133–135.

11 C.P. Oliveira, C.R. Kappel, E.R. Siqueira, et al. Effects of hepatitis C virus on cardiovascular risk in infected patients: a comparative study. Int. J. Cardiol. 164 (2013) 221–226.

12 M.J. Alter, Epidemiology of hepatitis C in the West, Semin. Liver Dis. 15 (1995) 5–14.

13 M. Barone, M.T. Viggiani, A. Amoruso, et al. Endothelial dysfunction correlates with liver fibrosis in chronic HCV infection, Gastroenterol. Res. Pract. 2015 (2015) 682174.

14 M. Fukui, Y. Kitagawa, N. Nakamura, et al. Hepatitis C virus and atherosclerosis in patients with type 2 diabetes, JAMA 289 (2003) 1245–1246.

15 L.E. Adinolfi, L. Restivo, R. Zampino, et al. Chronic HCV infection is a risk of atherosclerosis. Role of HCV and HCV-related steatosis, Atherosclerosis. 221 (2012) 496–502.

16 G. Targher, L. Bertolini, R. Padovani, et al. Differences and similarities in early atherosclerosis between patients with non-alcoholic steatohepatitis and chronic hepatitis B and C, J. Hepatol. 46 (2007) 1126–1132.

17 A.A. Butt, W. Xiaoqiang, M. Budoff, et al. Hepatitis C virus infection and the risk of coronary disease, Clin. Infect. Dis. 49 (2009) 225–232.

18 C. Vassalle, S. Masini, F. Bianchi, et al. Evidence for association between hepatitis C virus seropositivity and coronary artery disease, Heart. 90 (2004) 565–566.

19 M.S. Tsai, Y.C. Hsu, P.C. Yu, et al. Long-term risk of acute coronary syndrome in hepatitis C virus infected patients without antiviral treatment: A cohort study from an endemic area, Int. J. Cardiol. 181 (2015) 27–29.

20 H. Huang, R. Kang, Z. Zhao. Is hepatitis C associated with atherosclerotic burden? A systematic review and meta-analysis, PLoS One. 9 (2014) e106376.

21 H. He, R. Kang, Z. Zhao. Hepatitis C virus infection and risk of stroke: a systematic review and meta-analysis, PLoS One. 8 (2013) e81305.

22 L.E. Adinolfi, L. Restivo, B. Guerrera, et al. Chronic HCV infection is a risk factor of ischemic stroke, Atherosclerosis. 231 (2013) 22–26.

23 C.C. Wang, J.H. Kao. Hepatitis C virus infection, lipids, and coronary heart disease: a Pandora's box, Hepatology. 51 (2010) 343; author reply 343–344.

24 S. Petta, F.S. Macaluso, A. Craxi. Cardiovascular diseases and HCV infection: a simple association or more? Gut. 63 (2014) 369–375.

25 A. Mostafa, M.K. Mohamed, M. Saeed, et al. Hepatitis C infection and clearance: impact on atherosclerosis and cardiometabolic risk factors, Gut. 59 (2010) 1135–1140.

26 R.J. Wong, F. Kanwal, Z.M. Younossi, et al. Hepatitis C virus infection and coronary artery disease risk: a systematic review of the literature, Dig. Dis. Sci. 59 (2014) 1586–1593.

27 T. Roed, A.M. Lebech, A. Kjaer, et al. Hepatitis C virus infection and risk of coronary artery disease: a systematic review of the literature, Clin. Physiol. Funct. Imaging. 32 (2012) 421–430.

28 N. Ishizaka, Y. Ishizaka, E. Takahashi, et al. Increased prevalence of carotid atherosclerosis in hepatitis B virus carriers, Circulation. 105 (2002) 1028–1030.

29 N.V. Pothineni, R. Delongchamp, S. Vallurupalli, et al. Impact of hepatitis C seropositivity on the risk of coronary heart disease events, Am. J. Cardiol. 114 (2014) 1841–1845.

30 Y. Momiyama, R. Ohmori, R. Kato, et al. Lack of any association between persistent hepatitis B or C virus infection and coronary artery disease, Atherosclerosis. 181 (2005) 211–213.

31 S. Kiechl, G. Egger, M. Mayr, et al. Chronic infections and the risk of carotid atherosclerosis: prospective results from a large population study, Circulation. 103 (2001) 1064–1070.

32 K.A. Forde, K. Haynes, A.B. Troxel, et al. Risk of myocardial infarction associated with chronic hepatitis C virus infection: a population-based cohort study, J. Viral. Hepat. 19 (2012) 271–277.

33 A.H. Metwally, M.A. Elgamal. The relation between hepatitis C virus and coronary heart disease, Med. Hypotheses. 82 (2014) 505.

34 N.V. Pothineni, Y. Rochlani, S. Vallurupalli, et al. Comparison of angiographic burden of coronary artery disease in patients with versus without hepatitis C infection, Am. J. Cardiol. 116 (2015) 1041–1044.

35 C.L. Cheng, C.H. Lee, P.S. Chen, et al. Validation of acute myocardial infarction cases in the National Health Insurance Research Database in Taiwan, J. Epidemiol. 24 (2014) 500–507.

36 C.H. Chiang, W.C. Huang, J.S. Yang, et al. Five-year outcomes after acute myocardial

infarction in patients with and without diabetes mellitus in Taiwan, 1996-2005, Acta. Cardiol. Sin. 29 (2013) 387–394.

37 L.M. Sun, M.C. Lin, C.L. Lin, et al. Statin use reduces prostate cancer all-cause mortality: a nationwide population-based cohort study, Medicine (Baltimore). 94 (2015) e1644.

38 J.Y. Wang, C.Y. Wang, C.H. Tan, et al. Effect of different antipsychotic drugs on short-term mortality in stroke patients, Medicine (Baltimore). 93 (2014) e170.

39 P.L. Kuo, K.C. Lin, P.L. Tang, et al. Contribution of hepatitis B to long-term outcome among patients with acute myocardial infarction: a nationwide study, Medicine (Baltimore). 95 (2016) e2678.

40 N. Ishizaka, Y. Ishizaka, M. Yamkado. Atherosclerosis as a possible extrahepatic manifestation of chronic hepatitis C virus infection, Clin. Med. Insights Cardiol. 8 (2014) 1–5.

41 M.S. Abougergi, R. Karagozian, N.D. Grace, et al. ST elevation myocardial infarction mortality among patients with liver cirrhosis: a nationwide analysis across a decade, J. Clin. Gastroenterol. 49 (2015) 778–783.

42 E. Nilsson, H. Anderson, K. Sargenti, et al. Incidence, clinical presentation and mortality of liver cirrhosis in Southern Sweden: a 10-year population-based study, Aliment. Pharmacol. Ther. (2016)

43 CDC. Centers for Disease Control. Viral hepatitis surveillance— United States, 2013. http://www.cdc.gov/hepatitis/statistics/2013surveillance/pdfs/2013hepsurveillancerpt.pdf (accessed 03.05.16).

44 H. Innes, S.J. Hutchinson, N. Obel, et al. Liver mortality attributable to chronic hepatitis C virus infection in Denmark and Scotland: using spontaneous resolvers as the

benchmark comparator, Hepatology. 63 (2016) 1506–1516.

45 J. Grebely, K. Page, R. Sacks-Davis, et al. The effects of female sex, viral genotype, and IL28B genotype on spontaneous clearance of acute hepatitis C virus infection, Hepatology. 59 (2014) 109–120.

46 D. Siagris, M. Christofidou, G.J. Theocharis, et al. Serum lipid pattern in chronic hepatitis C: histological and virological correlations, J. Viral Hepat. 13 (2006) 56–61.

47 K.E. Corey, E. Kane, C. Munroe, et al. Hepatitis C virus infection and its clearance alter circulating lipids: implications for long-term follow-up, Hepatology. 50 (2009) 1030–1037.

48 D. Marzouk, J. Sass, I. Bakr, et al. A. Fontanet, Metabolic and cardiovascular risk profiles and hepatitis C virus infection in rural Egypt, Gut. 56 (2007) 1105–1110.

FOOTNOTES

Contributors: W-C H and G-Y M set up study concept and design. P-L T and H-C L acquire the data. P-L T, W-C, H, and J-S Y analyze and interpret the data and statistical analysis result. W-C H, S-H K, and W-T H draft the manuscript. G-Y M and H-T C perform critical revision of the manuscript for important intellectual content. W-C H and C-P L worked as study supervision.

FIGURE LEGENDS

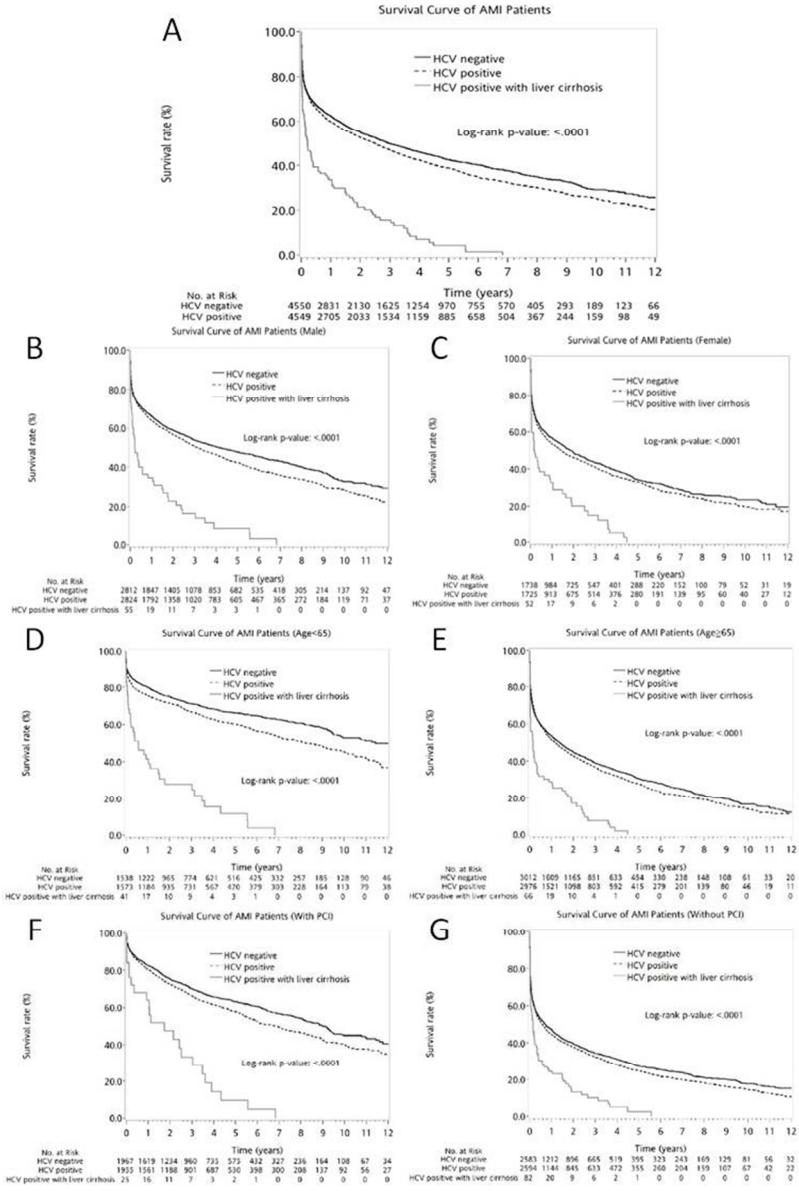
Figure 1. The 12-year Kaplan-Meier survival curves after the first AMI among the control group and the patients with HCV and those without liver cirrhosis (Panel A). Panel B shows the survival curve of the male subgroup. Panel C shows the survival curve of the female subgroup. The patients with liver cirrhosis had lower long-term survival rates than control group and male and female patients without cirrhosis. Additionally, the male AMI patients with HCV but without cirrhosis had higher mortality rates than the matched controls (log rank, *P*<.0001). However, there was no difference in long-term mortality rates between female patients in the HCV group and those in the control group (log rank, *P*=.10492). Further subgroup analysis by age and PCI was also demonstrated. Panel D shows the survival curve of younger patient (age <65 years) subgroup. Panel E shows the survival curve of elderly patient (age ≥65 years) subgroup. Panel F shows the survival curve of the PCI subgroup. Panel G shows the survival curve of the non-PCI subgroup. The patients with liver cirrhosis had lower long-term survival rates than those in the control group or those without cirrhosis in the younger patient (age <65 years), elderly patient, and PCI or non-PCI subgroups. The mortality rate was lower in matched controls than in patients with HCV but without cirrhosis in the younger (log rank, *P*<.0001), PCI (log rank, *P*<.0001), and non-PCI subgroups (log rank, *P*=.0003). However, the 12-year survival rates were comparable between elderly patients in the HCV and control groups (log rank, *P*=.4145).

AMI, acute myocardial infarction; HCV, hepatitis C virus, PCI, percutaneous coronary intervention

Figure 2. Forest plot evaluating the impact of HCV in different subgroups of patients after the

first AMI. HCV infection was found to influence the long-term outcomes of subgroups of male and younger patients, those with hypertension or dyslipidemia, those who underwent PCI, and those without previous stroke or chronic obstructive pulmonary disease.

AMI, acute myocardial infarction; HCV, hepatitis C virus; PCI, percutaneous coronary intervention



The 12-year Kaplan-Meier survival curves after the first AMI among the control group and the patients with HCV and those without liver cirrhosis (Panel A). Panel B shows the survival curve of the male subgroup. Panel C shows the survival curve of the female subgroup. The patients with liver cirrhosis had lower long-term survival rates than control group and male and female patients without cirrhosis. Additionally, the male AMI patients with HCV but without cirrhosis had higher mortality rates than the matched controls (log rank, P<.0001). However, there was no difference in long-term mortality rates between female patients in the HCV group and those in the control group (log rank, P=.10492). Further subgroup analysis by age and PCI was also demonstrated. Panel D shows the survival curve of younger patient (age <65 years) subgroup. Panel E shows the survival curve of elderly patient (age ≥65 years) subgroup. Panel F shows the survival curve of the PCI subgroup. Panel G shows the survival curve of the non-PCI subgroup. The patients with liver cirrhosis had lower long-term survival rates than those in the control group or those without cirrhosis in the younger patient (age <65 years), elderly patient, and PCI or non-PCI subgroups. The mortality rate was lower in matched controls than in patients with HCV but without cirrhosis in the younger (log rank,

P<.0001), PCI (log rank, P<.0001), and non-PCI subgroups (log rank, P=.0003). However, the 12-year survival rates were comparable between elderly patients in the HCV and control groups (log rank, P=.4145). AMI, acute myocardial infarction; HCV, hepatitis C virus, PCI, percutaneous coronary intervention

