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Complete List of Authors:	Wu, Victor Chien-Chia; Chang Gung Memorial Hospitalospital, Cardiology Chen, Tien-Hsing; Chang Gung Memorial Hospitalospital, cardiology Wu, Michael S; NewYork-Presbyterian Hospital/Weill Cornell Medical Center, Division of Cardiology Chen, Shao-Wei Chang, Chih-Hsiang; Chang Gung Memorial Hospital, nephrology Hsieh, Ming-Jer; Chang Gung Memorial Hospital Linkou Branch, Division of Cardiology Wang, Chao-Yung; Chang Gung Memorial Hospital Linkou Branch, Division of Cardiology Chang, Shang-Hung; Chang Gung Memorial Hospital Linkou Branch, Division of Cardiology Lin, Fen-Chiung; Chang Gung Memorial Hospital Linkou Branch, Division of Cardiology Wen, Ming-Shien; Chang Gung Memorial Hospital Linkou Branch, Division of Cardiology
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Ischemic Outcomes of Patients with Hypertrophic Cardiomyopathy and Acute Myocardial Infarction – A Propensity Score Matched 15-Year Nationwide Population-Based Study in Asia

Victor Chien-Chia Wu, MD[1*], Tien-Hsing Chen, MD[2*], Michael S Wu, MD[3], Shao-Wei Chen, MD[4], Chih-Hsiang Chang, MD[5], Ming-Jer Hsieh, MD[1], Chao-Yung Wang, MD[1], Shang-Hung Chang, MD[1], Fen-Chiung Lin, MD[1], Ming-Shien Wen, MD[1]

[1]Division of Cardiology, Chang Gung Memorial Hospital, Linkou Medical Center, Taoyuan City, Taiwan

[2]Department of Cardiology, Chang Gung Memorial Hospital, Keelung, Taiwan

[3]Division of Cardiology, Weill Cornell Medical Center, New York, USA

[4]Department of Cardiothoracic and Vascular Surgery, [5]Department of Nephrology, Chang Gung Memorial Hospital, Linkou Medical Center, Taoyuan City, Taiwan

Brief title: Ischemic Outcomes of Patients with HCM having AMI

*Authors contributed equally.

All authors have nothing to disclose

Address for correspondence:

Victor Chien-Chia Wu, MD

Department of Cardiology, Chang Gung Memorial Hospital, No. 5, Fuxing Street, Guishan District, Taoyuan City 33305, Taiwan

Tel: +886-3-3281200 x8115; fax: + 886-3-3281451

E-mail: victorcwu@hotmail.com

Objectives: Hypertrophic cardiomyopathy (HCM) has thickened myocardium with high burden for ischemia. However, conflicting data exists therefore we aimed to investigate the ischemic outcome of HCM patients with acute myocardial infarction (AMI).

Methods: Electronic medical records were retrieved from Taiwan National Health Insurance Research Database from 1997 to 2011. Patients were excluded for history of AMI, percutaneous coronary intervention (PCI), aortic valve disease, pericardial disease, congenital heart disease, venous thromboembolism, cardiovascular surgeries, device implantation, heart transplant, and on hemodialysis. AMI in patients with HCM were compared with propensity-matched AMI patients without HCM. Primary outcomes defined as in-hospital and 1-year cardiovascular events.

Results: There were 201,166 patients admitted due to AMI. After exclusion criteria, there were 177,058 patients with new-onset AMI (257 patients with HCM, 176,801 patients without HCM). After 1:4 propensity score matching for extensive comorbidities, the study population consisted of 257 patients with HCM and 1,028 patients without HCM. Patients with HCM having AMI received significantly less PCI, PCI with stenting, CABG, and had less episodes of shock and in-hospital death compared to patients without HCM having AMI. Specifically, patients with HCM having AMI occurred predominantly (82.5%) in the form of ischemia without requiring coronary stenting.

Conclusions: AMI patients with HCM had significantly better outcomes compared to those without HCM during in-hospital course and within 1 year follow up. In AMI patients with HCM, non-atherosclerotic microvascular disease seemed likely to be the mechanism for coronary ischemia.

Keywords: hypertrophic cardiomyopathy, acute myocardial infarction, outcome

Strengths and limitations of the study

- This is the largest study to directly compare the ischemic outcome of AMI in patients with and without HCM using extensively propensity score matched patients.
- In patients with and without HCM presenting with AMI, subsequent PCI, PCI with stenting, number of diseased vessels and/or CABG demonstrated severity and difference of ischemic burden between these two group of patients.
- In patients with and without HCM presenting with AMI, the ischemic difference between two groups were further corroborated with ischemic outcome of in-hospital hemodynamics, shock status, and mortality.
- Using ICD-9-CM codes for patient screening may miss some cases for conditions not coded correctly, but patients with AMI and HCM have definitive ICD codes therefore no exclusion of other cardiomyopathy is necessary.
- This study did not have baseline HCM population for clinical follow up till the occurrence of AMI, therefore the incidences and rates of those HCM patients studied for AMI may not include those that had died either due to severe ventricular arrhythmia or sudden death, thus selection bias.

Introduction

Hypertrophic cardiomyopathy (HCM) is defined by the presence of increased left ventricular (LV) wall thickness that is not solely explained by abnormal loading conditions [1]. It is the most common genetic disorder of the myocardium that affects 1 in 500 in the general population [2]. During systolic phase, the hypercontractile myocardium may obliterate the LV cavity and left ventricular outflow tract obstruction, causing chest pain, exercise intolerance, dizziness, and syncope. During diastolic phase, the excessively thickened myocardium decreases LV end-diastolic volume and restricts LV filling, resulting in increased LV end-diastolic pressure and decreased coronary flow reserve (CFR) [3].

Previous studies considered patients with HCM to have substantial cardiovascular risks, while there were also evidences noting patients HCM to have less clinically obvious symptoms thus evading diagnosis [4,5]. In a study that described clinical characteristics and outcomes of HCM, although HCM did not increase cardiovascular mortality rate, over one-third of patients with HCM experienced cardiovascular outcome [6]. In addition, a prospective study reported worse long-term survival in HCM patients with AMI compared to those non-HCM [7]. However, recently a large US population study showed that patients with HCM among those with acute myocardial infarction (AMI) presented at a later age and were also less likely to receive revascularization compared to patients without HCM [8]. In the end, HCM may progress along one or more of its major disease pathways: progressive heart failure (HF) due to dynamic LV outflow obstruction, LV diastolic dysfunction, atrial fibrillation (AF) with risk of stroke, and ventricular arrhythmia with risk of sudden death [9]. Therefore in this study, we aim to: (1) study the ischemic outcomes of patients with HCM and without HCM experiencing an AMI by

propensity score matching, and (2) clarify the prognostic difference in cardiovascular events between the two groups.

Methods

Study Patients

Taiwan's National Health Institute (NHI) Program started in 1995 and provides 99.5% coverage for the 23 million residents in Taiwan. The NHI Research Database (NHIRD) provides all dates of inpatient and outpatient services, diagnosis, prescriptions, examinations, operations, and expenditures, and data are updated biannually. With over 95% of Taiwan's population consists of Han Chinese, our study is considered of uniform ethnic background. The Institutional Review Board of Chang Gung Memorial Hospital Linkou Branch approved this study.

By searching electronic medical records from the NHIRD between January 1, 1997 and December 31, 2011, we retrieved all patients admitted due to AMI. AMI is defined as Third Universal Definition of AMI: (1) a rise and/or fall of cardiac biomarker with at least one value above the 99th percentile upper reference limit, with at least one of the following, (2) symptoms of ischemia, (3) new or presumed new significant ST segment-T wave changes or new left bundle branch block, (4) development of pathological Q waves in the ECG, (5) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, and (6) identification of an intracoronary thrombus by angiography or autopsy [10]. Using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes (as Appendix). Patients less than 18 years old were excluded. In addition, patients with history of AMI, percutaneous coronary intervention (PCI), aortic valve disease (AVD), pericardial disease, congenital heart disease (CHD), venous thromboembolism (VTE),

cardiovascular surgeries, device implantation, heart transplant, and on end-stage renal disease (ESRD) on dialysis were excluded. The remaining patients had their first ever AMI admission as the index admission. ICD-9-CM of 425.1 was to identify patients with HCM and was used previously in the large US population study [8]. We were further divided into HCM and non-HCM groups for further analysis.

Covariate and Study Outcomes

To effectively compare two groups of patients whose clinical presentation may be affected by comorbidities, we matched clinical characteristics of patients with HCM to patients without HCM. The matched variables include gender, age and clinical history of hypertension (HTN), hyperlipidemia (HL), diabetes mellitus (DM), HF, cerebrovascular accident (CVA), chronic kidney disease (CKD, defined as at least at moderate stage with creatinine clearance <60 mL/min/1.73 m^2), carotid artery disease, peripheral artery disease (PAD), AF/atrial flutter (AFL), chronic obstructive pulmonary disease (COPD), peptic ulcer disease (PUD), liver cirrhosis, malignancy,

The medical records of NHIRD listed primary diagnoses of the patients during admission. Definitions of cardiovascular death meet the criteria of Standardized Definitions for End Point Events in Cardiovascular Trials draft by the Food and Drug Administration [11]. Death was defined as the withdrawal of the patient from NHI Program. Causes of death were defined according to the primary discharge diagnosis of hospitalization within 3 months prior to death. Primary outcomes defined as in-hospital and 1-year cardiovascular events.

Statistical Analysis

We compared the baseline characteristics, comorbidities, intervention and medication between the study groups (HCM vs. non-HCM) using independent sample t-test for continuous variable or chi-square test for categorical variable. We compared the risk of categorical in-hospital outcomes (i.e. in-hospital death) between groups using logistic regression analysis and compared continuous outcomes (i.e. length of stay) using linear regression analysis. Because the risk of death between HCM and non-HCM groups was unbalanced, the incidence of long-term time to event outcome during the follow up between the HCM and non-HCM groups was compared using competing risk survival model with considering death as a competing risk [12]. We generated the plot of cumulative incidence rate using subdistribution hazard function for these time to event outcomes. As to all-cause mortality and cardiovascular death we used Cox proportional hazard model and generated the plot of incidence using regular proportions. All statistical analyses were carried out using commercial software (SAS 9.4, SAS Institute, Cary, NC).

Results

Study Population

There were 201,166 patients admitted due to AMI between 1997 and 2011 in Taiwan. After excluding patients with history of AMI, PCI, AVD, pericardial disease, CHD, VTE, cardiovascular surgeries, device implantation, heart transplant, and ESRD on dialysis, there were 177,058 patients with new-onset AMI where 257 patients were in HCM group and 176,801 patients in non-HCM group. Since there was an excess in number of those patients without HCM, after 1:4 propensity score matching for clinical variables of age and gender, and comorbidities of HTN, HL, DM, HF, CVA, CKD, carotid artery disease, PAD, AF/AFL, COPD, PUD, liver cirrhosis, malignancy,

and gout, there were 257 patients with HCM and 1,028 patients without HCM (Figure 1). Before matching, there were significant differences across clinical variables and comorbidities except HL, malignancy, and gout. After matching, there were no difference between the two groups (Table 1).

Clinical Characteristics

Table 2 shows the findings of AMI patients with HCM and without HCM during index admission. In terms of intervention, AMI patients with HCM were less likely to require intraaortic balloon bump (IABP) ($P = 0.002$) and a trend toward less likely to be intubated ($P = 0.065$) and receive temporary hemodialysis ($P = 0.063$). In terms of medication, AMI patients with HCM were more likely to be prescribed beta blocker ($P = 0.007$).

In-Hospital Outcome

Table 3 displays the results of in-hospital outcome. Patients HCM having AMI were significantly less likely to receive PCI (odds ratio [OR]: 0.46; 95% confidence interval [CI]: 0.32–0.65; p<0.001), less likely to have vessels intervened, less likely to receive PCI with stenting (OR: 0.33; 95% CI: 0.20–0.57; p<0.001), less likely to undergo coronary artery bypass surgery (CABG) (OR: 0.22; 95% CI, 0.05-0.90; p=0.036), and less episodes of shock (OR: 0.64; 95% CI: 0.48-0.86; p=0.003) and in-hospital death (OR: 0.46; 95% CI: 0.30–0.70; p<0.001) compared with patients without HCM having AMI. On the other hand, patients with HCM having AMI had significantly higher incidence in pacing device implantation (OR: 9.57; 95% CI: 2.46–37.26; p=0.001) and new-onset atrial fibrillation (OR: 3.22; 95% CI: 2.03–5.10; p<0.001).

Follow Up Outcome

Table 4 demonstrates the results of follow up outcome. During follow up of 1 year, patients without HCM having AMI had significantly worse all-cause mortality compared with patients without HCM having AMI (28.0% for HCM and 39.5% for non-HCM; hazard ratio [HR], 0.66; 95% CI, 0.51–0.85) (Table 4, Figure 2). However, patients with HCM having AMI conversely had higher mortality rate after 1-year follow up (33.9% for HCM and 19.3% for non-HCM, $P < 0.001$) as illustrated in Figure 2.

Discussion

Our study had several findings. (1) This is the first study to directly compare the ischemic outcome of patients with HCM and without HCM having AMI by extensive propensity score matching. (2) Patients with HCM having AMI had significantly lower rates of PCI, PCI with stenting, CABG, shock and in-hospital death. With the same regard, patients without HCM having AMI had significantly higher rates of one- and three-vessel coronary artery disease (CAD). (3) All-cause mortality was significantly higher within 1 year of follow up in patients without HCM having AMI, however reversed after 1 year to the end of follow up, possibly reflecting the high disease burden in HCM.

Previous Studies

In the investigation of AMI in the patients with HCM, the number of published papers were rather limited. There were two major studies that specifically addressed this gap in knowledge for our understanding on the supposedly ischemia-prone thickened

myocardium in the patients with HCM. The study that looked specifically at long-term survival of AMI in patients with HCM was published by a Chinese group that prospectively enrolled adult patients ≥18 years with HCM and AMI from 1997 to 2014 [7]. They also enrolled a control group constructed using age-, sex, and admission date-matched AMI patients without HCM in 1:1 ratio. The authors found patients with HCM exhibited worse long-term survival than patients without HCM. Kaplan-Meier survival curve showed worse outcome of those AMI patients with HCM after one year compared to those AMI patients without HCM [7].

In a large population-based study in US, discharge data of 5,901,827 patients with AMI during 2003-2011 were studied for the outcome of those with HCM (5,688 patients, 0.1%) and those without HCM [8]. The patients with HCM was older, more likely to be female, less likely to have traditional cardiovascular risk factors, less likely to present with ST-elevation myocardial infarction (STEMI), and more likely to present with non-ST-elevation myocardial infarction (NSTEMI). In addition, for these STEMI and NSTEMI in patients HCM, they were less likely to receive revascularization [8]. Since these patients with HCM were less likely to have traditional cardiovascular risk factors compared with patients without HCM, the authors postulates that it is reasonable that these AMIs were likely driven by non-atherosclerotic mechanisms through microvascular dysfunction. Without propensity score matching, the authors concluded that in the overall population with AMI, there was no difference in observed in-hospital mortality between patients with and without HCM [8].

Current Study

During the 15 years from 1997 to 2011, there were 201,166 patients admitted due to AMI and 257 patients had coexisting HCM (0.13%). This prevalence was similar to previous US study (0.10%) [8]. When comparing patients with HCM having AMI to patients without HCM having AMI, we found patients with HCM having AMI occurring at significantly older age (70.1±12.4 vs 67.3±14.0), more likely to be female (51.4% vs 30.8%), and less likely to have traditional cardiovascular risk factors such as DM (26.5% vs 34.7%), HL (19.8% vs 22.6%) but not HTN (68.5% vs 51.0%). Sincere there were also significant difference across comorbidities, we made extensive propensity score-matching that matched all clinical variables, comorbidities, and mean follow-up (Table 1).

As shown in Table 2, IABP was used significantly less in patients with HCM and there was a trend toward lower rates of intubation and temporary HD in patients with HCM as well. The cardiac performance and cardiovascular compromise seemed less likely to be affected in patients with HCM. The use of medications generally showed no significant difference between the groups except beta blockers were used more extensively in patients with HCM, reflecting the guideline suggested practice of beta-blockers as initial drug of choice in patients with HCM [1]. In this cohort of patients with AMI, the beta-blocker use was 52.5% in patients with HCM, and 43.1% in patients without HCM, which were higher than earlier reported 34% beta-blocker use after AMI in a review of ≥200,000 patient records in the Cooperative Cardiovascular Project [13] but lower than reported 88-92% in a more recent study involving patients with HCM having AMI [7].

The most important findings of our study were that patients with HCM having AMI had significantly less rates of PCI, intervened vessels, PCI with stenting, CABG, shock, and in-hospital death (Table 3) compared to patients without HCM having

AMI. Patients with HCM has higher rates of AMI in vessels requiring no coronary stenting compared to patients without HCM (82.5% vs 68.4%), suggesting microvascular disease, or lower CFR was probably responsible for the ischemia. Patients with HCM having AMI had significantly less rates of one- and three-vessel CAD disease compared to patients without HCM having AMI (13.2% vs 23.5%, P <0.001 and 0.4% vs 2.8%, P = 0.034). Therefore we would hypothesize that large vessel disease and more-proximal part of the coronary artery probably were responsible for the significantly higher rate of IABP use, shock, CABG, and in-hospital death in patients without HCM having AMI compared to patients with HCM having AMI. In the same regard, cumulative incidence of all-cause mortality was significantly higher in AMI patients without HCM within 1 year of follow up (Figure 2). The trend then reversed after 1 year to the end of follow up, suggesting coronary ischemia leading to myocardial infarction was not the cause of long-term mortality in patients with HCM. This results however, coincided with our understanding that there is indeed higher disease burden in patients with HCM.

In this study, the symptoms of angina and coronary ischemia presenting as AMI secondary to excessively thickened myocardium may not necessary lead to the finding of coronary obstruction. Indeed, angina symptoms in patients with HCM causes concerns if the chest discomfort are due to stenotic lesion or coronary ischemia. Previous study reported that these symptomatic patients with HCM had decrements in CRF [3], without evidence of a functional stenosis of the epicardial vessels [14-17]. Abnormal arterioles with decreased lumen were detected in HCM patients, suggesting that a structural change in the coronary arterial vascular tree might be related to this finding. In summary, compared to patients without HCM, patients with HCM were

significantly less likely to have coronary obstruction during AMI, CABG, shock, and in-hospital mortality.

Limitations

There are several limitations in epidemiologic data from NHIRD. First, using ICD-9-CM codes for patient screening may miss some cases for conditions not coded correctly, but patients with AMI and HCM have definitive ICD codes therefore no exclusion of other cardiomyopathy is necessary. Second, this study did not have baseline HCM population for clinical follow up till the occurrence of AMI, therefore the incidences and rates of those HCM patients studied for AMI may not include those that had died either due to severe ventricular arrhythmia or sudden death, thus selection bias. Third, in NHIRD study, there was no information on using gold standard CFR to confirm the microvascular dysfunction in these patient. Fourth while a small number of patients may not fulfill strict diagnostic criteria, Taiwan NHIRD has the most comprehensive electronic medical records covering 99.5% of insured residence and the study results is as complete as possible. Last, since our study consisted of uniform ethnic background, application of the results to other populations requires interpretation in the proper context.

Conclusions

This is the first study to directly compare the clinical outcomes of AMI patients with and without HCM using extensively propensity score-matched patients. AMI patients with HCM had significantly better outcomes compared to those without during in-hospital course and within 1 year follow up. In patients with HCM having AMI, non-

atherosclerotic microvascular disease seemed likely to be the mechanism for coronary ischemia.

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Contributorship

VCW, THC contributed to study conception and design.

VCW, THC, MSW acquired the data.

SWC, CHC, MJH, CYW, SHC contributed to analysis and interpretation of data.

VCW, THC drafted the manuscript.

FCL, MSW contributed to critical revision.

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Disclosures

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Data Sharing Statement

No additional data available.

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Figure Legends

Figure 1

Study design and screening criteria flow chart for 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.

Figure 2

Cumulative incidence of all-cause mortality in the AMI patients with and without HCM. The vertical dotted line separates follow-up to within and beyond 1 year.

Table 1. Baseline characteristics and comorbidities during the index admission before and after matching

	Before matching			After matching	
Variable	HCM (n = 257)	Non-HCM (n = 176,801)	P value	Non-HCM (n = 1,028)	P value
Clinical variables					
Age	70.1±12.4	67.3±14.0	0.001*	69.9±14.5	0.834
Gender (male)	125 (48.6)	122,422 (69.2)	<0.001*	481 (46.8)	0.595
Comorbidities					
Hypertension	176 (68.5)	90,160 (51.0)	<0.001*	704 (68.5)	1.000
Hyperlipidemia	51 (19.8)	40,020 (22.6)	0.285	204 (19.8)	1.000
Diabetes mellitus	68 (26.5)	61,284 (34.7)	0.007*	275 (26.8)	0.925
Heart failure	81 (31.5)	13,797 (7.8)	<0.001*	315 (30.6)	0.786
Cerebrovascular accident	51 (19.8)	23,218 (13.1)	0.001*	222 (21.6)	0.539
Chronic kidney disease	18 (7.0)	6,255 (3.5)	0.003*	78 (7.6)	0.750
Carotid artery disease	77 (30.0)	16,982 (9.6)	<0.001*	309 (30.1)	0.976
Peripheral artery disease	18 (7.0)	7,878 (4.5)	0.048*	75 (7.3)	0.872
Atrial fibrillation/atrial flutter	48 (18.7)	6,568 (3.7)	<0.001*	189 (18.4)	0.914
Chronic obstructive pulmonary disease	70 (27.2)	27,659 (15.6)	<0.001*	283 (27.5)	0.925
Peptic ulcer disease	57 (22.2)	20,022 (11.3)	<0.001*	221 (21.5)	0.813
Liver cirrhosis	12 (4.7)	3,360 (1.9)	0.001*	47 (4.6)	0.947
Malignancy	19 (7.4)	10,986 (6.2)	0.434	76 (7.4)	1.000
Gout	24 (9.3)	12,310 (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

* Denotes $P < 0.05$.

Table 2. Intervention and medication during the index admission

Variable	HCM (n = 257)	Non-HCM (n = 1,028)	P value
Intervention			
Intubation	41 (16.0)	217 (21.1)	0.065
Intraaortic balloon pump	4 (1.6)	65 (6.3)	0.002*
Extracorporeal membrane oxygenation	1 (0.4)	5 (0.5)	0.838
Temporary hemodialysis	5 (1.9)	46 (4.5)	0.063
Cardiac rehabilitation	8 (3.1)	50 (4.9)	0.227
Medications during admission			
Aspirin	196 (76.3)	757 (73.6)	0.390
Clopidogrel	120 (46.7)	519 (50.5)	0.277
ACEI/ARB	141 (54.9)	549 (53.4)	0.675
Beta blocker	135 (52.5)	443 (43.1)	0.007*
Calcium channel blocker	70 (27.2)	236 (23.0)	0.150
Diuretics	80 (31.1)	334 (32.5)	0.676
Spironolactone	19 (7.4)	87 (8.5)	0.577
Nitrates	51 (19.8)	219 (21.3)	0.608
Warfarin	18 (7.0)	49 (4.8)	0.149
Statin	49 (19.1)	237 (23.1)	0.169
Proton pump inhibitor	30 (11.7)	102 (9.9)	0.408

* Denotes $P < 0.05$.
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 3. In-hospital cardiovascular outcome

Variable	HCM (n = 257)	Non-HCM (n = 1,028)	HCM *vs*. Non-HCM	
			OR / *B* (95% CI)	*P* value
PCI	45 (17.5)	325 (31.6)	0.46 (0.32, 0.65)	<0.001*
Number of intervened vessels				
0 vessel	212 (82.5)	703 (68.4)	Reference	–
1 vessel	34 (13.2)	242 (23.5)	0.47 (0.32, 0.69)	<0.001*
2 vessels	10 (3.9)	54 (5.3)	0.61 (0.31, 1.23)	0.167
3 vessels	1 (0.4)	29 (2.8)	0.11 (0.02, 0.84)	0.034*
PCI with stenting	16 (6.2)	171 (16.6)	0.33 (0.20, 0.57)	<0.001*
CABG	2 (0.8)	36 (3.5)	0.22 (0.05, 0.90)	0.036*
Valvular surgery	3 (1.2)	3 (0.3)	4.04 (0.81, 20.11)	0.089
Pacing device implantation†	7 (2.7)	3 (0.3)	9.57 (2.46, 37.26)	0.001*
New onset of atrial fibrillation	35 (13.6)	48 (4.7)	3.22 (2.03, 5.10)	<0.001*
New onset of VTE	16 (6.2)	47 (4.6)	1.39 (0.77, 2.49)	0.274
Shock	75 (29.2)	402 (39.1)	0.64 (0.48, 0.86)	0.003*
In-hospital death	28 (10.9)	217 (21.1)	0.46 (0.30, 0.70)	<0.001*
ICU days	4.4±7.2	4.6±7.3	-0.21 (-1.20, 0.78)	0.677
Length of stay	13.7±25.1	12.3±20.6	1.39 (-1.56, 4.35)	0.355

* Denotes $P < 0.05$.
B, regression coefficient; CABG, coronary artery bypass graft; CI, confidence interval; ICU, intensive care unit; OR, odds ratio; PCI, percutaneous coronary intervention; VTE, venous thromboembolism.
† Includes pacemaker and implantable cardioverter defibrillator.

