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Contribution of Hepatitis B to Long-Term Outcome Among Patients With Acute Myocardial Infarction
A Nationwide Study

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Abstract: Although a possible association between hepatitis B and cardiovascular disease has been identified, the impact of viral hepatitis B on long-term prognosis after an acute myocardial infarction (AMI) is uncertain. Therefore, the aim of our study was to evaluate the specific impact of viral hepatitis B on survival after a first AMI through a retrospective analysis of data from the Taiwan National Health Insurance Research Database.

This was a nationwide, propensity score-matched case–control study of patients admitted to hospitals between January 2000 and December 2012 with a primary diagnosis of a first AMI. Among the 7671 prospective patients, 244 patients with a confirmed diagnosis of viral hepatitis B infection were identified. A propensity score, one-to-one matching technique was used to match 244 controls to the AMI group for analysis. Controls were matched on the following variables: sex, age, hypertension, dyslipidemia, diabetes, peripheral vascular disease, heart failure, cerebrovascular accidents, end-stage renal disease, chronic obstructive pulmonary disease, and percutaneous coronary intervention (PCI).

Overall, viral hepatitis B infection did not influence the 12-year survival rate ($P = 0.98$). However, survival was lower in female patients with viral hepatitis B infection compared to those without ($P = 0.03$; hazard ratio, 1.79; 95% confidence interval, 1.08–2.94). Inclusion of percutaneous coronary management improved survival, independent of sex, age, or hepatitis B status.

Hepatitis B infection might increase the mortality risk of female patients after a first AMI. PCI may improve the long-term survival of patients after a first AMI, regardless of sex, age, and hepatitis B status.

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Abbreviations: ACEI = angiotensin-converting enzyme inhibitors, AMI = acute myocardial infarction, ARB = angiotensin receptor blockers, CI = confidence interval, COPD = chronic obstructive pulmonary disease, ESRD = end-stage renal disease, HBV = hepatitis B viral infection, LMWH = low molecular weight heparin, NHI = national Health Insurance, NHIRD = National Health Insurance Research Database, PCI = percutaneous coronary intervention, SD = standard deviation.

INTRODUCTION

Cardiovascular disease is one of the leading causes of death worldwide. Previous studies showed infections played a possible role in the initiation and progression of atherosclerosis.[1,2] Viruses were shown to more frequently predispose to plaque rupture than bacteria.[3,4] Several viruses were identified to be associated with atherosclerosis or cardiovascular disease, including herpes viruses, cytomegalovirus, or hepatitis viruses.[3,5,6] However, the association between viral infection and acute coronary syndrome remains controversial.

Over the past few decades, viral hepatitis B has become endemic in Taiwan.[7] Viral hepatitis B is a chronic inflammatory disease which is associated with a high mortality rate,[8] as well as being a significant risk factor for atherosclerosis.[6] The link between viral hepatitis B and atherosclerosis could be associated with higher oxidative stress in hepatitis B infection.[9–11] Serum soluble urokinase plasminogen activator receptor and interferon-induced protein-10 were shown to increase in chronic hepatitis B infection with fibrosis,[12] which might contribute to acute myocardial infarction (AMI) or atherosclerosis.[13–16] Chronic viral hepatitis B increases soluble CD163 levels, which reflects macrophage activation and further induce atherosclerosis.[17,18] Furthermore, hepatitis B carriers tend to have relatively increased platelet activation and an atherothrombotic risk.[19] These findings in viral hepatitis B infection might further affect the prognosis of AMI.