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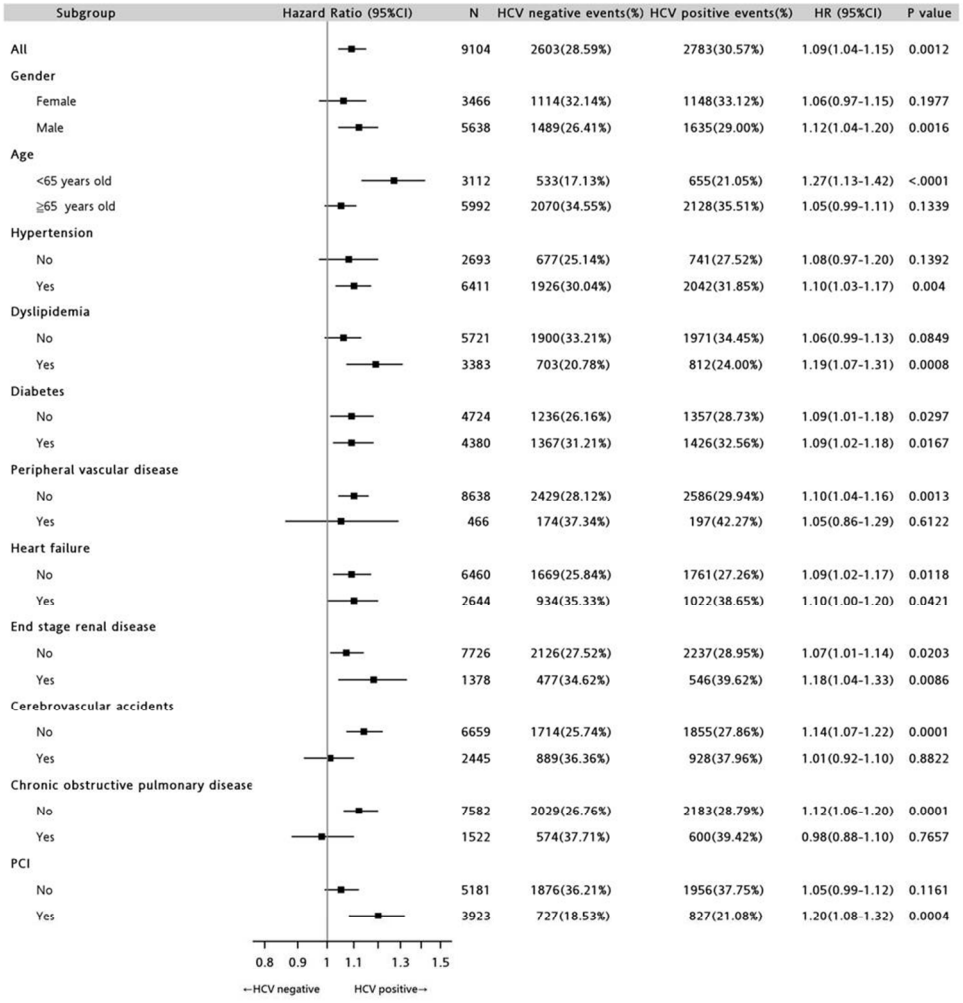

Forest plot evaluating the impact of HCV in different subgroups of patients after the first AMI. HCV infection was found to influence the long-term outcomes of subgroups of male and younger patients, those with hypertension or dyslipidemia, those who underwent PCI, and those without previous stroke or chronic obstructive pulmonary disease.
AMI, acute myocardial infarction; HCV, hepatitis C virus; PCI, percutaneous coronary intervention

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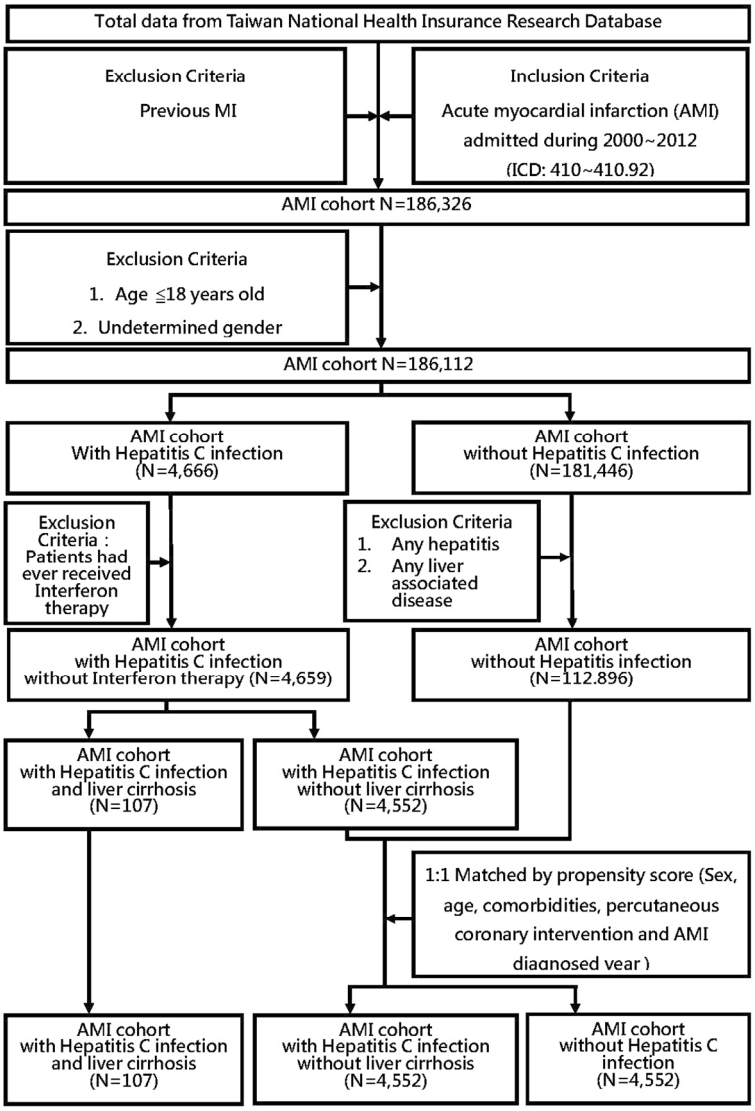

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1(Y)	(*a*) Indicate the study's design with a commonly used term in the title or the abstract(P1, 3)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found(P3)
Introduction		
Background/rationale	2(Y)	Explain the scientific background and rationale for the investigation being reported(P5)
Objectives	3(Y)	State specific objectives, including any prespecified hypotheses(P5)
Methods		
Study design	4(Y)	Present key elements of study design early in the paper(P6)
Setting	5(Y)	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection(P6)
Participants	6(Y)	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up(P6,7) *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls(P7) *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed(P6,7) *Case-control study*—For matched studies, give matching criteria and the number of controls per case(P7)
Variables	7(Y)	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable(P6,7)
Data sources/ measurement	8(Y)	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group(P6,7)
Bias	9(Y)	Describe any efforts to address potential sources of bias(P7)
Study size	10(Y)	Explain how the study size was arrived at(P6,7)
Quantitative variables	11(Y)	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why(P6,7)
Statistical methods	12(Y)	(*a*) Describe all statistical methods, including those used to control for confounding(P7)
		(*b*) Describe any methods used to examine subgroups and interactions(P8)
		(*c*) Explain how missing data were addressed(Nil)
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed(P6) *Case-control study*—If applicable, explain how matching of cases and controls was addressed(P7) *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses(P8)

Continued on next page

Results		
Participants	13(Y)	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed(P6,7)
		(b) Give reasons for non-participation at each stage(Nil)
		(c) Consider use of a flow diagram(available for attachment)
Descriptive data	14(Y)	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders(P8,10-12)
		(b) Indicate number of participants with missing data for each variable of interest(Nil)
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) (P13)
Outcome data	15(Y)	*Cohort study*—Report numbers of outcome events or summary measures over time(P13)
		Case-control study—Report numbers in each exposure category, or summary measures of exposure(P13)
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16(Y)	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included(P13-14)
		(*b*) Report category boundaries when continuous variables were categorized(P13-14)
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period(P13-14)
Other analyses	17(Y)	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses(P13-14)
Discussion		
Key results	18(Y)	Summarise key results with reference to study objectives(P16)
Limitations	19(Y)	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias(P19)
Interpretation	20(Y)	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence(P17-19)
Generalisability	21(Y)	Discuss the generalisability (external validity) of the study results(P19)
Other information		
Funding	22(Y)	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based(P19)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Impact of hepatitis C virus infection on long-term mortality after acute myocardial infarction: A nationwide population-based, propensity-matched cohort study

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Keywords:	acute myocardial infarction, case control study, hepatitis C, liver cirrhosis, propensity score

Impact of hepatitis C virus infection on long-term mortality after acute myocardial infarction: A nationwide population-based, propensity-matched cohort study

Kuo, Hung: Impact of hepatitis C virus on myocardial infarction

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These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Journal Subject Codes: Inflammation, Acute Coronary Syndrome

List of Abbreviations

ACEI, angiotensin-converting enzyme inhibitors; AMI, acute myocardial infarction; ARB, angiotensin receptor blockers; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CI, confidence interval; ESRD, end-stage renal disease; HCV, hepatitis C virus; ICD-9-CM, International Classification of Diseases, 9th edition, Clinical Modification; HR, hazard ratio; LMWH, low molecular weight heparin; NHI, National Health Insurance; NHIRD, National Health Insurance Research Database; PCI, percutaneous coronary intervention; SD, standard deviation

Word Count: 2715

ABSTRACT

Introduction: The influence of hepatitis C virus (HCV) infection on long-term outcomes of patients with acute myocardial infarction (AMI) is unclear. Therefore, this study aimed to analyse the impact of HCV infection on 12-year mortality rates after AMI using data from the Taiwan National Health Insurance Research Database (NHIRD).

Methods: NHIRD data for approximately 23,000,000 patients between January 2000 and December 2012 were analysed. A total of 186,112 cases of first AMI admission were identified. A total of 4,659 HCV-infected patients not receiving interferon therapy were enrolled and divided into those with (n = 107) or without (n = 4,552) cirrhosis. Using one-to-one matching, 4,552 matched controls were included in the final analysis.

Results: The 12-year mortality rate was significantly higher in AMI patients with HCV infection and cirrhosis than in those with HCV infection but without cirrhosis ($P < .0001$) or controls ($P < .0001$). Patients with HCV infection but without cirrhosis had significantly higher long-term mortality rates than the matched controls ($P < .0001$). The hazard ratio (HR) for mortality was higher in patients with HCV infection (hazard ratio [HR], 1.12; 95% confidence interval, 1.06–1.18). HCV influenced outcomes among the subgroups of patients who were male (HR, 1.15) and those who had hypertension (HR, 1.14).

Conclusions: HCV infection influenced the 12-year mortality rates of AMI patients, especially those who were male and those who had hypertension. Cirrhosis further increased the long-term mortality rates of AMI patients with HCV infection.

Keywords: acute myocardial infarction, case control study, hepatitis C, liver cirrhosis, propensity score

Strengths and limitations of this study:

1. We present a reliable and clear relationship between hepatitis C viral (HCV) infection and its impact on post-AMI patients using Taiwan National Health Insurance Research Database (NHIRD) data. The NHIRD is an enormous and unbiased record, as its data represent 93% of the medical institutions of Taiwan, which serve 99.9% of patients in Taiwan (approximately 23,000,000) over the past 12 years, making it representative of the general population in Taiwan.
2. The confounding factors were minimized by application of the propensity score–matching technique.
3. The diagnosis of the AMI population might not be confirmed owing to lacking information on the burden of atherosclerosis assessed, but previous studies confirmed the validity of AMI data in the NHIRD of Taiwan.
4. The NHIRD data might underestimate the HCV-infected population. Furthermore, the database does not include data on family history; actual cause of death; body weight; body height; smoking history; or lipid, viral load, and glucose levels, which are potential confounding factors. However, the size of the NHIRD database and use of the propensity score–matching technique could minimize the impact of these potential confounding factors.
5. Although a relationship between HCV infection and post-AMI mortality was found, the distinct cause-effect correlation remains vague and is pending further study for clarification.

INTRODUCTION

Acute myocardial infarction (AMI), one of the leading causes of death among men and women in Taiwan and worldwide, is now becoming increasingly more common in developed countries.[1] The coronary arteries of patients with AMI have lipid-rich cores after atherosclerosis plaque rupture that induce the formation of unstable platelet aggregates following an intermittent reduction in coronary flow and distal embolization.[2, 3] Despite advances in revascularization and medications, AMI can still trigger lethal arrhythmia, hemodynamic instability, or death. Therefore, assessing the risk factors of clinical outcomes after AMI remains an important research topic.[4-7] Infection has been hypothesized as a contributing risk factor of coronary artery disease (CAD).[8, 9] Several direct and indirect mechanisms have been proposed to explain the association between infectious agents and coronary heart disease.[9-11]

An estimated 2–3% of the global population is infected with the hepatitis C virus (HCV).[12] HCV infection was proposed to be associated with endothelial dysfunction,[13] atherosclerosis,[10, 14-16] CAD,[17-19] carotid artery disease,[20] and stroke.[21, 22] However, the association between HCV infection and CAD remains controversial.[23-27] Previous studies showed an association between the HCV core protein and carotid atherosclerosis[18] as well as between HCV seropositivity and CAD.[10, 28, 29] However, in a study of active-duty military personnel with a high prevalence of HCV infection, no association was found between HCV seropositivity and AMI.[9] Additionally, other studies reported no association between HCV infection and CAD,[30] carotid plaques,[31] or the risk of incident myocardial infarction.[32, 33] A recent study showed that patients with HCV infection had less obstructive CAD on coronary angiography.[34] Furthermore, the influence of HCV infection on the long-term outcomes of patients after AMI is unclear.

The present study aimed to analyse the impact of HCV infection on 12-year mortality after AMI using data from the Taiwan National Health Insurance Research Database (NHIRD).

MATERIAL AND METHODS

The National Health Insurance (NHI) program in Taiwan has financed the healthcare of more than 99% of its residents since 1995. The NHIRD includes detailed information from the medical records of patients admitted to hospitals, including their age, sex, diagnosis, prescriptions, interventions, and relevant survival data. This study was approved by the Human Research Committee of Kaohsiung Veterans General Hospital, Taiwan.

All patients who were admitted to hospitals with the main diagnosis of AMI (International Classification of Diseases, 9th edition, Clinical Modification [ICD-9-CM] codes 410–410.92) between January 2000 and December 2012 were identified from the NHIRD, which includes data for approximately 23,000,000 patients. Among these patients, those with a history of admission for AMI, whose sex was undetermined, or who were <18 years of age were excluded, and a total of 186,112 unique cases of AMI were identified (Supplementary Figure**)**.

Of the 186,112 patients, 4,666 with HCV infection (ICD-9-CM codes V02.62, 070.51, and 070.54) were identified. Among the remaining 181,446 patients, those with a history of hepatitis (ICD-9-CM codes V02.61, 070.30, 070.32, and 571.1) or other liver-associated diseases (ICD-9-CM codes 155, 070, 570, 571, 572, 573, 197.7, 230.8, 235.3, 789.1, and V02.6) were excluded, leaving 112,896 AMI controls (Supplementary Figure**)**.

Of the 4,666 AMI patients with HCV infection, those who had ever received interferon therapy were excluded to minimize the variables. Therefore, a total of 4,659 patients with HCV infection were enrolled and further divided into those with (n = 107) and those without (n =

4,552) liver cirrhosis. To minimize baseline differences between the AMI cohort with HCV infection but without liver cirrhosis and the control group, a propensity score–matching technique was used. One-to-one matching was performed using the following variables: sex, age, hypertension (IDC-9-CM codes 401–405), dyslipidemia (IDC-9-CM code 272), peripheral vascular disease (ICD-9-CM codes 443.9, 441, 441.9, 785.4, and V43.4 or procedure code 38.48), diabetes mellitus (ICD-9-CM code 250), heart failure (ICD-9-CM code 428), previous stroke (ICD-9-CM codes 430–437 and A290–A294), end-stage renal disease (ESRD; ICD-9-CM code 585), chronic obstructive pulmonary disease (ICD-9-CM codes 491, 492, and 496), and percutaneous coronary intervention (PCI, CD-9-CM procedure codes 36.0, 36.01, 36.02, 36.05, 36.06, and 36.09). The data from 4,552 AMI patients with HCV infection but without liver cirrhosis and from 4,552 matched controls were included in the final analysis (Supplementary Figure**)**.

For the outcome analysis, survival was defined as the time interval from the hospital admission date to the NHI coverage end date. Since the NHI premium is paid monthly, coverage can easily be discontinued at the time of death. Thus, the end date of NHI coverage is a valid proxy for mortality, which had a maximum error of 1 month.[35-39]

Statistical analysis

SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA) was used to extract and analyse the data. Descriptive statistics were calculated for all variables, with categorical data reported as percentile values and continuous data reported as mean and standard deviation. The paired *t*-test was used to compare continuous variables and the chi-squared test was used to compare categorical variables among the groups. Hazard ratios (HRs), confidence intervals (CIs),

and *P* values from Cox proportional hazards regression models are presented. Kaplan-Meier cumulative survival curves were constructed to compare survival among the groups. *P* values < .05 were considered statistically significant.