Table 4. Outcome during the follow up

Variable	HCM (n = 257)	Non-HCM (n = 1,028)	HCM *vs*. Non-HCM	
			HR (95% CI)	*P* value
1 year follow up				
Recurrent AMI	13 (5.1)	70 (6.8)	0.68 (0.37, 1.25)	0.214
HF hospitalization	17 (6.6)	66 (6.4)	1.02 (0.60, 1.74)	0.941
Systemic VTE	23 (8.9)	64 (6.2)	1.55 (0.75, 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, 0.85)	0.001*
CV death	46 (17.9)	211 (20.5)	0.83 (0.60, 1.14)	0.252
At the end of follow up				
Recurrent AMI	23 (8.9)	109 (10.6)	0.79 (0.50, 1.24)	0.299
HF hospitalization	35 (13.6)	112 (10.9)	1.24 (0.85, 1.80)	0.266
Systemic VTE	39 (15.2)	107 (10.4)	1.52 (0.97, 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, 1.16)	0.732
CV death	62 (24.1)	262 (25.5)	0.89 (0.67, 1.17)	0.401

* Denoted $P < 0.05$.
AMI, acute myocardial infarction; HR, hazard ratio; CI, confidence interval; CV, cardiovascular; HF, heart failure; VTE, venous thromboembolism; NA = not applicable.

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

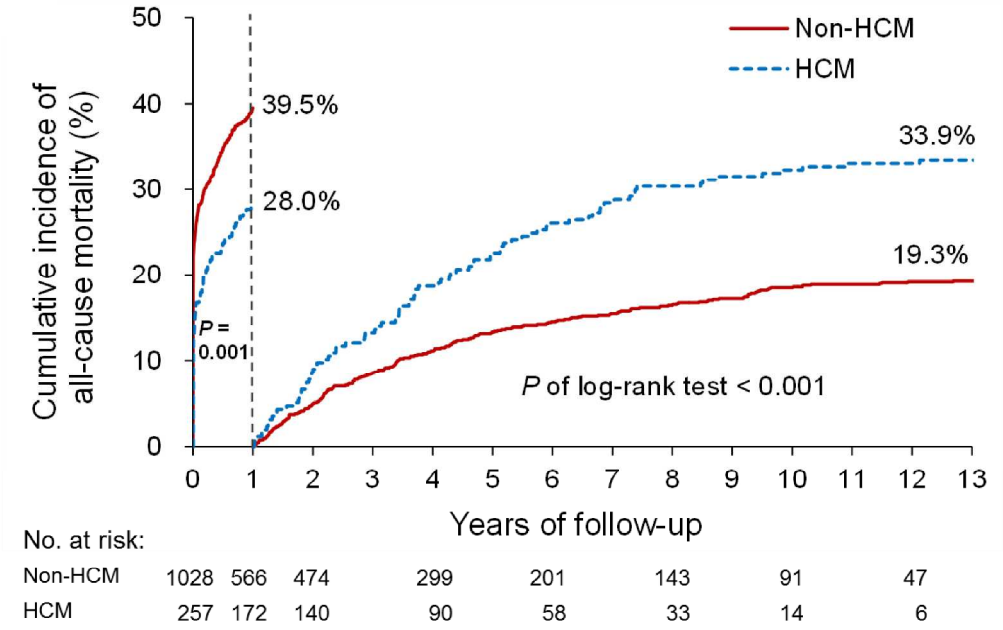

Figure 2. Cumulative incidence of all-cause mortality in the AMI patients with and without HCM. The vertical dotted line separates follow-up to within and beyond 1 year.

404x275mm (300 x 300 DPI)

Appendix. ICD-9-CM code used in the current study

Variable	Code
Acute myocardial infarction	410.xx
Aortic valve disease	424.1
Pericardial disease	423.xx
Congenital heart disease	745.xx–747.xx (Catastrophic illness card)
Venous thromboembolism	415.1x, 453.xx
Dialysis	585.xx (Catastrophic illness card)
Hypertrophic cardiomyopathy	425.1x
Hypertension	401.xx–405.xx
Hyperlipidemia	272.xx
Diabetes mellitus	250.xx
Heart failure	428.xx
Stroke	430.xx–437.xx
Chronic kidney disease	580.xx–589.xx, 403.xx–404.xx, 016.0x, 095.4x, 236.9x, 250.4x, 274.1x, 442.1x, 447.3x, 440.1x, 572.4x, 642.1x, 646.2x, 753.1x, 283.11, 403.01, 404.02, 446.21
Carotid artery disease	433.1x
Peripheral artery disease	440.0x, 440.2x, 440.3x, 440.8x, 440.9x, 443.xx, 444.0x, 444.22, 444.8x, 447.8x, 447.9x
Atrial fibrillation/atrial flutter	427.31, 427.32
Chronic obstructive pulmonary disease	491.xx, 492.xx, 496.xx
Peptic ulcer disease	531.xx–534.xx
Liver cirrhosis	571.2x, 571.5x, 571.6x
Malignancy	140.xx–208.xx
Gout	274.xx
Atrial fibrillation	427.31
Systemic thromboembolism	444.22, 444.81, 444.21, 557.0, 557.9, 557.1, 593.81, 444.89, 433.8, 444.9x, 415.1x, 433.xx, 434.xx, 435.xx, 436.xx, 437.xx

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 5
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5,6
Methods			
Study design	4	Present key elements of study design early in the paper	Page 6,7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Page 6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 6,7
Bias	9	Describe any efforts to address potential sources of bias	Page 14
Study size	10	Explain how the study size was arrived at	Page 8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 7,8
		(*b*) Describe any methods used to examine subgroups and interactions	n/a
		(*c*) Explain how missing data were addressed	n/a
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 8
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount)	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 3,4

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 4
		(*b*) Report category boundaries when continuous variables were categorized	Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page 9,10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 14
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 16

*Give information separately for exposed and unexposed groups.

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

BMJ Open

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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Keywords:	hypertrophic cardiomyopathy, acute myocardial infarction, outcome

Outcomes of Patients with Hypertrophic Cardiomyopathy and Acute Myocardial Infarction – A Propensity Score Matched 15-Year Nationwide Population-Based Study in Asia

Victor Chien-Chia Wu, MD[1*], Tien-Hsing Chen, MD[2*], Michael S Wu, MD[3], Shao-Wei Chen, MD[4], Chih-Hsiang Chang, MD[5], Chun-Wei Chang, MD[6], Ching-Chang Chen, MD[7],Ming-Jer Hsieh, MD[1], Chao-Yung Wang, MD[1], Shang-Hung Chang, MD[1], Fen-Chiung Lin, MD[1], Ming-Shien Wen, MD[1]

[1]Division of Cardiology, Chang Gung Memorial Hospital, Linkou Medical Center, Taoyuan City, Taiwan

[2]Department of Cardiology, Chang Gung Memorial Hospital, Keelung, Taiwan

[3]Divison of Cardiovascular Medicine, Miriam and Rhode Island Hospital, Warren Alpert School of Medicine, Brown University, Rhode Island, USA

[4]Department of Cardiothoracic and Vascular Surgery, [5]Department of Nephrology, [6]Department of Neurology, [7]Department of Neurosurgery, Chang Gung Memorial Hospital, Linkou Medical Center, Taoyuan City, Taiwan

Brief title: Outcomes of Patients with HCM having AMI

*Authors contributed equally.

All authors have nothing to disclose

Address for correspondence:

Victor Chien-Chia Wu, MD

Department of Cardiology, Chang Gung Memorial Hospital, No. 5, Fuxing Street, Guishan District, Taoyuan City 33305, Taiwan

Tel: +886-3-3281200 x8115; fax: + 886-3-3281451

E-mail: victorcwu@hotmail.com

Objectives: Hypertrophic cardiomyopathy (HCM) has thickened myocardium with high burden for ischemia. However, limited number of studies have been performed on the outcome of HCM patients with acute myocardial infarction (AMI).

Methods: Electronic medical records were retrieved from Taiwan National Health Insurance Research Database from 1997 to 2011. Patients were excluded for history of AMI, percutaneous coronary intervention (PCI), aortic valve disease, pericardial disease, congenital heart disease, venous thromboembolism, cardiovascular surgeries, device implantation, heart transplant, and on hemodialysis. AMI in patients with HCM were compared with propensity-matched AMI patients without HCM. Primary outcomes defined as in-hospital and 1-year cardiovascular events.

Results: There were 201,166 patients admitted due to AMI. After exclusion criteria, there were 177,058 patients with new-onset AMI (257 patients with HCM, 176,801 patients without HCM). After 1:4 propensity score matching for baseline characteristics, the study population consisted of 257 patients with HCM and 1,028 patients without HCM. Patients with HCM having AMI received significantly less PCI (odds ratio [OR], 0.46; 95% confidence interval [CI], 0.32-0.65), PCI with stenting (OR, 0.33; 95% CI, 0.20-0.57), CABG (OR, 0.22; 95% CI, 0.05-0.90), and had less episodes of shock (OR, 0.64; 95% CI, 0.48-0.86) and in-hospital death (OR, 0.46; 95% CI, 0.30-0.70) compared to patients without HCM having AMI. Specifically, patients with HCM having AMI occurred predominantly (82.5%) in the form of ischemia without requiring coronary stenting. Patients with HCM had a higher survival rate than those who did not (Hazard ratio, 0.66; 95% CI, 0.51-0.85) during the 1-year follow up.

Conclusions: This is the first study to directly compare the clinical outcomes of AMI patients with and without HCM using propensity score-matched patients. AMI

patients with HCM had significantly better outcomes compared to those without during in-hospital course and within 1 year follow up.

Keywords: hypertrophic cardiomyopathy, acute myocardial infarction, outcome

Strengths and limitations of the study

- This is the largest study to directly compare the outcome of AMI in patients with and without HCM using propensity score matched patients.
- In patients with and without HCM presenting with AMI, subsequent PCI, PCI with stenting, number of diseased vessels and/or CABG demonstrated severity and difference of ischemic burden between these two group of patients.
- In patients with and without HCM presenting with AMI, the difference between two groups were further corroborated with outcome of in-hospital hemodynamics, shock status, and mortality.
- Using ICD-9-CM codes for patient screening may miss some cases for conditions not coded correctly, but patients with AMI and HCM have definitive ICD codes therefore no exclusion of other cardiomyopathy is necessary.
- This study did not have baseline HCM population for clinical follow up till the occurrence of AMI, therefore the incidences and rates of those HCM patients studied for AMI may not include those that had died either due to severe ventricular arrhythmia or sudden death, thus selection bias.

Introduction

Hypertrophic cardiomyopathy (HCM) is defined by the presence of increased left ventricular (LV) wall thickness that is not solely explained by abnormal loading conditions [1]. It is the most common genetic disorder of the myocardium that affects 1 in 500 in the general population [2]. During systolic phase, the hypercontractile myocardium may obliterate the LV cavity and left ventricular outflow tract obstruction, causing chest pain, exercise intolerance, dizziness, and syncope. During diastolic phase, the excessively thickened myocardium decreases LV end-diastolic volume and restricts LV filling, resulting in increased LV end-diastolic pressure and decreased coronary flow reserve (CFR) [3].

Previous studies considered patients with HCM to have substantial cardiovascular risks, while there were also evidences noting patients HCM to have less clinically obvious symptoms thus evading diagnosis [4,5]. In a study that described clinical characteristics and outcomes of HCM, although HCM did not increase cardiovascular mortality rate, over one-third of patients with HCM experienced cardiovascular outcome [6]. In addition, a prospective study reported worse long-term survival in HCM patients with AMI compared to those non-HCM [7]. However, recently a large US population study showed that patients with HCM among those with acute myocardial infarction (AMI) presented at a later age and were also less likely to receive revascularization compared to patients without HCM [8]. In the end, HCM may progress with heart failure (HF) due to dynamic LV outflow obstruction, LV diastolic dysfunction, atrial fibrillation (AF) with risk of stroke, and ventricular arrhythmia with risk of sudden death. Therefore in this study, we aim to: (1) study the outcomes of patients with HCM and without HCM experiencing an AMI

by propensity score matching, and (2) clarify the prognostic difference in cardiovascular events between the two groups.

Methods

Study Patients

Taiwan's National Health Institute (NHI) Program started in 1995 and provides 99.5% coverage for the 23 million residents in Taiwan. The NHI Research Database (NHIRD) provides all dates of inpatient and outpatient services, diagnosis, prescriptions, examinations, operations, and expenditures, and data are updated biannually. With over 95% of Taiwan's population consists of Han Chinese, our study is considered of uniform ethnic background. The Institutional Review Board of Chang Gung Memorial Hospital Linkou Branch approved this study.

By searching electronic medical records from the NHIRD between January 1, 1997 and December 31, 2011, we retrieved all patients admitted due to AMI. AMI is defined as Third Universal Definition of AMI: (1) a rise and/or fall of cardiac biomarker with at least one value above the 99th percentile upper reference limit, with at least one of the following, (2) symptoms of ischemia, (3) new or presumed new significant ST segment-T wave changes or new left bundle branch block, (4) development of pathological Q waves in the ECG, (5) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, and (6) identification of an intracoronary thrombus by angiography or autopsy [9]. In our study, cardiogenic shock was defined as the use of (1) dopamine, (2) norepinephrine, (3) intra-aortic balloon pump, or (4) any combination of above medication and mechanical support. Using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes (as Appendix). Patients less than 18 years old were excluded. In

addition, patients with history of MI (AMI or old MI), percutaneous coronary intervention (PCI), aortic valve disease (AVD), pericardial disease, congenital heart disease (CHD), venous thromboembolism (VTE), cardiovascular surgeries, device implantation, heart transplant, and on end-stage renal disease (ESRD) on dialysis were excluded due to more complicated cardiovascular disease status, clinical course, and disease burden, with higher mortality rate by the disease per se. We therefore exclude these patients to have a purer or simplified comparison of the outcome between patients with and without HCM having AMI. The remaining patients had their first ever AMI admission as the index admission. ICD-9-CM of 425.1 was to identify patients with HCM and was used previously in the large US population study [8].

We were further divided into HCM and non-HCM groups for further analysis. According to 2011 ACCF/AHA Guideline, the definition of HCM, is a disease state characterized by unexplained left ventricular (LV) hypertrophy associated with nondilated ventricular chambers in the absence of another cardiac or systemic disease that itself would be capable of producing the magnitude of hypertrophy evident in a given patient [10]. And 2014 ESC Guideline simply defined HCM as the presence of increased left ventricular wall thickness that is not solely explained by abnormal loading conditions [11]. Clinically, HCM is usually recognized by maximal LV wall thickness ≥15 mm, with wall thickness of 13 to 14 mm considered borderline, particularly in the presence of other compelling information (e.g., family history of HCM), based on echocardiography [10].

Covariate and Study Outcomes

To effectively compare two groups of patients whose clinical presentation may be affected by comorbidities, we matched patients with HCM to patients without HCM using propensity score. Variables to calculate propensity score included gender, age, index date (admission date of the index AMI), and clinical history of hypertension (HTN), hyperlipidemia (HL), diabetes mellitus (DM), HF, cerebrovascular accident (CVA), chronic kidney disease (CKD, defined as at least at moderate stage with creatinine clearance <60 mL/min/1.73 m^2), carotid artery disease, peripheral artery disease (PAD), AF/atrial flutter (AFL), chronic obstructive pulmonary disease (COPD), peptic ulcer disease (PUD), liver cirrhosis, malignancy. The propensity score matching was processed using greedy nearest neighbor algorithm and the width of caliper was set as 0.2.

The medical records of NHIRD listed primary diagnoses of the patients during admission. Definitions of cardiovascular death meet the criteria of Standardized Definitions for End Point Events in Cardiovascular Trials draft by the Food and Drug Administration [12]. Death was defined as the withdrawal of the patient from NHI Program [13]. Causes of death were defined according to the primary discharge diagnosis of hospitalization within 3 months prior to death [13]. Primary outcomes defined as in-hospital and 1-year cardiovascular events.

Statistical Analysis

We compared the baseline characteristics, comorbidities, intervention and medication between the study groups (HCM vs. non-HCM) using independent sample t-test for continuous variable or chi-square test for categorical variable. We compared the risk of categorical in-hospital outcomes (i.e. in-hospital death) between groups using logistic regression analysis and compared continuous outcomes (i.e. length of stay)

using linear regression analysis. Because the risk of death between HCM and non-HCM groups was unbalanced, the incidence of long-term time to event outcome during the follow up between the HCM and non-HCM groups was compared using competing risk survival model with considering death as a competing risk [14]. We generated the plot of cumulative incidence rate using subdistribution hazard function for these time to event outcomes. As to all-cause mortality and cardiovascular death we used Cox proportional hazard model and generated the plot of incidence using regular proportions. All statistical analyses were carried out using commercial software (SAS 9.4, SAS Institute, Cary, NC).

Results

Study Population

There were 201,166 patients admitted due to AMI between 1997 and 2011 in Taiwan. After excluding patients with history of AMI, PCI, AVD, pericardial disease, CHD, VTE, cardiovascular surgeries, device implantation, heart transplant, and ESRD on dialysis, there were 177,058 patients with new-onset AMI where 257 patients were in HCM group and 176,801 patients in non-HCM group. Since there was an excess in number of those patients without HCM, after 1:4 propensity score matching for clinical variables of age and gender, and comorbidities of HTN, HL, DM, HF, CVA, CKD, carotid artery disease, PAD, AF/AFL, COPD, PUD, liver cirrhosis, malignancy, and gout, there were 257 patients with HCM and 1,028 patients without HCM (Figure 1). Before matching, there were significant differences across clinical variables and comorbidities except HL, malignancy, and gout. After matching, there were no difference between the two groups (Table 1).

Clinical Characteristics

Table 2 shows the findings of AMI patients with HCM and without HCM during index admission. In terms of intervention, AMI patients with HCM were less likely to require intraaortic balloon bump (IABP) ($P = 0.002$) and a trend toward less likely to be intubated ($P = 0.065$) and receive temporary hemodialysis ($P = 0.063$). In terms of medication, AMI patients with HCM were more likely to be prescribed beta blocker ($P = 0.007$).

In-Hospital Outcome

Table 3 displays the results of in-hospital outcome. Patients HCM having AMI were significantly less likely to receive PCI (odds ratio [OR]: 0.46; 95% confidence interval [CI]: 0.32–0.65; p<0.001), less likely to have vessels intervened, less likely to receive PCI with stenting (OR: 0.33; 95% CI: 0.20–0.57; p<0.001), less likely to undergo coronary artery bypass surgery (CABG) (OR: 0.22; 95% CI, 0.05-0.90; p=0.036), and less episodes of shock (OR: 0.64; 95% CI: 0.48-0.86; p=0.003) and in-hospital death (OR: 0.46; 95% CI: 0.30–0.70; p<0.001) compared with patients without HCM having AMI. On the other hand, patients with HCM having AMI had significantly higher incidence in pacing device implantation (OR: 9.57; 95% CI: 2.46–37.26; p=0.001) and new-onset atrial fibrillation (OR: 3.22; 95% CI: 2.03–5.10; p<0.001).

Follow Up Outcome

Figure 2A illustrates the Kaplan-Meier survival curves of HCM and non-HCM groups during the entire follow up. The risk of all-cause mortality was comparable between the two groups (crude hazard ratio [HR], 0.97; 95% CI, 0.81–1.16). However, it's

observed that the two curves crossed at year 6-7, reflecting the patients with HCM has an accelerated rate of death compared to patients without HCM, suggesting the death rate was not particularly related to the AMI. Observed from the Kaplan-Meier curves, the group difference (slope) achieve a maximum at year 1-2, so we used 1-year as the cut-point of landmark analysis. In-hospital death was included in 1-year mortality. During follow up of the first year, patients without HCM having AMI had significantly worse all-cause mortality compared with patients without HCM having AMI (28.0% for HCM and 39.5% for non-HCM; HR, 0.66; 95% CI, 0.51–0.85) (Table 4, Figure 2B). However, patients with HCM having AMI conversely had higher mortality rate after 1-year follow up (33.9% for HCM and 19.3% for non-HCM, $P < 0.001$) as illustrated in Figure 2B. In addition, similar results were found when the cut-point of landmark analysis was changed to 2-year or 3-year (data not shown).

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

Discussion

Our study had several findings. (1) This is the first study to directly compare the outcome of patients with HCM and without HCM having AMI by propensity score matching. (2) Patients with HCM having AMI had significantly lower rates of PCI, PCI with stenting, CABG, shock and in-hospital death. With the same regard, patients without HCM having AMI had significantly higher rates of one- and three-vessel coronary artery disease (CAD). (3) All-cause mortality was significantly higher

within 1 year of follow up in patients without HCM having AMI, however reversed after 1 year to the end of follow up, possibly reflecting the high disease burden in HCM.

Previous Studies

In the investigation of AMI in the patients with HCM, the number of published papers were rather limited. There were two major studies that specifically addressed this gap in knowledge for our understanding on the supposedly ischemia-prone thickened myocardium in the patients with HCM. The study that looked specifically at long-term survival of AMI in patients with HCM was published by a Chinese group that prospectively enrolled adult patients ≥18 years with HCM and AMI from 1997 to 2014 [7]. They also enrolled a control group constructed using age-, sex, and admission date-matched AMI patients without HCM in 1:1 ratio. The authors found patients with HCM exhibited worse long-term survival than patients without HCM. Kaplan-Meier survival curve showed worse outcome of those AMI patients with HCM after one year compared to those AMI patients without HCM [7].

In a large population-based study in US, discharge data of 5,901,827 patients with AMI during 2003-2011 were studied for the outcome of those with HCM (5,688 patients, 0.1%) and those without HCM [8]. The patients with HCM was older, more likely to be female, less likely to have traditional cardiovascular risk factors, less likely to present with ST-elevation myocardial infarction (STEMI), and more likely to present with non-ST-elevation myocardial infarction (NSTEMI). In addition, for these STEMI and NSTEMI in patients HCM, they were less likely to receive revascularization [8]. Since these patients with HCM were less likely to have traditional cardiovascular risk factors compared with patients without HCM, the

authors postulates that it is reasonable that these AMIs were likely driven by non-atherosclerotic mechanisms through microvascular dysfunction. Without propensity score matching, the authors concluded that in the overall population with AMI, there was no difference in observed in-hospital mortality between patients with and without HCM [8].

Current Study

During the 15 years from 1997 to 2011, there were 201,166 patients admitted due to AMI and 257 patients had coexisting HCM (0.13%). This prevalence was similar to previous US study (0.10%) [8]. When comparing patients with HCM having AMI to patients without HCM having AMI, we found patients with HCM having AMI occurring at significantly older age (70.1±12.4 vs 67.3±14.0), more likely to be female (51.4% vs 30.8%), and less likely to have traditional cardiovascular risk factors such as DM (26.5% vs 34.7%), HL (19.8% vs 22.6%) but not HTN (68.5% vs 51.0%). Sincere there were also significant difference across comorbidities, we made extensive propensity score-matching that matched all clinical variables, comorbidities, and mean follow-up (Table 1).

As shown in Table 2, IABP was used significantly less in patients with HCM and there was a trend toward lower rates of intubation and temporary HD in patients with HCM as well. The cardiac performance and cardiovascular compromise seemed less likely to be affected in patients with HCM. The use of medications generally showed no significant difference between the groups except beta blockers were used more extensively in patients with HCM, reflecting the guideline suggested practice of beta-blockers as initial drug of choice in patients with HCM [1]. In this cohort of patients with AMI, the beta-blocker use was 52.5% in patients with HCM, and 43.1%

in patients without HCM, which were higher than earlier reported 34% beta-blocker use after AMI in a review of ≥200,000 patient records in the Cooperative Cardiovascular Project [12] but lower than reported 88-92% in a more recent study involving patients with HCM having AMI [7].

The most important findings of our study were that patients with HCM having AMI had significantly less rates of PCI, intervened vessels, PCI with stenting, CABG, shock, and in-hospital death (Table 3) compared to patients without HCM having AMI. Patients with HCM has higher rates of AMI in vessels requiring no coronary stenting compared to patients without HCM (82.5% vs 68.4%). Patients with HCM having AMI had significantly less rates of one- and three-vessel CAD disease compared to patients without HCM having AMI (13.2% vs 23.5%, P <0.001 and 0.4% vs 2.8%, P = 0.034). In the same regard, cumulative incidence of all-cause mortality was significantly higher in AMI patients without HCM within 1 year of follow up (Figure 2). The trend then reversed after 1 year to the end of follow up, suggesting coronary ischemia leading to myocardial infarction was not the cause of long-term mortality in patients with HCM.

In summary, compared to patients without HCM, patients with HCM were significantly less likely to have coronary obstruction during AMI, CABG, shock, and in-hospital mortality.

Limitations

There are several limitations in epidemiologic data from NHIRD. First, the available NHIRD in this release was available from 1997 till 2011 and some information and practice may be outdated. However, the methods of treatment of HCM and the practice of PCI in AMI have not changed dramatically since then. Second, using ICD-

9-CM codes for patient screening may miss some cases for conditions not coded correctly, but patients with AMI and HCM have definitive ICD codes therefore no exclusion of other cardiomyopathy is necessary. Third, this study did not have baseline HCM population for clinical follow up till the occurrence of AMI, therefore the incidences and rates of those HCM patients studied for AMI may not include those that had died either due to severe ventricular arrhythmia or sudden death, thus selection bias. Fourth, using claim-based NHIRD for conducting a retrosepctive cohort study, the database does not provide additional information on examination report details such as laboratory, electrocardiographic, echocardiographic, or angiographic data. However, the NHIRD has data on PCI performed, number of intervened vessels, and number of stents placed.. Last, since our study consisted of uniform ethnic background, application of the results to other populations requires interpretation in the proper context.