TABLE 1. ICD-9-CM Code Used for Diagnosis in This Study

| Diagnosis	ICD-9-CM code
Acute myocardial infarction	410 to 410.92
Viral hepatitis B infection	V02.61, 070.30, 070.32
Any history of hepatitis	V02.62, 070.51, 070.54, 571.1
Other liver-associated diseases	571.2, 571.5, 571.6, 155, 070, 155, 570, 571, 572, 573, 197.7, 230.8, 235.3, 789.1, V02.6
Hypertension	401 to 405
Dyslipidemia	272
Diabetes	250
Peripheral vascular disease	443.9, 441, 441.9, 785.4, V43.4 or procedure 38.48
Cerebrovascular accidents	430 to 437 or A290 to A294
End-stage renal disease	585
Heart failure	428
Chronic obstructive pulmonary disease	491, 492 or 496
Percutaneous coronary intervention	Procedure codes 36.0, 36.01, 36.02, 36.05, 36.06, or 36.09
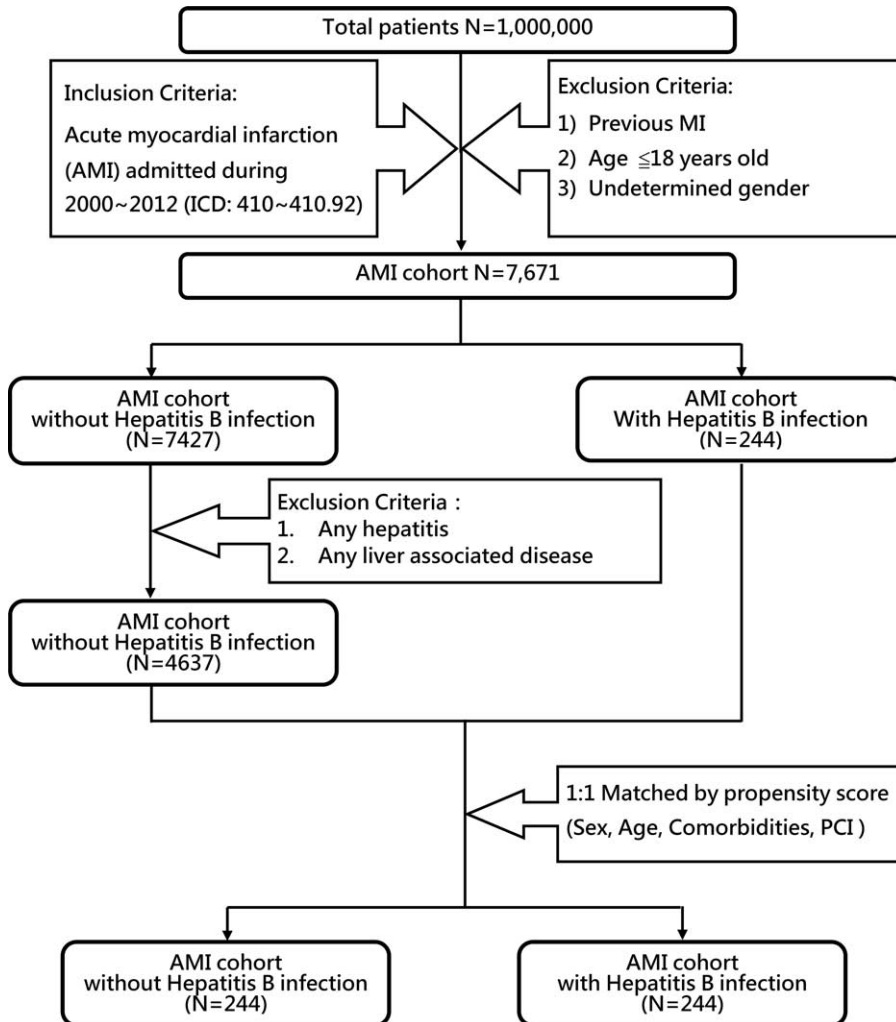
FIGURE 1. Flowchart of the identification of the study cohort. AMI = acute myocardial infarction; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Although a positive association between viral hepatitis and acute coronary syndrome or thrombus has been reported by some researchers,[6] others have not identified a clear association between hepatitis B infection and acute coronary syndrome.[20] Furthermore, the association between viral hepatitis and cardiovascular mortality, as well as of the impact of viral hepatitis on the prognosis of survival after an acute coronary syndrome, is currently unclear. Therefore, our aim was to evaluate the impact of viral hepatitis B on survival after an AMI in different genders through a retrospective analysis of data from the Taiwan National Health Insurance Research Database (NHIRD).

METHODS

Data Source

In Taiwan, the National Health Insurance Program has financed the healthcare of more than 99% residents of Taiwan since 1995. The NHIRD includes detailed information from the medical records of patients admitted to hospitals, including age, sex, diagnosis, intervention procedures, medication prescription, and relevant survival data. The NHIRD provides researchers with deidentified data. Our use of the NHIRD data was approved by our hospital's Human Research Committee.

TABLE 2. Characteristics of Overall Patients With First Hospitalized AMI With and Without Viral Hepatitis B Infection in This Propensity Score Matched Case–Control Study

Characteristics	Viral Hepatitis B Infection		*P*-Value
	No (N = 244)	Yes (N = 244)	
Male (%)	171 (70.08%)	180 (73.77%)	03646
Age (mean ± SD)	64.04 ± 13.85	63.82 ± 13.37	0.8609
Comorbidities			
Hypertension (%)	175 (71.72%)	159 (65.16%)	0.1191
Dyslipidemia (%)	81 (33.2%)	78 (31.97%)	0.7720
Diabetes (%)	108 (44.26%)	106 (43.44%)	0.8552
Peripheral vascular disease (%)	16 (6.56%)	11 (4.51%)	0.3222
Heart failure (%)	67 (27.46%)	52 (21.31%)	0.1138
End-stage renal disease (%)	30 (12.3%)	28 (11.48%)	0.7797
Cerebrovascular accidents (%)	58 (23.77%)	50 (20.49%)	0.3830
COPD (%)	26 (10.66%)	33 (13.52%)	0.3311
Liver cirrhosis (%)	0 (0%)	6 (2.46%)	0.0303
Medication			
Aspirin (%)	199 (81.56%)	195 (79.92%)	0.6461
Clopidogrel (%)	148 (60.66%)	166 (68.03%)	0.0889
Ticlopidine (%)	11 (4.51%)	5 (2.05%)	0.1272
ACEI (%)	135 (55.33%)	123 (50.41%)	0.2765
ARB (%)	54 (22.13%)	37 (15.16%)	0.0482
Statin (%)	92 (37.7%)	84 (34.43%)	0.4508
Beta blocker (%)	138 (56.56%)	126 (51.64%)	0.2757
Calcium channel blocker (%)	91 (37.3%)	69 (28.28%)	0.0339
Heparin (%)	157 (64.34%)	155 (63.52%)	0.8505
LMWH (%)	66 (27.05%)	75 (30.74%)	0.3687
Dopamine (%)	39 (15.98%)	42 (17.21%)	0.7151
Spironolactone (%)	22 (9.02%)	32 (13.11%)	0.1490
Nitrate (%)	199 (81.56%)	184 (75.41%)	0.0985
Nicorandil (%)	24 (9.84%)	22 (9.02%)	0.7567
Intervention			
Non-PCI (%)	113 (46.31%)	119 (48.77%)	0.5865
Non-PCI (% of male)	70 (40.94%)	74 (41.11%)	0.9734
Non-PCI (% of female)	43 (58.9%)	45 (70.31%)	0.1645
Non-PCI (% of age < 65)	51 (39.23%)	54 (42.19%)	0.6289
Non-PCI (% of Age ≥ 65)	62 (54.39%)	65 (56.03%)	0.8015
PCI (%)	131 (53.69%)	125 (51.23%)	0.5685
PCI (% of male)	101 (59.06%)	106 (58.89%)	0.9734
PCI (% of female)	30 (41.1%)	19 (29.69%)	0.1645
PCI (% of age < 65)	79 (60.77%)	74 (57.81%)	0.6289
PCI (% of age ≥ 65)	52 (45.61%)	51 (43.97%)	0.8015