RESULTS

Characteristics of the study group

The characteristics of the 4,552 patients with HCV infection but without cirrhosis and the 4,552 patients in the control group are presented in Table 1. The primary demographic variables of age, male to female distribution, and comorbidities were comparable among the groups. Additionally, the medications used were comparable among the groups except for antiplatelet medications (*P* = .0005) and statins (*P* = .0323), which were used more often in the control group than in the HCV-infected group (Table 1). The proportion of patients who underwent PCI was comparable between the HCV-infected without liver cirrhosis group (42.95%) and the control group (43.23%; *P* = .7832), independent of sex or age subgroup (Table 1).

Table 1. Characteristics of all patients with first hospitalized AMI with and without HCV infection in this propensity score–matched case control study

Characteristics	AMI cohort without HCV n = 4552 Group 1	AMI cohort with HCV but not liver cirrhosis n = 4552 Group 2	AMI cohort with HCV and liver cirrhosis n = 107 Group 3	*P* value Group 1 vs Group 2	*P* value Group 3 vs Group 2	*P* value Group 3 vs Group 1
Age < 65 years	1,538 (33.79%)	1,574 (34.58%)	41 (38.32%)	0.4264	0.4217	0.3278
Male participants	2,812 (61.78%)	2,826 (62.08%)	55 (51.4%)	0.7625	0.0246	0.0293
Comorbidity						
Hypertension	3,214 (70.61%)	3,197 (70.23%)	66 (61.68%)	0.6963	0.0563	0.0456
Dyslipidemia	1,680 (36.91%)	1,703 (37.41%)	20 (18.69%)	0.6179	<.0001	0.0001
Diabetes mellitus	2,217 (48.7%)	2,163 (47.52%)	70 (65.42%)	0.2573	0.0002	0.0006
Peripheral vascular disease	220 (4.83%)	246 (5.4%)	3 (2.8%)	0.2163	0.2371	0.3311

Heart failure	1,305 (28.67%)	1,339 (29.42%)	31 (28.97%)	0.4325	0.9207	0.9453
End-stage renal disease	681 (14.96%)	697 (15.31%)	13 (12.15%)	0.6399	0.3683	0.4195
Previous stroke	1,219 (26.78%)	1,226 (26.93%)	25 (23.36%)	0.3685	0.4103	0.4300
Chronic obstructive pulmonary disease	745 (16.37%)	777 (17.07%)	14 (13.08%)	0.3688	0.2778	0.3635
Medication						
Any antiplatelet	3,821 (83.94%)	3,695 (81.17%)	68 (63.55%)	0.0005	<.0001	<.0001
ACEI or ARB	2,571 (56.48%)	2,523 (55.43%)	32 (29.91%)	0.2109	<.0001	<.0001
Statin	1,288 (28.3%)	1,197 (26.3%)	13 (12.15%)	0.0323	0.0010	0.0002
Beta-blocker	2,191 (48.13%)	2,156 (47.36%)	36 (33.64%)	0.1627	0.0049	0.003
Calcium channel blocker	1,615 (35.48%)	1,631 (35.83%)	26 (24.3%)	0.7263	0.0138	0.0167
Heparin	2,579 (56.66%)	2,548 (55.98%)	40 (37.38%)	0.5124	0.0001	<.0001
Low molecular weight heparin	1,173 (25.77%)	1,151 (25.29%)	20 (18.69%)	0.3969	0.1201	0.0973
Dopamine	824 (18.1%)	762 (16.74%)	29 (27.1%)	0.1867	0.0048	0.0173
Epinephrine	227 (4.99%)	224 (4.92%)	8 (7.48%)	0.3848	0.2296	0.2447
Norepinephrine	601 (13.2%)	596 (13.09%)	19 (17.76%)	0.2768	0.1589	0.1704
Atropine	161 (3.54%)	146 (3.21%)	5 (4.67%)	0.3838	0.3975	0.4328

Nitrate	3,509 (77.09%)	3,508 (77.07%)	72 (67.29%)	0.9801	0.0178	0.0175
Nicorandil	381 (8.37%)	434 (9.53%)	9 (8.41%)	0.0517	0.6955	0.9878
PCI	1,968 (43.23%)	1,955 (42.95%)	25 (23.36%)	0.7832	<.0001	<.0001
PCI ratio in male patients	1,377 (48.97%)	1,372 (48.55%)	15 (27.27%)	0.7527	0.0018	0.0014
PCI ratio in female patients	591 (33.97%)	583 (33.78%)	10 (19.23%)	0.9069	0.0284	0.0266
PCI ratio in patients aged < 65 years	840 (54.62%)	842 (53.49%)	11 (26.83%)	0.5300	0.0007	0.0004
PCI ratio, age ≥ 65 years	1,128 (37.43%)	1,113 (37.37%)	14 (21.21%)	0.9673	0.0072	0.007

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention

Compared to Group 1 (matched control group) and Group 2 (HCV-infected patients without cirrhosis group), the 107 AMI patients with HCV infection and liver cirrhosis had a lower male ratio, lower prevalence of dyslipidemia, and higher prevalence of diabetes mellitus. Additionally, the medications used were significantly lower in Group 3 than in the other two groups, including antiplatelet, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, statins, beta-blockers, calcium channel blockers, heparin, and nitrate. The proportion of patients who underwent PCI was lower in the liver cirrhosis group than in Groups 1 and 2.

Outcome analysis

The 12-year survival rate was significantly lower in AMI patients with HCV infection and liver cirrhosis than in those with HCV infection but without liver cirrhosis (log rank, $P < .0001$) and control group (log rank, $P < .0001$). Furthermore, AMI patients with HCV infection but without liver cirrhosis had significantly lower long-term survival rates than the matched AMI controls (log rank, $P < .0001$).

In the subgroup analysis, the AMI patients with liver cirrhosis had lower long-term survival rates than the control group and the patients without cirrhosis regardless of sex, age, or PCI status (Figure 1). Among the male patients, the mortality rate was lower among the matched controls than among the patients without cirrhosis (log rank, $P < .0001$; Figure 1), those with younger age (log rank, $P < .0001$; Figure 1), those who underwent PCI (log rank, $P < .0001$; Figure 1), and those who did not undergo PCI (log rank, $P = .0003$; Figure 1). However, the 12-year survival rate was comparable between the HCV group without cirrhosis and the AMI control group for female (log rank, $P = .1049$; Figure 1) and elderly patients (log rank, $P = .4145$; Figure 1).

A Cox proportional hazard regression analysis was performed to evaluate the impact of factors including sex, age, comorbidities, PCI, HCV infection, antiplatelet, and statin use on the survival of patients admitted for a first AMI (Table 2). Overall, the HR for mortality was high for patients aged ≥ 65 years (HR, 2.22; 95% CI, 2.07–2.37) as well as those with diabetes (HR, 1.34; 95% CI, 1.27–1.42), peripheral vascular disease (HR, 1.28; 95% CI,1.15–1.43), heart failure (HR, 1.27; 95% CI, 1.20–1.34), ESRD (HR, 1.78; 95% CI, 1.66–1.91), previous stroke (HR, 1.32; 95% CI, 1.24–1.40), or chronic obstructive pulmonary disease (HR, 1.24; 95% CI, 1.16–1.33). Conversely, the HR was low for patients who underwent PCI (HR, 0.50; 95% CI, 0.47–0.53) and those taking antiplatelet (HR, 0.66; 95% CI, 0.61–0.70) or statin (HR, 0.79; 95% CI, 0.71–0.88) medication. Overall, HCV infection was associated with a higher risk for mortality (HR, 1.12; 95% CI, 1.06–1.18).

Table 2. Cox proportional hazard regression analysis in patients with first hospitalized AMI with versus those without HCV infection

Variable	All (n = 9104)		Male (n = 5652)		Female (n = 3452)	
	Hazard ratio	(95% CI)	Hazard ratio	(95% CI)	Hazard ratio	(95% CI)
Sex (male vs female)	1.00	(0.95-1.06)	-	-	-	-
Age (≧65 vs <65)	2.22	(2.07-2.37)*	2.43	(2.22-2.64)*	1.88	(1.68-2.11)*
Hypertension (yes vs no)	0.95	(0.89-1.01)	0.97	(0.89-1.05)	0.92	(0.82-1.02)
Dyslipidemia (yes vs no)	0.85	(0.77-0.93)*	0.87	(0.77-0.98)*	0.83	(0.72-0.95)*
Diabetes mellitus (yes vs no)	1.34	(1.27-1.42)*	1.36	(1.27-1.47)*	1.30	(1.19-1.42)*
Peripheral vascular disease (yes vs no)	1.28	(1.15-1.43)*	1.40	(1.21-1.61)*	1.16	(0.98-1.38)
Heart failure (yes vs no)	1.27	(1.20-1.34)*	1.26	(1.17-1.37)*	1.27	(1.17-1.39)*
End-stage renal disease (yes vs no)	1.78	(1.66-1.91)*	1.94	(1.76-2.14)*	1.62	(1.46-1.80)*
Previous stroke (yes vs no)	1.32	(1.24-1.40)*	1.32	(1.22-1.43)*	1.33	(1.21-1.46)*
Chronic obstructive pulmonary disease (yes vs no)	1.24	(1.16-1.33)*	1.25	(1.15-1.36)*	1.22	(1.08-1.38)*
Percutaneous coronary intervention (yes vs no)	0.50	(0.47-0.53)*	0.48	(0.44-0.52)*	0.53	(0.48-0.59)*
Antiplatelet drug (yes vs no)	0.66	(0.61-0.70)*	0.67	(0.61-0.73)*	0.64	(0.58-0.71)*
Statin (yes vs no)	0.79	(0.71-0.88)*	0.77	(0.66-0.89)*	0.82	(0.69-0.96)*
Hepatitis C (yes vs no)	1.12	(1.06-1.18)*	1.15	(1.07-1.24)*	1.07	(0.99-1.17)

*$P < 0.05$

In further gender subgroup analyses, HCV infection was found to influence the outcomes of male patients but not female patients (HR, 1.07; 95% CI, 0.99–1.17) (Figure 2). HCV infection also did not impact the outcomes of patients without hypertension (HR, 1.06; 95% CI, 0.95–1.17), with peripheral vascular disease (HR, 1.06; 95% CI, 0.87–1.31), with cerebrovascular accidents (HR, 1.06; 95% CI, 0.97–1.17), or with chronic obstructive pulmonary disease (HR, 1.01; 95% CI, 0.90–1.14) (Figure 2).

DISCUSSION

The present study showed that HCV infection influences the 12-year outcome of patients with AMI. To our knowledge, no previous study examined the impact of HCV infection on long-term outcomes after AMI. This study also showed that the survival rate was lower among the AMI patients with HCV infection and liver cirrhosis. Furthermore, HCV infection influenced long-term mortality among the subgroups of patients who were male and had hypertension.

Some studies did not identify an association between HCV seropositivity and myocardial infarction.[9, 32] However, the previous study population[9] included young healthy men (age < 50 years) from the US military, which limited the interpretation and generalizability of the results. Another study reported that HCV infection did not increase the risk of incident myocardial infarction among a large sample of patients from the United Kingdom.[32] The results of the present study are consistent with those of previous studies that linked HCV seropositivity with carotid[10, 40] or coronary atherosclerosis.[18] Our study included data from NHIRD and evaluated only those patients with first AMI. Additionally, the percentage of elderly patients was comparable between the HCV group (65.42%) and the control group (66.21%). Previous studies mainly investigated the prevalence of coronary events in patients with hepatitis.[9, 32] However,

our study investigated whether HCV infection influences the outcomes of patients after AMI, which makes it unique.

Tsai et al.[19] recently showed that the risk of developing acute coronary syndrome was greater in patients with than in those without HCV and that the risk was the highest in middle-aged patients. This previous study focused on the influence of HCV infection on the development of acute coronary syndrome, while our study focused on the influence of HCV infection on the outcomes of patients after AMI. Furthermore, the study by Tsai et al.[19] showed that comorbidities such as hypertension, diabetes, and dyslipidemia were more likely to be present in patients with than in those without HCV, which might be attributable to the higher acute coronary syndrome risk in these patients. However, these authors matched only patient age and sex. Using a propensity score–matching technique, our analyses controlled for several established cardiovascular risk factors and other important confounding variables that might influence patient outcomes after AMI, including sex, age, hypertension, dyslipidemia, peripheral vascular disease, diabetes mellitus, heart failure, previous stroke, ESRD, chronic obstructive pulmonary disease, and PCI. Therefore, our study ensured similar baseline characteristics among groups. Our exclusion criteria were also very strict. Patients with hepatitis, liver cirrhosis, or other liver diseases were excluded from the HCV infection without cirrhosis and control groups. These exclusions were not mentioned in the study by Tsai et al.[19] Considering these factors, our study accurately analysed the influence of HCV infection on patient outcomes after AMI.

A previous study analysed data from acute care hospitals across the United States in 1999 and 2009 and showed higher in-hospital mortality rates in ST elevation myocardial infarction patients with cirrhosis compared to patients without cirrhosis.[41] Our study also showed that HCV patients with cirrhosis had significant higher mortality rates than those without cirrhosis,

which was consistent with the study in the United States.[41] Unlike those studies, our study focused on HCV-related cirrhosis and further showed the impact of cirrhosis on long-term (12-year) outcomes. The higher mortality rates in cirrhosis patients in this study might have resulted from more cases of diabetes mellitus, lower PCI rates, and less use of medications, including antiplatelets, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, statins, and beta-blockers. The low PCI rate and use of life-saving medication in cirrhosis patients could be explained by the following. First, end-stage liver disease was shown to be associated with thrombocytopenia and coagulopathy predisposing patients to bleeding complications, especially in those with oesophageal varices.[42, 43] Furthermore, previous studies have shown that most patients with end-stage liver disease have higher INRs, high creatinine values, and lower haemoglobin levels.[42, 43] These cirrhotic patients might suffer from a higher frequency of peri-procedural bleeding, pseudoaneurysm formation, and the need for blood products.[42, 43]

Several studies have discussed the correlation between sex and outcomes in patients with liver disease. In a southern Sweden 10-year population-based study, female patients with liver cirrhosis had better prognosis than their male counterparts.[44] In a Centers for Disease Control 2013 surveillance, the HCV-related mortality rate for male patients was approximately 2.6 times that for female patients.[45] However, no previous studies showed the impact of sex on AMI patients with HCV. Our study was the first to show that HCV infection influenced long-term mortality in male but not female patients. Previous studies showed that spontaneous resolution was more common in female patients with HCV,[46, 47] which might be part of reason for the difference.

Interestingly, our study showed that antiplatelets and statins were less frequently used in the

HCV group than in the control group, which is consistent with the findings of a recent study.[34] The low use of antiplatelet medications and statins in patients with HCV could be secondary to physician concerns regarding liver disease and bleeding risk in these patients.[33, 34] Furthermore, several studies reported that patients with HCV tended to have low cholesterol and low-density lipoprotein levels.[17, 29, 32, 33, 48-50] Therefore, Cox proportional hazard regression analysis was used to adjust for possible confounding factors including antiplatelets and statins. After the analysis, HCV infection (HR, 1.12; 95% CI, 1.06–1.18; Table 2) still played a critical role in the long-term mortality of AMI patients.

The present study has some limitations. First, it was retrospective in design. Therefore, to minimize confounding factors between the HCV and control groups, we used a propensity score–matching technique and found that the characteristics of the controls and the patients with HCV but without cirrhosis did not differ. Matching of the groups further supports the results. Second, we did not confirm the presence of HCV infection, which may have slightly impacted the study results. However, the major strength of this study is that the data were obtained from the NHIRD, which includes data for approximately 23,000,000 patients over the past 12 years and is representative of the general population in Taiwan. Third, the database used here does not include data on family history; actual cause of death; body weight; body height; smoking history; lipid, viral load, and glucose levels; all are potential confounding factors. Fourth, there was no information on the burden of atherosclerosis assessed using coronary angiography or intracoronary ultrasonography. However, previous studies validated the AMI data in the NHIRD of Taiwan and confirmed the validity of its use for cardiovascular diseases.[35, 39]

CONCLUSION

HCV infection was demonstrated to influence the 12-year mortality of patients after AMI in this study. Additionally, the mortality rate was higher among the patients with HCV infection and liver cirrhosis. Furthermore, HCV infection influenced the long-term outcomes of patients after AMI among the subgroups of male patients and those with hypertension. Therefore, physicians should be aware of the impact of HCV infection in patients with AMI when choosing treatment strategies.

