Outcomes of patients with hypertrophic cardiomyopathy and acute myocardial infarction: a propensity score-matched, 15-year nationwide population-based study in Asia

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ABSTRACT

Objectives Hypertrophic cardiomyopathy (HCM) entails thickening of the myocardium and an increased risk of ischaemia. However, the prognosis of patients with HCM with acute myocardial infarction (AMI) is incompletely understood.

Methods Medical information was retrieved from the Taiwan National Health Insurance Research Database in 1997–2011. The exclusion criteria were patients <18 years old, and history of AMI, coronary intervention, aortic valve disease, disease of the pericardium, heart surgery, device implantation, venous thromboembolism, cardiac transplant, congenital heart disease and end-stage renal disease on dialysis. Patients with HCM with AMI were compared with propensity score (PS)-matched patients with AMI without HCM. The primary endpoints were in-hospital and 1-year cardiovascular events.

Results In total, 201 166 patients were admitted for AMI. There were 177 058 patients with new-onset AMI, 257 with HCM and 176 801 without HCM after exclusion criteria. Using 1:4 PS matching, the study population consisted of patients with AMI, 257 with HCM and 1028 without HCM. Patients with AMI with HCM received significantly less coronary intervention (OR=0.46; 95% CI 0.32 to 0.65; p<0.001), coronary intervention with stenting (OR=0.33; 95% CI 0.20 to 0.57; p<0.001) and coronary artery bypass graft surgery (OR=0.22; 95% CI 0.05 to 0.90; p=0.036), and fewer episodes of shock (OR=0.64; 95% CI 0.48 to 0.86; p=0.003) and in-hospital death (OR=0.46; 95% CI 0.30 to 0.70; p<0.001), compared with patients with AMI without HCM. Specifically, for patients with HCM with AMI, AMI occurred predominantly (82.5%) in the form of ischaemia without requiring coronary stenting. Patients with AMI with HCM had significantly better survival than patients without HCM (HR=0.66; 95% CI 0.51 to 0.85; p=0.001) during the 1-year follow-up.

Conclusions This is the first PS-matched study to compare the prognosis of patients with AMI with and without HCM. Compared with patients with AMI without HCM, patients with HCM had significantly better in-hospital and within 1-year outcomes.

Strengths and limitations of this study

- The prognosis of acute myocardial infarction (AMI) in patients with and without hypertrophic cardiomyopathy (HCM) is compared through propensity score matching.
- The clinical differences of patients with AMI with and without HCM were demonstrated by the percentage of patients who underwent percutaneous coronary intervention, stenting or coronary artery bypass graft, hence the difference in the severity of coronary artery disease between the two groups.
- Using the National Health Insurance (NHI) claims data is beneficial because the NHI programme provides uniform healthcare services to 99.5% of the population without financial restraints or selection bias; however, the data used for this study are old (1997–2011).
- The use of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for the study may occasionally result in missing cases if conditions were not coded correctly; however, patients with AMI and HCM have definite ICD codes and therefore no exclusion of other cardiomyopathy is necessary.
- This study did not have patients with baseline HCM to follow up until the occurrence of AMI; therefore, the incidence and rate of those patients with HCM studied for AMI may not include those who died due to severe ventricular arrhythmia or sudden death.

INTRODUCTION

Thickened myocardium which cannot be entirely attributed to excessive loading conditions is the hallmark of hypertrophic cardiomyopathy (HCM).1 HCM is the most common disorder that is affected by the myocardial gene expression in 0.2% of the general population.2 During the systolic
Phases, the hypercontractile myocardium may obliterate the left ventricular (LV) cavity and lead to LV outflow tract obstruction, causing chest pain, exercise intolerance, dizziness and syncope. During the diastolic phase, the excessively thickened myocardium reduces LV end-diastolic volume and restricts LV filling, resulting in increased LV end-diastolic pressure and decreased coronary flow reserve.