ACEI = angiotensin-converting enzyme inhibitors, AMI = acute myocardial infarction, ARB = angiotensin receptor blockers, COPD = chronic obstructive pulmonary disease, LMWH = low molecular weight heparin, PCI = percutaneous coronary intervention, SD = standard deviation.

Definition of AMI Population

Prospective participants were the 1 million patients admitted to hospitals in Taiwan, between January of 2000 and December of 2012, with a primary diagnosis of AMI. All ICD 9 codes used in this study are shown in Table 1. From this group, patients with a previous admission for AMI, whose sex was undetermined and who were younger than 18 years old were excluded, leaving 7671 unique cases of AMI (Figure 1).

Study Population

Among the 7671 identified cases of a first hospitalization for an AMI, 244 cases with viral hepatitis B infection were identified. Of the remaining 7427 cases, patients with any history of hepatitis or other liver-associated diseases were excluded, leaving 4637 AMI control cases for comparison (Figure 1). A propensity score matching technique was used to minimize baseline differences between the control group and the viral hepatitis B group. One-to-one matching was based on the following variables: sex, age, hypertension, dyslipidemia, diabetes, peripheral vascular disease, heart failure, cerebrovascular accidents, end-stage renal disease (ESRD), chronic obstructive pulmonary disease (COPD), and percutaneous coronary intervention (PCI). The data from 244 AMI patients with viral hepatitis B infection and 244 matched controls were, therefore, included in our final analysis (Figure 1).

Outcome Analysis

For analysis, survival was defined as the difference between the date of hospital admission and the end date of NHI coverage. As the NHI premium is paid on a monthly basis, coverage can easily be discontinued at the time of death and, therefore, the end date of NHI coverage provides a valid proxy measure of mortality, with a maximum error of 1 month.[21–24]

Statistical Analyses

Extraction of the data and statistical analysis were performed by SAS version 9.4 (SAS Institute, Inc., Cary, NC). Descriptive statistics were calculated for all variables, with categorical data reported as percentile values and continuous variables as a mean and standard deviation (SD). Between-group differences were evaluated by paired t test for continuous variables and Chi-squared test for categorical variables, with a P-value <0.05 considered statistically significant. Cox proportional hazard regression analysis was used to calculate the hazard ratio (HR), and associated 95% confidence intervals (95% CIs), for significant variables. Kaplan–Meier cumulative survival curves were constructed to compare survival between patients having received PCI management and those who had not, as well as to compare survival of patients with viral hepatitis B infection and the control group as a whole, and

TABLE 3. Characteristics of Male and Female Patients With First Hospitalized AMI With and Without Viral Hepatitis B Infection