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REFERENCES

1 C.P. Wong, S.Y. Loh, K.K. Loh, et al. Acute myocardial infarction: Clinical features and outcomes in young adults in Singapore, World J. Cardiol. 4 (2012) 206–210.

2 H.D. White, D.P. Chew. Acute myocardial infarction, Lancet. 372 (2008) 570–584.

3 J. Silvain, J.P. Collet, C. Nagaswami, et al. Composition of coronary thrombus in acute myocardial infarction, J. Am. Coll. Cardiol. 57 (2011) 1359–1367.

4 W.C. Huang, K.R. Chiou, C.P. Liu, et al. Multidetector row computed tomography can identify and characterize the occlusive culprit lesions in patients early (within 24 hours)

after acute myocardial infarction, Am. Heart J. 154 (2007) 914–922.

5 C.P. Liu, Y.H. Lin, M.S. Lin, et al. Evaluation of myocardial infarction patients after coronary revasculation by dual-phase multi-detector computed tomography: Now and in future, World J. Cardiol. 5 (2013) 115–118.

6 W.C. Huang, C.P. Liu, M.T. Wu, et al. Comparing culprit lesions in ST-segment elevation and non-ST-segment elevation acute coronary syndrome with 64-slice multidetector computed tomography, Eur. J. Radiol. 73 (2010) 74–81.

7 W.C. Huang, M.T. Wu, K.R. Chiou, et al. Assessing culprit lesions and active complex lesions in patients with early acute myocardial infarction by multidetector computed tomography, Circ. J. 72 (2008) 1806–1813.

8 F.J. Nieto. Infections and atherosclerosis: new clues from an old hypothesis? Am. J. Epidemiol. 148 (1998) 937–948.

9 C.M. Arcari, K.E. Nelson, D.M. Netski, et al. No association between hepatitis C virus seropositivity and acute myocardial infarction, Clin. Infect. Dis. 43 (2006) e53–56.

10 N. Ishizaka, Y. Ishizaka, E. Takahashi, et al. Association between hepatitis C virus seropositivity, carotid-artery plaque, and intima-media thickening, Lancet. 359 (2002)133–135.

11 C.P. Oliveira, C.R. Kappel, E.R. Siqueira, et al. Effects of hepatitis C virus on cardiovascular risk in infected patients: a comparative study. Int. J. Cardiol. 164 (2013) 221–226.

12 M.J. Alter. Epidemiology of hepatitis C in the West, Semin. Liver Dis. 15 (1995) 5–14.

13 M. Barone, M.T. Viggiani, A. Amoruso, et al. Endothelial dysfunction correlates with liver fibrosis in chronic HCV infection, Gastroenterol. Res. Pract. 2015 (2015) 682174.

14 M. Fukui, Y. Kitagawa, N. Nakamura, et al. Hepatitis C virus and atherosclerosis in patients with type 2 diabetes, JAMA 289 (2003) 1245–1246.

15 L.E. Adinolfi, L. Restivo, R. Zampino, et al. Chronic HCV infection is a risk of atherosclerosis. Role of HCV and HCV-related steatosis, Atherosclerosis. 221 (2012) 496–502.

16 G. Targher, L. Bertolini, R. Padovani, et al. Differences and similarities in early atherosclerosis between patients with non-alcoholic steatohepatitis and chronic hepatitis B and C, J. Hepatol. 46 (2007) 1126–1132.

17 A.A. Butt, W. Xiaoqiang, M. Budoff, et al. Hepatitis C virus infection and the risk of coronary disease, Clin. Infect. Dis. 49 (2009) 225–232.

18 C. Vassalle, S. Masini, F. Bianchi, et al. Evidence for association between hepatitis C virus seropositivity and coronary artery disease, Heart. 90 (2004) 565–566.

19 M.S. Tsai, Y.C. Hsu, P.C. Yu, et al. Long-term risk of acute coronary syndrome in hepatitis C virus infected patients without antiviral treatment: A cohort study from an endemic area, Int. J. Cardiol. 181 (2015) 27–29.

20 H. Huang, R. Kang, Z. Zhao. Is hepatitis C associated with atherosclerotic burden? A systematic review and meta-analysis, PLoS One. 9 (2014) e106376.

21 H. He, R. Kang, Z. Zhao. Hepatitis C virus infection and risk of stroke: a systematic review and meta-analysis, PLoS One. 8 (2013) e81305.

22 L.E. Adinolfi, L. Restivo, B. Guerrera, et al. Chronic HCV infection is a risk factor of ischemic stroke, Atherosclerosis. 231 (2013) 22–26.

23 C.C. Wang, J.H. Kao. Hepatitis C virus infection, lipids, and coronary heart disease: a Pandora's box, Hepatology. 51 (2010) 343; author reply 343–344.

24 S. Petta, F.S. Macaluso, A. Craxi. Cardiovascular diseases and HCV infection: a simple association or more? Gut. 63 (2014) 369–375.

25 A. Mostafa, M.K. Mohamed, M. Saeed, et al. Hepatitis C infection and clearance: impact on atherosclerosis and cardiometabolic risk factors, Gut. 59 (2010) 1135–1140.

26 R.J. Wong, F. Kanwal, Z.M. Younossi, et al. Hepatitis C virus infection and coronary artery disease risk: a systematic review of the literature, Dig. Dis. Sci. 59 (2014) 1586–1593.

27 T. Roed, A.M. Lebech, A. Kjaer, et al. Hepatitis C virus infection and risk of coronary artery disease: a systematic review of the literature, Clin. Physiol. Funct. Imaging. 32 (2012) 421–430.

28 N. Ishizaka, Y. Ishizaka, E. Takahashi, et al. Increased prevalence of carotid atherosclerosis in hepatitis B virus carriers, Circulation. 105 (2002) 1028–1030.

29 N.V. Pothineni, R. Delongchamp, S. Vallurupalli, et al. Impact of hepatitis C seropositivity on the risk of coronary heart disease events, Am. J. Cardiol. 114 (2014) 1841–1845.

30 Y. Momiyama, R. Ohmori, R. Kato, et al. Lack of any association between persistent hepatitis B or C virus infection and coronary artery disease, Atherosclerosis. 181 (2005) 211–213.

31 S. Kiechl, G. Egger, M. Mayr, et al. Chronic infections and the risk of carotid atherosclerosis: prospective results from a large population study, Circulation. 103 (2001) 1064–1070.

32 K.A. Forde, K. Haynes, A.B. Troxel, et al. Risk of myocardial infarction associated with chronic hepatitis C virus infection: a population-based cohort study, J. Viral. Hepat. 19

(2012) 271–277.

33 A.H. Metwally, M.A. Elgamal. The relation between hepatitis C virus and coronary heart disease, Med. Hypotheses. 82 (2014) 505.

34 N.V. Pothineni, Y. Rochlani, S. Vallurupalli, et al. Comparison of angiographic burden of coronary artery disease in patients with versus without hepatitis C infection, Am. J. Cardiol. 116 (2015) 1041–1044.

35 C.L. Cheng, C.H. Lee, P.S. Chen, et al. Validation of acute myocardial infarction cases in the National Health Insurance Research Database in Taiwan, J. Epidemiol. 24 (2014) 500–507.

36 C.H. Chiang, W.C. Huang, J.S. Yang, et al. Five-year outcomes after acute myocardial infarction in patients with and without diabetes mellitus in Taiwan, 1996-2005, Acta. Cardiol. Sin. 29 (2013) 387–394.

37 L.M. Sun, M.C. Lin, C.L. Lin, et al. Statin use reduces prostate cancer all-cause mortality: a nationwide population-based cohort study, Medicine (Baltimore). 94 (2015) e1644.

38 J.Y. Wang, C.Y. Wang, C.H. Tan, et al. Effect of different antipsychotic drugs on short-term mortality in stroke patients, Medicine (Baltimore). 93 (2014) e170.

39 P.L. Kuo, K.C. Lin, P.L. Tang, et al. Contribution of hepatitis B to long-term outcome among patients with acute myocardial infarction: a nationwide study, Medicine (Baltimore). 95 (2016) e2678.

40 N. Ishizaka, Y. Ishizaka, M. Yamkado. Atherosclerosis as a possible extrahepatic manifestation of chronic hepatitis C virus infection, Clin. Med. Insights Cardiol. 8 (2014) 1–5.

41 M.S. Abougergi, R. Karagozian, N.D. Grace, et al. ST elevation myocardial infarction

mortality among patients with liver cirrhosis: a nationwide analysis across a decade, J. Clin. Gastroenterol. 49 (2015) 778–783.

42 A. Marui, T. Kimura, S. Tanaka, et al. Coronary revascularization in patients with liver cirrhosis, Ann. Thorac. Surg. 91 (2011) 1393–1399.

43 V. Singh, N.J. Patel, A.P. Rodriguez, et al. Percutaneous coronary intervention in patients with end-stage liver disease, Am. J. Cardiol. 117 (2016) 1729–1734.

44 E. Nilsson, H. Anderson, K. Sargenti, et al. Incidence, clinical presentation and mortality of liver cirrhosis in Southern Sweden: a 10-year population-based study, Aliment. Pharmacol. Ther. (2016)

45 CDC. Centers for Disease Control. Viral hepatitis surveillance—United States, 2013. http://www.cdc.gov/hepatitis/statistics/2013surveillance/pdfs/2013hepsurveillancerpt.pdf (accessed 03.05.16).

46 H. Innes, S.J. Hutchinson, N. Obel, et al. Liver mortality attributable to chronic hepatitis C virus infection in Denmark and Scotland: using spontaneous resolvers as the benchmark comparator, Hepatology. 63 (2016) 1506–1516.

47 J. Grebely, K. Page, R. Sacks-Davis, et al. The effects of female sex, viral genotype, and IL28B genotype on spontaneous clearance of acute hepatitis C virus infection, Hepatology. 59 (2014) 109–120.

48 D. Siagris, M. Christofidou, G.J. Theocharis, et al. Serum lipid pattern in chronic hepatitis C: histological and virological correlations, J. Viral Hepat. 13 (2006) 56–61.

49 K.E. Corey, E. Kane, C. Munroe, et al. Hepatitis C virus infection and its clearance alter circulating lipids: implications for long-term follow-up, Hepatology. 50 (2009) 1030–1037.

50 D. Marzouk, J. Sass, I. Bakr, et al. A. Fontanet, Metabolic and cardiovascular risk profiles and hepatitis C virus infection in rural Egypt, Gut. 56 (2007) 1105–1110.

FOOTNOTES

Contributors: W-C H and G-Y M set up the study concept and design. P-L T and H-C L acquired the data. P-L T, W-C, H, and J-S Y analyzed and interpret the data and statistical analysis results. W-C H, S-H K, and W-T H drafted the manuscript. G-Y M and H-T C performed critical revisions of the manuscript for important intellectual content. W-C H and C-P L supervised the study.

FIGURE LEGENDS

Figure 1. The 12-year Kaplan-Meier survival curves after the first AMI among the control group and the patients with HCV and those without liver cirrhosis (Panel A). Panel B shows the survival curve of the male subgroup. Panel C shows the survival curve of the female subgroup. The patients with liver cirrhosis had lower long-term survival rates than the control group and the male and female patients without cirrhosis. Additionally, the male AMI patients with HCV but without cirrhosis had higher mortality rates than the matched controls (log rank, $P < .0001$). However, there was no difference in long-term mortality rates between female patients in the HCV group and those in the control group (log rank, $P = .10492$). Further subgroup analysis by age and PCI was also demonstrated. Panel D shows the survival curve of younger patient (age < 65 years) subgroup. Panel E shows the survival curve of elderly patient (age ≥ 65 years) subgroup. Panel F shows the survival curve of the PCI subgroup. Panel G shows the survival

curve of the non-PCI subgroup. The patients with liver cirrhosis had lower long-term survival rates than those in the control group or those without cirrhosis in the younger patient (age < 65 years), elderly patient, and PCI or non-PCI subgroups. The mortality rate was lower in the matched controls than in patients with HCV but without cirrhosis in the younger (log rank, $P < .0001$), PCI (log rank, $P < .0001$), and non-PCI (log rank, $P = .0003$) subgroups. However, the 12-year survival rates were comparable between elderly patients in the HCV and control groups (log rank, $P = .4145$).

AMI, acute myocardial infarction; HCV, hepatitis C virus, PCI, percutaneous coronary intervention

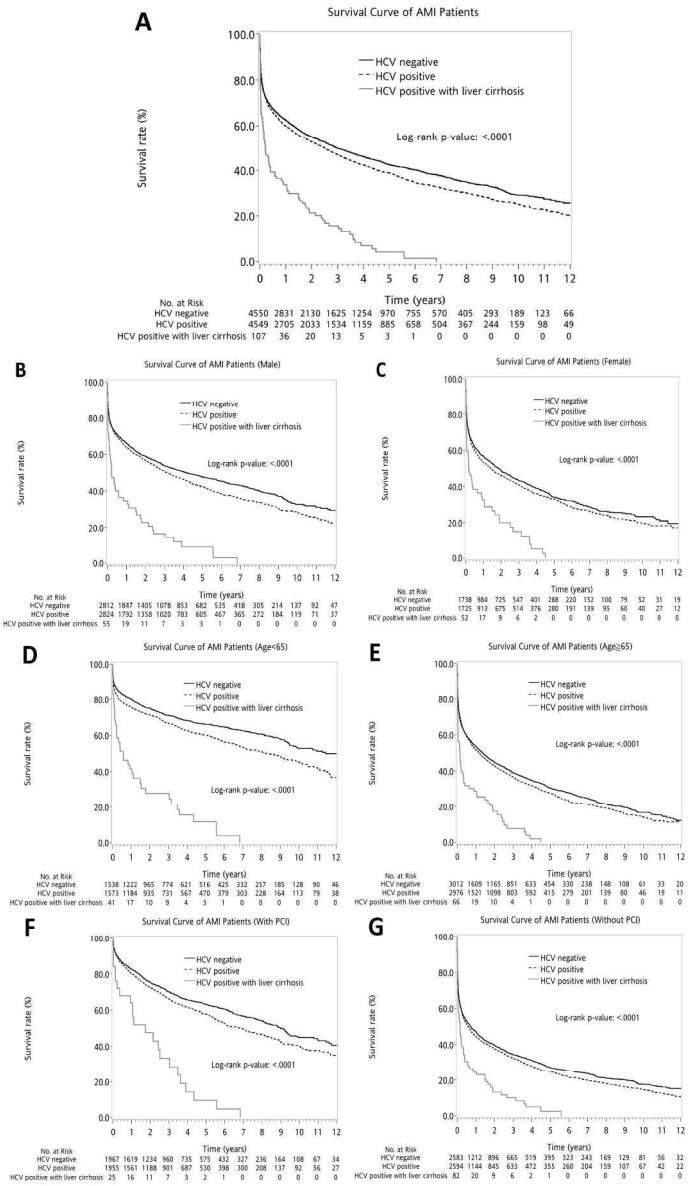
Figure 2. Forest plot evaluating the impact of HCV in different subgroups of patients after the first AMI. HCV infection influenced the long-term outcomes of subgroups of male, those with hypertension, and those without peripheral vascular disease, previous stroke, or chronic obstructive pulmonary disease.

AMI, acute myocardial infarction; HCV, hepatitis C virus; PCI, percutaneous coronary intervention

Supplementary Figure Flowchart of the establishment of the study cohort. The National Health Insurance Research Database data for approximately 23,000,000 patients between January 2000 and December 2012 were used in the analysis. A total of 186,112 cases of first AMI admission were identified. Of the 4,666 AMI patients with HCV, those who had ever received interferon therapy were excluded to minimize the variables. Therefore, a total of 4,659 patients were enrolled and further divided into those with liver cirrhosis (n=107) and those without liver

cirrhosis (n=4,552). One-to-one matching was performed, and 4,552 matched controls were included in the final analysis.

