Medicine

OBSERVATIONAL STUDY

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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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.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.9 The link between viral hepatitis B and atherosclerosis could be associated with higher oxidative stress in hepatitis B infection.10 Serum soluble urokinase plasminogen activator receptor and interferon-induced protein-10 were shown to increase in chronic hepatitis B infection with fibrosis,11 which might contribute to acute myocardial infarction (AMI) or atherosclerosis.12–16 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 atherosclerotic 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 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                        | No (N = 244) | Yes (N = 244) | P-Value |
|----------------------------------------|--------------|---------------|---------|
| Male (%)                               | 171 (70.08%) | 180 (73.77%)  | 0.3646  |
| 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

| Characteristics | [0,3-4] Viral Hepatitis B Infection in Male Patients | Viral Hepatitis B Infection in Female Patients |
|-----------------|----------------------------------------------------|-------------------------------------------------|
| Age (mean ± SD) | [62.44 ± 14.07, 61.79 ± 13.64, 0.6604] | [67.79 ± 12.62, 65.95 ± 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%), 0.0597]               | [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] |
| Nitrates (%)    | [140 (81.87%), 142 (78.89%), 0.4822]             | [59 (80.82%), 42 (65.63%), 0.0438]              |
| Nicorandil (%)  | [16 (9.56%), 19 (10.56%), 0.7079]                | [8 (10.96%), 3 (4.69%), 0.1778]                 |

ACEI = angiotensin-converting enzyme inhibitors, 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 ($P > 0.17$).

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 nitrates 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).

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
regression models constructed for group (ie, HBV and control) age, PCI, and comorbidities (Table 4). Overall, HRs for mortality were higher for patients ≥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 without hepatitis B (HR, 1.79; 95% CI, 1.08–2.94).

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 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. Sung et al reported that hepatitis B was not an independent risk factor for either myocardial infarction or coronary artery diseases. Tong et al 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 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 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) | Male (N = 351) | Female (N = 137) |
|------------------------------------------------|---------------|----------------|------------------|
| 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 (1.12–2.36) | 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) | 0.97 (0.39–2.4)  |
| 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\textsuperscript{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\textsuperscript{3} 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\textsuperscript{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\textsuperscript{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.\textsuperscript{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\textsuperscript{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.\textsuperscript{40–43} Nitrates were also shown to reduce mortality in patient early after myocardial infarction.\textsuperscript{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 intervention treatment\textsuperscript{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\textsuperscript{47} 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.\textsuperscript{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.

REFERENCES

1. Kiechl S, Egger G, Mayr M, et al. Chronic infections and the risk of carotid atherosclerosis: prospective results from a large population study. Circulation. 2001;103:1064–1070.
2. Shah PK. Link between infection and atherosclerosis: who are the culprits: viruses, bacteria, both, or neither? Circulation. 2001;103:5–6.
3. Epstein SE, Zhu J, Najafi AH, et al. Insights into the role of infection in atherogenesis and in plaque rupture. Circulation. 2009;119:3133–3141.
4. Wang CH, Chen CJ, Lee MH, et al. Chronic hepatitis B infection and risk of atherosclerosis-related mortality: a 17-year follow-up study based on 22 472 residents in Taiwan. Atherosclerosis. 2010;211:624–629.
5. Adam E, Melnick JL, Probstfield JL, et al. High levels of cytomegalovirus antibody in patients requiring vascular surgery for atherosclerosis. Lancet. 1987;2:291–293.
6. Ishizaka N, Ishizaka Y, Takahashi E, et al. Increased prevalence of carotid atherosclerosis in hepatitis B virus carriers. Circulation. 2002;105:1028–1030.
7. Ott JJ, Stevens GA, Groeger J, et al. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. Vaccine. 2012;30:2212–2219.
8. Ly KN, Xing J, Klevens RM, et al. The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. Ann Intern Med. 2012;156:271–278.
9. Karsen H, Binici I, Sunnetcioglu M, et al. Association of paroxysmal atrial fibrillation and atherosclerosis in patients with chronic hepatitis B. Afr Health Sci. 2012;11:148–152.
10. Demirag K, Yilmaz S, Ozdarendeli A, et al. Levels of plasma malondialdehyde and erythrocyte antioxidant enzyme activities in patients with chronic hepatitis B. Hepatogastroenterology. 2003;50:766–770.
11. Cai J, Han T, Nie C, et al. Biomarkers of oxidation stress, inflammation, necrosis and apoptosis are associated with hepatitis B-related acute-on-chronic liver failure. Clin Res Hepatol Gastroenterol. 2015.
12. Sevgi DY, Bayraktar B, Gunduz A, et al. Serum soluble urokinase-type plasminogen activator receptor and interferon-gamma-induced protein 10 levels correlate with significant fibrosis in chronic hepatitis B. Wien Klin Wochenschr. 2015.