Patients with HCM are considered to have substantial cardiovascular risk; however, they tend to have less clear symptoms, thus evading the diagnosis of ischaemia. In a study that described the clinical characteristics and prognosis of HCM, approximately one-third of patients with HCM had adverse cardiovascular outcomes without concomitant increased acute myocardial infarction (AMI) mortality rate. A prospective study reported patients with AMI with HCM had worse outcome compared with patients without HCM. A large US population study noted that patients with HCM presented with AMI at a later age, and these patients had received less cardiac catheterisation compared with non-HCM patients with AMI. Furthermore, HCM may progress to heart failure (HF) because of dynamic LV outflow obstruction, LV diastolic dysfunction, atrial fibrillation with subsequent risk of ischaemic stroke and ventricular arrhythmia with unexpected risk of sudden cardiac death. The aims of this study are thus to (1) investigate the prognosis of patients with and without HCM experiencing an AMI through propensity score matching, and (2) clarify the difference in cardiovascular events between the two groups.

METHODS

Study patients

In Taiwan, the National Health Insurance (NHI) programme was established in 1995, enrolling >99% of the island’s 23.5 million people. The NHI Research Database (NHIRD) stored all data on dates of inpatient and outpatient services, admission, clinic and emergency visit diagnoses, medications, medical and surgical procedures, and expenditures, and the data are updated twice a year. With Taiwan’s population consisting of greater than 95% of Han Chinese, the study is conducted within a nearly homogeneous ethnicity.

By retrieving medical information from the NHIRD in 1997–2011, all patients admitted for AMI were identified. In this study, AMI was referenced to the Third Universal Definition: elevated myocardial biomarkers with at least one value >99th percentile and at least one of the following criteria: (1) angina symptoms; (2) new ST-T wave changes or a new left bundle branch block; (3) a pathological Q wave; (4) evidence of recently viable myocardium loss or regional wall motion abnormality on imaging study; and (5) finding of coronary obstruction via cineangiography or autopsy. In addition, cardiogenic shock was defined as the use of (1) dopamine; (2) norepinephrine; (3) intra-aortic balloon pump; or (4) any combination of the aforementioned medications and mechanical support. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 425.1 (as in online supplementary table 1) was used to identify patients with HCM and has been used previously in a large US population study. We excluded patients <18 years old, and with history of AMI, coronary intervention, disease of the aortic valve, disease of the pericardium, heart surgery, device implantation, venous thromboembolism, cardiac transplant, congenital heart disease and end-stage renal disease on dialysis. The first-ever admission due to AMI in the remaining patients was considered as the index admission.

We divided patients into HCM and non-HCM groups for further analysis. In the 2011 American College of Cardiology Foundation/American Heart Association Guideline, HCM is diagnosed when an unexplained thickening of the LV myocardium was found not attributed to concurrent cardiac or systemic disease. In addition, the 2014 European Society of Cardiology Guideline simply defined HCM as an increased LV myocardial thickness unrelated to excessive loading. In clinical practice, HCM is identified when the LV wall thickness exceeds 15 mm or 13–14 mm (when family history is considered) on echocardiography.

Covariate and study outcomes

To effectively compare the two groups of patients whose clinical presentations may be affected by comorbidities, we matched patients with HCM to patients without HCM using propensity scores. The parameters included in the calculation of propensity scores were sex, age, index date (admission date of the index AMI), and clinical history of hypertension (HTN), hyperlipidaemia, diabetes mellitus (DM), HF, cerebrovascular accident, chronic kidney disease (creatinine clearance <60 mL/min/1.73 m²), carotid artery disease, peripheral artery disease, atrial fibrillation or atrial flutter, chronic obstructive pulmonary disease, peptic ulcer disease, liver cirrhosis, malignancy, and gout. The propensity score matching used the greedy nearest neighbour algorithm, and a calliper width was set at 0.2.

The medical records of the NHIRD listed the primary diagnoses of patients during admission. Cardiovascular death was previously defined by the Food and Drug Administration. Death was identified as the patient is withdrawn from the NHI programme. Causes of death were attributed to the primary discharge diagnoses in the preceding 3 months before death. The primary outcomes were in-hospital and 1-year cardiovascular events.