Conclusions

This is the first study to directly compare the clinical outcomes of AMI patients with and without HCM using propensity score-matched patients. AMI patients with HCM had significantly better outcomes compared to those without during in-hospital course and within 1 year follow up.

Acknowledgments

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Contributorship

VCW, THC contributed to study conception and design.

VCW, THC, MSW acquired the data.

SWC, CHC, CWC, CCC, MJH, CYW, SHC contributed to analysis and interpretation of data.

VCW, THC drafted the manuscript.

FCL, MSW contributed to critical revision.

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None.

Data Sharing Statement

No additional data available.

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Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report from the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011:124:2761-96.

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Figure Legends

Figure 1

Study design and screening criteria flow chart for 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.

Figure 2

Kaplan-Meier survival analysis of the AMI patients with and without HCM for the entire follow-up period (A). Due to the observed group difference (slope) achieved a maximum at year 1-2 in the Kaplan-Meier curves, using 1-year as the cut-point of landmark analysis, the Kaplan-Meier survival graph was shown with vertical dotted line separating follow-up to within and beyond 1 year (B).

Table 1. Baseline characteristics and comorbidities during the index admission before and after matching

	Before matching			After matching	
Variable	HCM (n = 257)	Non-HCM (n = 176,801)	P value	Non-HCM (n = 1,028)	P value
Clinical variables					
Age	70.1±12.4	67.3±14.0	0.001*	69.9±14.5	0.834
Gender (male)	125 (48.6)	122,422 (69.2)	<0.001*	481 (46.8)	0.595
Comorbidities					
Hypertension	176 (68.5)	90,160 (51.0)	<0.001*	704 (68.5)	1.000
Hyperlipidemia	51 (19.8)	40,020 (22.6)	0.285	204 (19.8)	1.000
Diabetes mellitus	68 (26.5)	61,284 (34.7)	0.007*	275 (26.8)	0.925
Heart failure	81 (31.5)	13,797 (7.8)	<0.001*	315 (30.6)	0.786
Cerebrovascular accident	51 (19.8)	23,218 (13.1)	0.001*	222 (21.6)	0.539
Chronic kidney disease	18 (7.0)	6,255 (3.5)	0.003*	78 (7.6)	0.750
Carotid artery disease	77 (30.0)	16,982 (9.6)	<0.001*	309 (30.1)	0.976
Peripheral artery disease	18 (7.0)	7,878 (4.5)	0.048*	75 (7.3)	0.872
Atrial fibrillation/atrial flutter	48 (18.7)	6,568 (3.7)	<0.001*	189 (18.4)	0.914
Chronic obstructive pulmonary disease	70 (27.2)	27,659 (15.6)	<0.001*	283 (27.5)	0.925
Peptic ulcer disease	57 (22.2)	20,022 (11.3)	<0.001*	221 (21.5)	0.813
Liver cirrhosis	12 (4.7)	3,360 (1.9)	0.001*	47 (4.6)	0.947
Malignancy	19 (7.4)	10,986 (6.2)	0.434	76 (7.4)	1.000
Gout	24 (9.3)	12,310 (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

* Denotes $P < 0.05$.

Table 2. Intervention and medication during the index admission

Variable	HCM (n = 257)	Non-HCM (n = 1,028)	P value
Intervention			
Intubation	41 (16.0)	217 (21.1)	0.065
Intraaortic balloon pump	4 (1.6)	65 (6.3)	0.002*
Extracorporeal membrane oxygenation	1 (0.4)	5 (0.5)	0.838
Temporary hemodialysis	5 (1.9)	46 (4.5)	0.063
Cardiac rehabilitation	8 (3.1)	50 (4.9)	0.227
Medications during admission			
Aspirin	196 (76.3)	757 (73.6)	0.390
Clopidogrel	120 (46.7)	519 (50.5)	0.277
ACEI/ARB	141 (54.9)	549 (53.4)	0.675
Beta blocker	135 (52.5)	443 (43.1)	0.007*
Calcium channel blocker	70 (27.2)	236 (23.0)	0.150
Diuretics	80 (31.1)	334 (32.5)	0.676
Spironolactone	19 (7.4)	87 (8.5)	0.577
Nitrates	51 (19.8)	219 (21.3)	0.608
Warfarin	18 (7.0)	49 (4.8)	0.149
Statin	49 (19.1)	237 (23.1)	0.169
Proton pump inhibitor	30 (11.7)	102 (9.9)	0.408

* Denotes $P < 0.05$.
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 3. In-hospital cardiovascular outcome

Variable	HCM (n = 257)	Non-HCM (n = 1,028)	HCM *vs*. Non-HCM	
			OR / *B* (95% CI)	*P* value
PCI	45 (17.5)	325 (31.6)	0.46 (0.32, 0.65)	<0.001*
Number of intervened vessels				
0 vessel	212 (82.5)	703 (68.4)	Reference	–
1 vessel	34 (13.2)	242 (23.5)	0.47 (0.32, 0.69)	<0.001*
2 vessels	10 (3.9)	54 (5.3)	0.61 (0.31, 1.23)	0.167
3 vessels	1 (0.4)	29 (2.8)	0.11 (0.02, 0.84)	0.034*
PCI with stenting	16 (6.2)	171 (16.6)	0.33 (0.20, 0.57)	<0.001*
CABG	2 (0.8)	36 (3.5)	0.22 (0.05, 0.90)	0.036*
Valvular surgery	3 (1.2)	3 (0.3)	4.04 (0.81, 20.11)	0.089
Pacing device implantation†	7 (2.7)	3 (0.3)	9.57 (2.46, 37.26)	0.001*
New onset of atrial fibrillation	35 (13.6)	48 (4.7)	3.22 (2.03, 5.10)	<0.001*
New onset of VTE	16 (6.2)	47 (4.6)	1.39 (0.77, 2.49)	0.274
Shock	75 (29.2)	402 (39.1)	0.64 (0.48, 0.86)	0.003*
In-hospital death	28 (10.9)	217 (21.1)	0.46 (0.30, 0.70)	<0.001*
ICU days	4.4±7.2	4.6±7.3	-0.21 (-1.20, 0.78)	0.677
Length of stay	13.7±25.1	12.3±20.6	1.39 (-1.56, 4.35)	0.355

* Denotes $P < 0.05$.

B, regression coefficient; CABG, coronary artery bypass graft; CI, confidence interval; ICU, intensive care unit; OR, odds ratio; PCI, percutaneous coronary intervention; VTE, venous thromboembolism.

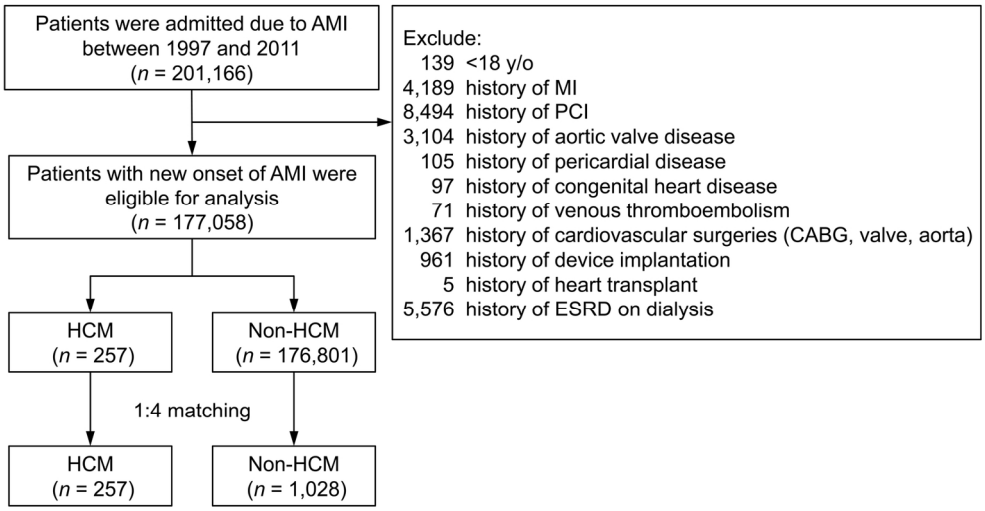
† Includes pacemaker and implantable cardioverter defibrillator.

Table 4. Outcome during the follow up

Variable	HCM (n = 257)	Non-HCM (n = 1,028)	HCM *vs*. Non-HCM HR (95% CI)	*P* value
1 year follow up				
Recurrent AMI	13 (5.1)	70 (6.8)	0.68 (0.37, 1.25)	0.214
HF hospitalization	17 (6.6)	66 (6.4)	1.02 (0.60, 1.74)	0.941
Systemic VTE	23 (8.9)	64 (6.2)	1.55 (0.75, 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, 0.85)	0.001*
CV death	46 (17.9)	211 (20.5)	0.83 (0.60, 1.14)	0.252
At the end of follow up				
Recurrent AMI	23 (8.9)	109 (10.6)	0.79 (0.50, 1.24)	0.299
HF hospitalization	35 (13.6)	112 (10.9)	1.24 (0.85, 1.80)	0.266
Systemic VTE	39 (15.2)	107 (10.4)	1.52 (0.97, 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, 1.16)	0.732
CV death	62 (24.1)	262 (25.5)	0.89 (0.67, 1.17)	0.401

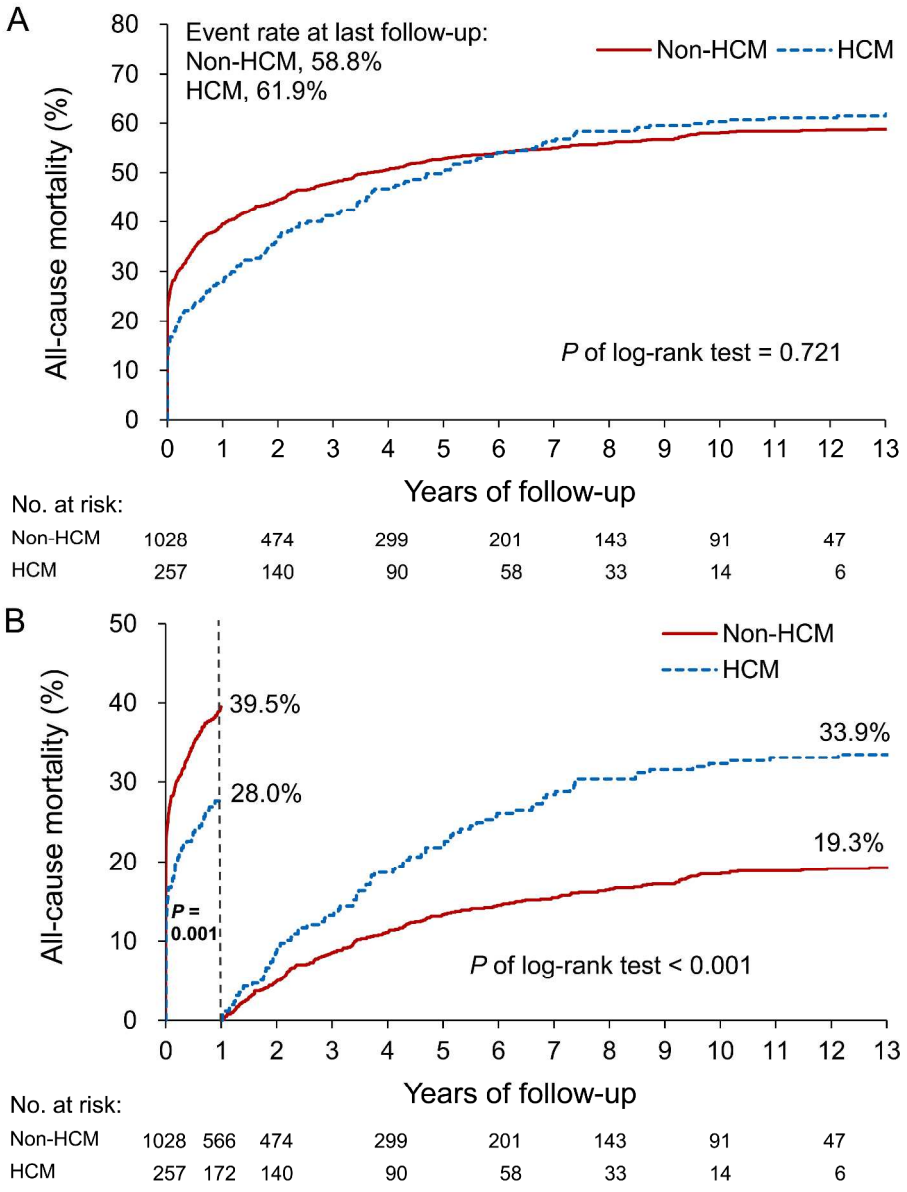
* Denoted $P < 0.05$.
AMI, acute myocardial infarction; HR, hazard ratio; CI, confidence interval; CV, cardiovascular; HF, heart failure; VTE, venous thromboembolism; NA = not applicable.

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



Study design and screening criteria flow chart for 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.

78x41mm (600 x 600 DPI)



Kaplan-Meier survival analysis of the AMI patients with and without HCM for the entire follow-up period (A). Due to the observed group difference (slope) achieved a maximum at year 1-2 in the Kaplan-Meier curves, using 1-year as the cut-point of landmark analysis, the Kaplan-Meier survival graph was shown with vertical dotted line separating follow-up to within and beyond 1 year (B).

416x542mm (300 x 300 DPI)

Appendix. ICD-9-CM code used in the current study

Variable	Code
Acute myocardial infarction	410.xx
Aortic valve disease	424.1
Pericardial disease	423.xx
Congenital heart disease	745.xx–747.xx (Catastrophic illness card)
Venous thromboembolism	415.1x, 453.xx
Dialysis	585.xx (Catastrophic illness card)
Hypertrophic cardiomyopathy	425.1x
Hypertension	401.xx–405.xx
Hyperlipidemia	272.xx
Diabetes mellitus	250.xx
Heart failure	428.xx
Stroke	430.xx–437.xx
Chronic kidney disease	580.xx–589.xx, 403.xx–404.xx, 016.0x, 095.4x, 236.9x, 250.4x, 274.1x, 442.1x, 447.3x, 440.1x, 572.4x, 642.1x, 646.2x, 753.1x, 283.11, 403.01, 404.02, 446.21
Carotid artery disease	433.1x
Peripheral artery disease	440.0x, 440.2x, 440.3x, 440.8x, 440.9x, 443.xx, 444.0x, 444.22, 444.8x, 447.8x, 447.9x
Atrial fibrillation/atrial flutter	427.31, 427.32
Chronic obstructive pulmonary disease	491.xx, 492.xx, 496.xx
Peptic ulcer disease	531.xx–534.xx
Liver cirrhosis	571.2x, 571.5x, 571.6x
Malignancy	140.xx–208.xx
Gout	274.xx
Atrial fibrillation	427.31
Systemic thromboembolism	444.22, 444.81, 444.21, 557.0, 557.9, 557.1, 593.81, 444.89, 433.8, 444.9x, 415.1x, 433.xx, 434.xx, 435.xx, 436.xx, 437.xx

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 5
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5,6
Methods			
Study design	4	Present key elements of study design early in the paper	Page 6,7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Page 6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 6,7
Bias	9	Describe any efforts to address potential sources of bias	Page 14
Study size	10	Explain how the study size was arrived at	Page 8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 7,8
		(*b*) Describe any methods used to examine subgroups and interactions	n/a
		(*c*) Explain how missing data were addressed	n/a
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 8
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount)	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 3,4

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 4
		(*b*) Report category boundaries when continuous variables were categorized	Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page 9,10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 14
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 16

*Give information separately for exposed and unexposed groups.

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

BMJ Open

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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Keywords:	hypertrophic cardiomyopathy, acute myocardial infarction, outcome

Outcomes of Patients with Hypertrophic Cardiomyopathy and Acute Myocardial Infarction: A Propensity Score-Matched 15-Year Nationwide Population-Based Study in Asia

Victor Chien-Chia Wu, MD[1*], Tien-Hsing Chen, MD[2*], Michael Wu, MD[3], Shao-Wei Chen, MD[4], Chih-Hsiang Chang, MD[5], Chun-Wei Chang, MD[6], Ching-Chang Chen, MD[7], Katie Pei-Hsuan Wu, MD[8], Ming-Jer Hsieh, MD[1], Chao-Yung Wang, MD[1], Shang-Hung Chang, MD[1], Fen-Chiung Lin, MD[1], I-Chang Hsieh, MD[1], Pao-Hsien Chu, MD[1], Ming-Shien Wen, MD[1]

[1]Division of Cardiology, Chang Gung Memorial Hospital, Linkou Medical Center, Taoyuan City, Taiwan

[2]Department of Cardiology, Chang Gung Memorial Hospital, Keelung, Taiwan

[3]Divison of Cardiovascular Medicine, Miriam and Rhode Island Hospital, Warren Alpert School of Medicine, Brown University, Rhode Island, USA

[4]Department of Cardiothoracic and Vascular Surgery, [5]Department of Nephrology, [6]Department of Neurology, [7]Department of Neurosurgery, [8]Department of Physical Medicine and Rehabilitation, Chang Gung Memorial Hospital, Linkou Medical Center, Taoyuan City, Taiwan

Brief title: Outcomes of HCM Patients with AMI

*Authors contributed equally.

All authors have nothing to disclose

Address for correspondence:

Victor Chien-Chia Wu, MD, FESC

Department of Cardiology, Chang Gung Memorial Hospital, No. 5, Fuxing Street, Guishan District, Taoyuan City 33305, Taiwan

Tel: +886-3-3281200 x8115; fax: + 886-3-3281451

E-mail: victorcwu@hotmail.com

Objectives: Hypertrophic cardiomyopathy (HCM) entails thickening of the myocardium and an increased risk of ischemia. However, studies of the outcomes of acute myocardial infarction (AMI) in patients with HCM are limited.

Methods: Electronic medical records were retrieved from the Taiwan National Health Insurance Research Database from 1997 to 2011. Exclusion criteria were a history of AMI, percutaneous coronary intervention (PCI), aortic valve disease, pericardial disease, congenital heart disease, venous thromboembolism, cardiovascular surgeries, device implantation, heart transplant, and hemodialysis. HCM patients with AMI were compared with propensity score-matched AMI patients without HCM. Primary outcomes were defined as in-hospital and 1-year cardiovascular events.

Results: In total, 201,166 patients were admitted for AMI. After exclusion, there were 177,058 patients with new-onset AMI (257 with HCM, 176,801 without HCM). After 1:4 propensity score matching, the study population comprised 257 AMI patients with HCM and 1,028 AMI patients without HCM. HCM patients with AMI received significantly less PCI (odds ratio [OR]=0.46; 95% confidence interval [CI]=0.32–0.65; P <0.001), PCI with stenting (OR=0.33; 95% CI=0.20–0.57; P <0.001), and coronary artery bypass graft (OR=0.22; 95% CI=0.05–0.90; P=0.036), as well as had fewer episodes of shock (OR,=0.64; 95% CI=0.48–0.86; P=0.003) and in-hospital death (OR=0.46; 95% CI=0.30–0.70; P <0.001) compared with AMI patients without HCM. Specifically, for HCM patients with AMI, AMI occurred predominantly (82.5%) in the form of ischemia without requiring coronary stenting. Patients with HCM had a higher survival rate than did those without (hazard ratio=0.66; 95% CI=0.51–0.85; P=0.001) during the 1-year follow-up.

Conclusions: This is the first study to directly compare the clinical outcomes of AMI patients with and without HCM through propensity score matching. AMI patients

with HCM had significantly better outcomes than did AMI patients without HCM during the in-hospital course and within the 1-year follow-up period.

Keywords: hypertrophic cardiomyopathy, acute myocardial infarction, outcome

Strengths and limitations of this study

- This is the first study to directly compare the outcomes of AMI in patients with and without HCM through propensity score matching.
- The differences in outcomes in AMI patients with HCM and without HCM were demonstrated by percentage of patients underwent PCI, stenting, or coronary artery bypass graft, thence the difference in the severity of coronary artery disease between the two groups.
- Using the National Health Insurance claims data is beneficial because the NHI program provides uniform health care services to 99.5% of the population without financial restraints or selection bias, however with the limitation of the usage of older database during 1997-2011.
- Using ICD-9-CM codes for patient screening may have resulted in missing some cases if conditions were not coded correctly. However, patients with AMI and HCM have definitive ICD codes; 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 incidences and rates of those HCM patients studied for AMI may not include those that died due to severe ventricular arrhythmia or had sudden death.

Introduction

Hypertrophic cardiomyopathy (HCM) is defined by the presence of increased left ventricular (LV) wall thickness that is not solely explained by abnormal loading conditions.[1] HCM is the most common genetic disorder of the myocardium that affects 1 in 500 in a general population.[2] During the systolic phase, the hypercontractile myocardium may obliterate the 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.[3]

Although patients with HCM are considered to have a substantial cardiovascular risk, they tend to have less clear symptoms thus evading the diagnosis of ischemia.[4,5] In a study that described the clinical characteristics and outcomes of HCM, although HCM did not increase the cardiovascular mortality rate, over one-third of patients with HCM experienced cardiovascular outcomes.[6] A prospective study reported worse long-term survival of acute myocardial infarction (AMI) in patients with HCM compared with AMI in patients without HCM.[7] In addition, a large US population study reported that patients with HCM presented with AMI at a later age, and they were less likely to receive revascularization compared with patients without HCM.[8] Furthermore, HCM may progress to heart failure (HF) because of dynamic LV outflow obstruction, LV diastolic dysfunction, atrial fibrillation (AF) with the risk of stroke, and ventricular arrhythmia with the risk of sudden death. Therefore, in this study, we aimed to (1) investigate the outcomes of patients with and without HCM experiencing an AMI through propensity score-

matching and (2) clarify the prognostic difference in cardiovascular events between the two groups.

Methods

Study patients

Taiwan's National Health Insurance (NHI) program, which was launched in 1995, covers 99.5% of the 23 million residents of Taiwan. The NHI Research Database (NHIRD) provides all dates of inpatient and outpatient services, diagnosis, prescriptions, examinations, operations, and expenditures, and the data are updated biannually. With over 95% of Taiwan's population consisting of Han Chinese, our study can be considered of an uniform ethnic background. The Institutional Review Board of Chang Gung Memorial Hospital Linkou Branch approved this study.

By searching electronic medical records from the NHIRD between January 1, 1997, and December 31, 2011, we identified all patients admitted for AMI. In this study, AMI was defined using the Third Universal Definition of AMI: a rise or fall of cardiac biomarkers with at least one value above the 99th percentile upper reference limit with at least one of the following: (1) symptoms of ischemia; (2) new or presumed new significant ST segment-T wave changes or a new left bundle branch block; (3) development of pathological Q waves in ECG; (4) imaging evidence of new loss of the viable myocardium or new regional wall motion abnormality; and (5) identification of an intracoronary thrombus through angiography or autopsy.[9] 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 medication and mechanical support. The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code 425.1

(Supplementary Table 1) was used to identify patients with HCM and was used previously in a large US population study.[8] Patients aged below 18 years were excluded. In addition, patients with a history of MI (AMI or old MI), percutaneous coronary intervention (PCI), aortic valve disease (AVD), pericardial disease, congenital heart disease (CHD), venous thromboembolism (VTE), cardiovascular surgeries, device implantation, heart transplant, or end-stage renal disease (ESRD) on dialysis were excluded. The remaining patients had their first-ever AMI admission as the index admission.

We further divided patients into HCM and non-HCM groups for further analysis. According to the 2011 ACCF/AHA Guideline, HCM is a disease state characterized by unexplained LV hypertrophy associated with nondilated ventricular chambers in the absence of another cardiac or systemic disease that itself would be capable of producing the magnitude of hypertrophy evident in a given patient.[10] In addition, the 2014 ESC Guideline simply defined HCM as the presence of increased LV wall thickness that is not solely explained by abnormal loading conditions.[11] Clinically, HCM is usually recognized by a maximal LV wall thickness ≥15 mm, with 13–14 mm considered borderline, particularly in the presence of other compelling information (e.g., a family history of HCM), based on echocardiography.[10]

Covariate and study outcomes

To effectively compare two groups of patients whose clinical presentations may be affected by comorbidities, we matched patients with HCM to patients without HCM by using propensity scores. 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), hyperlipidemia (HL), diabetes mellitus (DM), HF,

cerebrovascular accident (CVA), chronic kidney disease (CKD; at least at moderate stage with creatinine clearance <60 mL/min/1.73 m^2), carotid artery disease, peripheral artery disease (PAD), AF/atrial flutter (AFL), chronic obstructive pulmonary disease (COPD), peptic ulcer disease (PUD), liver cirrhosis, and malignancy. The propensity score matching was processed using the greedy nearest neighbor algorithm, and the caliper width was set as 0.2 of the standard deviation of the logit of the propensity score.

The medical records of the NHIRD listed the primary diagnoses of patients during admission. Cardiovascular death was defined according to the criteria of Standardized Definitions for End Point Events in Cardiovascular Trials drafted by the Food and Drug Administration.[12] Death was defined as the withdrawal of a patient from the NHI program.[13] Causes of death were defined according to the primary discharge diagnosis of hospitalization within 3 months prior to death.[13] Primary outcomes were defined as in-hospital and 1-year cardiovascular events.