13. Persson M, Ostling G, Smith G, et al. Soluble urokinase plasminogen activator receptor: a risk factor for carotid plaque, stroke, and coronary artery disease. Stroke. 2014;45:18–23.

14. Rasmussen L, Knudsen A, Katzenstein TL, et al. Soluble urokinase plasminogen activator receptor (suPAR) is a novel, independent predictive marker of myocardial infarction in HIV-1-infected patients: a nested case-control study. HIV Med. 2015.

15. Sorensen MH, Gerke O, Eugen-Olsen J, et al. Soluble urokinase plasminogen activator receptor is in contrast to high-sensitive C-reactive-protein associated with coronary artery calcifications in healthy middle-aged subjects. Atherosclerosis. 2014;237:60–66.

16. Edsfeldt A, Nitulescu M, Gruftman H, et al. Soluble urokinase plasminogen activator receptor is independently associated with fibrosis in patients with chronic viral hepatitis B and C. Hепатоло́гия. 2014;60:521–530.

17. Aristotelis LP, Moller HJ, Bailey B, et al. The monocytic lineage specific soluble CD163 is a plasma marker of coronary atherosclerosis. Atherosclerosis. 2006;184:342–347.

18. Turhan O, Coban E, Inan D, et al. Increased mean platelet volume in chronic hepatitis B patients with inactive disease. Med Sci Monit. 2010;16:CR202–CR205.

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

20. Cheng CL, Lee CH, Chen PS, et al. Validation of acute myocardial infarction cases in the National Health Insurance Research Database in Taiwan. J Epidemiol. 2014;24:500–507.

21. Chiang CH, Huang WC, Yang JS, et al. Five-year outcomes after acute myocardial infarction in patients with and without diabetes mellitus in Taiwan, 1996–2005. Acta Cardiol Sin. 2013;29:387–394.

22. Sun LM, Lin MC, Lin CL, et al. Statin use reduces prostate cancer all-cause mortality: a nationwide population-based cohort study. Medicine (Baltim). 2015;94:e1644.

23. Fang JY, Wang CY, Tan CH, et al. Effect of different antipsychotic drugs on short-term mortality in stroke patients. Medicine (Baltim). 2014;93:e170.

24. Ghotsalou R, Aslanabadi N, Ghojazadeh M. Hepatitis B virus infection and the risk of coronary atherosclerosis. Ann Acad Med Singapore. 2008;37:913–915.

25. Voizke H, Schwan C, Wolff B, et al. Hepatitis B and C virus infection and the risk of atherosclerosis in a general population. Atherosclerosis. 2004;174:99–103.

26. Sung J, Song YM, Choi YH, et al. Hepatitis B virus seropositivity and the risk of stroke and myocardial infarction. Stroke. 2007;38:1436–1441.

27. Tong DY, Wang XY, Xu CF, et al. Hepatitis B virus infection and coronary atherosclerosis: results from a population with relatively high prevalence of hepatitis B virus. World J Gastroenterol. 2005;11:1292–1296.

28. Bilara F, Rinaldi R, Bocciolotti V, et al. Chronic viral hepatitis: a prospective factor against atherosclerosis. A study with echo-color Doppler of the carotid and femoral arteries and the abdominal aorta. Gastroenterol Clin Biol. 2002;26:1001–1004.