Statistical analysis

Clinical characteristics in terms of clinical variables, comorbidities, mean follow-up years, interventions and medications during admission were compared between HCM and non-HCM groups using t-test for continuous variables and χ² test for categorical variables. In-hospital events (eg, in-hospital death) were compared by
logistic regression analysis, and continuous outcomes (e.g., length of stay) were compared using linear regression analysis. Because the risk of death between the HCM and non-HCM groups was imbalance, the incidence of long-term time-to-event outcomes during the follow-up was compared using death in the competing risk model.\textsuperscript{14} Using subdistribution hazard functions, cumulative incidence rates were plotted. Cox proportional hazards models for generating cumulative incidence functions were performed for all-cause mortality.

| Table 1 Baseline characteristics and comorbidities during the index admission before and after matching |
|-----------------|------------------|------------------|------------------|
| Variable         | Before matching  | After matching   | P values         |
| HCM (n=257)     | Non-HCM (n=176801) | P values         | Non-HCM (n=1028) |
| Clinical variables |                  |                  |                  |
| Age              | 70.1±12.4        | 67.3±14.0        | 0.001*           | 69.9±14.5        | 0.834 |
| Gender (male)    | 125 (48.6)       | 122422 (69.2)    | <0.001*          | 481 (46.8)       | 0.595 |
| Comorbidities    |                  |                  |                  |
| Hypertension     | 176 (68.5)       | 90160 (51.0)     | <0.001*          | 704 (68.5)       | 1.000 |
| Hyperlipidaemia  | 51 (19.8)        | 40020 (22.6)     | 0.285            | 204 (19.8)       | 1.000 |
| Diabetes mellitus| 68 (26.5)        | 61284 (34.7)     | 0.007*           | 275 (26.8)       | 0.925 |
| Heart failure    | 81 (31.5)        | 13797 (7.8)      | <0.001*          | 315 (30.6)       | 0.786 |
| Cerebrovascular accident | 51 (19.8)     | 23218 (13.1)     | 0.001*           | 222 (21.6)       | 0.539 |
| Chronic kidney disease | 18 (7.0)      | 6255 (3.5)       | 0.003*           | 78 (7.6)        | 0.750 |
| Carotid artery disease | 77 (30.0)   | 16982 (9.6)      | <0.001*          | 309 (30.1)       | 0.976 |
| Peripheral artery disease | 18 (7.0) | 7878 (4.5)       | 0.048*           | 75 (7.3)        | 0.872 |
| Atrial fibrillation/atrial flutter | 48 (18.7) | 6568 (3.7)       | <0.001*          | 189 (18.4)       | 0.914 |
| Chronic obstructive pulmonary disease | 70 (27.2) | 27659 (15.6)     | <0.001*          | 283 (27.5)       | 0.925 |
| Peptic ulcer disease | 57 (22.2) | 20022 (11.3)     | <0.001*          | 221 (21.5)       | 0.813 |
| Liver cirrhosis  | 12 (4.7)         | 3360 (1.9)       | 0.001*           | 47 (4.6)        | 0.947 |
| Malignancy       | 19 (7.4)         | 10986 (6.2)      | 0.434            | 76 (7.4)        | 1.000 |
| Gout             | 24 (9.3)         | 12310 (7.0)      | 0.135            | 98 (9.5)        | 0.924 |
| Mean follow-up years | 3.4±3.4       | 3.7±4.0          | 0.220            | 3.1±3.8         | 0.223 |

*P<0.05. HCM, hypertrophic cardiomyopathy.

Figure 1 Study design and flow chart of the inclusion of patients with acute myocardial infarction (AMI) and the selection of those patients with and without hypertrophic cardiomyopathy (HCM) for propensity score matching. CABG, coronary artery bypass graft; ESRD, end-stage renal disease; MI, myocardial infarction; PCI, percutaneous coronary intervention.
Since there was a crossing between HCM and non-HCM all-cause mortality survival curves, inverse probability of treatment weighting with log-rank test was used to compare the study groups. Therefore, a landmark analysis of all-cause mortality using cut-points of 1 year (main result), 2 years and 3 years was performed. Statistical analyses were all performed using commercial statistics software (SAS V.9.4). All tests were two-tailed, and statistics was considered significant when p<0.05.