Statistical analysis

We compared baseline characteristics, comorbidities, interventions, and medication between the study groups (HCM vs. non-HCM) using the independent 2-sample *t* test for continuous variables or the chi-square test for categorical variables. We compared the risk of categorical in-hospital outcomes (e.g., in-hospital death) between the groups by using logistic regression analysis and compared continuous outcomes (e.g., length of stay) by using linear regression analysis. Because the risk of death between the HCM and non-HCM groups was unbalanced, the incidence of long-term time-to-event outcomes during the follow-up between the groups was compared using a competing risk survival model that considered death as a competing risk.[14] We

generated the plot of the cumulative incidence rate by using subdistribution hazard functions for time-to-event outcomes. Subsequently, we used Cox proportional hazards models to generate cumulative incidence functions for all-cause and cardiovascular mortality.

Because the survival curves of all-cause mortality during the overall follow-up period in the HCM and non-HCM groups crossed, a log-rank test with inverse probability of treatment weighting was used to compare the study groups.[15] Therefore, a landmark analysis of all-cause mortality by using cut-points of 1 year (main result), 2 years, and 3 years was performed. All statistical analyses were carried out using commercial software (SAS 9.4 (SAS Institute, Cary, NC). All tests were 2-tailed, and statistical significance was defined as $P < 0.05$.

Sensitivity analysis

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

Patient and public involvement

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

Results

Study population

In total, 201,166 patients were admitted for AMI between 1997 and 2011 in Taiwan. After excluding patients with a history of AMI, PCI, AVD, pericardial disease, CHD, VTE, cardiovascular surgeries, device implantation, heart transplant, and ESRD on dialysis, 177,058 patients remained with new-onset AMI, of which 257 and 176,801 patients were included in the HCM and non-HCM groups, respectively. Because the number of patients without HCM was excessive, after 1:4 propensity score matching for clinical variables of age, sex, and comorbidities, namely HTN, HL, DM, HF, CVA, CKD, carotid artery disease, PAD, AF/AFL, COPD, PUD, liver cirrhosis, malignancy, and gout, 257 patients with HCM and 1,028 patients without HCM remained (Figure 1). Before matching, significant differences existed across clinical variables and comorbidities except for HL, malignancy, and gout. After matching, no difference was observed between the two groups (Table 1).

Clinical characteristics

Table 2 presents the findings of AMI patients with and without HCM during index admission. In terms of intervention, AMI patients with HCM were less likely to require an intra-aortic balloon bump (IABP, $P = 0.002$) and exhibited a trend toward being less likely to be intubated ($P = 0.065$) and receive temporary hemodialysis ($P =$

0.063). In terms of medication, AMI patients with HCM were more likely to be prescribed beta-blockers ($P = 0.007$).

In-hospital outcomes

Table 3 displays the results of in-hospital outcomes. HCM patients with AMI were significantly less likely to receive PCI (odds ratio [OR], 0.46; 95% confidence interval [CI], 0.32–0.65; $P < 0.001$), have vessels intervened, receive PCI with stenting (OR, 0.33; 95% CI, 0.20–0.57; $P < 0.001$), undergo CABG (OR, 0.22; 95% CI, 0.05–0.90; $P = 0.036$), and experience episodes of shock (OR, 0.64; 95% CI, 0.48–0.86; $P = 0.003$) and in-hospital death (OR, 0.46; 95% CI, 0.30–0.70; $P < 0.001$) compared with non-HCM patients with AMI. However, HCM patients with AMI had a significantly higher incidence of pacing device implantation (OR, 9.57; 95% CI, 2.46–37.26; $P = 0.001$) and new-onset AF (OR, 3.22; 95% CI, 2.03–5.10; $P < 0.001$).

Follow-up outcomes

Figure 2A illustrates the Kaplan–Meier survival curves of the HCM and non-HCM groups during the entire follow-up. The risk of all-cause mortality was comparable between the two groups (crude hazard ratio [HR], 0.97; 95% CI, 0.81–1.16). However, the two curves crossed at year 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 year 1–2; thus, we used 1-year as the cutoff point in the landmark analysis. In-hospital death was included in 1-year mortality. During the first-year follow-up, non-HCM patients with AMI had significantly poor all-cause mortality compared with patients without HCM having

AMI (28.0% for HCM and 39.5% for non-HCM; HR, 0.66; 95% CI, 0.51–0.85; Table 4, Fig. 2B). By contrast, HCM patients with AMI had a higher mortality rate after the 1-year follow-up (33.9% for HCM and 19.3% for non-HCM, $P < 0.001$; Fig. 2B). In addition, similar results were found when the cutoff point of the landmark analysis was changed to 2 or 3 year (data not shown).

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

Discussion

Some of the highlights and important findings of this study are as follows. (1) This is the first study to directly compare the outcomes of HCM and non-HCM patients with AMI by using propensity score matching. (2) HCM patients with AMI had significantly lower rates of PCI, PCI with stenting, CABG, shock, and in-hospital death. Similarly, non-HCM patients with AMI had significantly higher rates of one- and three-vessel coronary artery disease (CAD). (3) All-cause mortality was significantly higher within 1 year of follow-up in non-HCM patients with AMI; however, this was reversed after 1 year until the end of the follow-up, possibly reflecting the high disease burden of HCM.

Relevant studies

Regarding investigations of AMI in patients with HCM, the number of published papers is limited. Two major studies have specifically addressed this knowledge gap and enhanced our understanding of the supposedly ischemia-prone thickened

myocardium in patients with HCM. The study that focused specifically on the long-term survival of AMI in patients with HCM was published by a Chinese group that prospectively enrolled adult patients aged ≥18 years with HCM and AMI from 1997 to 2014.[7] Furthermore, they enrolled age,- sex-, and admission date-matched AMI patients without HCM in 1:1 ratio as controls. The findings indicated that patients with HCM exhibited poorer long-term survival than did patients without HCM. A Kaplan–Meier survival curve showed poorer outcomes for AMI patients with HCM after 1 year than for those without HCM.[7]

In a large population-based study conducted in the United States, discharge data of 5,901,827 patients with AMI during 2003–2011 were studied for the outcomes of those with HCM (5,688 patients, 0.1%) and those without HCM.[8] Patients with HCM were older, more likely to be female, less likely to have traditional cardiovascular risk factors, less likely to present with ST-elevation myocardial infarction (STEMI), and more likely to present with non-ST-elevation myocardial infarction (NSTEMI). In addition, patients with HCM were less likely to receive revascularization for STEMI and NSTEMI.[8] Because these patients with HCM were less likely to have traditional cardiovascular risk factors compared with patients without HCM, the authors postulated that these AMIs were likely driven by nonatherosclerotic mechanisms through microvascular dysfunction. Without propensity score matching, the authors concluded that in the overall population with AMI, no difference existed in observed in-hospital mortality between patients with and 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 those patients had coexisting HCM (0.13%). This prevalence was similar to that reported in a previous US study (0.10%).[8] When comparing our two study groups, we found that AMI in patients with HCM occurred at a significantly older age (70.1 ± 12.4 vs. 67.3 ± 14.0 years), and these patients were more likely to be female (51.4% vs. 30.8%) and less likely to have traditional cardiovascular risk factors such as DM (26.5% vs. 34.7%) and HL (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 toward lower rates of intubation and temporary HD in these patients. The cardiac performance and cardiovascular compromise appeared to be less likely affected in patients with HCM. 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.[1] 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 earlier reported 34% beta-blocker use after AMI in a review of ≥200,000 patient records in the Cooperative Cardiovascular Project,[12] but lower than the reported 88%–92% beta-blocker use in a more recent study involving HCM patients with AMI.[7]

Our study's crucial findings were that HCM patients with AMI had significantly lower rates of PCI, intervened vessels, PCI with stenting, CABG, shock, and in-hospital death (Table 3) than did HCM patients without AMI. Patients with

HCM had a higher rate of AMI in vessels requiring no coronary stenting than did patients without HCM (82.5% vs. 68.4%). HCM patients with AMI had significantly lower rates of one- and three-vessel CAD disease compared with non-HCM patients without AMI (13.2% vs. 23.5%, $P < 0.001$ and 0.4% vs 2.8%, $P = 0.034$). Similarly, the cumulative incidence of all-cause mortality was significantly higher in AMI patients without HCM within 1 year of follow-up (Fig. 2). Subsequently, the trend reversed after 1 year until the end of follow-up, suggesting coronary ischemia leading to myocardial infarction was not the cause of long-term mortality in patients with HCM.

In summary, AMI patients with HCM were significantly less likely to have coronary obstruction as well as receive PCI/CABG, shock, and in-hospital mortality, compared with AMI 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, using ICD-9-CM codes for patient screening may result in missing some cases for conditions not coded correctly. 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 incidences and rates of those HCM patients studied for AMI may not include those that died either due to severe ventricular arrhythmia or had sudden death, causing

selection bias. Fourth, the claims-based NHIRD does not provide additional information on examination report details such as laboratory, electrocardiographic, echocardiographic, or angiographic data. However, the NHIRD has data on PCI performed, number of intervened vessels, and number of stents placed. Last, because our study population comprised of patients with uniform ethnic background, application of the results to other populations requires interpretation within proper contexts.

Conclusions

This is the first study to directly compare the clinical outcomes of AMI patients with HCM and AMI patients without HCM using propensity score matching. AMI patients with HCM had significantly better outcomes than did AMI patients without HCM during the in-hospital course and within 1-year follow-up. However, patients with HCM still had poor long-term outcomes.

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Contributorship

VCW, THC, and MW contributed to the study's conception and design.

VCW and THC acquired the data.

SWC, CHC, CWC, CCC, KPW, MJH, CYW, and SHC contributed to the analysis and interpretation of data.

VCW, THC, and MW drafted the manuscript.

FCL, ICH, PHC, and MSW contributed to critical revision.

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Disclosures

None.

Data Sharing Statement

No additional data available.

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Figure Legends

Figure 1

Study design and flow chart for 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.

Figure 2

Kaplan–Meier survival analysis of AMI patients with and without HCM for the entire follow-up period (A). Because the observed group difference (slope) achieved the maximum at year 1–2 in Kaplan–Meier curves, using 1-year as the cutoff point of landmark analysis, the Kaplan–Meier survival graph is presented with a vertical dotted line separating the follow-up to within and beyond 1 year (B).

Table 1. Baseline characteristics and comorbidities during the index admission before and after matching

	Before matching			After matching	
Variable	HCM (n = 257)	Non-HCM (n = 176,801)	P value	Non-HCM (n = 1,028)	P value
Clinical variables					
Age	70.1±12.4	67.3±14.0	0.001*	69.9±14.5	0.834
Gender (male)	125 (48.6)	122,422 (69.2)	<0.001*	481 (46.8)	0.595
Comorbidities					
Hypertension	176 (68.5)	90,160 (51.0)	<0.001*	704 (68.5)	1.000
Hyperlipidemia	51 (19.8)	40,020 (22.6)	0.285	204 (19.8)	1.000
Diabetes mellitus	68 (26.5)	61,284 (34.7)	0.007*	275 (26.8)	0.925
Heart failure	81 (31.5)	13,797 (7.8)	<0.001*	315 (30.6)	0.786
Cerebrovascular accident	51 (19.8)	23,218 (13.1)	0.001*	222 (21.6)	0.539
Chronic kidney disease	18 (7.0)	6,255 (3.5)	0.003*	78 (7.6)	0.750
Carotid artery disease	77 (30.0)	16,982 (9.6)	<0.001*	309 (30.1)	0.976
Peripheral artery disease	18 (7.0)	7,878 (4.5)	0.048*	75 (7.3)	0.872
Atrial fibrillation/atrial flutter	48 (18.7)	6,568 (3.7)	<0.001*	189 (18.4)	0.914
Chronic obstructive pulmonary disease	70 (27.2)	27,659 (15.6)	<0.001*	283 (27.5)	0.925
Peptic ulcer disease	57 (22.2)	20,022 (11.3)	<0.001*	221 (21.5)	0.813
Liver cirrhosis	12 (4.7)	3,360 (1.9)	0.001*	47 (4.6)	0.947
Malignancy	19 (7.4)	10,986 (6.2)	0.434	76 (7.4)	1.000
Gout	24 (9.3)	12,310 (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

* Denotes $P < 0.05$.

Table 2. Intervention and medication during the index admission

Variable	HCM (n = 257)	Non-HCM (n = 1,028)	P value
Intervention			
Intubation	41 (16.0)	217 (21.1)	0.065
Intraaortic balloon pump	4 (1.6)	65 (6.3)	0.002*
Extracorporeal membrane oxygenation	1 (0.4)	5 (0.5)	0.838
Temporary hemodialysis	5 (1.9)	46 (4.5)	0.063
Cardiac rehabilitation	8 (3.1)	50 (4.9)	0.227
Medications during admission			
Aspirin	196 (76.3)	757 (73.6)	0.390
Clopidogrel	120 (46.7)	519 (50.5)	0.277
ACEI/ARB	141 (54.9)	549 (53.4)	0.675
Beta blocker	135 (52.5)	443 (43.1)	0.007*
Calcium channel blocker	70 (27.2)	236 (23.0)	0.150
Diuretics	80 (31.1)	334 (32.5)	0.676
Spironolactone	19 (7.4)	87 (8.5)	0.577
Nitrates	51 (19.8)	219 (21.3)	0.608
Warfarin	18 (7.0)	49 (4.8)	0.149
Statin	49 (19.1)	237 (23.1)	0.169
Proton pump inhibitor	30 (11.7)	102 (9.9)	0.408

* Denotes $P < 0.05$.
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 3. Clinical course during hospitalization

Variable	HCM (n = 257)	Non-HCM (n = 1,028)	HCM *vs*. Non-HCM	
			OR / *B* (95% CI)	*P* value
PCI	45 (17.5)	325 (31.6)	0.46 (0.32, 0.65)	<0.001*
Number of intervened vessels				
0 vessel	212 (82.5)	703 (68.4)	Reference	–
1 vessel	34 (13.2)	242 (23.5)	0.47 (0.32, 0.69)	<0.001*
2 vessels	10 (3.9)	54 (5.3)	0.61 (0.31, 1.23)	0.167
3 vessels	1 (0.4)	29 (2.8)	0.11 (0.02, 0.84)	0.034*
PCI with stenting	16 (6.2)	171 (16.6)	0.33 (0.20, 0.57)	<0.001*
CABG	2 (0.8)	36 (3.5)	0.22 (0.05, 0.90)	0.036*
Valvular surgery	3 (1.2)	3 (0.3)	4.04 (0.81, 20.11)	0.089
Pacing device implantation†	7 (2.7)	3 (0.3)	9.57 (2.46, 37.26)	0.001*
New onset of atrial fibrillation	35 (13.6)	48 (4.7)	3.22 (2.03, 5.10)	<0.001*
New onset of VTE	16 (6.2)	47 (4.6)	1.39 (0.77, 2.49)	0.274
Shock	75 (29.2)	402 (39.1)	0.64 (0.48, 0.86)	0.003*
In-hospital death	28 (10.9)	217 (21.1)	0.46 (0.30, 0.70)	<0.001*
ICU days	4.4±7.2	4.6±7.3	-0.21 (-1.20, 0.78)	0.677
Length of stay	13.7±25.1	12.3±20.6	1.39 (-1.56, 4.35)	0.355

* Denotes $P < 0.05$.

B, regression coefficient; CABG, coronary artery bypass graft; CI, confidence interval; ICU, intensive care unit; OR, odds ratio; PCI, percutaneous coronary intervention; VTE, venous thromboembolism.

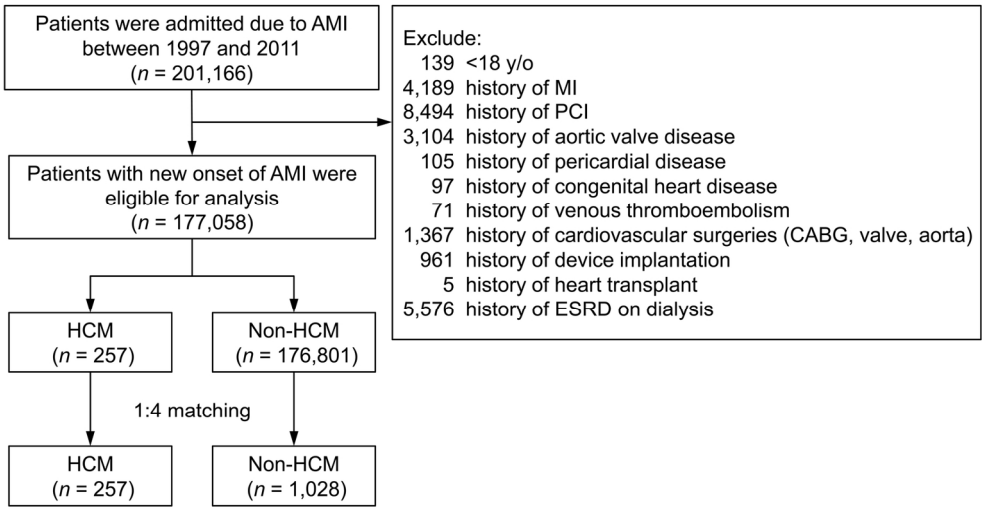
† Includes pacemaker and implantable cardioverter defibrillator.

Table 4. Outcome during the follow up

Variable	HCM (n = 257)	Non-HCM (n = 1,028)	HCM *vs*. Non-HCM HR (95% CI)	*P* value
1 year follow up				
Recurrent AMI	13 (5.1)	70 (6.8)	0.68 (0.37, 1.25)	0.214
HF hospitalization	17 (6.6)	66 (6.4)	1.02 (0.60, 1.74)	0.941
Systemic VTE	23 (8.9)	64 (6.2)	1.55 (0.75, 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, 0.85)	0.001*
CV death	46 (17.9)	211 (20.5)	0.83 (0.60, 1.14)	0.252
At the end of follow up				
Recurrent AMI	23 (8.9)	109 (10.6)	0.79 (0.50, 1.24)	0.299
HF hospitalization	35 (13.6)	112 (10.9)	1.24 (0.85, 1.80)	0.266
Systemic VTE	39 (15.2)	107 (10.4)	1.52 (0.97, 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, 1.16)	0.732
CV death	62 (24.1)	262 (25.5)	0.89 (0.67, 1.17)	0.401

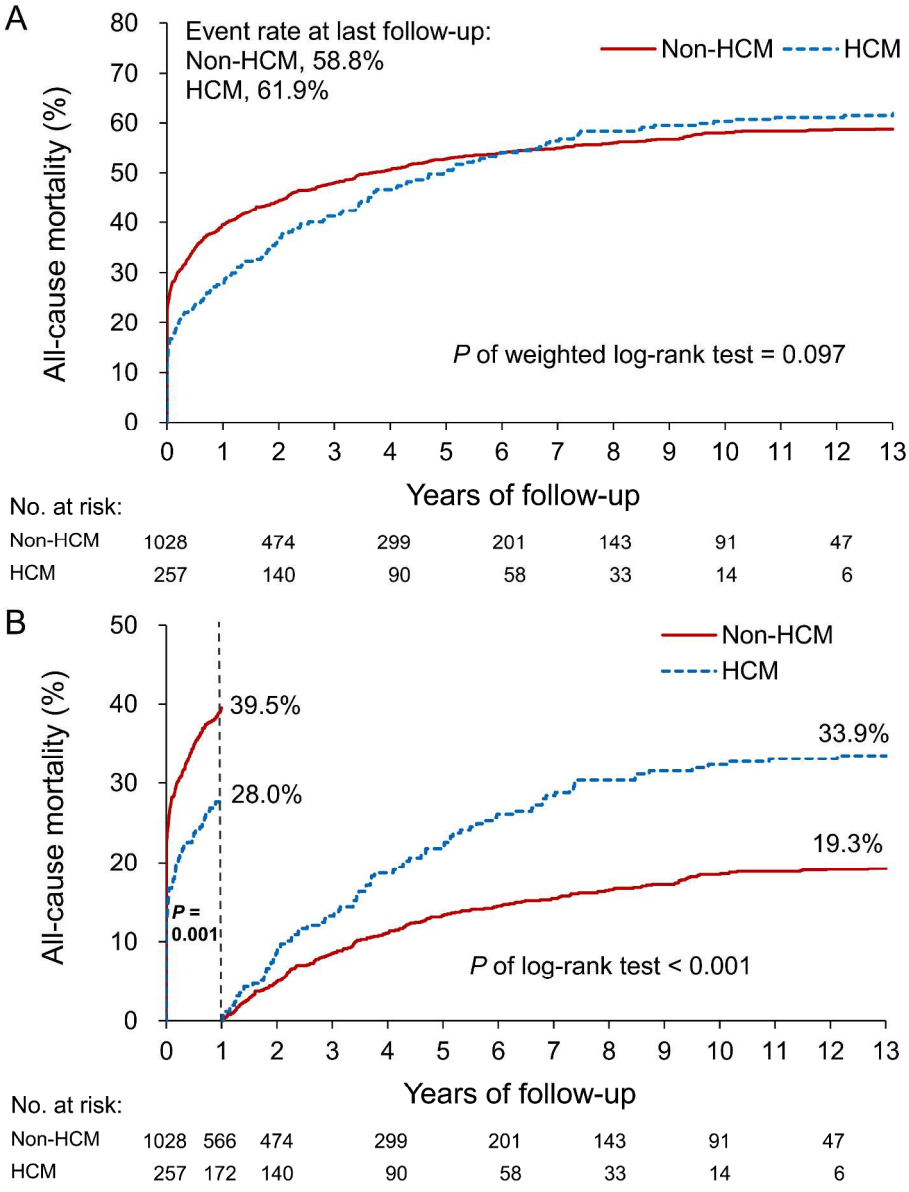
* Denoted $P < 0.05$.
AMI, acute myocardial infarction; HR, hazard ratio; CI, confidence interval; CV, cardiovascular; HF, heart failure; VTE, venous thromboembolism; NA = not applicable.

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



Study design and flow chart for 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.

78x41mm (600 x 600 DPI)



Kaplan–Meier survival analysis of AMI patients with and without HCM for the entire follow-up period (A). Because the observed group difference (slope) achieved the maximum at year 1–2 in Kaplan–Meier curves, using 1-year as the cutoff point of landmark analysis, the Kaplan–Meier survival graph is presented with a vertical dotted line separating the follow-up to within and beyond 1 year (B).

343x449mm (300 x 300 DPI)

Supplementary Table 1. ICD-9-CM code used in the current study

Variable	Code
Acute myocardial infarction	410.xx
Aortic valve disease	424.1
Pericardial disease	423.xx
Congenital heart disease	745.xx–747.xx (Catastrophic illness card)
Venous thromboembolism	415.1x, 453.xx
Dialysis	585.xx (Catastrophic illness card)
Hypertrophic cardiomyopathy	425.1x
Hypertension	401.xx–405.xx
Hyperlipidemia	272.xx
Diabetes mellitus	250.xx
Heart failure	428.xx
Stroke	430.xx–437.xx
Chronic kidney disease	580.xx–589.xx, 403.xx–404.xx, 016.0x, 095.4x, 236.9x, 250.4x, 274.1x, 442.1x, 447.3x, 440.1x, 572.4x, 642.1x, 646.2x, 753.1x, 283.11, 403.01, 404.02, 446.21
Carotid artery disease	433.1x
Peripheral artery disease	440.0x, 440.2x, 440.3x, 440.8x, 440.9x, 443.xx, 444.0x, 444.22, 444.8x, 447.8x, 447.9x
Atrial fibrillation/atrial flutter	427.31, 427.32
Chronic obstructive pulmonary disease	491.xx, 492.xx, 496.xx
Peptic ulcer disease	531.xx–534.xx
Liver cirrhosis	571.2x, 571.5x, 571.6x
Malignancy	140.xx–208.xx
Gout	274.xx
Atrial fibrillation	427.31
Systemic thromboembolism	444.22, 444.81, 444.21, 557.0, 557.9, 557.1, 593.81, 444.89, 433.8, 444.9x, 415.1x, 433.xx, 434.xx, 435.xx, 436.xx, 437.xx

Supplementary Table 2. Intervention and medication during the index admission after propensity score matching without matching the index date (sensitivity analysis I)

Variable	HCM (n = 257)	Non-HCM (n = 1,028)	P value#
Intervention			
Intubation	41 (16.0)	247 (24.0)	0.005*
Intraaortic balloon pump	4 (1.6)	65 (6.3)	0.002*
Extracorporeal membrane oxygenation	1 (0.4)	11 (1.1)	0.310
Temporary hemodialysis	5 (1.9)	44 (4.3)	0.080
Cardiac rehabilitation	8 (3.1)	46 (4.5)	0.330
Medications during admission			
Aspirin	196 (76.3)	761 (74.0)	0.462
Clopidogrel	120 (46.7)	528 (51.4)	0.181
ACEI/ARB	141 (54.9)	582 (56.6)	0.613
Beta blocker	135 (52.5)	454 (44.2)	0.016*
Calcium channel blocker	70 (27.2)	225 (21.9)	0.068
Diuretics	80 (31.1)	330 (32.1)	0.765
Spironolactone	19 (7.4)	92 (8.9)	0.427
Nitrates	51 (19.8)	228 (22.2)	0.417
Warfarin	18 (7.0)	52 (5.1)	0.219
Statin	49 (19.1)	223 (21.7)	0.357
Proton pump inhibitor	30 (11.7)	118 (11.5)	0.930

* Denotes $P < 0.05$.
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Adjusted for year of index admission.