29. Suver SO, Boschi-Pinto C, Trichopoulos D. Infection with hepatitis B and C viruses, social class and cancer. IARC Sci Publ. 1997:319–324.

30. Cheng CC, Huang WC, Chiu KR, et al. Higher body mass index and outcome of acute myocardial infarction—is there an obesity paradox? Acta Cardiol Sin. 2013;29:413–420.

31. Huang WC, Lin TW, Chiu KR, et al. The effect of intensified low density lipoprotein cholesterol reduction on recurrent myocardial infarction and cardiovascular mortality. Acta Cardiol Sin. 2013;29:404–412.

32. Hung CC, Huang WC, Chiu KR, et al. Chronic kidney disease, but not diabetes, can predict 30-day outcomes in patients with ST-Elevation myocardial infarction after primary percutaneous coronary intervention: a single-center experience. Acta Cardiol Sin. 2013;29:395–403.

33. Vaccarino V, Krumholz HM, Berkman LF, et al. Sex differences in mortality after myocardial infarction. Is there evidence for an increased risk for women? Circulation. 1995;91:1861–1871.

34. Milcev C, Dormont B, Durand-Zaleski I, et al. Gender differences in hospital mortality and use of percutaneous coronary intervention in acute myocardial infarction: microsimulation analysis of the 1999 nationwide French hospitals database. Circulation. 2007;115:833–839.

35. Anderson RD, Pepine CJ. Gender differences in the treatment for acute myocardial infarction: bias or biology? Circulation. 2007;115:823–826.

36. Bairey Merz CN, Shaw LJ, Reis SE, et al. Insights from the NHLBI-Sponsored Women’s Ischemia Syndrome Evaluation (WISE) Study: Part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. J Am Coll Cardiol. 2006;47:S21–S29.

37. Shaw LJ, Bairey Merz CN, Pepine CJ, et al. Insights from the NHLBI-Sponsored Women’s Ischemia Syndrome Evaluation (WISE) Study: Part I: gender differences in traditional and novel risk factors, symptom evaluation, and gender-optimized diagnostic strategies. J Am Coll Cardiol. 2006;47:S4–S20.

38. Bonino F, Marcellin P, Lau GK, et al. Predicting response to peginterferon alpha-2a, lamivudine and the two combined for HBsAg-negative chronic hepatitis B. Gut. 2007;56:699–705.

39. Roberts R, Rogers WJ, Mueller HS, et al. Immediate versus deferred beta-blockade following thrombolytic therapy in patients with acute myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI) II-B Study. Circulation. 1991;83:422–437.

40. Freemantle N, Cleland J, Young P, et al. Harrison J. beta Blockade after myocardial infarction: systematic review and meta regression analysis. BMJ. 1999;318:1730–1737.

41. Kontos MC, Diercks DB, Ho PM, et al. Treatment and outcomes in patients with myocardial infarction treated with acute beta-blocker therapy: results from the American College of Cardiology’s NCDR (§). Am Heart J. 2011;161:864–870.

42. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130:2354–2394.

43. Yusuf S, Collins R, MacMahon S, et al. Effect of intravenous nitrates on mortality in acute myocardial infarction: an overview of the randomised trials. Lancet. 1988;1:1088–1092.

44. Gasior M, Pres D, Gierlotka M, et al. The influence of diabetes on in-hospital and long-term mortality in patients with myocardial infarction complicated by cardiogenic shock: results from the PL-ACS registry. Kardiol Pol. 2012;70:1215–1224.
46. Anderson JL, Adams CD, Antman EM, et al. 2011 ACCF/AHA Focused Update Incorporated Into the ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011;123:e426–e579.

47. O’Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127:529–555.

48. Tarantino G, Citro V, Conca P, et al. What are the implications of the spontaneous spleno-renal shunts in liver cirrhosis? *BMC Gastroenterol*. 2009;9:89.

49. Tarantino G, Citro V, Esposito P, et al. Blood ammonia levels in liver cirrhosis: a clue for the presence of portosystemic collateral veins. *BMC Gastroenterol*. 2009;9:21.