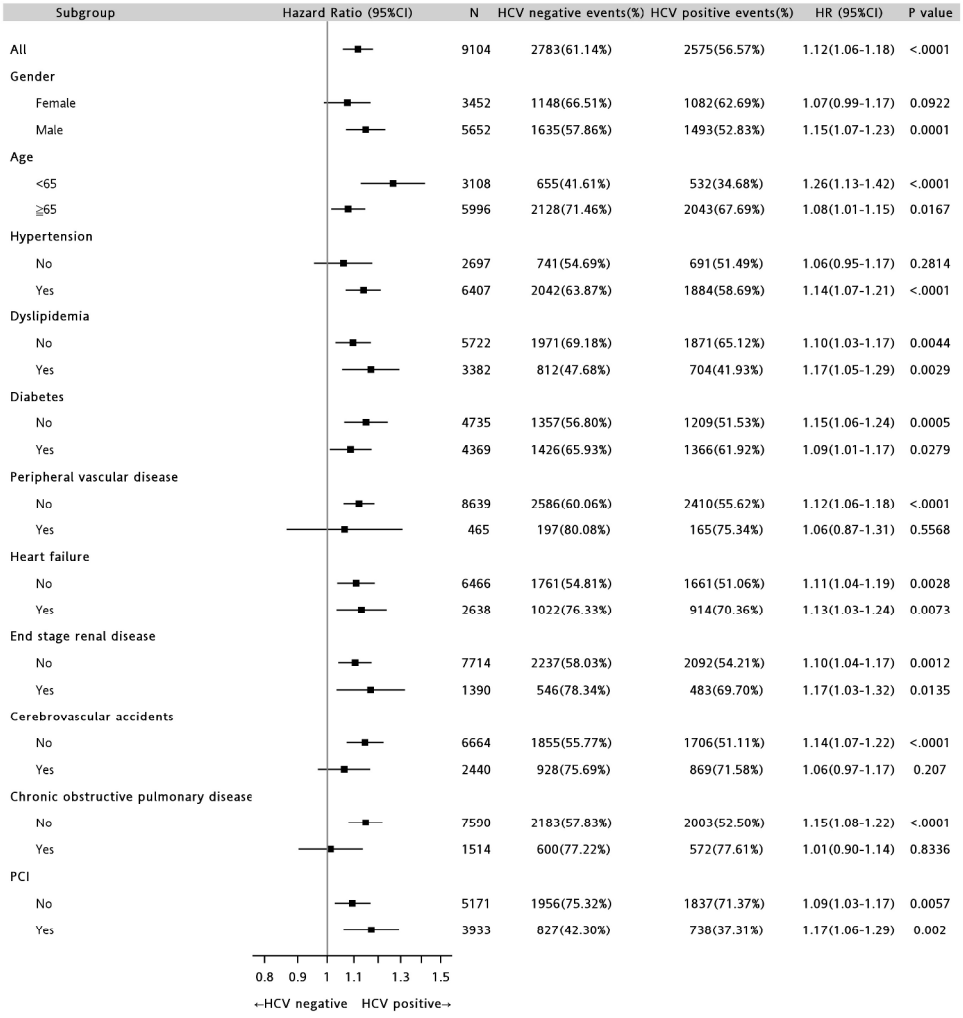
AMI, acute myocardial infarction; HCV, hepatitis C virus



The 12-year Kaplan-Meier survival curves after the first AMI among the control group and the patients with HCV and those without liver cirrhosis (Panel A). Panel B shows the survival curve of the male subgroup. Panel C shows the survival curve of the female subgroup. The patients with liver cirrhosis had lower long-term survival rates than the control group and the male and female patients without cirrhosis. Additionally, the male AMI patients with HCV but without cirrhosis had higher mortality rates than the matched controls (log rank, P < .0001). However, there was no difference in long-term mortality rates between female patients in the HCV group and those in the control group (log rank, P = .10492). Further subgroup analysis by age and PCI was also demonstrated. Panel D shows the survival curve of younger patient (age < 65 years) subgroup. Panel E shows the survival curve of elderly patient (age ≥ 65 years) subgroup. Panel F shows the survival curve of the PCI subgroup. Panel G shows the survival curve of the non-PCI subgroup. The patients with liver cirrhosis had lower long-term survival rates than those in the control group or those without cirrhosis in the younger patient (age < 65 years), elderly patient, and PCI or non-PCI subgroups. The mortality rate was lower in the matched controls than in patients with HCV but without cirrhosis in the

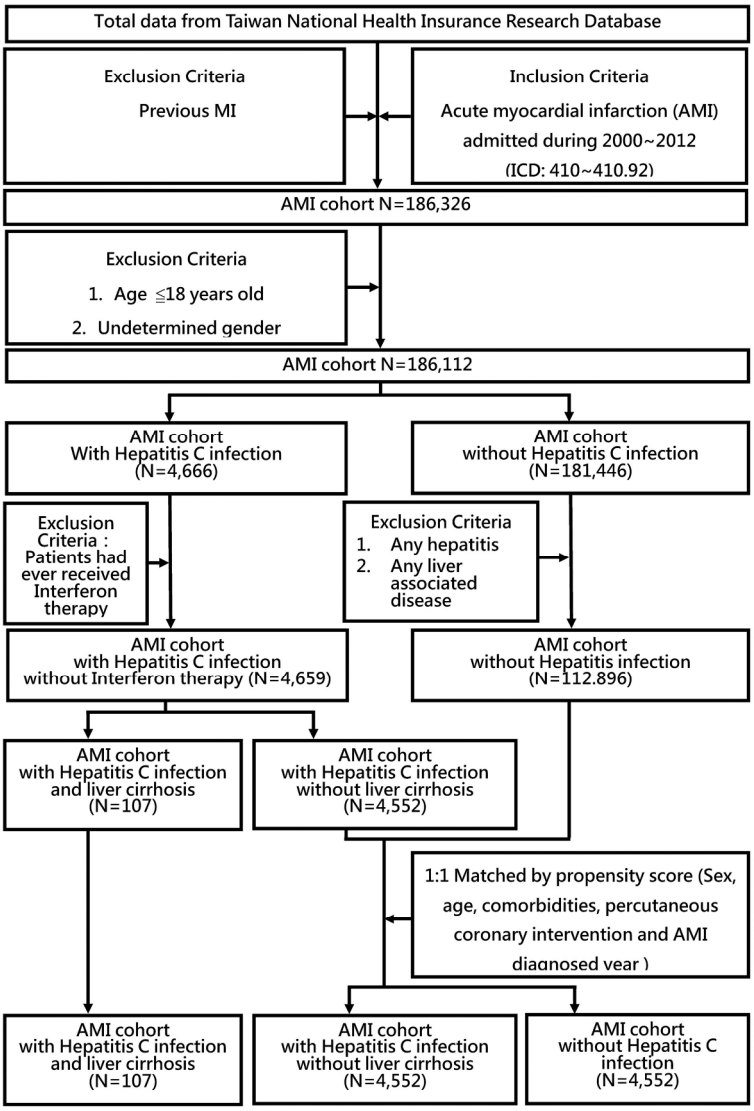
younger (log rank, P < .0001), PCI (log rank, P < .0001), and non-PCI (log rank, P = .0003) subgroups. However, the 12-year survival rates were comparable between elderly patients in the HCV and control groups (log rank, P = .4145).
AMI, acute myocardial infarction; HCV, hepatitis C virus, PCI, percutaneous coronary intervention

249x394mm (300 x 300 DPI)



Forest plot evaluating the impact of HCV in different subgroups of patients after the first AMI. HCV infection influenced the long-term outcomes of subgroups of male, those with hypertension, and those without peripheral vascular disease, previous stroke, or chronic obstructive pulmonary disease.
AMI, acute myocardial infarction; HCV, hepatitis C virus; PCI, percutaneous coronary intervention

241x254mm (300 x 300 DPI)



Flowchart of the establishment of the study cohort. The National Health Insurance Research Database data for approximately 23,000,000 patients between January 2000 and December 2012 were used in the analysis. A total of 186,112 cases of first AMI admission were identified. Of the 4,666 AMI patients with HCV, those who had ever received interferon therapy were excluded to minimize the variables. Therefore, a total of 4,659 patients were enrolled and further divided into those with liver cirrhosis (n=107) and those without liver cirrhosis (n=4,552). One-to-one matching was performed, and 4,552 matched controls were included in the final analysis.
AMI, acute myocardial infarction; HCV, hepatitis C virus

111x157mm (600 x 600 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1(Y)	(*a*) Indicate the study's design with a commonly used term in the title or the abstract(P1, 3)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found(P3)
Introduction		
Background/rationale	2(Y)	Explain the scientific background and rationale for the investigation being reported(P5)
Objectives	3(Y)	State specific objectives, including any prespecified hypotheses(P5)
Methods		
Study design	4(Y)	Present key elements of study design early in the paper(P6)
Setting	5(Y)	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection(P6)
Participants	6(Y)	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up(P6,7) *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls(P7) *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed(P6,7) *Case-control study*—For matched studies, give matching criteria and the number of controls per case(P7)
Variables	7(Y)	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable(P6,7)
Data sources/ measurement	8(Y)	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group(P6,7)
Bias	9(Y)	Describe any efforts to address potential sources of bias(P7)
Study size	10(Y)	Explain how the study size was arrived at(P6,7)
Quantitative variables	11(Y)	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why(P6,7)
Statistical methods	12(Y)	(*a*) Describe all statistical methods, including those used to control for confounding(P7)
		(*b*) Describe any methods used to examine subgroups and interactions(P8)
		(*c*) Explain how missing data were addressed(Nil)
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed(P6) *Case-control study*—If applicable, explain how matching of cases and controls was addressed(P7) *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses(P8)

Continued on next page

Results		
Participants	13(Y)	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed(P6,7)
		(b) Give reasons for non-participation at each stage(Nil)
		(c) Consider use of a flow diagram(available for attachment)
Descriptive data	14(Y)	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders(P8,10-12)
		(b) Indicate number of participants with missing data for each variable of interest(Nil)
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) (P13)
Outcome data	15(Y)	*Cohort study*—Report numbers of outcome events or summary measures over time(P13)
		Case-control study—Report numbers in each exposure category, or summary measures of exposure(P13)
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16(Y)	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included(P13-14)
		(*b*) Report category boundaries when continuous variables were categorized(P13-14)
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period(P13-14)
Other analyses	17(Y)	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses(P13-14)
Discussion		
Key results	18(Y)	Summarise key results with reference to study objectives(P16)
Limitations	19(Y)	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias(P19)
Interpretation	20(Y)	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence(P17-19)
Generalisability	21(Y)	Discuss the generalisability (external validity) of the study results(P19)
Other information		
Funding	22(Y)	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based(P19)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Impact of hepatitis C virus infection on long-term mortality after acute myocardial infarction: A nationwide population-based, propensity-matched cohort study in Taiwan

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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Cardiovascular medicine, Gastroenterology and hepatology, Health services research, Infectious diseases, Epidemiology
Keywords:	acute myocardial infarction, case control study, hepatitis C, liver cirrhosis, propensity score

Impact of hepatitis C virus infection on long-term mortality after acute myocardial infarction: A nationwide population-based, propensity-matched cohort study in Taiwan

Kuo, Hung: Impact of hepatitis C virus on myocardial infarction

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Journal Subject Codes: Inflammation, Acute Coronary Syndrome

List of Abbreviations

ACEI, angiotensin-converting enzyme inhibitors; AMI, acute myocardial infarction; ARB, angiotensin receptor blockers; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CI, confidence interval; ESRD, end-stage renal disease; HCV, hepatitis C virus; ICD-9-CM, International Classification of Diseases, 9th edition, Clinical Modification; HR, hazard ratio; LMWH, low molecular weight heparin; NHI, National Health Insurance; NHIRD, National Health Insurance Research Database; PCI, percutaneous coronary intervention; SD, standard deviation

Word Count: 2894

ABSTRACT

Introduction: The influence of hepatitis C virus (HCV) infection on long-term outcomes of patients with acute myocardial infarction (AMI) is unclear. Therefore, this study aimed to analyse the impact of HCV infection on 12-year mortality rates after AMI using data from the Taiwan National Health Insurance Research Database (NHIRD).

Methods: NHIRD data for approximately 23,000,000 patients between January 2000 and December 2012 were analysed. A total of 186,112 cases of first AMI admission were identified. A total of 4,659 HCV-infected patients not receiving interferon therapy were enrolled and divided into those with (n = 107) or without (n = 4,552) cirrhosis. Using one-to-one matching, 4,552 matched controls were included in the final analysis.

Results: The 12-year mortality rate was significantly higher in AMI patients with HCV infection and cirrhosis than in those with HCV infection but without cirrhosis ($P < .0001$) or controls ($P < .0001$). Patients with HCV infection but without cirrhosis had significantly higher long-term mortality rates than the matched controls ($P < .0001$). The hazard ratio (HR) for mortality was higher in patients with HCV infection (hazard ratio [HR], 1.12; 95% confidence interval, 1.06–1.18). HCV influenced outcomes among the subgroups of patients who were male (HR, 1.15) and those who had hypertension (HR, 1.14).

Conclusions: HCV infection influenced the 12-year mortality rates of AMI patients, especially those who were male and those who had hypertension. Cirrhosis further increased the long-term mortality rates of AMI patients with HCV infection.

Keywords: acute myocardial infarction, case control study, hepatitis C, liver cirrhosis, propensity score

Strengths and limitations of this study:

1. This cohort study was based on Taiwan National Health Insurance Research Database (NHIRD) data a representative sample of approximately 23,000,000 subjects from 93% of the medical institutions of Taiwan over the past 12 years.
2. The diagnosis of the AMI population might not be confirmed owing to lacking information on the burden of atherosclerosis assessed.

This cohort study based on NHIRD data might underestimate the HCV-infected population.

3. The database does not include data on family history; actual cause of death; body weight; body height; smoking history; or lipid, viral load, and glucose levels, all of which might be potential confounding factors.
4. The distinct cause-effect correlation remains vague and is pending further study for clarification.

INTRODUCTION

Acute myocardial infarction (AMI), one of the leading causes of death among men and women in Taiwan and worldwide, is now becoming increasingly more common in developed countries.[1] The coronary arteries of patients with AMI have lipid-rich cores after atherosclerosis plaque rupture that induce the formation of unstable platelet aggregates following an intermittent reduction in coronary flow and distal embolization.[2, 3] Despite advances in revascularization and medications, AMI can still trigger lethal arrhythmia, hemodynamic instability, or death. Therefore, assessing the risk factors of clinical outcomes after AMI remains an important research topic.[4-7] Infection has been hypothesized as a contributing risk factor of coronary artery disease (CAD).[8, 9] Several direct and indirect mechanisms have been proposed to explain the association between infectious agents and coronary heart disease.[9-11]

An estimated 2–3% of the global population is infected with the hepatitis C virus (HCV).[12] HCV infection was proposed to be associated with endothelial dysfunction,[13] atherosclerosis,[10, 14-16] CAD,[17-19] carotid artery disease,[20] and stroke.[21, 22] However, the association between HCV infection and CAD remains controversial.[23-27] Previous studies showed an association between the HCV core protein and carotid atherosclerosis[18] as well as between HCV seropositivity and CAD.[10, 28, 29] However, in a study of active-duty military personnel with a high prevalence of HCV infection, no association was found between HCV seropositivity and AMI.[9] Additionally, other studies reported no association between HCV infection and CAD,[30] carotid plaques,[31] or the risk of incident myocardial infarction.[32, 33] A recent study showed that patients with HCV infection had less obstructive CAD on coronary angiography.[34] Furthermore, the influence of HCV infection on the long-term outcomes of patients after AMI is unclear.

The present study aimed to analyse the impact of HCV infection on 12-year mortality after AMI using data from the Taiwan National Health Insurance Research Database (NHIRD).

MATERIAL AND METHODS

The National Health Insurance (NHI) program in Taiwan has financed the healthcare of more than 99% of its residents since 1995. The NHIRD includes detailed information from the medical records of patients admitted to hospitals, including their age, sex, diagnosis, prescriptions, interventions, and relevant survival data. This study was approved by the Human Research Committee of Kaohsiung Veterans General Hospital, Taiwan.