Supplementary Table 3. In-hospital cardiovascular outcome after propensity score matching without matching the index date (sensitivity analysis I)

Variable	HCM (n = 257)	Non-HCM (n = 1,028)	HCM *vs*. Non-HCM#	
			OR / *B* (95% CI)	*P* value
PCI	45 (17.5)	311 (30.3)	0.49 (0.34, 0.70)	<0.001*
Number of intervened vessels				
0 vessel	212 (82.5)	717 (69.7)	Reference	–
1 vessel	34 (13.2)	226 (22.0)	0.51 (0.34, 0.76)	<0.001*
2 vessels	10 (3.9)	57 (5.5)	0.60 (0.30, 1.20)	0.146
3 vessels	1 (0.4)	28 (2.7)	0.12 (0.02, 0.86)	0.035*
PCI with stenting	16 (6.2)	181 (17.6)	0.30 (0.17, 0.51)	<0.001*
CABG	2 (0.8)	31 (3.0)	0.26 (0.06, 1.10)	0.067
Valvular surgery	3 (1.2)	6 (0.6)	2.06 (0.50, 8.49)	0.315
Pacing device implantation†	7 (2.7)	3 (0.3)	9.68 (2.43, 38.47)	0.001*
New onset of atrial fibrillation	35 (13.6)	32 (3.1)	5.15 (3.09, 8.57)	<0.001*
New onset of VTE	16 (6.2)	55 (5.4)	1.28 (0.72, 2.29)	0.405
Shock	75 (29.2)	433 (42.1)	0.58 (0.43, 0.78)	<0.001*
In-hospital death	28 (10.9)	223 (21.7)	0.44 (0.29, 0.67)	<0.001*
ICU days	4.4±7.2	4.6±7.8	-0.24 (-1.29, 0.81)	0.824
Length of stay	13.7±25.1	12.9±20.1	0.78 (-2.11, 3.68)	0.550

* Denotes $P < 0.05$.
B, regression coefficient; CABG, coronary artery bypass graft; CI, confidence interval; ICU, intensive care unit; OR, odds ratio; PCI, percutaneous coronary intervention; VTE, venous thromboembolism.
† Includes pacemaker and implantable cardioverter defibrillator.

Adjusted for year of index admission.

Supplementary Table 4. Outcome during the follow up after propensity score matching without matching the index date (sensitivity analysis I)

Variable	HCM (n = 257)	Non-HCM (n = 1,028)	HCM *vs*. Non-HCM#	
			HR (95% CI)	*P* value
1 year follow up				
Recurrent AMI	13 (5.1)	69 (6.7)	0.70 (0.38, 1.28)	0.249
HF hospitalization	17 (6.6)	61 (5.9)	1.10 (0.65, 1.88)	0.717
Systemic VTE	23 (8.9)	63 (6.1)	2.62 (1.06, 6.48)	0.036*
Heart transplant	0 (0.0)	0 (0.0)	NA	NA
All-cause mortality	72 (28.0)	407 (39.6)	0.59 (0.46, 0.76)	<0.001*
CV death	46 (17.9)	217 (21.1)	0.74 (0.54, 1.02)	0.067
At the end of follow up				
Recurrent AMI	23 (8.9)	100 (9.7)	0.86 (0.54, 1.37)	0.528
HF hospitalization	35 (13.6)	101 (9.8)	1.41 (0.96, 2.07)	0.083
Systemic VTE	39 (15.2)	108 (10.5)	1.77 (1.09, 2.88)	0.022*
Heart transplant	0 (0.0)	0 (0.0)	NA	NA
All-cause mortality	159 (61.9)	604 (58.8)	0.82 (0.69, 0.98)	0.031*
CV death	62 (24.1)	246 (23.9)	0.84 (0.63, 1.11)	0.220

* Denoted $P < 0.05$.
AMI, acute myocardial infarction; HR, hazard ratio; CI, confidence interval; CV, cardiovascular; HF, heart failure; VTE, venous thromboembolism; NA = not applicable.

#Additional adjusted for percutaneous coronary intervention, coronary artery bypass graft and pacing device during the index admission and the index year.

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

Supplementary Table 5. Intervention and medication during the index admission using multivariable regression adjustment (sensitivity analysis II)#

Variable	HCM (n = 257)	Non-HCM (n = 176,801)	P value
Intervention			
Intubation	41 (16.0)	34,182 (19.3)	0.170
Intraaortic balloon pump	4 (1.6)	11,882 (6.7)	0.001*
Extracorporeal membrane oxygenation	1 (0.4)	932 (0.5)	0.760
Temporary hemodialysis	5 (1.9)	5,877 (3.3)	0.218
Cardiac rehabilitation	8 (3.1)	8,076 (4.6)	0.264
Medications during admission			
Aspirin	196 (76.3)	139,396 (78.8)	0.312
Clopidogrel	120 (46.7)	98,802 (55.9)	0.003*
ACEI/ARB	141 (54.9)	106,910 (60.5)	0.066
Beta blocker	135 (52.5)	87,549 (49.5)	0.335
Calcium channel blocker	70 (27.2)	35,653 (20.2)	0.005*
Diuretics	80 (31.1)	48,383 (27.4)	0.176
Spironolactone	19 (7.4)	13,274 (7.5)	0.944
Nitrates	51 (19.8)	41,146 (23.3)	0.194
Warfarin	18 (7.0)	6,388 (3.6)	0.004*
Statin	49 (19.1)	50,907 (28.8)	0.001*
Proton pump inhibitor	30 (11.7)	14,352 (8.1)	0.037*

* Denotes $P < 0.05$.
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Adjusted for sex, gender and 14 comorbidities listed in Table 1.

Supplementary Table 6. In-hospital cardiovascular outcome using multivariable regression adjustment (sensitivity analysis II)#

Variable	HCM (n = 257)	Non-HCM (n = 176,801)	HCM *vs*. Non-HCM OR / *B* (95% CI)	*P* value
PCI	45 (17.5)	73,391 (41.5)	0.44 (0.31, 0.61)	<0.001*
Number of intervened vessels				
0 vessel	212 (82.5)	103,410 (58.5)	Reference	–
1 vessel	34 (13.2)	55,066 (31.1)	0.45 (0.31, 0.66)	<0.001*
2 vessels	10 (3.9)	11,924 (6.7)	0.57 (0.30, 1.08)	0.085
3 vessels	1 (0.4)	6,401 (3.6)	0.11 (0.02, 0.77)	0.026*
PCI with stenting	16 (6.2)	39,233 (22.2)	0.31 (0.18, 0.53)	<0.001*
CABG	2 (0.8)	6,759 (3.8)	0.25 (0.06, 1.002)	0.0503
Valvular surgery	3 (1.2)	756 (0.4)	2.12 (0.67, 6.69)	0.200
Pacing device implantation†	7 (2.7)	549 (0.3)	8.04 (3.73, 17.31)	<0.001*
New onset of atrial fibrillation	35 (13.6)	6,543 (3.7)	4.57 (3.15, 6.63)	<0.001*
New onset of VTE	16 (6.2)	7,242 (4.1)	1.50 (0.89, 2.52)	0.127
Shock	75 (29.2)	63,077 (35.7)	0.64 (0.49, 0.85)	0.002*
In-hospital death	28 (10.9)	29,396 (16.6)	0.46 (0.30, 0.69)	<0.001*
ICU days	4.4±7.2	4.4±7.1	0.04 (-0.81, 0.89)	0.595
Length of stay	13.7±25.1	11.1±17.3	2.66 (0.60, 4.72)	0.360

* Denotes $P < 0.05$.
B, regression coefficient; CABG, coronary artery bypass graft; CI, confidence interval; ICU, intensive care unit; OR, odds ratio; PCI, percutaneous coronary intervention; VTE, venous thromboembolism.
† Includes pacemaker and implantable cardioverter defibrillator.
# Adjusted for sex, gender and 14 comorbidities listed in Table 1.

Supplementary Table 7. Outcome during the follow up using multivariable regression adjustment (sensitivity analysis II)#

Variable	HCM (*n* = 257)	Non-HCM (*n* = 176,801)	HCM *vs*. Non-HCM	
			HR (95% CI)	*P* value
1 year follow up				
Recurrent AMI	13 (5.1)	13,774 (7.8)	0.68 (0.38, 1.19)	0.174
HF hospitalization	17 (6.6)	7,790 (4.4)	0.98 (0.60, 1.60)	0.946
Systemic VTE	23 (8.9)	9,496 (5.4)	2.08 (1.12, 3.86)	0.021*
Heart transplant	0 (0.0)	89 (0.1)	NA	NA
All-cause mortality	72 (28.0)	54,007 (30.5)	0.69 (0.55, 0.87)	0.002*
CV death	46 (17.9)	29,667 (16.8)	0.85 (0.64, 1.14)	0.284
At the end of follow up				
Recurrent AMI	23 (8.9)	20,316 (11.5)	0.85 (0.56, 1.28)	0.429
HF hospitalization	35 (13.6)	15,708 (8.9)	1.16 (0.82, 1.62)	0.405
Systemic VTE	39 (15.2)	18,155 (10.3)	1.67 (1.13, 2.47)	0.010*
Heart transplant	0 (0.0)	188 (0.1)	NA	NA
All-cause mortality	159 (61.9)	88,884 (50.3)	0.93 (0.79, 1.08)	0.338
CV death	62 (24.1)	36,481 (20.6)	0.93 (0.72, 1.19)	0.539

* Denoted $P < 0.05$.
AMI, acute myocardial infarction; HR, hazard ratio; CI, confidence interval; CV, cardiovascular; HF, heart failure; VTE, venous thromboembolism; NA = not applicable.

The analysis considers death as a competing risk except for all-cause mortality and CV death.
Adjusted for sex, gender and 14 comorbidities listed in Table 1.

Supplementary Table 8. Outcome during the follow up after propensity score matching using classical Cox proportional hazard model (sensitivity analysis III)

Variable	HCM (*n* = 257)	Non-HCM (*n* = 1,028)	HCM *vs*. Non-HCM HR (95% CI)	HCM *vs*. Non-HCM *P* value
1 year follow up				
Recurrent AMI	13 (5.1)	70 (6.8)	0.63 (0.34, 1.16)	0.136
HF hospitalization	17 (6.6)	66 (6.4)	0.88 (0.52, 1.50)	0.643
Systemic VTE	23 (8.9)	64 (6.2)	1.31 (0.63, 2.71)	0.473
Heart transplant	0 (0.0)	1 (0.1)	NA	NA
All-cause mortality	72 (28.0)	406 (39.5)	0.66 (0.51, 0.85)	0.001*
CV death	46 (17.9)	211 (20.5)	0.83 (0.60, 1.14)	0.252
At the end of follow up				
Recurrent AMI	23 (8.9)	109 (10.6)	0.72 (0.46, 1.14)	0.165
HF hospitalization	35 (13.6)	112 (10.9)	1.10 (0.76, 1.62)	0.609
Systemic VTE	39 (15.2)	107 (10.4)	1.38 (0.88, 2.17)	0.162
Heart transplant	0 (0.0)	1 (0.1)	NA	NA
All-cause mortality	159 (61.9)	604 (58.8)	0.97 (0.81, 1.16)	0.732
CV death	62 (24.1)	262 (25.5)	0.89 (0.67, 1.17)	0.401

* Denoted $P < 0.05$.

AMI, acute myocardial infarction; HR, hazard ratio; CI, confidence interval; CV, cardiovascular; HF, heart failure; VTE, venous thromboembolism; NA = not applicable.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 6
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 6,7
Methods			
Study design	4	Present key elements of study design early in the paper	Page 7,8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 7,8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 7,8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Page 7,8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 7,8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 7,8
Bias	9	Describe any efforts to address potential sources of bias	Page 16
Study size	10	Explain how the study size was arrived at	Page 11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 7,8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 9,10
		(*b*) Describe any methods used to examine subgroups and interactions	n/a
		(*c*) Explain how missing data were addressed	n/a
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 11
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1,2
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount)	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 3,4

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 4
		(*b*) Report category boundaries when continuous variables were categorized	Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page 9,10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 16,17
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 16,17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 18

*Give information separately for exposed and unexposed groups.

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

BMJ Open

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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Complete List of Authors:	Wu, Victor Chien-Chia; Chang Gung Memorial Hospital Linkou Branch, Division of Cardiology Chen, Tien-Hsing; Chang Gung Memorial Hospital Keelung Branch, Department of Cardiology Wu, Michael; Miriam and Rhode Island Hospital, Division of Cardiovascular Medicine Chen, Shao-Wei ; Chang Gung Memorial Hospital Linkou Branch, Department of Cardiothoracic and Vascular Surgery Chang, Chih-Hsiang; Chang Gung Memorial Hospital Linkou Branch, Department of Nephrology Chang, Chun-Wei; Chang Gung Memorial Hospital Linkou Branch, Department of Neurology Chen, Ching-Chang; Chang Gung Memorial Hospital Linkou Branch, Department of Neurosurgery Wu, Katie P; Chang Gung Memorial Hospital Linkou Branch, Division of Cardiology Hsieh, Ming-Jer; Chang Gung Memorial Hospital Linkou Branch, Division of Cardiology Wang, Chao-Yung; Chang Gung Memorial Hospital Linkou Branch, Division of Cardiology Chang, Shang-Hung; Chang Gung Memorial Hospital Linkou Branch, Division of Cardiology Lin, Fen-Chiung; Chang Gung Memorial Hospital Linkou Branch, Division of Cardiology Hsieh, I-Chang; Chang Gung Memorial Hospital Linkou Branch, Division of Cardiology Chu, Pao-Hsien ; Chang Gung Memorial Hospital and University, Cardiology Wen, Ming-Shien; Chang Gung Memorial Hospital Linkou Branch, Division of Cardiology
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Outcomes of Patients with Hypertrophic Cardiomyopathy and Acute Myocardial Infarction: A Propensity Score-Matched 15-Year Nationwide Population-Based Study in Asia

Victor Chien-Chia Wu, MD[1*], Tien-Hsing Chen, MD[2*], Michael Wu, MD[3], Shao-Wei Chen, MD[4], Chih-Hsiang Chang, MD[5], Chun-Wei Chang, MD[6], Ching-Chang Chen, MD[7], Katie Pei-Hsuan Wu, MD[8], Ming-Jer Hsieh, MD[1], Chao-Yung Wang, MD[1], Shang-Hung Chang, MD[1], Fen-Chiung Lin, MD[1], I-Chang Hsieh, MD[1], Pao-Hsien Chu, MD[1], Ming-Shien Wen, MD[1]

[1]Division of Cardiology, Chang Gung Memorial Hospital, Linkou Medical Center, Taoyuan City, Taiwan

[2]Department of Cardiology, Chang Gung Memorial Hospital, Keelung, Taiwan

[3]Divison of Cardiovascular Medicine, Miriam and Rhode Island Hospital, Warren Alpert School of Medicine, Brown University, Rhode Island, USA

[4]Department of Cardiothoracic and Vascular Surgery, [5]Department of Nephrology, [6]Department of Neurology, [7]Department of Neurosurgery, [8]Department of Physical Medicine and Rehabilitation, Chang Gung Memorial Hospital, Linkou Medical Center, Taoyuan City, Taiwan

Brief title: Outcomes of HCM Patients with AMI

*Authors contributed equally.

All authors have nothing to disclose

Address for correspondence:

Victor Chien-Chia Wu, MD, FESC

Department of Cardiology, Chang Gung Memorial Hospital, No. 5, Fuxing Street, Guishan District, Taoyuan City 33305, Taiwan

Tel: +886-3-3281200 x8115; fax: + 886-3-3281451

E-mail: victorcwu@hotmail.com

Objectives: Hypertrophic cardiomyopathy (HCM) entails thickening of the myocardium and an increased risk of ischemia. However, studies of the outcomes of acute myocardial infarction (AMI) in patients with HCM are limited.

Methods: Electronic medical records were retrieved from the Taiwan National Health Insurance Research Database from 1997 to 2011. Exclusion criteria were a history of AMI, percutaneous coronary intervention (PCI), aortic valve disease, pericardial disease, congenital heart disease, venous thromboembolism, cardiovascular surgeries, device implantation, heart transplant, and hemodialysis. HCM patients with AMI were compared with propensity score-matched AMI patients without HCM. Primary outcomes were defined as in-hospital and 1-year cardiovascular events.

Results: In total, 201,166 patients were admitted for AMI. After exclusion, there were 177,058 patients with new-onset AMI (257 with HCM, 176,801 without HCM). After 1:4 propensity score matching, the study population was comprised of 257 AMI patients with HCM and 1,028 AMI patients without HCM. HCM patients with AMI received significantly less PCI (odds ratio [OR]=0.46; 95% confidence interval [CI]=0.32–0.65; *P* <0.001), PCI with stenting (OR=0.33; 95% CI=0.20–0.57; *P* <0.001), and coronary artery bypass graft (OR=0.22; 95% CI=0.05–0.90; *P*=0.036), as well as had fewer episodes of shock (OR,=0.64; 95% CI=0.48–0.86; *P*=0.003) and in-hospital death (OR=0.46; 95% CI=0.30–0.70; *P* <0.001) compared with AMI patients without HCM. Specifically, for HCM patients with AMI, AMI occurred predominantly (82.5%) in the form of ischemia without requiring coronary stenting. Patients with HCM had a higher survival rate than did those without (hazard ratio=0.66; 95% CI=0.51–0.85; *P*=0.001) during the 1-year follow-up.

Conclusions: This is the first study to directly compare the clinical outcomes of AMI patients with and without HCM through propensity score matching. AMI patients

with HCM had significantly better outcomes than did AMI patients without HCM during the in-hospital course and within the 1-year follow-up period.

Keywords: hypertrophic cardiomyopathy, acute myocardial infarction, outcome

Strengths and limitations of this study

- This is the first study to directly compare the outcomes of AMI in patients with and without HCM through propensity score matching.
- The differences in outcomes in AMI patients with HCM and without HCM were demonstrated by the percentage of patients who underwent PCI, 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 program provides uniform health care services to 99.5% of the population without financial restraints or selection bias; however, the data utilized for this study are old (1997-2011).
- Using ICD-9-CM codes for patient screening may have resulted in missing cases if conditions were not coded correctly, however patients with AMI and HCM have definitive ICD codes 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 incidences and rates of those HCM patients studied for AMI may not include those who died due to severe ventricular arrhythmia or had sudden death.

Introduction

Hypertrophic cardiomyopathy (HCM) is hallmarked by the increase in left ventricular (LV) wall thickness that cannot be entirely attributed to the excessive loading conditions.[1] HCM is the most common genetic disorder of the myocardium that affects 1 in 500 of the general population.[2] During the systolic phase, the hypercontractile myocardium may obliterate the 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.[3]

Patients with HCM are considered to have a substantial cardiovascular risk, however they tend to have less clear symptoms thus evading the diagnosis of ischemia.[4,5] In a study that described the clinical characteristics and prognosis of HCM, approximately 1/3 of patients with HCM had adverse cardiovascular outcomes without concomitant increased acute myocardial infarction (AMI) mortality rate.[6] A prospective study reported worse long-term survival of AMI in HCM patients compared with AMI in non-HCM patients.[7] A large US population study noted that HCM patients presented with AMI at a later age, and these patients had received less cardiac catheterization compared with non-HCM patients with AMI.[8] Furthermore, HCM may progress to heart failure (HF) because of dynamic LV outflow obstruction, LV diastolic dysfunction, atrial fibrillation (AF) with the risk of stroke, and ventricular arrhythmia with the risk of sudden death. Therefore, in this study, we aimed to (1) investigate the outcomes of patients with and without HCM experiencing an AMI through propensity score-matching and (2) clarify the prognostic difference in cardiovascular events between the two groups.

Methods

Study patients

The health insurance program in Taiwan established in 1995, named National Health Insurance (NHI), covers over 99% of the 23.5 million residents. The NHI Research Database (NHIRD) stored all data of 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 consisted of greater than 95% of Han Chinese, the study is conducted within a nearly homogenous ethnicity. The Institutional Review Board of Chang Gung Memorial Hospital Linkou Branch approved this study.

By searching electronic medical records from the NHIRD between January 1, 1997, and December 31, 2011, we identified all patients admitted for AMI. In this study, AMI was defined using the Third Universal Definition of AMI: a rise or fall of cardiac biomarkers with at least one value above the 99th percentile upper reference limit with at least one of the following: (1) symptoms of ischemia; (2) new or presumed new significant ST segment-T wave changes or a new left bundle branch block; (3) development of pathological Q waves in ECG; (4) imaging evidence of new loss of the viable myocardium or new regional wall motion abnormality; and (5) identification of an intracoronary thrombus through angiography or autopsy.[9] 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 medication and mechanical support. The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code 425.1 (Supplementary Table 1) was used to identify patients with HCM and was used

previously in a large US population study.[8] Patients aged below 18 years were excluded. In addition, patients with a history of MI (AMI or old MI), percutaneous coronary intervention (PCI), aortic valve disease (AVD), pericardial disease, congenital heart disease (CHD), venous thromboembolism (VTE), cardiovascular surgeries, device implantation, heart transplant, or end-stage renal disease (ESRD) on dialysis were excluded. The remaining patients had their first-ever AMI admission as the index admission.

We divided patients into HCM and non-HCM groups for further analysis. According to the 2011 ACCF/AHA Guideline, HCM is a disease state characterized by unexplained LV hypertrophy associated with nondilated ventricular chambers in the absence of another cardiac or systemic disease that itself would be capable of producing the magnitude of hypertrophy evident in a given patient.[10] In addition, the 2014 ESC Guideline simply defined HCM as the presence of increased LV wall thickness that is not solely explained by abnormal loading conditions.[11] Clinically, HCM is usually recognized by a maximal LV wall thickness ≥15 mm, with 13–14 mm considered borderline, particularly in the presence of other compelling information (e.g., a family history of HCM), based on echocardiography.[10]

Covariate and study outcomes

To effectively compare two groups of patients whose clinical presentations may be affected by comorbidities, we matched patients with HCM to patients without HCM by using propensity scores. 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), hyperlipidemia, diabetes mellitus (DM), HF, cerebrovascular accident (CVA), chronic kidney disease (CKD; at least at moderate

stage with creatinine clearance <60 mL/min/1.73 m^2), carotid artery disease, peripheral artery disease (PAD), AF/atrial flutter (AFL), chronic obstructive pulmonary disease (COPD), peptic ulcer disease (PUD), liver cirrhosis, and malignancy. The propensity score matching was processed using the greedy nearest neighbor algorithm, and the caliper width was set as 0.2 of the standard deviation of the logit of the propensity score.

The medical records of the NHIRD listed the primary diagnoses of patients during admission. Cardiovascular death was defined according to the criteria of Standardized Definitions for End Point Events in Cardiovascular Trials drafted by the Food and Drug Administration.[12] Death was defined as the withdrawal of a patient from the NHI program.[13] Causes of death were defined according to the primary discharge diagnoses of hospitalization within 3 months prior to death.[13] Primary outcomes were defined as in-hospital and 1-year cardiovascular events.

Statistical analysis

We compared baseline characteristics, comorbidities, interventions, and medication between the study groups (HCM vs. non-HCM) using the independent 2-sample *t* test for continuous variables or the chi-square test for categorical variables. We compared the risk of categorical in-hospital outcomes (e.g., in-hospital death) between the groups by using logistic regression analysis and compared continuous outcomes (e.g., length of stay) by using linear regression analysis. Because the risk of death between the HCM and non-HCM groups was unbalanced, the incidence of long-term time-to-event outcomes during the follow-up between the groups was compared using a competing risk survival model that considered death as a competing risk.[14] We generated the plot of the cumulative incidence rate by using subdistribution

hazard functions for time-to-event outcomes. Subsequently, we used Cox proportional hazards models to generate cumulative incidence functions for all-cause and cardiovascular mortality.

Because the survival curves of all-cause mortality during the overall follow-up period in the HCM and non-HCM groups crossed, a log-rank test with inverse probability of treatment weighting was used to compare the study groups.[15] Therefore, a landmark analysis of all-cause mortality by using cut-points of 1 year (main result), 2 years, and 3 years was performed. All statistical analyses were carried out using commercial software (SAS 9.4 (SAS Institute, Cary, NC). All tests were 2-tailed, and statistical significance was defined as $P < 0.05$.

Sensitivity analysis

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

Patient and public involvement

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

Results

Study population

In total, 201,166 patients were admitted for AMI between 1997 and 2011 in Taiwan. After excluding patients with a history of AMI, PCI, AVD, pericardial disease, CHD, VTE, cardiovascular surgeries, device implantation, heart transplant, and ESRD on dialysis, 177,058 patients remained with new-onset AMI, of which 257 and 176,801 patients were included in the HCM and non-HCM groups, respectively. Because the number of patients without HCM was excessive, after 1:4 propensity score matching for clinical variables of age, sex, and comorbidities, namely HTN, hyperlipidemia, DM, HF, CVA, CKD, carotid artery disease, PAD, AF/AFL, COPD, PUD, liver cirrhosis, malignancy, and gout, 257 patients with HCM and 1,028 patients without HCM remained (Figure 1). Before matching, significant differences existed across clinical variables and comorbidities except for hyperlipidemia, malignancy, and gout. After matching, no difference was observed between the two groups (Table 1).

Clinical characteristics

Table 2 presents the findings of AMI patients with and without HCM during index admission. In terms of intervention, AMI patients with HCM were less likely to require an intra-aortic balloon bump (IABP, $P = 0.002$) and exhibited a trend toward being less likely to be intubated ($P = 0.065$) and receive temporary hemodialysis ($P =$

0.063). In terms of medication, AMI patients with HCM were more likely to be prescribed beta-blockers ($P = 0.007$).