Characteristics	[0,3-4]Viral Hepatitis B Infection in Male Patients			Viral Hepatitis B Infection in Female Patients		
	No (N = 171)	Yes (N = 180)	*P*-Value	No (N = 73)	Yes (N = 64)	*P*-Value
Age (mean ± SD)	62.44 ± 14.07	61.79 ± 13.64	0.6604	67.79 ± 12.62	69.55± 10.72	0.3845
Comorbidities						
Hypertension (%)	116 (67.84%)	112 (62.22%)	0.2705	59 (80.82%)	47 (73.44%)	0.3027
Dyslipidemia (%)	55 (32.16%)	65 (36.11%)	0.4358	26 (35.62%)	13 (20.31%)	0.0477
Diabetes (%)	62 (36.26%)	69 (38.33%)	0.6877	46 (63.01%)	37 (57.81%)	0.5342
Peripheral vascular disease (%)	8 (4.68%)	9 (5%)	0.8884	8 (10.96%)	2 (3.13%)	0.1041
Heart failure (%)	36 (21.05%)	32 (17.78%)	0.4378	31 (42.47%)	20 (31.25%)	0.1755
End-stage renal disease (%)	17 (9.94%)	14 (7.78%)	0.4752	13 (17.81%)	14 (21.88%)	0.5505
Cerebrovascular accidents (%)	33 (19.3%)	34 (18.89%)	0.9223	25 (34.25%)	16 (25%)	0.2383
COPD (%)	20 (11.7%)	26 (14.44%)	0.4456	6 (8.22%)	7 (10.94%)	0.588
Liver cirrhosis (%)	0 (0%)	2 (1.11%)	0.4989	0 (0%)	4 (6.25%)	0.0452
Medication						
Aspirin (%)	147 (85.96%)	153 (85%)	0.7976	52 (71.23%)	42 (65.63%)	0.4804
Clopidogrel (%)	108 (63.16%)	126 (70%)	0.1741	40 (54.79%)	40 (62.5%)	0.3613
Ticlopidine (%)	9 (5.26%)	4 (2.22%)	0.1316	2 (2.74%)	1 (1.56%)	1
ACEI (%)	104 (60.82%)	105 (58.33%)	0.6354	31 (42.47%)	18 (28.13%)	0.0806
ARB (%)	30 (17.54%)	25 (13.89%)	0.3464	24 (32.88%)	12 (18.75%)	0.0609
Statin (%)	68 (39.77%)	69 (38.33%)	0.7833	24 (32.88%)	15 (23.44%)	0.2219
Beta blocker (%)	96 (56.14%)	102 (56.67%)	0.9208	42 (57.53%)	24 (37.5%)	0.0192
Calcium channel blocker (%)	62 (36.26%)	48 (26.67%)	0.0529	29 (39.73%)	21 (32.81%)	0.4017
Heparin (%)	115 (67.25%)	115 (63.89%)	0.5076	42 (57.53%)	40 (62.5%)	0.5541
LMWH (%)	51 (29.82%)	57 (31.67%)	0.7086	15 (20.55%)	18 (28.13%)	0.3008
Dopamine (%)	25 (14.62%)	22 (12.22%)	0.5097	14 (19.18%)	20 (31.25%)	0.1027
Spironolactone (%)	12 (7.02%)	25 (13.89%)	0.0361	10 (13.7%)	7 (10.94%)	0.6248
Nitrate (%)	140 (81.87%)	142 (78.89%)	0.4822	59 (80.82%)	42 (65.63%)	0.0438
Nicorandil (%)	16 (9.36%)	19 (10.56%)	0.7079	8 (10.96%)	3 (4.69%)	0.1778

ACEI = angiotensin-converting enzyme inhibitors, AMI = acute myocardial infarction, ARB = angiotensin receptor blockers, COPD = chronic obstructive pulmonary disease, LMWH = low molecular weight heparin, SD = standard deviation.

for male and female patients separately. Log-rank tests with a $P < 0.05$ were considered statistically significant.

RESULTS

Descriptive Characteristics of Study Group

The descriptive characteristics of the 244 patients forming the AMI group with viral hepatitis B (HBV group) and the 244 matched controls (control group), including types of medication used, are listed in Table 2. Groups were comparable on the primary demographic variables of age, distribution of male and female patients, and comorbidities ($P \geq 0.11$). Only 6 patients in the HBV group (2.46%) had liver cirrhosis. Medications used were comparable between groups, except for a higher use of calcium channel blockers ($P = 0.03$) and angiotensin receptor blockers (ARB) ($P = 0.05$) by the patients in the control group.

We further investigated the proportion of patients in each group receiving PCI, controlling for hepatitis B status, age and sex, as a means of clarifying factors which may affect physicians' and patients' attitude to perform PCI (Table 2). The proportion of patients receiving PCI procedures was comparable for the HBV and control groups, with 125 of 244 (51.2%) patients in the control group and 131 of 244 patients (53.7%) in the HBV group having received PCI management, independent of sex or age subgroups ($P \geq 0.17$).

Sex-specific group characteristics are reported in Table 3. For male patients, the HBV ($n = 171$) and control ($n = 180$) groups were comparable in terms of age, comorbidities, liver cirrhosis, and medication use. However, female patients in the control group ($n = 73$) had a higher percentage of dyslipidemia, and use of beta blockers and nitrate than patients in the HBV group ($n = 64$). In contrast, female HBV patients had higher percentage of liver cirrhosis ($P = 0.05$).

Survival Analysis

Overall, the 12-year survival rate was comparable for the HBV and control groups (log rank $P = 0.98$; Figure 2, panel A). Patients in the HBV and control groups were subdivided into a younger (age < 65 years) and older (age ≥ 65 years) category to evaluate the interactive effects of hepatitis B infection and age on survival. The Kaplan–Meier cumulative survival curves were comparable for the younger (log rank $P = 0.92$) and older (log rank $P = 0.96$) patients in both the HBV and control groups (Figure 2, panels B and C). However, sex-specific differences in survival rate were identified. Although survival was comparable for male patients in both the HBV and control groups (log rank $P = 0.33$; Figure 3, panel A), the rate of mortality was higher for female patients in the HBV group, compared to female patients in the control group (log rank $P = 0.03$; Figure 3, panel B). Overall, survival rate for male patients after an AMI was higher than for female patients, regardless of group (HBV group, log rank $P < 0.001$; Figure 3, panel C; control group, log rank $P = 0.05$, Figure 3, panel D).