Sensitivity analysis

Three sensitivity analyses were additionally performed to assess the robustness and increase the generalisability of findings. First, the index AMI admission date was not included in the propensity score; instead, the index year was adjusted in the regression model (online supplementary tables 2–3). Furthermore, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) and pacing device during the index admission and index year were adjusted in the analysis of survival outcomes (online supplementary table 4). Second, the sample size of the propensity score-matched cohort was notably small, which may limit the external generalisability of the findings. Using the whole cohort, we performed a traditional multivariable regression adjusting for age, sex and the 14 comorbidities from table 1 (online supplementary tables 5–7). Third, we performed the classic Cox proportional hazards model rather than the competing risk model in survival analyses (online supplementary table 8).

Patient and public involvement

Due to the nature of this database research study, the patient and the public were not directly involved in the investigation.

RESULTS

Study population

In total, 201 166 patients were admitted for AMI between 1997 and 2011 in Taiwan. After exclusion criteria, the remaining 177 058 patients with AMI were separated into those with HCM and those without HCM. The 257 patients with AMI with HCM and 176 801 patients without HCM were 1:4 propensity score-matched, and the final study population consisted of 257 patients with HCM and 1028 patients without HCM (figure 1). Before matching, significant differences existed between the two groups and there was no difference after matching (table 1).

Clinical characteristics

Table 2 presents the findings on patients with AMI with and without HCM during index admission. In terms of intervention, patients with AMI with HCM had significantly less intra-aortic balloon pump (IABP, p=0.002) placed and had trends towards less intubation (p=0.065) and received temporary haemodialysis (p=0.063). In terms of medication, patients with AMI with HCM had significantly more prescriptions of beta-blockers (p=0.007).

In-hospital outcomes

Table 3 shows the results of in-hospital cardiovascular outcomes. Patients with AMI with HCM had significantly less PCI (OR=0.46; 95% CI 0.32 to 0.65; p<0.001), vessels intervened, PCI with stenting (OR=0.33; 95% CI 0.20 to 0.57; p<0.001), CABG (OR=0.22; 95% CI 0.05 to 0.90; p=0.036), shock (OR=0.64; 95% CI 0.48 to 0.86; p=0.003) and died during hospitalisation (OR=0.46; 95% CI 0.30 to 0.70; p<0.001) compared with patients with AMI without HCM. However, patients with AMI with HCM had significantly more pacing device implantation (OR=9.57; 95% CI 2.46 to 37.26; p=0.001) and new-onset atrial fibrillation (OR=3.22; 95% CI 2.03 to 5.10; p<0.001).

Follow-up outcomes

Figure 2A shows the Kaplan-Meier survival curves of patients with AMI with and without HCM during the entire follow-up. The risk of all-cause mortality was similar between the two groups of patients with AMI (crude HR, 0.97; 95% CI 0.81 to 1.16). However, the two curves crossed at years 6–7, reflecting that patients with HCM had an accelerated rate of death compared with
patients without HCM and suggesting that the death rate was not particularly related to AMI. The Kaplan-Meier curves revealed that the group difference (slope) achieved the maximum at years 1–2; thus, we used 1 year as the cut-off point in the landmark analysis. In-hospital death was included in 1-year mortality, and during the first-year follow-up patients with AMI without HCM had significantly higher all-cause mortality compared with patients with HCM (28.0% for HCM and 39.5% for non-HCM; HR, 0.66; 95% CI 0.51 to 0.85; table 4, figure 2B). By contrast, patients with AMI with HCM had a higher mortality rate after 1-year follow-up (33.9% for HCM and 19.3% for non-HCM, p<0.001; figure 2B). In addition, similar results were found when the cut-off point of the landmark analysis was changed to 2 or 3 years (data not shown).