In-hospital outcomes

Table 3 displays the results of in-hospital outcomes. HCM patients with AMI were significantly less likely to receive PCI (odds ratio [OR], 0.46; 95% confidence interval [CI], 0.32–0.65; $P < 0.001$), have vessels intervened, receive PCI with stenting (OR, 0.33; 95% CI, 0.20–0.57; $P < 0.001$), undergo CABG (OR, 0.22; 95% CI, 0.05–0.90; $P = 0.036$), experience episodes of shock (OR, 0.64; 95% CI, 0.48–0.86; $P = 0.003$), and die during hospitalization (OR, 0.46; 95% CI, 0.30–0.70; $P < 0.001$) compared with non-HCM patients with AMI. However, HCM patients with AMI had a significantly higher incidence of pacing device implantation (OR, 9.57; 95% CI, 2.46–37.26; $P = 0.001$) and new-onset AF (OR, 3.22; 95% CI, 2.03–5.10; $P < 0.001$).

Follow-up outcomes

Figure 2A illustrates the Kaplan–Meier survival curves of the HCM and non-HCM groups during the entire follow-up. The risk of all-cause mortality was comparable between the two groups (crude hazard ratio [HR], 0.97; 95% CI, 0.81–1.16). However, the two curves crossed at year 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 year 1–2; thus, we used 1-year as the cutoff point in the landmark analysis. In-hospital death was included in 1-year mortality. During the first-year follow-up, non-HCM patients with AMI had

significantly poor all-cause mortality compared with patients without HCM having AMI (28.0% for HCM and 39.5% for non-HCM; HR, 0.66; 95% CI, 0.51–0.85; Table 4, Fig. 2B). By contrast, HCM patients with AMI had a higher mortality rate after the 1-year follow-up (33.9% for HCM and 19.3% for non-HCM, $P < 0.001$; Fig. 2B). In addition, similar results were found when the cutoff point of the landmark analysis was changed to 2 or 3 year (data not shown).

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

Discussion

Some of the highlights and important findings of this study are as follows. (1) This is the first study to directly compare the outcomes of HCM and non-HCM patients with AMI by using propensity score matching. (2) HCM patients with AMI had significantly lower rates of PCI, PCI with stenting, CABG, shock, and in-hospital death. Similarly, non-HCM patients with AMI had significantly higher rates of one- and three-vessel coronary artery disease (CAD). (3) All-cause mortality was significantly higher within 1 year of follow-up in non-HCM patients with AMI; however, this was reversed after 1 year until the end of the follow-up, possibly reflecting the high disease burden of HCM.

Relevant studies

The number of published papers regarding investigations of AMI in patients with HCM is limited. Two major studies have specifically addressed this knowledge gap

and enhanced our understanding of the supposedly ischemia-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 that had underlying HCM with incident AMI from 1997 to 2014.[7] Furthermore, they enrolled age-, sex-, and admission date-matched non-HCM patients with incident AMI in 1:1 ratio as controls. The findings indicated that HCM patients had less optimistic long-term outcome than did matched non-HCM patients. A Kaplan–Meier survival curve showed poorer outcomes for AMI patients with HCM after 1 year than for those without HCM.[7]

In a large population-based study conducted in the United States, discharge data of 5,901,827 patients with AMI during 2003–2011 were studied for the outcomes of those with HCM (5,688 patients, 0.1%) and those without HCM.[8] Patients with HCM were of elder age, higher percentage of female, and had less traditional cardiovascular risk factors. They were more likely to present with non-ST-elevation myocardial infarction (NSTEMI) but less likely ST-elevation myocardial infarction (STEMI). In addition, HCM patients had less cardiac catheterization for NSTEMI and STEMI.[8] Since these HCM patients with AMI had less traditional cardiovascular risk factors compared with non-HCM patients with AMI, the authors postulated that these AMIs were probably caused by non-atherosclerotic mechanisms, such as microvascular dysfunction. Without propensity score matching, the authors concluded that there was no difference in the observed in-hospital mortality between HCM patients with AMI and non-HCM patients with AMI.[8]

Present study

During the 15 years from 1997 to 2011, 201,166 patients were admitted for AMI in Taiwan, and 257 of those patients had coexisting HCM (0.13%). This prevalence was similar to that reported in a previous US study (0.10%).[8] When comparing our two study groups, we found that AMI in patients with HCM occurred at a significantly older age (70.1 ± 12.4 vs. 67.3 ± 14.0 years), and these patients were more likely to be female (51.4% vs. 30.8%) and less likely to have traditional cardiovascular risk factors such as DM (26.5% vs. 34.7%) and hyperlipidemia (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 toward lower rates of intubation and temporary hemodialysis 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 (Supplementary Table 2) and were not significant when using multivariable regression adjustment (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.[1] 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 earlier reported 34% beta-blocker use after AMI in a review of ≥200,000 patient records in the Cooperative Cardiovascular Project,[12] but lower than the reported 88%–92% beta-blocker use in a more recent study involving HCM patients

with AMI.[7] This result was reproduced in sensitivity analysis I (Supplementary Table 2) but not in sensitivity analysis II (Supplementary Table 5).

Our study's crucial findings were that HCM patients with AMI had significantly lower rates of PCI, intervened vessels, PCI with stenting, CABG, shock, and in-hospital death (Table 3) than did HCM patients without AMI. Patients with HCM had a higher rate of AMI in vessels requiring no coronary stenting than did patients without HCM (82.5% vs. 68.4%). HCM patients with AMI had significantly lower rates of one- and three-vessel CAD disease compared with non-HCM patients with AMI (13.2% vs. 23.5%, $P < 0.001$ and 0.4% vs 2.8%, $P = 0.034$). In addition, HCM patients with AMI had approximately half the rate of in-hospital mortality compared with non-HCM patients with AMI, yet the ICU and overall lengths of stay did not differ significantly between the groups. Both sensitivity analysis I and II generated similar results as the primary analysis (Supplementary Table 3 and 6). Similarly, the cumulative incidence of all-cause mortality was significantly higher in AMI patients without HCM within 1 year of follow-up (Fig. 2) and this result was replicated in our sensitivity analyses (Supplementary Table 4 and 7). Subsequently, the trend reversed after 1 year until the end of follow-up, suggesting coronary ischemia leading to myocardial infarction was not the cause of long-term mortality in patients with HCM.

In summary, AMI patients with HCM were significantly less likely to have coronary obstruction as well as receive PCI/CABG, shock, and in-hospital mortality, compared with AMI 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, using ICD-9-CM codes for patient screening may result in missing cases for conditions not coded correctly. 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 incidences and rates of those HCM patients studied for AMI may not include those who died either due to severe ventricular arrhythmia or had sudden death, causing selection bias. Fourth, the claims-based NHIRD does not provide additional information on examination report details such as laboratory, electrocardiographic, echocardiographic, or angiographic data. However, the NHIRD has data on PCI performed, number of intervened vessels, and number of stents placed. Last, because our study population was comprised of patients with uniform ethnic background, application of the results to other populations requires interpretation within proper contexts.

Conclusions

This is the first study to directly compare the clinical outcomes of AMI patients with HCM and AMI patients without HCM using propensity score matching. AMI patients with HCM had significantly better outcomes than did AMI patients without HCM during the in-hospital course and within 1-year follow-up. However, patients with HCM still had worse long-term outcomes.

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Contributorship

VCW, THC, and MW contributed to the study's conception and design.

VCW and THC acquired the data.

SWC, CHC, CWC, CCC, KPW, MJH, CYW, and SHC contributed to the analysis and interpretation of data.

VCW, THC, and MW drafted the manuscript.

FCL, ICH, PHC, and MSW contributed to critical revision.

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Disclosures

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Data Sharing Statement

No additional data available.

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Figure Legends

Figure 1

Study design and flow chart for 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.

Figure 2

Kaplan–Meier survival analysis of AMI patients with and without HCM for the entire follow-up period (A). Because the observed group difference (slope) achieved the maximum at year 1–2 in Kaplan–Meier curves, using 1-year as the cutoff point of landmark analysis, the Kaplan–Meier survival graph is presented with a vertical dotted line separating the follow-up to within and beyond 1 year (B).

Table 1. Baseline characteristics and comorbidities during the index admission before and after matching

	Before matching			After matching	
Variable	HCM (n = 257)	Non-HCM (n = 176,801)	P value	Non-HCM (n = 1,028)	P value
Clinical variables					
Age	70.1±12.4	67.3±14.0	0.001*	69.9±14.5	0.834
Gender (male)	125 (48.6)	122,422 (69.2)	<0.001*	481 (46.8)	0.595
Comorbidities					
Hypertension	176 (68.5)	90,160 (51.0)	<0.001*	704 (68.5)	1.000
Hyperlipidemia	51 (19.8)	40,020 (22.6)	0.285	204 (19.8)	1.000
Diabetes mellitus	68 (26.5)	61,284 (34.7)	0.007*	275 (26.8)	0.925
Heart failure	81 (31.5)	13,797 (7.8)	<0.001*	315 (30.6)	0.786
Cerebrovascular accident	51 (19.8)	23,218 (13.1)	0.001*	222 (21.6)	0.539
Chronic kidney disease	18 (7.0)	6,255 (3.5)	0.003*	78 (7.6)	0.750
Carotid artery disease	77 (30.0)	16,982 (9.6)	<0.001*	309 (30.1)	0.976
Peripheral artery disease	18 (7.0)	7,878 (4.5)	0.048*	75 (7.3)	0.872
Atrial fibrillation/atrial flutter	48 (18.7)	6,568 (3.7)	<0.001*	189 (18.4)	0.914
Chronic obstructive pulmonary disease	70 (27.2)	27,659 (15.6)	<0.001*	283 (27.5)	0.925
Peptic ulcer disease	57 (22.2)	20,022 (11.3)	<0.001*	221 (21.5)	0.813
Liver cirrhosis	12 (4.7)	3,360 (1.9)	0.001*	47 (4.6)	0.947
Malignancy	19 (7.4)	10,986 (6.2)	0.434	76 (7.4)	1.000
Gout	24 (9.3)	12,310 (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

* Denotes $P < 0.05$.

Table 2. Intervention and medication during the index admission

Variable	HCM (n = 257)	Non-HCM (n = 1,028)	P value
Intervention			
Intubation	41 (16.0)	217 (21.1)	0.065
Intraaortic balloon pump	4 (1.6)	65 (6.3)	0.002*
Extracorporeal membrane oxygenation	1 (0.4)	5 (0.5)	0.838
Temporary hemodialysis	5 (1.9)	46 (4.5)	0.063
Cardiac rehabilitation	8 (3.1)	50 (4.9)	0.227
Medications during admission			
Aspirin	196 (76.3)	757 (73.6)	0.390
Clopidogrel	120 (46.7)	519 (50.5)	0.277
ACEI/ARB	141 (54.9)	549 (53.4)	0.675
Beta blocker	135 (52.5)	443 (43.1)	0.007*
Calcium channel blocker	70 (27.2)	236 (23.0)	0.150
Diuretics	80 (31.1)	334 (32.5)	0.676
Spironolactone	19 (7.4)	87 (8.5)	0.577
Nitrates	51 (19.8)	219 (21.3)	0.608
Warfarin	18 (7.0)	49 (4.8)	0.149
Statin	49 (19.1)	237 (23.1)	0.169
Proton pump inhibitor	30 (11.7)	102 (9.9)	0.408

* Denotes $P < 0.05$.
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 3. Clinical course during hospitalization

Variable	HCM (n = 257)	Non-HCM (n = 1,028)	HCM *vs*. Non-HCM	
			OR / *B* (95% CI)	*P* value
PCI	45 (17.5)	325 (31.6)	0.46 (0.32, 0.65)	<0.001*
Number of intervened vessels				
0 vessel	212 (82.5)	703 (68.4)	Reference	–
1 vessel	34 (13.2)	242 (23.5)	0.47 (0.32, 0.69)	<0.001*
2 vessels	10 (3.9)	54 (5.3)	0.61 (0.31, 1.23)	0.167
3 vessels	1 (0.4)	29 (2.8)	0.11 (0.02, 0.84)	0.034*
PCI with stenting	16 (6.2)	171 (16.6)	0.33 (0.20, 0.57)	<0.001*
CABG	2 (0.8)	36 (3.5)	0.22 (0.05, 0.90)	0.036*
Valvular surgery	3 (1.2)	3 (0.3)	4.04 (0.81, 20.11)	0.089
Pacing device implantation†	7 (2.7)	3 (0.3)	9.57 (2.46, 37.26)	0.001*
New onset of atrial fibrillation	35 (13.6)	48 (4.7)	3.22 (2.03, 5.10)	<0.001*
New onset of VTE	16 (6.2)	47 (4.6)	1.39 (0.77, 2.49)	0.274
Shock	75 (29.2)	402 (39.1)	0.64 (0.48, 0.86)	0.003*
In-hospital death	28 (10.9)	217 (21.1)	0.46 (0.30, 0.70)	<0.001*
ICU days	4.4±7.2	4.6±7.3	-0.21 (-1.20, 0.78)	0.677
Length of stay	13.7±25.1	12.3±20.6	1.39 (-1.56, 4.35)	0.355

* Denotes $P < 0.05$.

B, regression coefficient; CABG, coronary artery bypass graft; CI, confidence interval; ICU, intensive care unit; OR, odds ratio; PCI, percutaneous coronary intervention; VTE, venous thromboembolism.

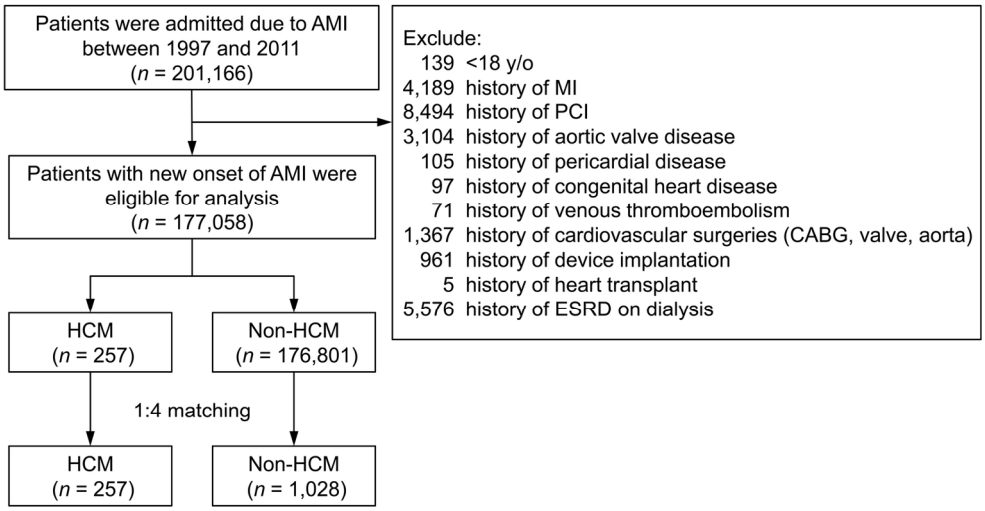
† Includes pacemaker and implantable cardioverter defibrillator.

Table 4. Outcome during the follow up

Variable	HCM (n = 257)	Non-HCM (n = 1,028)	HCM *vs*. Non-HCM HR (95% CI)	*P* value
1 year follow up				
Recurrent AMI	13 (5.1)	70 (6.8)	0.68 (0.37, 1.25)	0.214
HF hospitalization	17 (6.6)	66 (6.4)	1.02 (0.60, 1.74)	0.941
Systemic VTE	23 (8.9)	64 (6.2)	1.55 (0.75, 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, 0.85)	0.001*
CV death	46 (17.9)	211 (20.5)	0.83 (0.60, 1.14)	0.252
At the end of follow up				
Recurrent AMI	23 (8.9)	109 (10.6)	0.79 (0.50, 1.24)	0.299
HF hospitalization	35 (13.6)	112 (10.9)	1.24 (0.85, 1.80)	0.266
Systemic VTE	39 (15.2)	107 (10.4)	1.52 (0.97, 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, 1.16)	0.732
CV death	62 (24.1)	262 (25.5)	0.89 (0.67, 1.17)	0.401

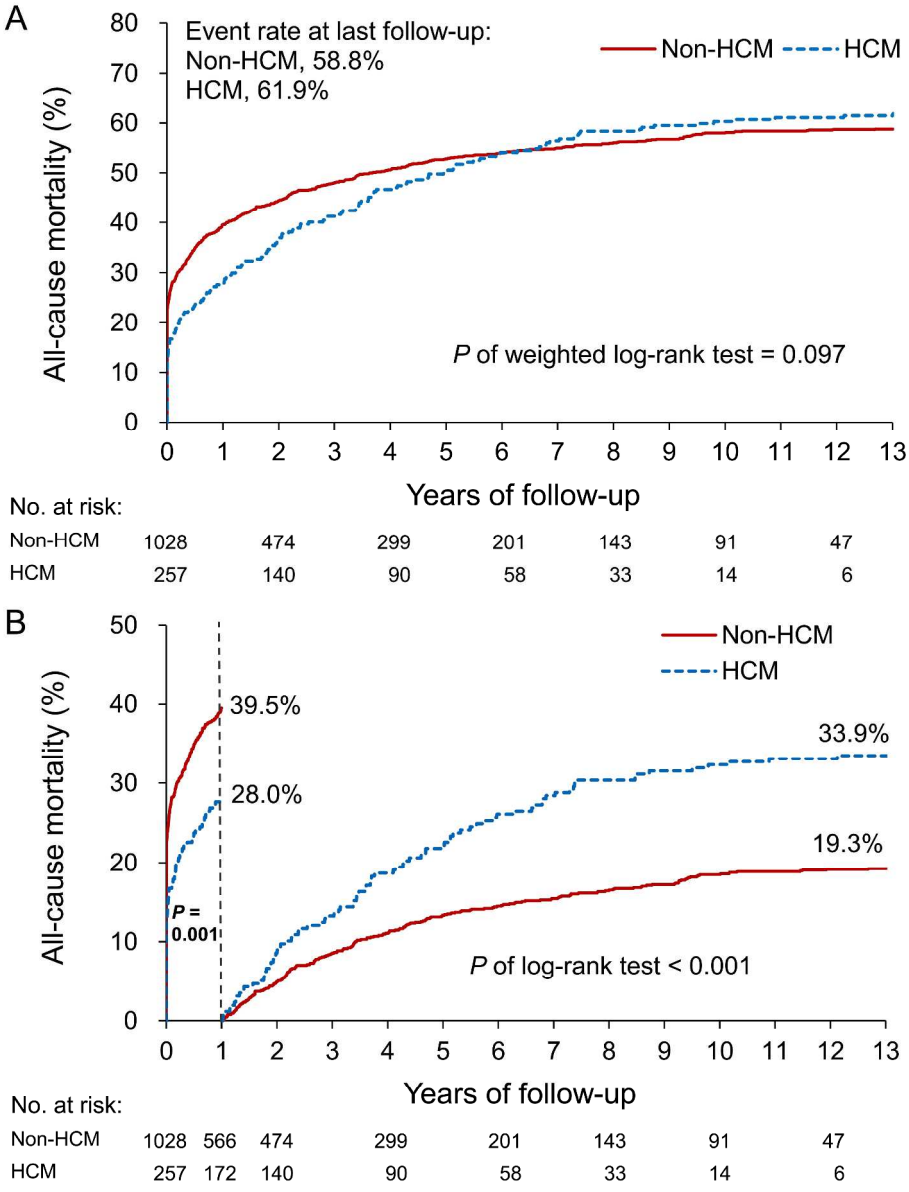
* Denoted $P < 0.05$.
AMI, acute myocardial infarction; HR, hazard ratio; CI, confidence interval; CV, cardiovascular; HF, heart failure; VTE, venous thromboembolism; NA = not applicable.

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



Study design and flow chart for 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.

78x41mm (600 x 600 DPI)



Kaplan–Meier survival analysis of AMI patients with and without HCM for the entire follow-up period (A). Because the observed group difference (slope) achieved the maximum at year 1–2 in Kaplan–Meier curves, using 1-year as the cutoff point of landmark analysis, the Kaplan–Meier survival graph is presented with a vertical dotted line separating the follow-up to within and beyond 1 year (B).

343x449mm (300 x 300 DPI)

Supplementary Table 1. ICD-9-CM code used in the current study

Variable	Code
Acute myocardial infarction	410.xx
Aortic valve disease	424.1
Pericardial disease	423.xx
Congenital heart disease	745.xx–747.xx (Catastrophic illness card)
Venous thromboembolism	415.1x, 453.xx
Dialysis	585.xx (Catastrophic illness card)
Hypertrophic cardiomyopathy	425.1x
Hypertension	401.xx–405.xx
Hyperlipidemia	272.xx
Diabetes mellitus	250.xx
Heart failure	428.xx
Stroke	430.xx–437.xx
Chronic kidney disease	580.xx–589.xx, 403.xx–404.xx, 016.0x, 095.4x, 236.9x, 250.4x, 274.1x, 442.1x, 447.3x, 440.1x, 572.4x, 642.1x, 646.2x, 753.1x, 283.11, 403.01, 404.02, 446.21
Carotid artery disease	433.1x
Peripheral artery disease	440.0x, 440.2x, 440.3x, 440.8x, 440.9x, 443.xx, 444.0x, 444.22, 444.8x, 447.8x, 447.9x
Atrial fibrillation/atrial flutter	427.31, 427.32
Chronic obstructive pulmonary disease	491.xx, 492.xx, 496.xx
Peptic ulcer disease	531.xx–534.xx
Liver cirrhosis	571.2x, 571.5x, 571.6x
Malignancy	140.xx–208.xx
Gout	274.xx
Atrial fibrillation	427.31
Systemic thromboembolism	444.22, 444.81, 444.21, 557.0, 557.9, 557.1, 593.81, 444.89, 433.8, 444.9x, 415.1x, 433.xx, 434.xx, 435.xx, 436.xx, 437.xx

Supplementary Table 2. Intervention and medication during the index admission after propensity score matching without matching the index date (sensitivity analysis I)

Variable	HCM (n = 257)	Non-HCM (n = 1,028)	P value#
Intervention			
Intubation	41 (16.0)	247 (24.0)	0.005*
Intraaortic balloon pump	4 (1.6)	65 (6.3)	0.002*
Extracorporeal membrane oxygenation	1 (0.4)	11 (1.1)	0.310
Temporary hemodialysis	5 (1.9)	44 (4.3)	0.080
Cardiac rehabilitation	8 (3.1)	46 (4.5)	0.330
Medications during admission			
Aspirin	196 (76.3)	761 (74.0)	0.462
Clopidogrel	120 (46.7)	528 (51.4)	0.181
ACEI/ARB	141 (54.9)	582 (56.6)	0.613
Beta blocker	135 (52.5)	454 (44.2)	0.016*
Calcium channel blocker	70 (27.2)	225 (21.9)	0.068
Diuretics	80 (31.1)	330 (32.1)	0.765
Spironolactone	19 (7.4)	92 (8.9)	0.427
Nitrates	51 (19.8)	228 (22.2)	0.417
Warfarin	18 (7.0)	52 (5.1)	0.219
Statin	49 (19.1)	223 (21.7)	0.357
Proton pump inhibitor	30 (11.7)	118 (11.5)	0.930

* Denotes $P < 0.05$.
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Adjusted for year of index admission.

Supplementary Table 3. In-hospital cardiovascular outcome after propensity score matching without matching the index date (sensitivity analysis I)

Variable	HCM (n = 257)	Non-HCM (n = 1,028)	HCM *vs*. Non-HCM#	
			OR / *B* (95% CI)	*P* value
PCI	45 (17.5)	311 (30.3)	0.49 (0.34, 0.70)	<0.001*
Number of intervened vessels				
0 vessel	212 (82.5)	717 (69.7)	Reference	–
1 vessel	34 (13.2)	226 (22.0)	0.51 (0.34, 0.76)	<0.001*
2 vessels	10 (3.9)	57 (5.5)	0.60 (0.30, 1.20)	0.146
3 vessels	1 (0.4)	28 (2.7)	0.12 (0.02, 0.86)	0.035*
PCI with stenting	16 (6.2)	181 (17.6)	0.30 (0.17, 0.51)	<0.001*
CABG	2 (0.8)	31 (3.0)	0.26 (0.06, 1.10)	0.067
Valvular surgery	3 (1.2)	6 (0.6)	2.06 (0.50, 8.49)	0.315
Pacing device implantation†	7 (2.7)	3 (0.3)	9.68 (2.43, 38.47)	0.001*
New onset of atrial fibrillation	35 (13.6)	32 (3.1)	5.15 (3.09, 8.57)	<0.001*
New onset of VTE	16 (6.2)	55 (5.4)	1.28 (0.72, 2.29)	0.405
Shock	75 (29.2)	433 (42.1)	0.58 (0.43, 0.78)	<0.001*
In-hospital death	28 (10.9)	223 (21.7)	0.44 (0.29, 0.67)	<0.001*
ICU days	4.4±7.2	4.6±7.8	-0.24 (-1.29, 0.81)	0.824
Length of stay	13.7±25.1	12.9±20.1	0.78 (-2.11, 3.68)	0.550

* Denotes $P < 0.05$.
B, regression coefficient; CABG, coronary artery bypass graft; CI, confidence interval; ICU, intensive care unit; OR, odds ratio; PCI, percutaneous coronary intervention; VTE, venous thromboembolism.
† Includes pacemaker and implantable cardioverter defibrillator.

Adjusted for year of index admission.