Overall, PCI management improved survival outcomes after AMI in both the HBV (log rank $P < 0.001$; Figure 4, panel A) and control (log rank $P < 0.001$; Figure 4, panel B) groups. The survival rate of patients who had received PCI management was comparable among patients in the HBV and control groups (log rank $P = 0.37$; Figure 4, panel C). Similarly, the rate of survival among patients who did not receive PCI management was comparable for both the HBV and control groups (log rank $P = 0.55$; Figure 4, panel D).
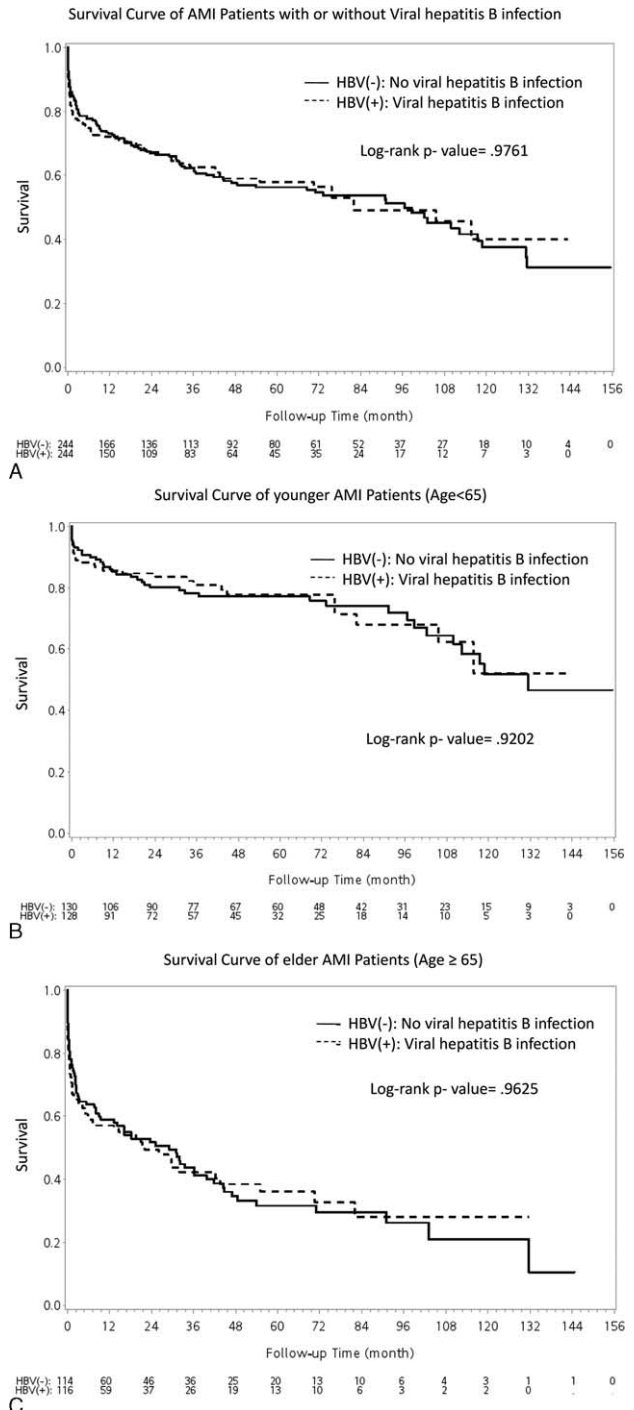

FIGURE 2. Kaplan–Meier survival curve after first acute myocardial infarction (AMI) for the age-specific subanalysis. Panel A, comparison of survival between patients with and without a viral hepatitis B infection; panel B, comparison of survival in younger patients, <65 years, with and without viral hepatitis B infection; panel C, comparison of survival in older patients ≥65 years, with and without viral hepatitis B infection.