Table 4 demonstrates the results of the follow-up outcomes. No group difference was found in terms of recurrent AMI, HF hospitalisation, systemic venous thromboembolism, heart transplant and cardiovascular death during either 1 year or the entire follow-up period.

Sensitivity analysis

Both sensitivity analyses I and II had results similar to the primary analysis (online supplementary tables 3 and 6). Similarly, patients with AMI with HCM had significantly lower all-cause mortality within 1 year of follow-up (figure 2), which was replicated in our sensitivity analyses (online supplementary tables 4 and 7).

DISCUSSION

The following are some highlights and important findings from this study: (1) This is the first study to compare the outcomes of patients with AMI with and without HCM using propensity score matching. (2) Patients with AMI with HCM had significantly lower number of coronary interventions (PCI, intervened vessels, PCI with stenting, CABG), shock and in-hospital death. Similarly, AMI without HCM had significantly higher number of one-vessel and three-vessel coronary artery disease. (3) Patients with AMI without HCM had significantly higher all-cause mortality within 1 year of follow-up; however, this was reversed after 1 year until the end of the follow-up, possibly reflecting the inherently high disease burden of HCM.

Relevant studies

The number of published papers that investigate AMI in patients with HCM is limited. Two major studies have specifically addressed this knowledge gap and enhanced our understanding of the supposedly ischaemia-prone thickened myocardium in patients with HCM. The study that focused specifically on the prognosis of AMI in patients with HCM was published by a Chinese group that prospectively enrolled patients aged ≥18 years who had underlying HCM with incident AMI from 1997 to 2014.7

Further, they enrolled age-matched, sex-matched and admission date-matched non-HCM patients with incident AMI in 1:1 ratio as controls. The findings indicated
that patients with HCM had less optimistic long-term outcome than did matched non-HCM patients. A Kaplan-Meier survival curve showed poorer outcomes for patients with AMI with HCM after 1 year than for those without HCM.7

In a population study from the USA, the discharge data of 5 901 827 patients with AMI during 2003–2011 were studied for the outcomes of those with HCM (5688 patients, 0.1%) and those without HCM.8 Patients with HCM were older, more likely to be female and had less number of traditional cardiovascular risks. These patients had higher percentage of non-ST elevation myocardial infarction but lower percentage of ST-elevation myocardial infarction. In addition, patients with HCM had less cardiac catheterisation for AMI.8 Since patients with AMI with HCM had less traditional cardiovascular risks as opposed to patients without HCM, the authors postulated that these AMIs were probably caused by non-atherosclerotic mechanisms, such as microvascular dysfunction. Without using propensity score matching, the authors noted that there was no difference in terms of in-hospital mortality between patients with AMI with HCM and those without HCM.8

**Present study**

During the 15 years from 1997 to 2011, 201 166 patients were admitted for AMI in Taiwan, and 257 of these patients had coexisting HCM (0.13%). This prevalence rate was similar to the study reported in the USA (0.10%).8 Our study also showed that patients with AMI with HCM were older (70.1±12.4 vs 67.3±14.0 years), and a high percentage of these patients were female (51.4%)}
vs 30.8%) and had traditional cardiovascular risks such as DM (26.5% vs 34.7%) and hyperlipidaemia (19.8% vs 22.6%), but not HTN (68.5% vs 51.0%). Because significant differences existed across comorbidities, we used propensity score matching that matched sex, age, 14 comorbidities and the index admission date (table 1).

As shown in table 2, IABP was used significantly less in patients with HCM, and a trend occurred towards lower rates of intubation and temporary haemodialysis in these patients. The cardiac performance and cardiovascular compromise appeared to be less likely affected in patients with HCM. However, these results exhibited a trend in the sensitivity analysis without matching the index date (online supplementary table 2) and were not significant when using multivariable regression adjustment (online supplementary table 5). The use of medication did not significantly differ between the groups, except for beta-blockers being used more extensively in patients with HCM, reflecting the guideline-suggested practice of beta-blockers as the initial drug of choice for patients with HCM. Among patients with AMI, beta-blocker use was 52.5% in patients with HCM and 43.1% in patients without HCM, which were higher than the previously reported 34% beta-blocker use after AMI in a review, but lower than the reported 88%–92% beta-blocker in patients with AMI with HCM recently. This result was reproduced in sensitivity analysis I (online supplementary table 2) but not in sensitivity analysis II (online supplementary table 5).