Supplementary Table 4. Outcome during the follow up after propensity score matching without matching the index date (sensitivity analysis I)

Variable	HCM (n = 257)	Non-HCM (n = 1,028)	HCM *vs*. Non-HCM#	
			HR (95% CI)	*P* value
1 year follow up				
Recurrent AMI	13 (5.1)	69 (6.7)	0.70 (0.38, 1.28)	0.249
HF hospitalization	17 (6.6)	61 (5.9)	1.10 (0.65, 1.88)	0.717
Systemic VTE	23 (8.9)	63 (6.1)	2.62 (1.06, 6.48)	0.036*
Heart transplant	0 (0.0)	0 (0.0)	NA	NA
All-cause mortality	72 (28.0)	407 (39.6)	0.59 (0.46, 0.76)	<0.001*
CV death	46 (17.9)	217 (21.1)	0.74 (0.54, 1.02)	0.067
At the end of follow up				
Recurrent AMI	23 (8.9)	100 (9.7)	0.86 (0.54, 1.37)	0.528
HF hospitalization	35 (13.6)	101 (9.8)	1.41 (0.96, 2.07)	0.083
Systemic VTE	39 (15.2)	108 (10.5)	1.77 (1.09, 2.88)	0.022*
Heart transplant	0 (0.0)	0 (0.0)	NA	NA
All-cause mortality	159 (61.9)	604 (58.8)	0.82 (0.69, 0.98)	0.031*
CV death	62 (24.1)	246 (23.9)	0.84 (0.63, 1.11)	0.220

* Denoted $P < 0.05$.
AMI, acute myocardial infarction; HR, hazard ratio; CI, confidence interval; CV, cardiovascular; HF, heart failure; VTE, venous thromboembolism; NA = not applicable.

#Additional adjusted for percutaneous coronary intervention, coronary artery bypass graft and pacing device during the index admission and the index year.

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

Supplementary Table 5. Intervention and medication during the index admission using multivariable regression adjustment (sensitivity analysis II)#

Variable	HCM (n = 257)	Non-HCM (n = 176,801)	P value
Intervention			
Intubation	41 (16.0)	34,182 (19.3)	0.170
Intraaortic balloon pump	4 (1.6)	11,882 (6.7)	0.001*
Extracorporeal membrane oxygenation	1 (0.4)	932 (0.5)	0.760
Temporary hemodialysis	5 (1.9)	5,877 (3.3)	0.218
Cardiac rehabilitation	8 (3.1)	8,076 (4.6)	0.264
Medications during admission			
Aspirin	196 (76.3)	139,396 (78.8)	0.312
Clopidogrel	120 (46.7)	98,802 (55.9)	0.003*
ACEI/ARB	141 (54.9)	106,910 (60.5)	0.066
Beta blocker	135 (52.5)	87,549 (49.5)	0.335
Calcium channel blocker	70 (27.2)	35,653 (20.2)	0.005*
Diuretics	80 (31.1)	48,383 (27.4)	0.176
Spironolactone	19 (7.4)	13,274 (7.5)	0.944
Nitrates	51 (19.8)	41,146 (23.3)	0.194
Warfarin	18 (7.0)	6,388 (3.6)	0.004*
Statin	49 (19.1)	50,907 (28.8)	0.001*
Proton pump inhibitor	30 (11.7)	14,352 (8.1)	0.037*

* Denotes $P < 0.05$.
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Adjusted for sex, gender and 14 comorbidities listed in Table 1.

Supplementary Table 6. In-hospital cardiovascular outcome using multivariable regression adjustment (sensitivity analysis II)#

Variable	HCM (n = 257)	Non-HCM (n = 176,801)	HCM *vs*. Non-HCM OR / *B* (95% CI)	*P* value
PCI	45 (17.5)	73,391 (41.5)	0.44 (0.31, 0.61)	<0.001*
Number of intervened vessels				
0 vessel	212 (82.5)	103,410 (58.5)	Reference	–
1 vessel	34 (13.2)	55,066 (31.1)	0.45 (0.31, 0.66)	<0.001*
2 vessels	10 (3.9)	11,924 (6.7)	0.57 (0.30, 1.08)	0.085
3 vessels	1 (0.4)	6,401 (3.6)	0.11 (0.02, 0.77)	0.026*
PCI with stenting	16 (6.2)	39,233 (22.2)	0.31 (0.18, 0.53)	<0.001*
CABG	2 (0.8)	6,759 (3.8)	0.25 (0.06, 1.002)	0.0503
Valvular surgery	3 (1.2)	756 (0.4)	2.12 (0.67, 6.69)	0.200
Pacing device implantation†	7 (2.7)	549 (0.3)	8.04 (3.73, 17.31)	<0.001*
New onset of atrial fibrillation	35 (13.6)	6,543 (3.7)	4.57 (3.15, 6.63)	<0.001*
New onset of VTE	16 (6.2)	7,242 (4.1)	1.50 (0.89, 2.52)	0.127
Shock	75 (29.2)	63,077 (35.7)	0.64 (0.49, 0.85)	0.002*
In-hospital death	28 (10.9)	29,396 (16.6)	0.46 (0.30, 0.69)	<0.001*
ICU days	4.4±7.2	4.4±7.1	0.04 (-0.81, 0.89)	0.595
Length of stay	13.7±25.1	11.1±17.3	2.66 (0.60, 4.72)	0.360

* Denotes $P < 0.05$.
B, regression coefficient; CABG, coronary artery bypass graft; CI, confidence interval; ICU, intensive care unit; OR, odds ratio; PCI, percutaneous coronary intervention; VTE, venous thromboembolism.
† Includes pacemaker and implantable cardioverter defibrillator.
# Adjusted for sex, gender and 14 comorbidities listed in Table 1.

Supplementary Table 7. Outcome during the follow up using multivariable regression adjustment (sensitivity analysis II)#

Variable	HCM (*n* = 257)	Non-HCM (*n* = 176,801)	HCM *vs*. Non-HCM	
			HR (95% CI)	*P* value
1 year follow up				
Recurrent AMI	13 (5.1)	13,774 (7.8)	0.68 (0.38, 1.19)	0.174
HF hospitalization	17 (6.6)	7,790 (4.4)	0.98 (0.60, 1.60)	0.946
Systemic VTE	23 (8.9)	9,496 (5.4)	2.08 (1.12, 3.86)	0.021*
Heart transplant	0 (0.0)	89 (0.1)	NA	NA
All-cause mortality	72 (28.0)	54,007 (30.5)	0.69 (0.55, 0.87)	0.002*
CV death	46 (17.9)	29,667 (16.8)	0.85 (0.64, 1.14)	0.284
At the end of follow up				
Recurrent AMI	23 (8.9)	20,316 (11.5)	0.85 (0.56, 1.28)	0.429
HF hospitalization	35 (13.6)	15,708 (8.9)	1.16 (0.82, 1.62)	0.405
Systemic VTE	39 (15.2)	18,155 (10.3)	1.67 (1.13, 2.47)	0.010*
Heart transplant	0 (0.0)	188 (0.1)	NA	NA
All-cause mortality	159 (61.9)	88,884 (50.3)	0.93 (0.79, 1.08)	0.338
CV death	62 (24.1)	36,481 (20.6)	0.93 (0.72, 1.19)	0.539

* Denoted $P < 0.05$.
AMI, acute myocardial infarction; HR, hazard ratio; CI, confidence interval; CV, cardiovascular; HF, heart failure; VTE, venous thromboembolism; NA = not applicable.

The analysis considers death as a competing risk except for all-cause mortality and CV death.
Adjusted for sex, gender and 14 comorbidities listed in Table 1.

Supplementary Table 8. Outcome during the follow up after propensity score matching using classical Cox proportional hazard model (sensitivity analysis III)

Variable	HCM (*n* = 257)	Non-HCM (*n* = 1,028)	HCM *vs*. Non-HCM HR (95% CI)	HCM *vs*. Non-HCM *P* value
1 year follow up				
Recurrent AMI	13 (5.1)	70 (6.8)	0.63 (0.34, 1.16)	0.136
HF hospitalization	17 (6.6)	66 (6.4)	0.88 (0.52, 1.50)	0.643
Systemic VTE	23 (8.9)	64 (6.2)	1.31 (0.63, 2.71)	0.473
Heart transplant	0 (0.0)	1 (0.1)	NA	NA
All-cause mortality	72 (28.0)	406 (39.5)	0.66 (0.51, 0.85)	0.001*
CV death	46 (17.9)	211 (20.5)	0.83 (0.60, 1.14)	0.252
At the end of follow up				
Recurrent AMI	23 (8.9)	109 (10.6)	0.72 (0.46, 1.14)	0.165
HF hospitalization	35 (13.6)	112 (10.9)	1.10 (0.76, 1.62)	0.609
Systemic VTE	39 (15.2)	107 (10.4)	1.38 (0.88, 2.17)	0.162
Heart transplant	0 (0.0)	1 (0.1)	NA	NA
All-cause mortality	159 (61.9)	604 (58.8)	0.97 (0.81, 1.16)	0.732
CV death	62 (24.1)	262 (25.5)	0.89 (0.67, 1.17)	0.401

* Denoted $P < 0.05$.

AMI, acute myocardial infarction; HR, hazard ratio; CI, confidence interval; CV, cardiovascular; HF, heart failure; VTE, venous thromboembolism; NA = not applicable.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 6
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 6,7
Methods			
Study design	4	Present key elements of study design early in the paper	Page 7,8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 7,8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 7,8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Page 7,8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 7,8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 7,8
Bias	9	Describe any efforts to address potential sources of bias	Page 16
Study size	10	Explain how the study size was arrived at	Page 11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 7,8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 9,10
		(*b*) Describe any methods used to examine subgroups and interactions	n/a
		(*c*) Explain how missing data were addressed	n/a
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 11
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1,2
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount)	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 3,4

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 4
		(*b*) Report category boundaries when continuous variables were categorized	Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page 9,10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 16,17
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 16,17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 18

*Give information separately for exposed and unexposed groups.

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

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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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Keywords:	hypertrophic cardiomyopathy, acute myocardial infarction, outcome

Outcomes of Patients with Hypertrophic Cardiomyopathy and Acute Myocardial Infarction: A Propensity Score-Matched 15-Year Nationwide Population-Based Study in Asia

Victor Chien-Chia Wu, MD[1*], Tien-Hsing Chen, MD[2*], Michael Wu, MD[3], Shao-Wei Chen, MD[4], Chih-Hsiang Chang, MD[5], Chun-Wei Chang, MD[6], Ching-Chang Chen, MD[7], Katie Pei-Hsuan Wu, MD[8], Ming-Jer Hsieh, MD[1], Chao-Yung Wang, MD[1], Shang-Hung Chang, MD[1], Fen-Chiung Lin, MD[1], I-Chang Hsieh, MD[1], Pao-Hsien Chu, MD[1], Ming-Shien Wen, MD[1]

[1]Division of Cardiology, Chang Gung Memorial Hospital, Linkou Medical Center, Taoyuan City, Taiwan

[2]Department of Cardiology, Chang Gung Memorial Hospital, Keelung, Taiwan

[3]Divison of Cardiovascular Medicine, Miriam and Rhode Island Hospital, Warren Alpert School of Medicine, Brown University, Rhode Island, USA

[4]Department of Cardiothoracic and Vascular Surgery, [5]Department of Nephrology, [6]Department of Neurology, [7]Department of Neurosurgery, [8]Department of Physical Medicine and Rehabilitation, Chang Gung Memorial Hospital, Linkou Medical Center, Taoyuan City, Taiwan

Brief title: Outcomes of HCM Patients with AMI

*Authors contributed equally.

All authors have nothing to disclose

Address for correspondence:

Victor Chien-Chia Wu, MD, FESC

Department of Cardiology, Chang Gung Memorial Hospital, No. 5, Fuxing Street, Guishan District, Taoyuan City 33305, Taiwan

Tel: +886-3-3281200 x8115; fax: + 886-3-3281451

E-mail: victorcwu@hotmail.com

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

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

Results: In total, 201,166 patients were admitted for AMI. There were 177,058 new-onset AMI patients with 257 HCM and 176,801 without HCM after exclusion criteria. Using 1:4 PS matching, the study population consisted of AMI patients with 257 HCM and 1,028 without HCM. AMI patients with HC received significantly less coronary intervention (odds ratio [OR]=0.46; 95% confidence interval [CI]=0.32–0.65; *P* <0.001), coronary intervention with stenting (OR=0.33; 95% CI=0.20–0.57; *P* <0.001), and coronary artery bypass graft surgery (OR=0.22; 95% CI=0.05–0.90; *P*=0.036), fewer episodes of shock (OR,=0.64; 95% CI=0.48–0.86; *P*=0.003) and in-hospital death (OR=0.46; 95% CI=0.30–0.70; *P* <0.001) compared with AMI patients without HCM. Specifically, for HCM patients with AMI, AMI occurred predominantly (82.5%) in the form of ischemia without requiring coronary stenting. AMI patients with HCM had significantly better survival than AMI patients without HCM (hazard ratio=0.66; 95% CI=0.51–0.85; *P*=0.001) during the 1-year follow-up.

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

Keywords: hypertrophic cardiomyopathy, acute myocardial infarction, outcome

Strengths and limitations of this study

- The prognosis of AMI in patients with HCM and without HCM through is compared propensity score matching.
- The clinical differences of AMI patients with HCM and without HCM were demonstrated by the percentage of patients who underwent PCI, 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 program provides uniform health care services to 99.5% of the population without financial restraints or selection bias; however, the data utilized for this study are old (1997-2011).
- The use of ICD-9-CM codes for study may occasionally resulted in missing cases if conditions were not coded correctly, however patients with AMI and HCM have definitive ICD codes 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 incidences and rates of those HCM patients studied for AMI may not include those who died due to severe ventricular arrhythmia or had sudden death.

Introduction

Thickened myocardium that cannot be entirely attributed to the 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 phase, the hypercontractile myocardium may obliterate the 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.[3]

Patients with HCM are considered to have a substantial cardiovascular risk, however they tend to have less clear symptoms thus evading the diagnosis of ischemia.[4,5] In a study that described the clinical characteristics and prognosis of HCM, approximately 1/3 of patients with HCM had adverse cardiovascular outcomes without concomitant increased acute myocardial infarction (AMI) mortality rate.[6] A prospective study reported AMI in HCM patients had worse outcome compared to AMI patients without HCM.[7] A large US population study noted that HCM patients presented with AMI at a later age, and these patients had received less cardiac catheterization compared with non-HCM patients with AMI.[8] Furthermore, HCM may progress to heart failure (HF) because of dynamic LV outflow obstruction, LV diastolic dysfunction, atrial fibrillation with subsequent risk of ischemic 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 HCM 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) program was established in 1995, enrolling >99% of the island's 23.5 million people. The NHI Research Database (NHIRD) stored all data of 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 consisted of greater than 95% of Han Chinese, the study is conducted within a nearly homogenous ethnicity. The Institutional Review Board of our hospital, Chang Gung Memorial Hospital, Linkou Medical Center, approved this study.

By retrieving medical information from NHIRD during 1997-2011, all patients admitted for AMI were identified. In this study, AMI was referenced to the Third Universal Definition: an elevated of myocardial biomarkers with at least 1 value >99%-tile and at least 1 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.[9] 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 medication and mechanical support. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 425.1 (as in Supplementary Table 1) was used to identify patients with HCM and was used previously in a large US population study.[8] We excluded patients <18 years old, history of AMI, coronary intervention, disease of aortic valve, disease of 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 ACCF/AHA Guideline, HCM is diagnosed when unexplained thickening of LV myocardium was found not attributed to concurrent cardiac or systemic disease.[10] In addition, the 2014 ESC Guideline simply defined HCM as increased LV myocardial thickness unrelated to excessive loading.[11] In clinical practice, HCM is identified when LV wall thickness exceeds 15 mm, or 13-14 mm (when family history is considered) on echocardiography.[10]

Covariate and study outcomes

To effectively compare two groups of patients whose clinical presentations may be affected by comorbidities, we matched patients with HCM to patients without HCM by using propensity scores. 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), hyperlipidemia, diabetes mellitus (DM), HF, cerebrovascular accident, chronic kidney disease (creatinine clearance <60 mL/min/1.73 m^2), 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 neighbor algorithm, and a caliper width was set at 0.2.

The medical records of the NHIRD listed the primary diagnoses of patients during admission. Cardiovascular death previously defined by the Food and Drug

Administration.[12] Death was identified as the patient is withdrawn from the NHI program.[13] Causes of death were attributed to be the primary discharge diagnoses in the preceding 3 months before death.[13] 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 via *t* test for continuous variables and chi-square test for categorical variables. In-hospital events (e.g., in-hospital death) were compared by logistic regression analysis and continuous outcomes (e.g., length of stay) were compared by 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.[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.

Since there was a crossing between HCM and non-HCM all-cause mortality survival curves, inverse probability of treatment weighting with log-rank test were used to compare the study groups.[15] Therefore, a landmark analysis of all-cause mortality by 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 9.4, SAS Institute, Cary, NC). All tests were 2-tailed, and statistics was considered significant when $P < 0.05$.

Sensitivity analysis

There were three sensitivity analyses performed additionally to assess the robustness of findings and increase the generalizability 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 (Supplementary Tables 2–3). Furthermore, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), and pacing device during the index admission and index year was adjusted in the analysis of survival outcomes (Supplementary Table 4). Second, the sample size of the propensity score-matched cohort was notably small, which may limit the external generalizability of findings. Using the whole cohort, we performed a traditional multivariable regression adjusting age, sex, and the 14 comorbidities from Table 1 (Supplementary Tables 5-7). Third, we performed the classic Cox proportional hazards model rather than the competing risk model in survival analyses (Supplementary Table 8).

Patient and public involvement

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

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 AMI patients were separated into those with HCM and those without HCM. The 257 AMI patients with HCM and 176,801 AMI patients without HCM were 1:4 propensity score matched, the final

study population consisted of 257 AMI patients with HCM and 1,028 AMI 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 of AMI patients with HCM and AMI patients without HCM during index admission. In terms of intervention, AMI patients with HCM had significantly less intra-aortic balloon bump (IABP, $P = 0.002$) placed and had trends toward less intubation ($P = 0.065$) and receive temporary hemodialysis ($P = 0.063$). In terms of medication, AMI patients with HCM had significantly more prescription of beta-blockers ($P = 0.007$).

In-hospital outcomes

Table 3 showed the results of in-hospital cardiovascular outcomes. AMI patients with HCM had significantly less PCI (odds ratio [OR], 0.46; 95% confidence interval [CI], 0.32–0.65; $P < 0.001$), vessels intervened, PCI with stenting (OR, 0.33; 95% CI, 0.20–0.57; $P < 0.001$), CABG (OR, 0.22; 95% CI, 0.05–0.90; $P = 0.036$), shock (OR, 0.64; 95% CI, 0.48–0.86; $P = 0.003$), and die during hospitalization (OR, 0.46; 95% CI, 0.30–0.70; $P < 0.001$) compared with AMI patients without HCM. However, AMI patients with HCM had significantly more pacing device implantation (OR, 9.57; 95% CI, 2.46–37.26; $P = 0.001$) and new-onset AF (OR, 3.22; 95% CI, 2.03–5.10; $P < 0.001$).

Follow-up outcomes

Figure 2A shows the Kaplan–Meier survival curves of AMI patients with HCM and AMI patients without-HCM during the entire follow-up. The risk of all-cause mortality was similar between the two AMI patients groups (crude hazard ratio [HR], 0.97; 95% CI, 0.81–1.16). However, the two curves crossed at year 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 year 1–2; thus, we used 1-year as the cutoff point in the landmark analysis. In-hospital death was included in 1-year mortality. And during the first-year follow-up, AMI patients without HCM had significantly higher all-cause mortality compared with AMI with HCM (28.0% for HCM and 39.5% for non-HCM; HR, 0.66; 95% CI, 0.51–0.85; Table 4, Fig. 2B). By contrast, AMI patients with HCM had a higher mortality rate after the 1-year follow-up (33.9% for HCM and 19.3% for non-HCM, $P < 0.001$; Fig. 2B). In addition, similar results were found when the cutoff point of the landmark analysis was changed to 2 or 3 year (data not shown).

Table 4 demonstrates the results of follow-up outcomes. No group difference was found in terms of recurrent AMI, HF hospitalization, 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 (Supplementary Table 3 and 6). Similarly, AMI patients with HCM had significantly lower all-cause mortality within 1 year of follow-up (Fig. 2), which was replicated in our sensitivity analyses (Supplementary Table 4 and 7).

Discussion

Some highlights and important findings from this study are: (1) This is the first study to compare the outcomes of AMI patients with HCM and AMI patients without HCM using propensity score matching. (2) AMI patients 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- and three-vessel coronary artery disease (CAD). (3) AMI patients 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 regarding investigations of AMI in patients with HCM is limited. Two major studies have specifically addressed this knowledge gap and enhanced our understanding of the supposedly ischemia-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 that had underlying HCM with incident AMI from 1997 to 2014.[7] Furthermore, they enrolled age-, sex-, and admission date-matched non-HCM patients with incident AMI in 1:1 ratio as controls. The findings indicated that HCM patients had less optimistic long-term outcome than did matched non-HCM patients. A Kaplan–Meier survival curve showed poorer outcomes for AMI patients with HCM after 1 year than for those without HCM.[7]

In a population study from United States, the discharge data of 5,901,827

patients with AMI during 2003–2011 were studied for the outcomes of those with HCM (5,688 patients, 0.1%) and those without HCM.[8] Patients with HCM were older, more likely to 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, HCM patients had less cardiac catheterization for AMI.[8] Since AMI patients with HCM had less traditional cardiovascular risks as opposed to with AMI 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 AMI patients with HCM and AMI patients 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 those patients had coexisting HCM (0.13%). This prevalence rate was similar to the study reported in US (0.10%).[8] Out study also showed that AMI patients with HCM were older (70.1 ± 12.4 vs. 67.3 ± 14.0 years), and these patients had higher percentage of female (51.4% vs. 30.8%) and had traditional cardiovascular risks such as DM (26.5% vs. 34.7%) and hyperlipidemia (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 toward lower rates of intubation and temporary hemodialysis 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 (Supplementary Table 2) and were not significant when using multivariable regression adjustment (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.[1] 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,[12] but lower than the reported 88%–92% beta-blocker in AMI patients with HCM recently.[7] This result was reproduced in sensitivity analysis I (Supplementary Table 2) but not in sensitivity analysis II (Supplementary Table 5).

The key findings of current study were that AMI patients with HCM had significantly less coronary interventions (including PCI, intervened vessels, coronary stenting, CABG), cardiogenic shock, and in-hospital death (Table 3) than did AMI patients without HCM. AMI patients with HCM had less number of intervened vessels whether it to be a 1 vessel, 2 vessel, or 3 vessel disease. In addition, AMI patients with HCM had approximately half the number of patients died during index hospitalization compared with AMI patients without HCM. Both sensitivity analyses I and II results were similar to the primary analysis (Supplementary Table 3 and 6). Similarly, AMI patients with HCM had significantly lower all-cause mortality within 1 year of follow-up (Fig. 2), which was replicated in our sensitivity analyses (Supplementary Table 4 and 7). Subsequently, the trend reversed after 1 year until the end of follow-up, suggesting coronary ischemia and myocardial infarction were not the reason for mortality in patients with HCM during extended follow-up.

In summary, out study showed that AMI patients with HCM had significantly less coronary obstruction as well as necessary coronary interventions, shock, in-hospital mortality, and 1-year all-cause mortality compared to AMI 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 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 incidences and rates of those HCM patients studied for AMI may not include those who died either due to severe ventricular arrhythmia or had 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, NHIRD has data on coronary intervention performed, number of intervened vessels, and number of stents placed. Last, because our study population was comprised of 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 AMI patients with HCM and AMI patients without HCM. Compared to AMI patients without HCM, AMI patients with HCM had significantly better in-hospital and within 1-year outcomes.

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Contributorship

VCW, THC, and MW contributed to the study's conception and design.

VCW and THC acquired the data.

SWC, CHC, CWC, CCC, KPW, MJH, CYW, and SHC contributed to the analysis and interpretation of data.

VCW, THC, and MW drafted the manuscript.

FCL, ICH, PHC, and MSW contributed to critical revision.

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Disclosures

None.

Data Sharing Statement

No additional data available.

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Figure Legends

Figure 1

Study design and flow chart for 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.

Figure 2

Kaplan–Meier survival analysis of AMI patients with and without HCM for the entire follow-up period (A). Because the observed group difference (slope) achieved the maximum at year 1–2 in Kaplan–Meier curves, using 1-year as the cutoff point of landmark analysis, the Kaplan–Meier survival graph is presented with a vertical dotted line separating the follow-up to within and beyond 1 year (B).

Table 1. Baseline characteristics and comorbidities during the index admission before and after matching

	Before matching			After matching	
Variable	HCM (n = 257)	Non-HCM (n = 176,801)	P value	Non-HCM (n = 1,028)	P value
Clinical variables					
Age	70.1±12.4	67.3±14.0	0.001*	69.9±14.5	0.834
Gender (male)	125 (48.6)	122,422 (69.2)	<0.001*	481 (46.8)	0.595
Comorbidities					
Hypertension	176 (68.5)	90,160 (51.0)	<0.001*	704 (68.5)	1.000
Hyperlipidemia	51 (19.8)	40,020 (22.6)	0.285	204 (19.8)	1.000
Diabetes mellitus	68 (26.5)	61,284 (34.7)	0.007*	275 (26.8)	0.925
Heart failure	81 (31.5)	13,797 (7.8)	<0.001*	315 (30.6)	0.786
Cerebrovascular accident	51 (19.8)	23,218 (13.1)	0.001*	222 (21.6)	0.539
Chronic kidney disease	18 (7.0)	6,255 (3.5)	0.003*	78 (7.6)	0.750
Carotid artery disease	77 (30.0)	16,982 (9.6)	<0.001*	309 (30.1)	0.976
Peripheral artery disease	18 (7.0)	7,878 (4.5)	0.048*	75 (7.3)	0.872
Atrial fibrillation/atrial flutter	48 (18.7)	6,568 (3.7)	<0.001*	189 (18.4)	0.914
Chronic obstructive pulmonary disease	70 (27.2)	27,659 (15.6)	<0.001*	283 (27.5)	0.925
Peptic ulcer disease	57 (22.2)	20,022 (11.3)	<0.001*	221 (21.5)	0.813
Liver cirrhosis	12 (4.7)	3,360 (1.9)	0.001*	47 (4.6)	0.947
Malignancy	19 (7.4)	10,986 (6.2)	0.434	76 (7.4)	1.000
Gout	24 (9.3)	12,310 (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

* Denotes $P < 0.05$.