Cox proportional hazard regression analysis was performed to further evaluate the impact of viral hepatitis B on the survival of patients admitted for a first AMI, with separate
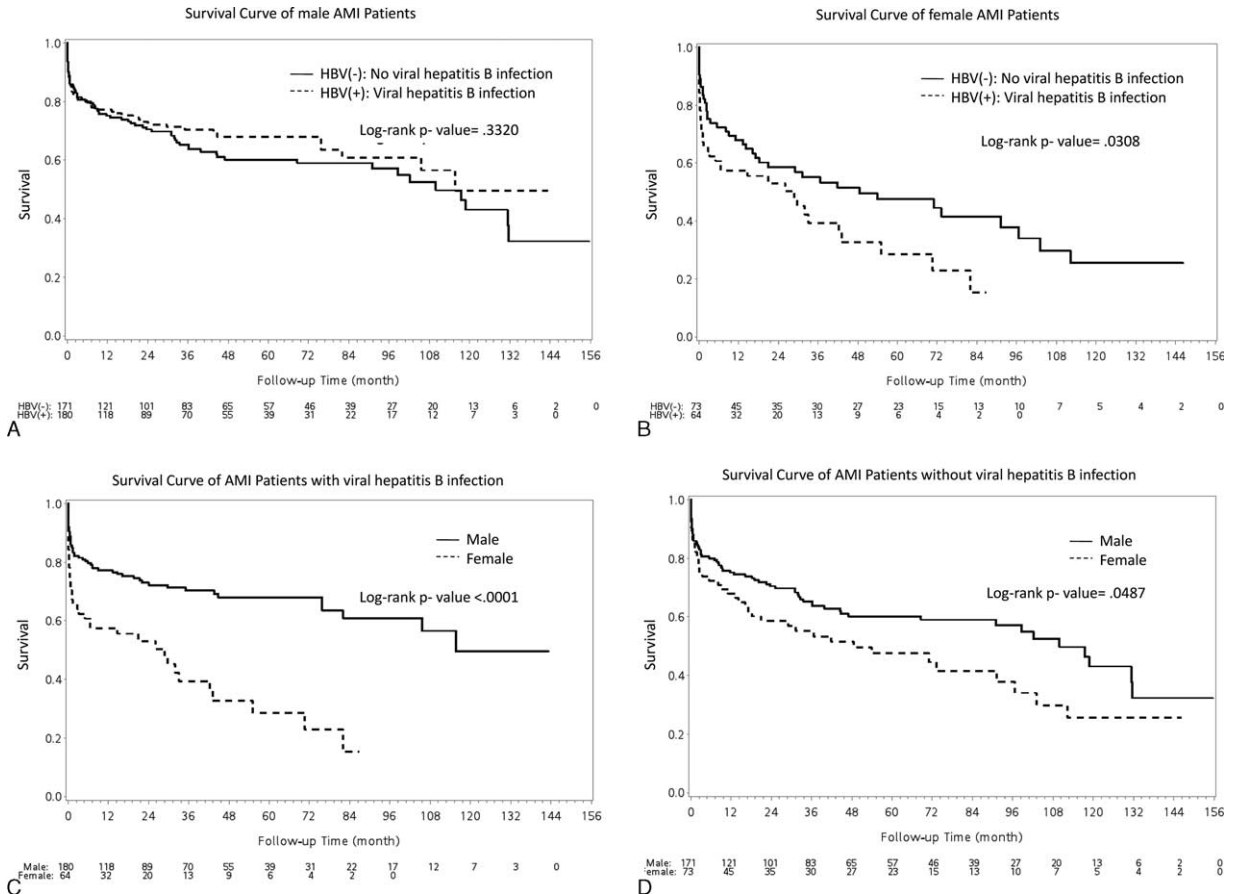
FIGURE 3. Kaplan–Meier survival curve after first acute myocardial infarction (AMI) for the sex subanalysis. Panel A, comparison of survival of male patients, with and without viral hepatitis B infection; panel B, comparison of survival of female patients, with and without viral hepatitis B infection; panel C, comparison of survival between male and female patients, with viral hepatitis B infection; and panel D, comparison of survival between male and female patients, without viral hepatitis B infection.

regression models constructed for group (ie, HBV and control) age, PCI, and comorbidities (Table 4). Overall, HRs for mortality were higher for patients $\geq$65 years (HR, 2.54; 95% CI, 1.83–3.51), as well as for patients with diabetes (HR, 1.57; 95% CI, 1.17–2.11), peripheral vascular disease (HR, 2.01; 95% CI, 1.2–3.36), and heart failure (HR, 1.48; 95% CI, 1.07–2.03). HRs were lower for patients who had undergone PCI management (HR, 0.35; 95% CI, 0.26–0.48). Although viral hepatitis did not influence mortality rate for male patients, the HR of mortality was higher for female patients with viral hepatitis B, compared to female patients without hepatitis B (HR, 1.79; 95% CI, 1.08–2.94).

DISCUSSION

To our knowledge, this is the first study to evaluate the impact of hepatitis B on the long-term outcomes of patients admitted to hospital after a first AMI. Our analysis provides evidence that viral hepatitis is not a significant risk factor of the survival of male patients following a first AMI but may influence survival in female patients. An important outcome of our retrospective study was the finding of an overall higher survival of male patients, compared to female patients after an AMI, independent of hepatitis status. Furthermore, PCI management improved outcomes for all patient groups, compared to conservative therapy.

The possible impact of hepatitis on cardiovascular diseases, such as atherosclerosis, coronary artery diseases, and myocardial infarction, has been reported by different researchers Ishizaka et al[6] postulated the possible contribution of infection agents associated with hepatitis B infection to the formation of atherosclerosis. In contrast, studies conducted by Kiechl et al and Volzke et al did not identify an obvious association between hepatitis and atherosclerosis.[1,25,26] Sung et al[27] reported that hepatitis B was not an independent risk factor for either myocardial infarction or coronary artery diseases. Tong et al[28] corroborated this finding, reported that hepatitis B infection did not relate to coronary atherosclerosis or to C-reactive protein (CRP), a blood marker of inflammation. In fact, Bilora et al[29] reported that chronic active hepatitis B may actually be a protective factor against carotid atherosclerosis. Thus, the evidence relating hepatitis B infection to cardiovascular diseases remains controversial.