In summary, our study showed that patients with AMI with HCM had significantly less coronary obstruction, as well as necessary coronary interventions, shock, in-hospital mortality and 1-year all-cause mortality, compared with patients without HCM.

Limitations

This study has several limitations related to the epidemiological data obtained from the NHIRD. First, the data available in the NHIRD is for the period between 1997 and 2011; thus, some information and practices may be outdated. However, the treatment methods for HCM and the practice of PCI in AMI have not changed dramatically since then. Second, retrieving medical information using ICD-9-CM codes may suffer from missed cases or

| Variable               | HCM (n=257) | Non-HCM (n=1028) | HCM vs non-HCM HR (95% CI) | P values |
|------------------------|------------|------------------|----------------------------|----------|
| 1-year follow-up       |            |                  |                            |          |
| Recurrent AMI          | 13 (5.1)   | 70 (6.8)         | 0.68 (0.37 to 1.25)        | 0.214    |
| HF hospitalisation     | 17 (6.6)   | 66 (6.4)         | 1.02 (0.60 to 1.74)        | 0.941    |
| Systemic VTE          | 23 (8.9)   | 64 (6.2)         | 1.55 (0.75 to 3.21)        | 0.236    |
| Heart transplant       | 0 (0.0)    | 1 (0.1)          | NA                        | NA       |
| All-cause mortality    | 72 (28.0)  | 406 (39.5)       | 0.66 (0.51 to 0.85)        | 0.001*   |
| CV death               | 46 (17.9)  | 211 (20.5)       | 0.83 (0.60 to 1.14)        | 0.252    |
| At the end of follow-up|            |                  |                            |          |
| Recurrent AMI          | 23 (8.9)   | 109 (10.6)       | 0.79 (0.50 to 1.24)        | 0.299    |
| HF hospitalisation     | 35 (13.6)  | 112 (10.9)       | 1.24 (0.85 to 1.80)        | 0.266    |
| Systemic VTE          | 39 (15.2)  | 107 (10.4)       | 1.52 (0.97 to 2.38)        | 0.068    |
| Heart transplant       | 0 (0.0)    | 1 (0.1)          | NA                        | NA       |
| All-cause mortality    | 159 (61.9) | 604 (58.8)       | 0.97 (0.81 to 1.16)        | 0.732    |
| CV death               | 62 (24.1)  | 262 (25.5)       | 0.89 (0.67 to 1.17)        | 0.401    |

The analysis considers death as a competing risk except for all-cause mortality and CV death.

*P<0.05.

AMI, acute myocardial infarction; CV, cardiovascular; HCM, hypertrophic cardiomyopathy; HF, heart failure; NA, not applicable.; VTE, venous thromboembolism.
incorrectly coded conditions. However, because patients with AMI and HCM have definitive ICD codes, no exclusion of other cardiomyopathy is necessary. Third, this study did not have a baseline HCM population for clinical follow-up until the occurrence of AMI; therefore, the incidence and rate of those patients with HCM studied for AMI may not include those who died either due to severe ventricular arrhythmia or sudden death, causing selection bias. Fourth, the claims-based insurance database does not offer laboratory data values or examination report details. On the other hand, the NHIRD has data on coronary intervention performed, number of intervened vessels and number of stents placed. Last, because our study population comprised patients with uniform ethnic background, application of the results to other populations requires interpretation within proper contexts.

CONCLUSIONS
This is the first propensity-matched study to compare the prognosis of patients with AMI with and without HCM. Compared with patients with AMI without HCM, patients with HCM had significantly better in-hospital and within 1-year outcomes.

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