All patients who were admitted to hospitals with the main diagnosis of AMI (International Classification of Diseases, 9th edition, Clinical Modification [ICD-9-CM] codes 410–410.92) between January 2000 and December 2012 were identified from the NHIRD, which includes data for approximately 23,000,000 patients. Among these patients, those with a history of admission for AMI, whose sex was undetermined, or who were <18 years of age were excluded, and a total of 186,112 unique cases of AMI were identified (Supplementary Figure**)**.

Of the 186,112 patients, 4,666 with HCV infection (ICD-9-CM codes V02.62, 070.51, and 070.54) were identified. Among the remaining 181,446 patients, those with a history of hepatitis (ICD-9-CM codes V02.61, 070.30, 070.32, and 571.1) or other liver-associated diseases (ICD-9-CM codes 155, 070, 570, 571, 572, 573, 197.7, 230.8, 235.3, 789.1, and V02.6) were excluded, leaving 112,896 AMI controls (Supplementary Figure**)**.

Of the 4,666 AMI patients with HCV infection, those who had ever received interferon therapy were excluded to minimize the variables. Therefore, a total of 4,659 patients with HCV infection were enrolled and further divided into those with (n = 107) and those without (n =

4,552) liver cirrhosis. To minimize baseline differences between the AMI cohort with HCV infection but without liver cirrhosis and the control group, a propensity score–matching technique was used. One-to-one matching was performed using the following variables: sex, age, hypertension (IDC-9-CM codes 401–405), dyslipidemia (IDC-9-CM code 272), peripheral vascular disease (ICD-9-CM codes 443.9, 441, 441.9, 785.4, and V43.4 or procedure code 38.48), diabetes mellitus (ICD-9-CM code 250), heart failure (ICD-9-CM code 428), previous stroke (ICD-9-CM codes 430–437 and A290–A294), end-stage renal disease (ESRD; ICD-9-CM code 585), chronic obstructive pulmonary disease (ICD-9-CM codes 491, 492, and 496), and percutaneous coronary intervention (PCI, CD-9-CM procedure codes 36.0, 36.01, 36.02, 36.05, 36.06, and 36.09). The data from 4,552 AMI patients with HCV infection but without liver cirrhosis and from 4,552 matched controls were included in the final analysis (Supplementary Figure**)**.

For the outcome analysis, survival was defined as the time interval from the hospital admission date to the NHI coverage end date. Since the NHI premium is paid monthly, coverage can easily be discontinued at the time of death. Thus, the end date of NHI coverage is a valid proxy for mortality, which had a maximum error of 1 month. [35-39]

Statistical analysis

SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA) was used to extract and analyse the data. Descriptive statistics were calculated for all variables, with categorical data reported as percentile values and continuous data reported as mean and standard deviation. The paired *t*-test was used to compare continuous variables and the chi-squared test was used to compare categorical variables among the groups. Hazard ratios (HRs), confidence intervals (CIs),

and *P* values from Cox proportional hazards regression models are presented. Kaplan-Meier cumulative survival curves were constructed to compare survival among the groups. *P* values < .05 were considered statistically significant.

RESULTS

Characteristics of the study group

The characteristics of the 4,552 patients with HCV infection but without cirrhosis and the 4,552 patients in the control group are presented in Table 1. The primary demographic variables of age, male to female distribution, and comorbidities were comparable among the groups. Additionally, the medications used were comparable among the groups except for antiplatelet medications ($P = .0005$) and statins ($P = .0323$), which were used more often in the control group than in the HCV-infected group (Table 1). The proportion of patients who underwent PCI was comparable between the HCV-infected without liver cirrhosis group (42.95%) and the control group (43.23%; $P = .7832$), independent of sex or age subgroup (Table 1).

Table 1. Characteristics of all patients with first hospitalized AMI with and without HCV infection in this propensity score–matched case control study

Characteristics	AMI cohort without HCV n = 4552 Group 1	AMI cohort with HCV but not liver cirrhosis n = 4552 Group 2	AMI cohort with HCV and liver cirrhosis n = 107 Group 3	*P* value Group 1 vs Group 2	*P* value Group 3 vs Group 2	*P* value Group 3 vs Group 1
Age < 65 years	1,538 (33.79%)	1,574 (34.58%)	41 (38.32%)	0.4264	0.4217	0.3278
Male participants	2,812 (61.78%)	2,826 (62.08%)	55 (51.4%)	0.7625	0.0246	0.0293
Comorbidity						
Hypertension	3,214 (70.61%)	3,197 (70.23%)	66 (61.68%)	0.6963	0.0563	0.0456
Dyslipidemia	1,680 (36.91%)	1,703 (37.41%)	20 (18.69%)	0.6179	<.0001	0.0001
Diabetes mellitus	2,217 (48.7%)	2,163 (47.52%)	70 (65.42%)	0.2573	0.0002	0.0006
Peripheral vascular disease	220 (4.83%)	246 (5.4%)	3 (2.8%)	0.2163	0.2371	0.3311

Heart failure	1,305 (28.67%)	1,339 (29.42%)	31 (28.97%)	0.4325	0.9207	0.9453
End-stage renal disease	681 (14.96%)	697 (15.31%)	13 (12.15%)	0.6399	0.3683	0.4195
Previous stroke	1,219 (26.78%)	1,226 (26.93%)	25 (23.36%)	0.3685	0.4103	0.4300
Chronic obstructive pulmonary disease	745 (16.37%)	777 (17.07%)	14 (13.08%)	0.3688	0.2778	0.3635
Medication						
Any antiplatelet	3,821 (83.94%)	3,695 (81.17%)	68 (63.55%)	0.0005	<.0001	<.0001
ACEI or ARB	2,571 (56.48%)	2,523 (55.43%)	32 (29.91%)	0.2109	<.0001	<.0001
Statin	1,288 (28.3%)	1,197 (26.3%)	13 (12.15%)	0.0323	0.0010	0.0002
Beta-blocker	2,191 (48.13%)	2,156 (47.36%)	36 (33.64%)	0.1627	0.0049	0.003
Calcium channel blocker	1,615 (35.48%)	1,631 (35.83%)	26 (24.3%)	0.7263	0.0138	0.0167
Heparin	2,579 (56.66%)	2,548 (55.98%)	40 (37.38%)	0.5124	0.0001	<.0001
Low molecular weight heparin	1,173 (25.77%)	1,151 (25.29%)	20 (18.69%)	0.3969	0.1201	0.0973
Dopamine	824 (18.1%)	762 (16.74%)	29 (27.1%)	0.1867	0.0048	0.0173
Epinephrine	227 (4.99%)	224 (4.92%)	8 (7.48%)	0.3848	0.2296	0.2447
Norepinephrine	601 (13.2%)	596 (13.09%)	19 (17.76%)	0.2768	0.1589	0.1704
Atropine	161 (3.54%)	146 (3.21%)	5 (4.67%)	0.3838	0.3975	0.4328

Nitrate	3,509 (77.09%)	3,508 (77.07%)	72 (67.29%)	0.9801	0.0178	0.0175
Nicorandil	381 (8.37%)	434 (9.53%)	9 (8.41%)	0.0517	0.6955	0.9878
PCI	1,968 (43.23%)	1,955 (42.95%)	25 (23.36%)	0.7832	<.0001	<.0001
PCI ratio in male patients	1,377 (48.97%)	1,372 (48.55%)	15 (27.27%)	0.7527	0.0018	0.0014
PCI ratio in female patients	591 (33.97%)	583 (33.78%)	10 (19.23%)	0.9069	0.0284	0.0266
PCI ratio in patients aged < 65 years	840 (54.62%)	842 (53.49%)	11 (26.83%)	0.5300	0.0007	0.0004
PCI ratio, age ≥ 65 years	1,128 (37.43%)	1,113 (37.37%)	14 (21.21%)	0.9673	0.0072	0.007

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention

Compared to Group 1 (matched control group) and Group 2 (HCV-infected patients without cirrhosis group), the 107 AMI patients with HCV infection and liver cirrhosis had a lower male ratio, lower prevalence of dyslipidemia, and higher prevalence of diabetes mellitus. Additionally, the medications used were significantly lower in Group 3 than in the other two groups, including antiplatelet, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, statins, beta-blockers, calcium channel blockers, heparin, and nitrate. The proportion of patients who underwent PCI was lower in the liver cirrhosis group than in Groups 1 and 2.

Outcome analysis

The 12-year survival rate was significantly lower in AMI patients with HCV infection and liver cirrhosis than in those with HCV infection but without liver cirrhosis (log rank, $P < .0001$) and control group (log rank, $P < .0001$). Furthermore, AMI patients with HCV infection but without liver cirrhosis had significantly lower long-term survival rates than the matched AMI controls (log rank, $P < .0001$).

In the subgroup analysis, the AMI patients with liver cirrhosis had lower long-term survival rates than the control group and the patients without cirrhosis regardless of sex, age, or PCI status (Figure 1). Among the male patients, the mortality rate was lower among the matched controls than among the patients without cirrhosis (log rank, $P < .0001$; Figure 1), those with younger age (log rank, $P < .0001$; Figure 1), those who underwent PCI (log rank, $P < .0001$; Figure 1), and those who did not undergo PCI (log rank, $P = .0003$; Figure 1). However, the 12-year survival rate was comparable between the HCV group without cirrhosis and the AMI control group for female (log rank, $P = .1049$; Figure 1) and elderly patients (log rank, $P = .4145$; Figure 1).

A Cox proportional hazard regression analysis was performed to evaluate the impact of factors including sex, age, comorbidities, PCI, HCV infection, antiplatelet, and statin use on the survival of patients admitted for a first AMI (Table 2). Overall, the HR for mortality was high for patients aged ≥ 65 years (HR, 2.22; 95% CI, 2.07–2.37) as well as those with diabetes (HR, 1.34; 95% CI, 1.27–1.42), peripheral vascular disease (HR, 1.28; 95% CI,1.15–1.43), heart failure (HR, 1.27; 95% CI, 1.20–1.34), ESRD (HR, 1.78; 95% CI, 1.66–1.91), previous stroke (HR, 1.32; 95% CI, 1.24–1.40), or chronic obstructive pulmonary disease (HR, 1.24; 95% CI, 1.16–1.33). Conversely, the HR was low for patients who underwent PCI (HR, 0.50; 95% CI, 0.47–0.53) and those taking antiplatelet (HR, 0.66; 95% CI, 0.61–0.70) or statin (HR, 0.79; 95% CI, 0.71–0.88) medication. Overall, HCV infection was associated with a higher risk for mortality (HR, 1.12; 95% CI, 1.06–1.18).

Table 2. Cox proportional hazard regression analysis in patients with first hospitalized AMI with versus those without HCV infection

Variable	All (n = 9104)		Male (n = 5652)		Female (n = 3452)	
	Hazard ratio	(95% CI)	Hazard ratio	(95% CI)	Hazard ratio	(95% CI)
Sex (male vs female)	1.00	(0.95-1.06)	-	-	-	-
Age (≧65 vs <65)	2.22	(2.07-2.37)*	2.43	(2.22-2.64)*	1.88	(1.68-2.11)*
Hypertension (yes vs no)	0.95	(0.89-1.01)	0.97	(0.89-1.05)	0.92	(0.82-1.02)
Dyslipidemia (yes vs no)	0.85	(0.77-0.93)*	0.87	(0.77-0.98)*	0.83	(0.72-0.95)*
Diabetes mellitus (yes vs no)	1.34	(1.27-1.42)*	1.36	(1.27-1.47)*	1.30	(1.19-1.42)*
Peripheral vascular disease (yes vs no)	1.28	(1.15-1.43)*	1.40	(1.21-1.61)*	1.16	(0.98-1.38)
Heart failure (yes vs no)	1.27	(1.20-1.34)*	1.26	(1.17-1.37)*	1.27	(1.17-1.39)*
End-stage renal disease (yes vs no)	1.78	(1.66-1.91)*	1.94	(1.76-2.14)*	1.62	(1.46-1.80)*
Previous stroke (yes vs no)	1.32	(1.24-1.40)*	1.32	(1.22-1.43)*	1.33	(1.21-1.46)*
Chronic obstructive pulmonary disease (yes vs no)	1.24	(1.16-1.33)*	1.25	(1.15-1.36)*	1.22	(1.08-1.38)*
Percutaneous coronary intervention (yes vs no)	0.50	(0.47-0.53)*	0.48	(0.44-0.52)*	0.53	(0.48-0.59)*
Antiplatelet drug (yes vs no)	0.66	(0.61-0.70)*	0.67	(0.61-0.73)*	0.64	(0.58-0.71)*
Statin (yes vs no)	0.79	(0.71-0.88)*	0.77	(0.66-0.89)*	0.82	(0.69-0.96)*
Hepatitis C (yes vs no)	1.12	(1.06-1.18)*	1.15	(1.07-1.24)*	1.07	(0.99-1.17)

*$P < 0.05$

In further gender subgroup analyses, HCV infection was found to influence the outcomes of male patients but not female patients (HR, 1.07; 95% CI, 0.99–1.17) (Figure 2). HCV infection also did not impact the outcomes of patients without hypertension (HR, 1.06; 95% CI, 0.95–1.17), with peripheral vascular disease (HR, 1.06; 95% CI, 0.87–1.31), with cerebrovascular accidents (HR, 1.06; 95% CI, 0.97–1.17), or with chronic obstructive pulmonary disease (HR, 1.01; 95% CI, 0.90–1.14) (Figure 2).

DISCUSSION

The present study showed that HCV infection influences the 12-year outcome of patients with AMI. To our knowledge, no previous study examined the impact of HCV infection on long-term outcomes after AMI. This study also showed that the survival rate was lower among the AMI patients with HCV infection and liver cirrhosis. Furthermore, HCV infection influenced long-term mortality among the subgroups of patients who were male and had hypertension.

Some studies did not identify an association between HCV seropositivity and myocardial infarction.[9, 32] However, the previous study population[9] included young healthy men (age < 50 years) from the US military, which limited the interpretation and generalizability of the results. Another study reported that HCV infection did not increase the risk of incident myocardial infarction among a large sample of patients from the United Kingdom.[32] The results of the present study are consistent with those of previous studies that linked HCV seropositivity with carotid[10, 40] or coronary atherosclerosis.[18] Our study included data from NHIRD and evaluated only those patients with first AMI. Additionally, the percentage of elderly patients was comparable between the HCV group (65.42%) and the control group (66.21%). Previous studies mainly investigated the prevalence of coronary events in patients with hepatitis. [9, 32] However,

our study investigated whether HCV infection influences the outcomes of patients after AMI, which makes it unique.

Tsai et al.[19] recently showed that the risk of developing acute coronary syndrome was greater in patients with than in those without HCV and that the risk was the highest in middle-aged patients. This previous study focused on the influence of HCV infection on the development of acute coronary syndrome, while our study focused on the influence of HCV infection on the outcomes of patients after AMI. Furthermore, the study by Tsai et al.[19] showed that comorbidities such as hypertension, diabetes, and dyslipidemia were more likely to be present in patients with than in those without HCV, which might be attributable to the higher acute coronary syndrome risk in these patients. However, these authors matched only patient age and sex. Using a propensity score–matching technique, our analyses controlled for several established cardiovascular risk factors and other important confounding variables that might influence patient outcomes after AMI, including sex, age, hypertension, dyslipidemia, peripheral vascular disease, diabetes mellitus, heart failure, previous stroke, ESRD, chronic obstructive pulmonary disease, and PCI. Therefore, our study ensured similar baseline characteristics among groups. Our exclusion criteria were also very strict. Patients with hepatitis, liver cirrhosis, or other liver diseases were excluded from the HCV infection without cirrhosis and control groups. These exclusions were not mentioned in the study by Tsai et al.[19] Considering these factors, our study accurately analysed the influence of HCV infection on patient outcomes after AMI.