Although various studies have tried to further our understanding of the relationship between hepatitis B infection and the risk of cardiovascular diseases, to the best of our knowledge, our study is the first to specifically evaluate the impact of hepatitis B infection on the survival rate of AMI. In their retrospective study, Wang et al[4] did not identify an impact of hepatitis B seropositivity on cardiovascular-related mortality during 17-year follow-up in Taiwan. However, it is important to
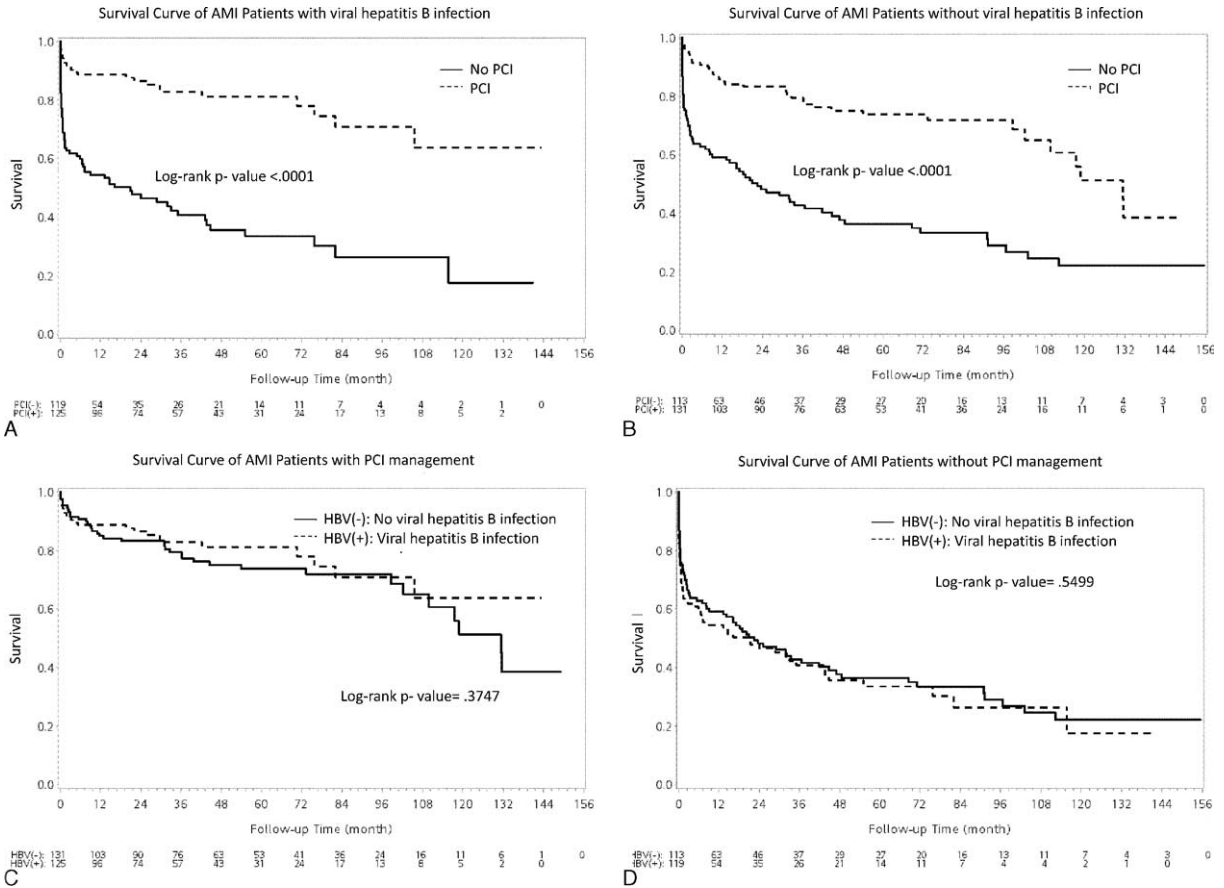
FIGURE 4. Kaplan–Meier survival curve after first acute myocardial infarction (AMI) for subanalysis of percutaneous coronary intervention (PCI). Panel A, comparison of survival of patients, with viral hepatitis B infection, with and without PCI management; panel B, comparison of survival of patients without viral hepatitis B infection, with and without PCI management; panel C, comparison of survival of patients, with and without viral hepatitis B infection, receiving PCI management; and panel D, comparison of survival of patients, with and without viral hepatitis B infection, who had not received PCI management.

TABLE 4. Cox Proportional Hazard Regression in Patients With First Hospitalized AMI With and Without Viral Hepatitis B Infection