A previous study analysed data from acute care hospitals across the United States in 1999 and 2009 and showed higher in-hospital mortality rates in ST elevation myocardial infarction patients with cirrhosis compared to patients without cirrhosis.[41] Our study also showed that HCV patients with cirrhosis had significant higher mortality rates than those without cirrhosis,

which was consistent with the study in the United States.[41] Unlike those studies, our study focused on HCV-related cirrhosis and further showed the impact of cirrhosis on long-term (12-year) outcomes. The higher mortality rates in cirrhosis patients in this study might have resulted from more cases of diabetes mellitus, lower PCI rates, and less use of medications, including antiplatelets, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, statins, and beta-blockers, and HCV infection itself with or without liver cirrhosis. Other than HCV infection, the PCI intervention and life-saving medication were well recognized prognostic factor, which influence long term outcome through numerous facets, which was also shown in Table 2. First, the revascularization might save cardiac muscle for better residual cardiac function.[42] Second, antiplatelets prescription may provide better coronary artery protection.[43] Third, medication such as ACEI, ARB, and beta-blockers can prevent post AMI cardiac remodelling, and further preserve better cardiac function.[44] Fourth, all the medications mentioned above can reduce the associated cardiovascular disease risks by controlling metabolic disease. The intergroup difference over lower PCI rates and less use of medications could cause the mortality difference, by themselves without HCV infection related. The low PCI rate and use of life-saving medication in cirrhosis patients could be explained by the following. End-stage liver disease was shown to be associated with thrombocytopenia and coagulopathy predisposing patients to bleeding complications, especially in those with oesophageal varices.[45, 46] Furthermore, previous studies have shown that most patients with end-stage liver disease have higher INRs, high creatinine values, and lower haemoglobin levels.[45, 46] These cirrhotic patients might suffer from a higher frequency of peri-procedural bleeding, pseudoaneurysm formation, and the need for blood products.[45, 46]

Several studies have discussed the correlation between sex and outcomes in patients with

liver disease. In a southern Sweden 10-year population-based study, female patients with liver cirrhosis had better prognosis than their male counterparts.[47] In a Centers for Disease Control 2013 surveillance, the HCV-related mortality rate for male patients was approximately 2.6 times that for female patients.[48] However, no previous studies showed the impact of sex on AMI patients with HCV. Our study was the first to show that HCV infection influenced long-term mortality in male but not female patients. Previous studies showed that spontaneous resolution was more common in female patients with HCV, [49, 50] which might be part of reason for the difference.

Interestingly, our study showed that antiplatelets and statins were less frequently used in the HCV group than in the control group, which is consistent with the findings of a recent study.[34] The low use of antiplatelet medications and statins in patients with HCV could be secondary to physician concerns regarding liver disease and bleeding risk in these patients.[33,34] Furthermore, several studies reported that patients with HCV tended to have low cholesterol and low-density lipoprotein levels, which might partially explain the low prescription of statins.[17, 29, 32, 33, 51-53] Therefore, to unveil the real weight over each individual factor, Cox proportional hazard regression analysis was used to adjust for possible confounding factors including antiplatelets and statins. After the analysis, HCV infection (HR, 1.12; 95% CI, 1.06–1.18; Table 2) still played a critical role in the long-term mortality of AMI patients.

The present study has some limitations. First, it was retrospective in design. Therefore, to minimize confounding factors between the HCV and control groups, we used a propensity score–matching technique and found that the characteristics of the controls and the patients with HCV but without cirrhosis did not differ. Matching of the groups further supports the results. Second, ICD-9-CM codes for diagnosis of HCV infection were made by positive anti-HCV

serology test in NHIRD databases. Previous study showed the validity of adopting the positive anti-HCV serology result as positive HCV infection was accepted and confirmed. [54-56] Whereas the database did not provide available confirmatory viral load, which may have slightly underestimate the HCV-infected population. However, the major strength of this study is that the data were obtained from the NHIRD, which includes data for approximately 23,000,000 patients over the past 12 years and is representative of the general population in Taiwan. Third, the database used here does not include data on family history; actual cause of death; body weight; body height; smoking history; lipid, viral load, and glucose levels; all are potential confounding factors. Fourth, there was no information on the burden of atherosclerosis assessed using coronary angiography or intracoronary ultrasonography. However, previous studies validated the AMI data in the NHIRD of Taiwan and confirmed the validity of its use for cardiovascular diseases. [35, 39]

CONCLUSION

HCV infection was demonstrated to influence the 12-year mortality of patients after AMI in this study. Additionally, the mortality rate was higher among the patients with HCV infection and liver cirrhosis. Furthermore, HCV infection influenced the long-term outcomes of patients after AMI among the subgroups of male patients and those with hypertension. Therefore, physicians should be aware of the impact of HCV infection in patients with AMI when choosing treatment strategies.

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Data Sharing: No additional data are available.

REFERENCES

1 C.P. Wong, S.Y. Loh, K.K. Loh, et al. Acute myocardial infarction: Clinical features and outcomes in young adults in Singapore, World J. Cardiol. 4 (2012) 206–210.

2 H.D. White, D.P. Chew. Acute myocardial infarction, Lancet. 372 (2008) 570–584.

3 J. Silvain, J.P. Collet, C. Nagaswami, et al. Composition of coronary thrombus in acute myocardial infarction, J. Am. Coll. Cardiol. 57 (2011) 1359–1367.

4 W.C. Huang, K.R. Chiou, C.P. Liu, et al. Multidetector row computed tomography can identify and characterize the occlusive culprit lesions in patients early (within 24 hours) after acute myocardial infarction, Am. Heart J. 154 (2007) 914–922.

5 C.P. Liu, Y.H. Lin, M.S. Lin, et al. Evaluation of myocardial infarction patients after coronary revasculation by dual-phase multi-detector computed tomography: Now and in future, World J. Cardiol. 5 (2013) 115–118.

6 W.C. Huang, C.P. Liu, M.T. Wu, et al. Comparing culprit lesions in ST-segment elevation and non-ST-segment elevation acute coronary syndrome with 64-slice multidetector computed tomography, Eur. J. Radiol. 73 (2010) 74–81.

7 W.C. Huang, M.T. Wu, K.R. Chiou, et al. Assessing culprit lesions and active complex lesions in patients with early acute myocardial infarction by multidetector computed

tomography, Circ. J. 72 (2008) 1806–1813.

8 F.J. Nieto. Infections and atherosclerosis: new clues from an old hypothesis? Am. J. Epidemiol. 148 (1998) 937–948.

9 C.M. Arcari, K.E. Nelson, D.M. Netski, et al. No association between hepatitis C virus seropositivity and acute myocardial infarction, Clin. Infect. Dis. 43 (2006) e53–56.

10 N. Ishizaka, Y. Ishizaka, E. Takahashi, et al. Association between hepatitis C virus seropositivity, carotid-artery plaque, and intima-media thickening, Lancet. 359 (2002)133–135.

11 C.P. Oliveira, C.R. Kappel, E.R. Siqueira, et al. Effects of hepatitis C virus on cardiovascular risk in infected patients: a comparative study. Int. J. Cardiol. 164 (2013) 221–226.

12 M.J. Alter. Epidemiology of hepatitis C in the West, Semin. Liver Dis. 15 (1995) 5–14.

13 M. Barone, M.T. Viggiani, A. Amoruso, et al. Endothelial dysfunction correlates with liver fibrosis in chronic HCV infection, Gastroenterol. Res. Pract. 2015 (2015) 682174.

14 M. Fukui, Y. Kitagawa, N. Nakamura, et al. Hepatitis C virus and atherosclerosis in patients with type 2 diabetes, JAMA 289 (2003) 1245–1246.

15 L.E. Adinolfi, L. Restivo, R. Zampino, et al. Chronic HCV infection is a risk of atherosclerosis. Role of HCV and HCV-related steatosis, Atherosclerosis. 221 (2012) 496–502.

16 G. Targher, L. Bertolini, R. Padovani, et al. Differences and similarities in early atherosclerosis between patients with non-alcoholic steatohepatitis and chronic hepatitis B and C, J. Hepatol. 46 (2007) 1126–1132.

17 A.A. Butt, W. Xiaoqiang, M. Budoff, et al. Hepatitis C virus infection and the risk of

coronary disease, Clin. Infect. Dis. 49 (2009) 225–232.

18 C. Vassalle, S. Masini, F. Bianchi, et al. Evidence for association between hepatitis C virus seropositivity and coronary artery disease, Heart. 90 (2004) 565–566.

19 M.S. Tsai, Y.C. Hsu, P.C. Yu, et al. Long-term risk of acute coronary syndrome in hepatitis C virus infected patients without antiviral treatment: A cohort study from an endemic area, Int. J. Cardiol. 181 (2015) 27–29.

20 H. Huang, R. Kang, Z. Zhao. Is hepatitis C associated with atherosclerotic burden? A systematic review and meta-analysis, PLoS One. 9 (2014) e106376.

21 H. He, R. Kang, Z. Zhao. Hepatitis C virus infection and risk of stroke: a systematic review and meta-analysis, PLoS One. 8 (2013) e81305.

22 L.E. Adinolfi, L. Restivo, B. Guerrera, et al. Chronic HCV infection is a risk factor of ischemic stroke, Atherosclerosis. 231 (2013) 22–26.

23 C.C. Wang, J.H. Kao. Hepatitis C virus infection, lipids, and coronary heart disease: a Pandora's box, Hepatology. 51 (2010) 343; author reply 343–344.

24 S. Petta, F.S. Macaluso, A. Craxi. Cardiovascular diseases and HCV infection: a simple association or more? Gut. 63 (2014) 369–375.

25 A. Mostafa, M.K. Mohamed, M. Saeed, et al. Hepatitis C infection and clearance: impact on atherosclerosis and cardiometabolic risk factors, Gut. 59 (2010) 1135–1140.

26 R.J. Wong, F. Kanwal, Z.M. Younossi, et al. Hepatitis C virus infection and coronary artery disease risk: a systematic review of the literature, Dig. Dis. Sci. 59 (2014) 1586–1593.

27 T. Roed, A.M. Lebech, A. Kjaer, et al. Hepatitis C virus infection and risk of coronary artery disease: a systematic review of the literature, Clin. Physiol. Funct. Imaging. 32

(2012) 421–430.

28 N. Ishizaka, Y. Ishizaka, E. Takahashi, et al. Increased prevalence of carotid atherosclerosis in hepatitis B virus carriers, Circulation. 105 (2002) 1028–1030.

29 N.V. Pothineni, R. Delongchamp, S. Vallurupalli, et al. Impact of hepatitis C seropositivity on the risk of coronary heart disease events, Am. J. Cardiol. 114 (2014) 1841–1845.

30 Y. Momiyama, R. Ohmori, R. Kato, et al. Lack of any association between persistent hepatitis B or C virus infection and coronary artery disease, Atherosclerosis. 181 (2005) 211–213.

31 S. Kiechl, G. Egger, M. Mayr, et al. Chronic infections and the risk of carotid atherosclerosis: prospective results from a large population study, Circulation. 103 (2001) 1064–1070.

32 K.A. Forde, K. Haynes, A.B. Troxel, et al. Risk of myocardial infarction associated with chronic hepatitis C virus infection: a population-based cohort study, J. Viral. Hepat. 19 (2012) 271–277.

33 A.H. Metwally, M.A. Elgamal. The relation between hepatitis C virus and coronary heart disease, Med. Hypotheses. 82 (2014) 505.

34 N.V. Pothineni, Y. Rochlani, S. Vallurupalli, et al. Comparison of angiographic burden of coronary artery disease in patients with versus without hepatitis C infection, Am. J. Cardiol. 116 (2015) 1041–1044.

35 C.L. Cheng, C.H. Lee, P.S. Chen, et al. Validation of acute myocardial infarction cases in the National Health Insurance Research Database in Taiwan, J. Epidemiol. 24 (2014) 500–507.

36 C.H. Chiang, W.C. Huang, J.S. Yang, et al. Five-year outcomes after acute myocardial infarction in patients with and without diabetes mellitus in Taiwan, 1996-2005, Acta. Cardiol. Sin. 29 (2013) 387–394.

37 L.M. Sun, M.C. Lin, C.L. Lin, et al. Statin use reduces prostate cancer all-cause mortality: a nationwide population-based cohort study, Medicine (Baltimore). 94 (2015) e1644.

38 J.Y. Wang, C.Y. Wang, C.H. Tan, et al. Effect of different antipsychotic drugs on short-term mortality in stroke patients, Medicine (Baltimore). 93 (2014) e170.

39 P.L. Kuo, K.C. Lin, P.L. Tang, et al. Contribution of hepatitis B to long-term outcome among patients with acute myocardial infarction: a nationwide study, Medicine (Baltimore). 95 (2016) e2678.

40 N. Ishizaka, Y. Ishizaka, M. Yamkado. Atherosclerosis as a possible extrahepatic manifestation of chronic hepatitis C virus infection, Clin. Med. Insights Cardiol. 8 (2014) 1–5.

41 M.S. Abougergi, R. Karagozian, N.D. Grace, et al. ST elevation myocardial infarction mortality among patients with liver cirrhosis: a nationwide analysis across a decade, J. Clin. Gastroenterol. 49 (2015) 778–783.

42 K.C. Allman, L.J. Shaw, R. Hachamovitch, et al. Myocardial Viability Testing and Impact of Revascularization on Prognosis in Patients With Coronary Artery Disease and Left Ventricular Dysfunction: A Meta-Analysis, JACC. 39 (2002) 1151-1158.

43 Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients, BMJ. 324(2002) 71-86.

44 B. Pitt, H. White, J. N, et al. Eplerenone Reduces Mortality 30 Days After Randomization Following Acute Myocardial Infarction in Patients With Left Ventricular Systolic Dysfunction and Heart Failure, JACC. 46 (2005) 425-431.

45 A. Marui, T. Kimura, S. Tanaka, et al. Coronary revascularization in patients with liver cirrhosis, Ann. Thorac. Surg. 91 (2011) 1393–1399.

46 V. Singh, N.J. Patel, A.P. Rodriguez, et al. Percutaneous coronary intervention in patients with end-stage liver disease, Am. J. Cardiol. 117 (2016) 1729–1734.

47 E. Nilsson, H. Anderson, K. Sargenti, et al. Incidence, clinical presentation and mortality of liver cirrhosis in Southern Sweden: a 10-year population-based study, Aliment. Pharmacol. Ther. (2016)

48 CDC. Centers for Disease Control. Viral hepatitis surveillance—United States, 2013. http://www.cdc.gov/hepatitis/statistics/2013surveillance/pdfs/2013hepsurveillancerpt.pdf (accessed 03.05.16).

49 H. Innes, S.J. Hutchinson, N. Obel, et al. Liver mortality attributable to chronic hepatitis C virus infection in Denmark and Scotland: using spontaneous resolvers as the benchmark comparator, Hepatology. 63 (2016) 1506–1516.

50 J. Grebely, K. Page, R. Sacks-Davis, et al. The effects of female sex, viral genotype, and IL28B genotype on spontaneous clearance of acute hepatitis C virus infection, Hepatology. 59 (2014) 109–120.

51 D. Siagris, M. Christofidou, G.J. Theocharis, et al. Serum lipid pattern in chronic hepatitis C: histological and virological correlations, J. Viral Hepat. 13 (2006) 56–61.

52 K.E. Corey, E. Kane, C. Munroe, et al. Hepatitis C virus infection and its clearance alter

circulating lipids: implications for long-term follow-up, Hepatology. 50 (2009) 1030–1037.

53 D. Marzouk, J. Sass, I. Bakr, et al. A. Fontanet, Metabolic and cardiovascular risk profiles and hepatitis C virus infection in rural Egypt, Gut. 56 (2007) 1105–1110.

54 C.W. Shepard, L. Finelli, M.J. Alter. Global epidemiology of hepatitis C virus infection, Lancet Infect Dis. 5(2005) 558-567.

55 K.M. Hanafiah, J. Groeger, A.D. Flaxman, et al. Global Epidemiology of Hepatitis C Virus Infection: New Estimates of Age-Specific Antibody to HCV Seroprevalence, Hepatology. 57 (2013) 1333–1342.

56 Y.C. Chen, H.Y. Lin, C.Y. Li, et al. A nationwide cohort study suggests that hepatitis C virus infection is associated with increased risk of chronic kidney disease. Kidney International. 85(2014) 1200–1207.

FOOTNOTES

Contributors: W-C H and G-Y M set up the study concept and design. P-L T and H-C L acquired the data. P-L T, W-C, H, and J-S Y analyzed and interpret the data and statistical analysis results. W-C H, S-H K, and W-T H drafted the manuscript. G-Y M and H-T C performed critical revisions of the manuscript for important intellectual content. W-C H and C-P L supervised the study.

FIGURE LEGENDS

Figure 1. The 12-year Kaplan-Meier survival curves after the first AMI among the control group and the patients with HCV and those without liver cirrhosis (Panel A). Panel B shows the survival curve of the male subgroup. Panel C shows the survival curve of the female subgroup. The patients with liver cirrhosis had lower long-term survival rates than the control group and the male and female patients without cirrhosis. Additionally, the male AMI patients with HCV but without cirrhosis had higher mortality rates than the matched controls (log rank, $P < .0001$). However, there was no difference in long-term mortality rates between female patients in the HCV group and those in the control group (log rank, $P = .10492$). Further subgroup analysis by age and PCI was also demonstrated. Panel D shows the survival curve of younger patient (age < 65 years) subgroup. Panel E shows the survival curve of elderly patient (age ≥ 65 years) subgroup. Panel F shows the survival curve of the PCI subgroup. Panel G shows the survival curve of the non-PCI subgroup. The patients with liver cirrhosis had lower long-term survival rates than those in the control group or those without cirrhosis in the younger patient (age < 65 years), elderly patient, and PCI or non-PCI subgroups. The mortality rate was lower in the matched controls than in patients with HCV but without cirrhosis in the younger (log rank, $P < .0001$), PCI (log rank, $P < .0001$), and non-PCI (log rank, $P = .0003$) subgroups. However, the 12-year survival rates were comparable between elderly patients in the HCV and control groups (log rank, $P = .4145$).

AMI, acute myocardial infarction; HCV, hepatitis C virus, PCI, percutaneous coronary intervention

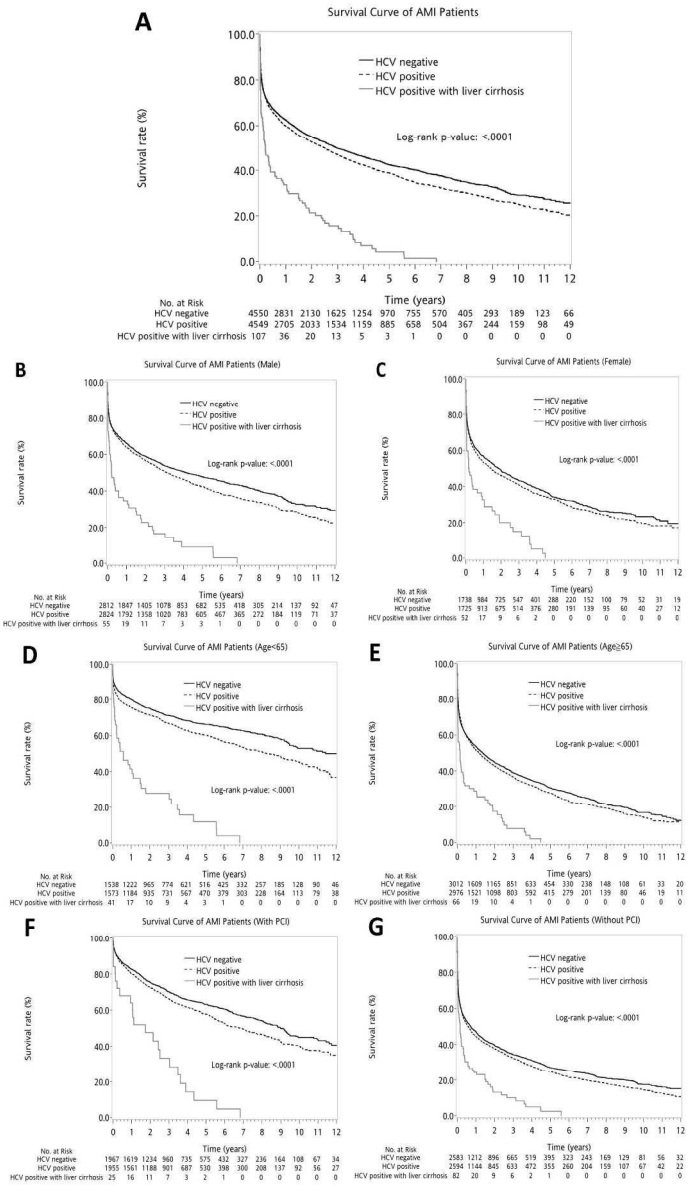
Figure 2. Forest plot evaluating the impact of HCV in different subgroups of patients after the first AMI. HCV infection influenced the long-term outcomes of subgroups of male, those with

hypertension, and those without peripheral vascular disease, previous stroke, or chronic obstructive pulmonary disease.

AMI, acute myocardial infarction; HCV, hepatitis C virus; PCI, percutaneous coronary intervention

Supplementary Figure Flowchart of the establishment of the study cohort. The National Health Insurance Research Database data for approximately 23,000,000 patients between January 2000 and December 2012 were used in the analysis. A total of 186,112 cases of first AMI admission were identified. Of the 4,666 AMI patients with HCV, those who had ever received interferon therapy were excluded to minimize the variables. Therefore, a total of 4,659 patients were enrolled and further divided into those with liver cirrhosis (n=107) and those without liver cirrhosis (n=4,552). One-to-one matching was performed, and 4,552 matched controls were included in the final analysis.

AMI, acute myocardial infarction; HCV, hepatitis C virus



The 12-year Kaplan-Meier survival curves after the first AMI among the control group and the patients with HCV and those without liver cirrhosis (Panel A). Panel B shows the survival curve of the male subgroup. Panel C shows the survival curve of the female subgroup. The patients with liver cirrhosis had lower long-term survival rates than the control group and the male and female patients without cirrhosis. Additionally, the male AMI patients with HCV but without cirrhosis had higher mortality rates than the matched controls (log rank, P < .0001). However, there was no difference in long-term mortality rates between female patients in the HCV group and those in the control group (log rank, P = .10492). Further subgroup analysis by age and PCI was also demonstrated. Panel D shows the survival curve of younger patient (age < 65 years) subgroup. Panel E shows the survival curve of elderly patient (age ≥ 65 years) subgroup. Panel F shows the survival curve of the PCI subgroup. Panel G shows the survival curve of the non-PCI subgroup. The patients with liver cirrhosis had lower long-term survival rates than those in the control group or those without cirrhosis in the younger patient (age < 65 years), elderly patient, and PCI or non-PCI subgroups. The mortality rate was lower in the matched controls than in patients with HCV but without cirrhosis in the

younger (log rank, P < .0001), PCI (log rank, P < .0001), and non-PCI (log rank, P = .0003) subgroups. However, the 12-year survival rates were comparable between elderly patients in the HCV and control groups (log rank, P = .4145).
AMI, acute myocardial infarction; HCV, hepatitis C virus, PCI, percutaneous coronary intervention

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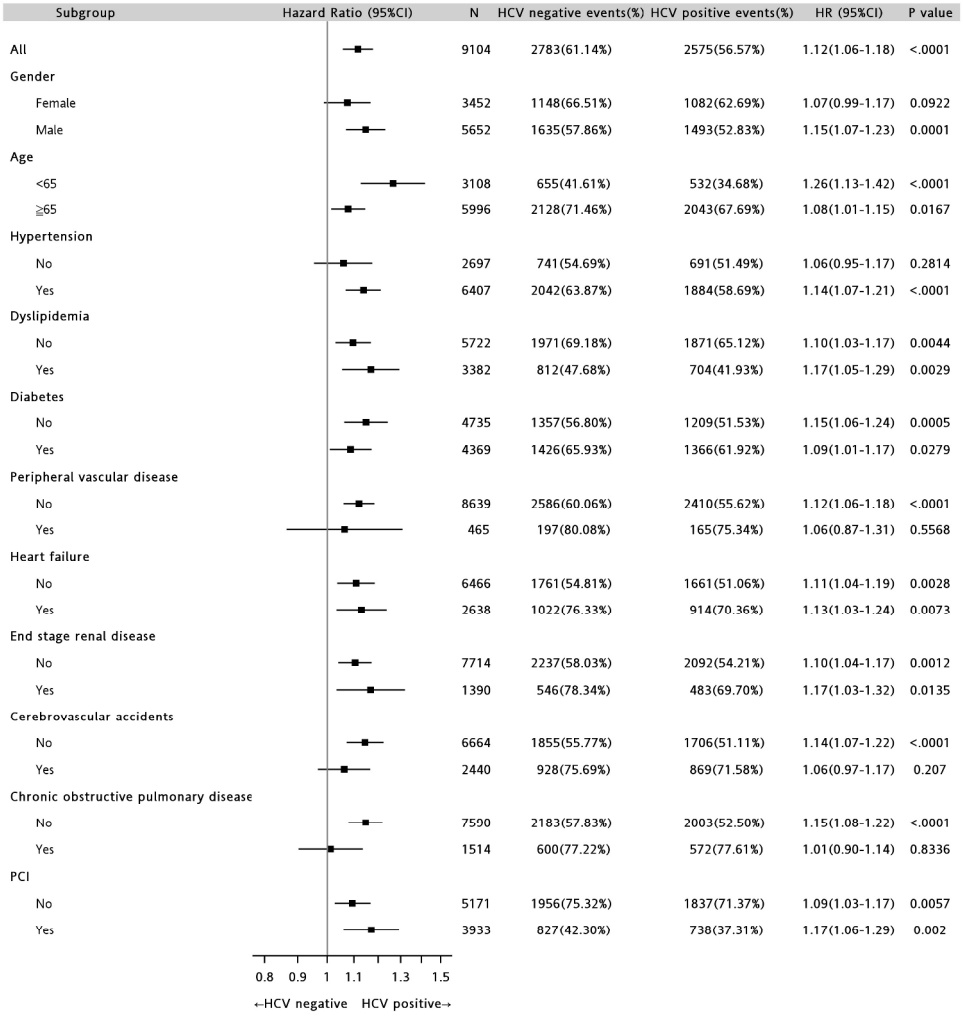

Forest plot evaluating the impact of HCV in different subgroups of patients after the first AMI. HCV infection influenced the long-term outcomes of subgroups of male, those with hypertension, and those without peripheral vascular disease, previous stroke, or chronic obstructive pulmonary disease.
AMI, acute myocardial infarction; HCV, hepatitis C virus; PCI, percutaneous coronary intervention

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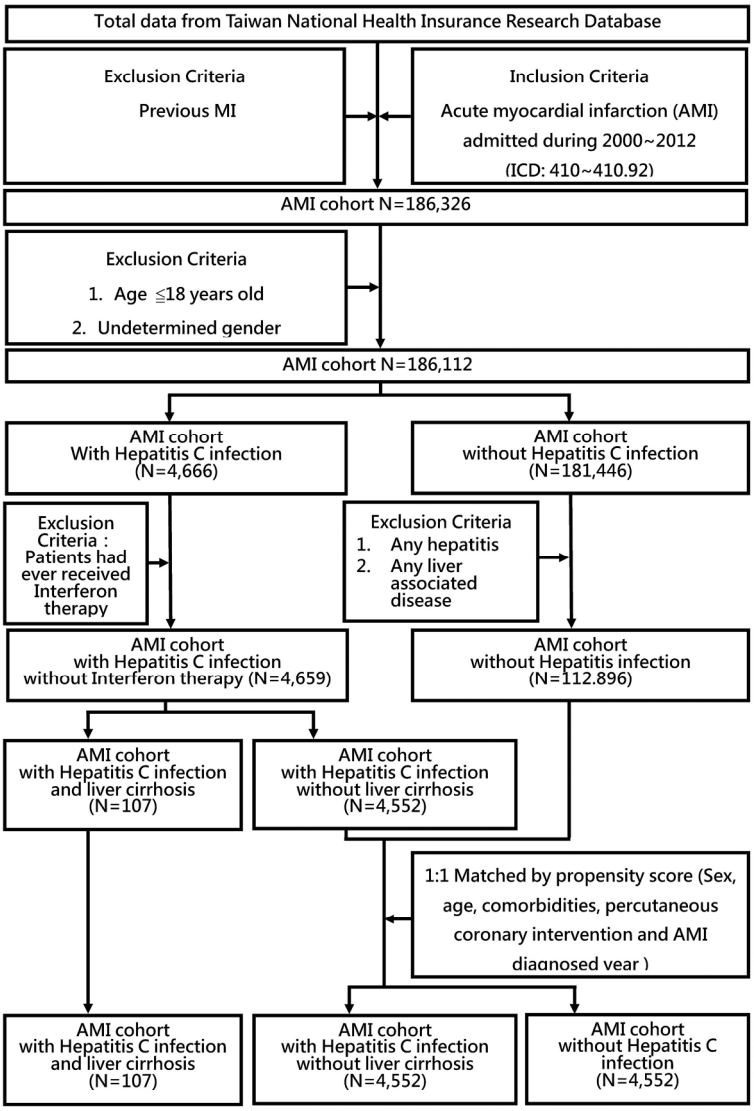

Flowchart of the establishment of the study cohort. The National Health Insurance Research Database data for approximately 23,000,000 patients between January 2000 and December 2012 were used in the analysis. A total of 186,112 cases of first AMI admission were identified. Of the 4,666 AMI patients with HCV, those who had ever received interferon therapy were excluded to minimize the variables. Therefore, a total of 4,659 patients were enrolled and further divided into those with liver cirrhosis (n=107) and those without liver cirrhosis (n=4,552). One-to-one matching was performed, and 4,552 matched controls were included in the final analysis.
AMI, acute myocardial infarction; HCV, hepatitis C virus

111x157mm (600 x 600 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1(Y)	(*a*) Indicate the study's design with a commonly used term in the title or the abstract(P1, 3)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found(P3)
Introduction		
Background/rationale	2(Y)	Explain the scientific background and rationale for the investigation being reported(P5)
Objectives	3(Y)	State specific objectives, including any prespecified hypotheses(P5)
Methods		
Study design	4(Y)	Present key elements of study design early in the paper(P6)
Setting	5(Y)	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection(P6)
Participants	6(Y)	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up(P6,7) *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls(P7) *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed(P6,7) *Case-control study*—For matched studies, give matching criteria and the number of controls per case(P7)
Variables	7(Y)	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable(P6,7)
Data sources/ measurement	8(Y)	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group(P6,7)
Bias	9(Y)	Describe any efforts to address potential sources of bias(P7)
Study size	10(Y)	Explain how the study size was arrived at(P6,7)
Quantitative variables	11(Y)	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why(P6,7)
Statistical methods	12(Y)	(*a*) Describe all statistical methods, including those used to control for confounding(P7)
		(*b*) Describe any methods used to examine subgroups and interactions(P8)
		(*c*) Explain how missing data were addressed(Nil)
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed(P6) *Case-control study*—If applicable, explain how matching of cases and controls was addressed(P7) *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses(P8)

Continued on next page

Results		
Participants	13(Y)	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed(P6,7)
		(b) Give reasons for non-participation at each stage(Nil)
		(c) Consider use of a flow diagram(available for attachment)
Descriptive data	14(Y)	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders(P8,10-12)
		(b) Indicate number of participants with missing data for each variable of interest(Nil)
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) (P13)
Outcome data	15(Y)	*Cohort study*—Report numbers of outcome events or summary measures over time(P13)
		Case-control study—Report numbers in each exposure category, or summary measures of exposure(P13)
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16(Y)	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included(P13-14)
		(*b*) Report category boundaries when continuous variables were categorized(P13-14)
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period(P13-14)
Other analyses	17(Y)	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses(P13-14)
Discussion		
Key results	18(Y)	Summarise key results with reference to study objectives(P16)
Limitations	19(Y)	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias(P19)
Interpretation	20(Y)	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence(P17-19)
Generalisability	21(Y)	Discuss the generalisability (external validity) of the study results(P19)
Other information		
Funding	22(Y)	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based(P19)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.