Variables	All (N = 488) HR (95% CI)	Male (N = 351) HR (95% CI)	Female (N = 137) HR (95% CI)
Age (≥65 vs. <65)	2.54 (1.83–3.51)	2.41 (1.61–3.59)	2.41 (1.33–4.39)
Hypertension (yes vs. no)	0.96 (0.69–1.33)	0.8 (0.53–1.21)	1.68 (0.89–3.16)
Dyslipidemia (yes vs. no)	0.68 (0.47–1.02)	0.66 (0.36–1.07)	0.98 (0.56–1.73)
Diabetes (yes vs. no)	1.57 (1.17–2.11)	1.61 (1.1–2.36)	1.18 (0.71–1.95)
Peripheral vascular disease (yes vs. no)	2.01 (1.2–3.36)	2.57 (1.36–4.86)	2.02 (0.85–4.84)
Heart failure (yes vs. no)	1.48 (1.07–2.03)	1.23 (0.81–1.89)	1.99 (1.16–3.4)
End-stage renal disease (yes vs. no)	1.45 (0.98–2.15)	2.15 (1.26–3.68)	0.85 (0.46–1.58)
Cerebrovascular accidents (yes vs. no)	1.07 (0.78–1.47)	1.17 (0.76–1.8)	0.99 (0.59–1.66)
COPD (yes vs. no)	1.27 (0.88–1.83)	1.8 (1.14–2.84)	0.64 (0.32–1.29)
Liver cirrhosis (yes vs. no)	1.23 (0.38–3.99)	—	2.93 (0.79–10.9)
PCI (yes vs. no)	0.35 (0.26–0.48)	0.32 (0.22–0.46)	0.43 (0.25–0.75)
Hepatitis B (yes vs. no)	1.19 (0.89–1.58)	0.99 (0.69–1.42)	1.79 (1.08–2.94)

AMI = acute myocardial infarction, CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, PCI = percutaneous coronary intervention.

note that over the period in which Wang et al conducted their research, full-coverage through the NHI program was not available to all citizens of Taiwan, and accessibility to medical resources was limited. When we further consider findings by Stuver et al[30] of a strong association between chronic HBV infection and low socioeconomic class, it is possible that patients with a hepatitis B infection in the 1990s might not have received adequate treatment when admitted for cardiovascular emergencies in Taiwan. As well, the baseline characteristics of the study group in Wang et al's[4] study were quite different from ours.

A distinct strength of our study is that we conducted a retrospective analysis over a time period when NHI was available to nearly most citizens of Taiwan and patients could receive appropriate management, regardless of socioeconomic status. The one-to-one matching strategy for factors known to influence survival post-AMI[22,31–33] was also necessary to confirm that hepatitis B infection has no impact on the long-term outcome in patients with first hospitalized AMI, despite higher use of calcium channel blockers and ARB in control group.

Women have a well-documented higher risk for AMI-associated mortality[34–36] which has been attributed to older age at the time of the first AMI, with age being an independent risk factor for lower functional status and a higher prevalence of risk factors for mortality.[37,38] Outcomes of our study confirmed a higher AMI-related mortality rate for women compared to men, regardless of hepatitis B status. In agreement with previous studies, female patients in our study were older than male patients and had a higher prevalence of hypertension, diabetes, heart failure, ESRD, and cerebrovascular disease. In agreement with Bonino et al,[39] we identified a negative influence of hepatitis B on the survival rate of female patients after a first AMI. Hepatitis B infection, therefore, might contribute to inflammatory mechanism that affects the outcomes of treatments for AMI.

In patient after AMI, beta-blockers are effective in long-term secondary prevention.[40–43] Nitrates were also shown to reduce mortality in patient early after myocardial infarction.[43,44] In this study, we also found that use of beta blocker and nitrate was lower in the female hepatitis B patient than the corresponding control group, which could be contributed to insignificant lower percentage of hypertension and heart failure in female hepatitis B patients (Table 3). The different percentage use of beta blocker and nitrate could partly explain the favorable outcome in female hepatitis B group. Furthermore, female HBV patients in this study had higher percentage of liver cirrhosis (Table 3), which also might partly contribute to the worst outcome. However, a comprehensive understanding of identified sex-specific impact of hepatitis B on AMI-related outcomes requires further investigation.

Our study provides evidence that PCI may be the most important factor in determining outcome of patients after a first AMI, regardless of age, sex, and hepatitis B status. These results emphasize the importance of providing adequate PCI management to patients meeting the current guidelines for interventional treatment,[45–47] regardless of hepatitis B status.

The limitations of our study should be noted in the interpretation of results for practice. First, although the prevalence of hepatitis B infection in Taiwan is high, the number of patients admitted for a first AMI with a concurrent hepatitis B infection over the 12-year period of the study was relatively low. As the NHIRD is used for billing purposes, in many situations, only the diagnoses related to active treatment

provision is recorded. Therefore, the prevalence of hepatitis B infection may have been under-reported. Cheng et al[21] conducted a validation study of the NHIRD confirming the accuracy of reporting of cardiovascular diseases. A similar validation process for hepatitis B infection is warranted. Secondly, previous publications showed Child–Pugh classification might influence the outcomes of patients.[48,49] However, liver function tests data were not available in the NHIRD. Therefore, Child–Pugh classification was not shown in this study and individual differences in hepatitis B viral load were also not included in the analysis. Thirdly, left ventricular ejection fraction, Killip grade, and myocardial injury biomarkers (eg, peak values of CK, CK-MB, and Troponin I) were not available in the NHIRD data. Although a propensity score matching technique was used to minimize confounding factors between the HBV and control groups, future prospective studies are required to confirm findings.

CONCLUSIONS

In this nationwide retrospective study, using matched case–control we provide evidence of a possible effect of hepatitis B infection on the survival of women after a first AMI. Independent of sex and hepatitis status, PCI management plays an important role in the long-term outcome of AMI patients.

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