Table 2. Intervention and medication during the index admission

Variable	HCM (n = 257)	Non-HCM (n = 1,028)	P value
Intervention			
Intubation	41 (16.0)	217 (21.1)	0.065
Intraaortic balloon pump	4 (1.6)	65 (6.3)	0.002*
Extracorporeal membrane oxygenation	1 (0.4)	5 (0.5)	0.838
Temporary hemodialysis	5 (1.9)	46 (4.5)	0.063
Cardiac rehabilitation	8 (3.1)	50 (4.9)	0.227
Medications during admission			
Aspirin	196 (76.3)	757 (73.6)	0.390
Clopidogrel	120 (46.7)	519 (50.5)	0.277
ACEI/ARB	141 (54.9)	549 (53.4)	0.675
Beta blocker	135 (52.5)	443 (43.1)	0.007*
Calcium channel blocker	70 (27.2)	236 (23.0)	0.150
Diuretics	80 (31.1)	334 (32.5)	0.676
Spironolactone	19 (7.4)	87 (8.5)	0.577
Nitrates	51 (19.8)	219 (21.3)	0.608
Warfarin	18 (7.0)	49 (4.8)	0.149
Statin	49 (19.1)	237 (23.1)	0.169
Proton pump inhibitor	30 (11.7)	102 (9.9)	0.408

* Denotes $P < 0.05$.
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 3. Clinical course during hospitalization

Variable	HCM (n = 257)	Non-HCM (n = 1,028)	HCM *vs*. Non-HCM	
			OR / *B* (95% CI)	*P* value
PCI	45 (17.5)	325 (31.6)	0.46 (0.32, 0.65)	<0.001*
Number of intervened vessels				
0 vessel	212 (82.5)	703 (68.4)	Reference	–
1 vessel	34 (13.2)	242 (23.5)	0.47 (0.32, 0.69)	<0.001*
2 vessels	10 (3.9)	54 (5.3)	0.61 (0.31, 1.23)	0.167
3 vessels	1 (0.4)	29 (2.8)	0.11 (0.02, 0.84)	0.034*
PCI with stenting	16 (6.2)	171 (16.6)	0.33 (0.20, 0.57)	<0.001*
CABG	2 (0.8)	36 (3.5)	0.22 (0.05, 0.90)	0.036*
Valvular surgery	3 (1.2)	3 (0.3)	4.04 (0.81, 20.11)	0.089
Pacing device implantation†	7 (2.7)	3 (0.3)	9.57 (2.46, 37.26)	0.001*
New onset of atrial fibrillation	35 (13.6)	48 (4.7)	3.22 (2.03, 5.10)	<0.001*
New onset of VTE	16 (6.2)	47 (4.6)	1.39 (0.77, 2.49)	0.274
Shock	75 (29.2)	402 (39.1)	0.64 (0.48, 0.86)	0.003*
In-hospital death	28 (10.9)	217 (21.1)	0.46 (0.30, 0.70)	<0.001*
ICU days	4.4±7.2	4.6±7.3	-0.21 (-1.20, 0.78)	0.677
Length of stay	13.7±25.1	12.3±20.6	1.39 (-1.56, 4.35)	0.355

* Denotes $P < 0.05$.

B, regression coefficient; CABG, coronary artery bypass graft; CI, confidence interval; ICU, intensive care unit; OR, odds ratio; PCI, percutaneous coronary intervention; VTE, venous thromboembolism.

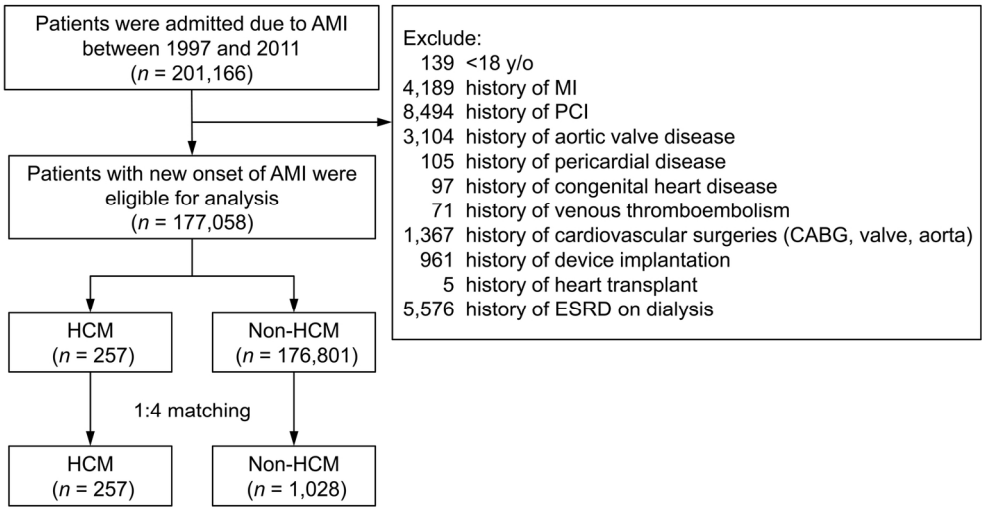
† Includes pacemaker and implantable cardioverter defibrillator.

Table 4. Outcome during the follow up

Variable	HCM (n = 257)	Non-HCM (n = 1,028)	HCM *vs*. Non-HCM HR (95% CI)	*P* value
1 year follow up				
Recurrent AMI	13 (5.1)	70 (6.8)	0.68 (0.37, 1.25)	0.214
HF hospitalization	17 (6.6)	66 (6.4)	1.02 (0.60, 1.74)	0.941
Systemic VTE	23 (8.9)	64 (6.2)	1.55 (0.75, 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, 0.85)	0.001*
CV death	46 (17.9)	211 (20.5)	0.83 (0.60, 1.14)	0.252
At the end of follow up				
Recurrent AMI	23 (8.9)	109 (10.6)	0.79 (0.50, 1.24)	0.299
HF hospitalization	35 (13.6)	112 (10.9)	1.24 (0.85, 1.80)	0.266
Systemic VTE	39 (15.2)	107 (10.4)	1.52 (0.97, 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, 1.16)	0.732
CV death	62 (24.1)	262 (25.5)	0.89 (0.67, 1.17)	0.401

* Denoted $P < 0.05$.
AMI, acute myocardial infarction; HR, hazard ratio; CI, confidence interval; CV, cardiovascular; HF, heart failure; VTE, venous thromboembolism; NA = not applicable.

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



Study design and flow chart for 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.

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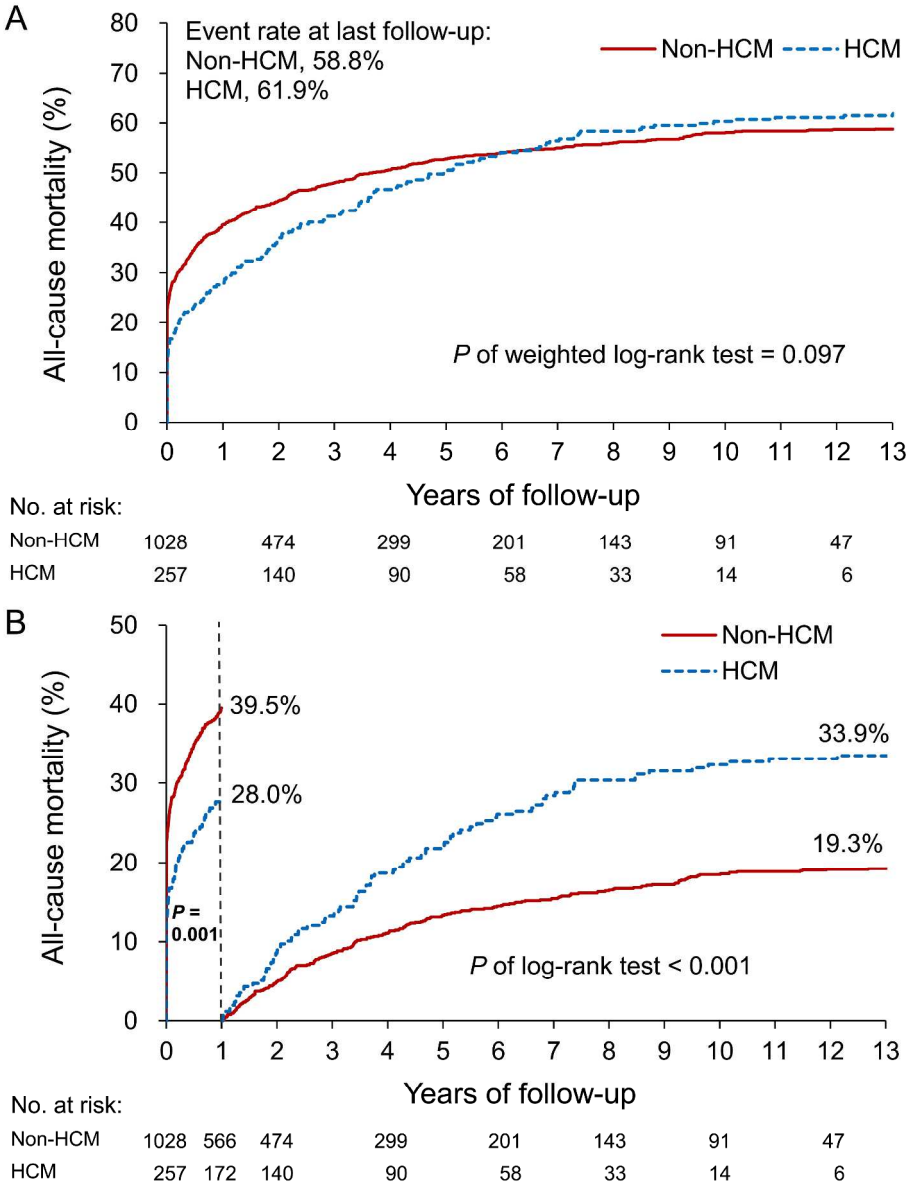

Kaplan–Meier survival analysis of AMI patients with and without HCM for the entire follow-up period (A). Because the observed group difference (slope) achieved the maximum at year 1–2 in Kaplan–Meier curves, using 1-year as the cutoff point of landmark analysis, the Kaplan–Meier survival graph is presented with a vertical dotted line separating the follow-up to within and beyond 1 year (B).

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Supplementary Table 1. ICD-9-CM code used in the current study

Variable	Code
Acute myocardial infarction	410.xx
Aortic valve disease	424.1
Pericardial disease	423.xx
Congenital heart disease	745.xx–747.xx (Catastrophic illness card)
Venous thromboembolism	415.1x, 453.xx
Dialysis	585.xx (Catastrophic illness card)
Hypertrophic cardiomyopathy	425.1x
Hypertension	401.xx–405.xx
Hyperlipidemia	272.xx
Diabetes mellitus	250.xx
Heart failure	428.xx
Stroke	430.xx–437.xx
Chronic kidney disease	580.xx–589.xx, 403.xx–404.xx, 016.0x, 095.4x, 236.9x, 250.4x, 274.1x, 442.1x, 447.3x, 440.1x, 572.4x, 642.1x, 646.2x, 753.1x, 283.11, 403.01, 404.02, 446.21
Carotid artery disease	433.1x
Peripheral artery disease	440.0x, 440.2x, 440.3x, 440.8x, 440.9x, 443.xx, 444.0x, 444.22, 444.8x, 447.8x, 447.9x
Atrial fibrillation/atrial flutter	427.31, 427.32
Chronic obstructive pulmonary disease	491.xx, 492.xx, 496.xx
Peptic ulcer disease	531.xx–534.xx
Liver cirrhosis	571.2x, 571.5x, 571.6x
Malignancy	140.xx–208.xx
Gout	274.xx
Atrial fibrillation	427.31
Systemic thromboembolism	444.22, 444.81, 444.21, 557.0, 557.9, 557.1, 593.81, 444.89, 433.8, 444.9x, 415.1x, 433.xx, 434.xx, 435.xx, 436.xx, 437.xx

Supplementary Table 2. Intervention and medication during the index admission after propensity score matching without matching the index date (sensitivity analysis I)

Variable	HCM (n = 257)	Non-HCM (n = 1,028)	P value#
Intervention			
Intubation	41 (16.0)	247 (24.0)	0.005*
Intraaortic balloon pump	4 (1.6)	65 (6.3)	0.002*
Extracorporeal membrane oxygenation	1 (0.4)	11 (1.1)	0.310
Temporary hemodialysis	5 (1.9)	44 (4.3)	0.080
Cardiac rehabilitation	8 (3.1)	46 (4.5)	0.330
Medications during admission			
Aspirin	196 (76.3)	761 (74.0)	0.462
Clopidogrel	120 (46.7)	528 (51.4)	0.181
ACEI/ARB	141 (54.9)	582 (56.6)	0.613
Beta blocker	135 (52.5)	454 (44.2)	0.016*
Calcium channel blocker	70 (27.2)	225 (21.9)	0.068
Diuretics	80 (31.1)	330 (32.1)	0.765
Spironolactone	19 (7.4)	92 (8.9)	0.427
Nitrates	51 (19.8)	228 (22.2)	0.417
Warfarin	18 (7.0)	52 (5.1)	0.219
Statin	49 (19.1)	223 (21.7)	0.357
Proton pump inhibitor	30 (11.7)	118 (11.5)	0.930

* Denotes $P < 0.05$.
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Adjusted for year of index admission.

Supplementary Table 3. In-hospital cardiovascular outcome after propensity score matching without matching the index date (sensitivity analysis I)

Variable	HCM (n = 257)	Non-HCM (n = 1,028)	HCM *vs*. Non-HCM#	
			OR / *B* (95% CI)	*P* value
PCI	45 (17.5)	311 (30.3)	0.49 (0.34, 0.70)	<0.001*
Number of intervened vessels				
0 vessel	212 (82.5)	717 (69.7)	Reference	–
1 vessel	34 (13.2)	226 (22.0)	0.51 (0.34, 0.76)	<0.001*
2 vessels	10 (3.9)	57 (5.5)	0.60 (0.30, 1.20)	0.146
3 vessels	1 (0.4)	28 (2.7)	0.12 (0.02, 0.86)	0.035*
PCI with stenting	16 (6.2)	181 (17.6)	0.30 (0.17, 0.51)	<0.001*
CABG	2 (0.8)	31 (3.0)	0.26 (0.06, 1.10)	0.067
Valvular surgery	3 (1.2)	6 (0.6)	2.06 (0.50, 8.49)	0.315
Pacing device implantation†	7 (2.7)	3 (0.3)	9.68 (2.43, 38.47)	0.001*
New onset of atrial fibrillation	35 (13.6)	32 (3.1)	5.15 (3.09, 8.57)	<0.001*
New onset of VTE	16 (6.2)	55 (5.4)	1.28 (0.72, 2.29)	0.405
Shock	75 (29.2)	433 (42.1)	0.58 (0.43, 0.78)	<0.001*
In-hospital death	28 (10.9)	223 (21.7)	0.44 (0.29, 0.67)	<0.001*
ICU days	4.4±7.2	4.6±7.8	-0.24 (-1.29, 0.81)	0.824
Length of stay	13.7±25.1	12.9±20.1	0.78 (-2.11, 3.68)	0.550

* Denotes $P < 0.05$.
B, regression coefficient; CABG, coronary artery bypass graft; CI, confidence interval; ICU, intensive care unit; OR, odds ratio; PCI, percutaneous coronary intervention; VTE, venous thromboembolism.
† Includes pacemaker and implantable cardioverter defibrillator.

Adjusted for year of index admission.

Supplementary Table 4. Outcome during the follow up after propensity score matching without matching the index date (sensitivity analysis I)

Variable	HCM (n = 257)	Non-HCM (n = 1,028)	HCM *vs*. Non-HCM#	
			HR (95% CI)	*P* value
1 year follow up				
Recurrent AMI	13 (5.1)	69 (6.7)	0.70 (0.38, 1.28)	0.249
HF hospitalization	17 (6.6)	61 (5.9)	1.10 (0.65, 1.88)	0.717
Systemic VTE	23 (8.9)	63 (6.1)	2.62 (1.06, 6.48)	0.036*
Heart transplant	0 (0.0)	0 (0.0)	NA	NA
All-cause mortality	72 (28.0)	407 (39.6)	0.59 (0.46, 0.76)	<0.001*
CV death	46 (17.9)	217 (21.1)	0.74 (0.54, 1.02)	0.067
At the end of follow up				
Recurrent AMI	23 (8.9)	100 (9.7)	0.86 (0.54, 1.37)	0.528
HF hospitalization	35 (13.6)	101 (9.8)	1.41 (0.96, 2.07)	0.083
Systemic VTE	39 (15.2)	108 (10.5)	1.77 (1.09, 2.88)	0.022*
Heart transplant	0 (0.0)	0 (0.0)	NA	NA
All-cause mortality	159 (61.9)	604 (58.8)	0.82 (0.69, 0.98)	0.031*
CV death	62 (24.1)	246 (23.9)	0.84 (0.63, 1.11)	0.220

* Denoted $P < 0.05$.
AMI, acute myocardial infarction; HR, hazard ratio; CI, confidence interval; CV, cardiovascular; HF, heart failure; VTE, venous thromboembolism; NA = not applicable.

#Additional adjusted for percutaneous coronary intervention, coronary artery bypass graft and pacing device during the index admission and the index year.

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

Supplementary Table 5. Intervention and medication during the index admission using multivariable regression adjustment (sensitivity analysis II)#

Variable	HCM (n = 257)	Non-HCM (n = 176,801)	P value
Intervention			
Intubation	41 (16.0)	34,182 (19.3)	0.170
Intraaortic balloon pump	4 (1.6)	11,882 (6.7)	0.001*
Extracorporeal membrane oxygenation	1 (0.4)	932 (0.5)	0.760
Temporary hemodialysis	5 (1.9)	5,877 (3.3)	0.218
Cardiac rehabilitation	8 (3.1)	8,076 (4.6)	0.264
Medications during admission			
Aspirin	196 (76.3)	139,396 (78.8)	0.312
Clopidogrel	120 (46.7)	98,802 (55.9)	0.003*
ACEI/ARB	141 (54.9)	106,910 (60.5)	0.066
Beta blocker	135 (52.5)	87,549 (49.5)	0.335
Calcium channel blocker	70 (27.2)	35,653 (20.2)	0.005*
Diuretics	80 (31.1)	48,383 (27.4)	0.176
Spironolactone	19 (7.4)	13,274 (7.5)	0.944
Nitrates	51 (19.8)	41,146 (23.3)	0.194
Warfarin	18 (7.0)	6,388 (3.6)	0.004*
Statin	49 (19.1)	50,907 (28.8)	0.001*
Proton pump inhibitor	30 (11.7)	14,352 (8.1)	0.037*

* Denotes $P < 0.05$.
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Adjusted for sex, gender and 14 comorbidities listed in Table 1.

Supplementary Table 6. In-hospital cardiovascular outcome using multivariable regression adjustment (sensitivity analysis II)#

Variable	HCM (n = 257)	Non-HCM (n = 176,801)	HCM *vs*. Non-HCM OR / *B* (95% CI)	*P* value
PCI	45 (17.5)	73,391 (41.5)	0.44 (0.31, 0.61)	<0.001*
Number of intervened vessels				
0 vessel	212 (82.5)	103,410 (58.5)	Reference	–
1 vessel	34 (13.2)	55,066 (31.1)	0.45 (0.31, 0.66)	<0.001*
2 vessels	10 (3.9)	11,924 (6.7)	0.57 (0.30, 1.08)	0.085
3 vessels	1 (0.4)	6,401 (3.6)	0.11 (0.02, 0.77)	0.026*
PCI with stenting	16 (6.2)	39,233 (22.2)	0.31 (0.18, 0.53)	<0.001*
CABG	2 (0.8)	6,759 (3.8)	0.25 (0.06, 1.002)	0.0503
Valvular surgery	3 (1.2)	756 (0.4)	2.12 (0.67, 6.69)	0.200
Pacing device implantation†	7 (2.7)	549 (0.3)	8.04 (3.73, 17.31)	<0.001*
New onset of atrial fibrillation	35 (13.6)	6,543 (3.7)	4.57 (3.15, 6.63)	<0.001*
New onset of VTE	16 (6.2)	7,242 (4.1)	1.50 (0.89, 2.52)	0.127
Shock	75 (29.2)	63,077 (35.7)	0.64 (0.49, 0.85)	0.002*
In-hospital death	28 (10.9)	29,396 (16.6)	0.46 (0.30, 0.69)	<0.001*
ICU days	4.4±7.2	4.4±7.1	0.04 (-0.81, 0.89)	0.595
Length of stay	13.7±25.1	11.1±17.3	2.66 (0.60, 4.72)	0.360

* Denotes $P < 0.05$.
B, regression coefficient; CABG, coronary artery bypass graft; CI, confidence interval; ICU, intensive care unit; OR, odds ratio; PCI, percutaneous coronary intervention; VTE, venous thromboembolism.
† Includes pacemaker and implantable cardioverter defibrillator.
# Adjusted for sex, gender and 14 comorbidities listed in Table 1.

Supplementary Table 7. Outcome during the follow up using multivariable regression adjustment (sensitivity analysis II)#

Variable	HCM (*n* = 257)	Non-HCM (*n* = 176,801)	HCM *vs*. Non-HCM	
			HR (95% CI)	*P* value
1 year follow up				
Recurrent AMI	13 (5.1)	13,774 (7.8)	0.68 (0.38, 1.19)	0.174
HF hospitalization	17 (6.6)	7,790 (4.4)	0.98 (0.60, 1.60)	0.946
Systemic VTE	23 (8.9)	9,496 (5.4)	2.08 (1.12, 3.86)	0.021*
Heart transplant	0 (0.0)	89 (0.1)	NA	NA
All-cause mortality	72 (28.0)	54,007 (30.5)	0.69 (0.55, 0.87)	0.002*
CV death	46 (17.9)	29,667 (16.8)	0.85 (0.64, 1.14)	0.284
At the end of follow up				
Recurrent AMI	23 (8.9)	20,316 (11.5)	0.85 (0.56, 1.28)	0.429
HF hospitalization	35 (13.6)	15,708 (8.9)	1.16 (0.82, 1.62)	0.405
Systemic VTE	39 (15.2)	18,155 (10.3)	1.67 (1.13, 2.47)	0.010*
Heart transplant	0 (0.0)	188 (0.1)	NA	NA
All-cause mortality	159 (61.9)	88,884 (50.3)	0.93 (0.79, 1.08)	0.338
CV death	62 (24.1)	36,481 (20.6)	0.93 (0.72, 1.19)	0.539

* Denoted $P < 0.05$.
AMI, acute myocardial infarction; HR, hazard ratio; CI, confidence interval; CV, cardiovascular; HF, heart failure; VTE, venous thromboembolism; NA = not applicable.

The analysis considers death as a competing risk except for all-cause mortality and CV death.
Adjusted for sex, gender and 14 comorbidities listed in Table 1.

Supplementary Table 8. Outcome during the follow up after propensity score matching using classical Cox proportional hazard model (sensitivity analysis III)

Variable	HCM (*n* = 257)	Non-HCM (*n* = 1,028)	HCM *vs*. Non-HCM HR (95% CI)	HCM *vs*. Non-HCM *P* value
1 year follow up				
Recurrent AMI	13 (5.1)	70 (6.8)	0.63 (0.34, 1.16)	0.136
HF hospitalization	17 (6.6)	66 (6.4)	0.88 (0.52, 1.50)	0.643
Systemic VTE	23 (8.9)	64 (6.2)	1.31 (0.63, 2.71)	0.473
Heart transplant	0 (0.0)	1 (0.1)	NA	NA
All-cause mortality	72 (28.0)	406 (39.5)	0.66 (0.51, 0.85)	0.001*
CV death	46 (17.9)	211 (20.5)	0.83 (0.60, 1.14)	0.252
At the end of follow up				
Recurrent AMI	23 (8.9)	109 (10.6)	0.72 (0.46, 1.14)	0.165
HF hospitalization	35 (13.6)	112 (10.9)	1.10 (0.76, 1.62)	0.609
Systemic VTE	39 (15.2)	107 (10.4)	1.38 (0.88, 2.17)	0.162
Heart transplant	0 (0.0)	1 (0.1)	NA	NA
All-cause mortality	159 (61.9)	604 (58.8)	0.97 (0.81, 1.16)	0.732
CV death	62 (24.1)	262 (25.5)	0.89 (0.67, 1.17)	0.401

* Denoted $P < 0.05$.

AMI, acute myocardial infarction; HR, hazard ratio; CI, confidence interval; CV, cardiovascular; HF, heart failure; VTE, venous thromboembolism; NA = not applicable.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 6
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 6,7
Methods			
Study design	4	Present key elements of study design early in the paper	Page 7,8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 7,8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 7,8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Page 7,8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 7,8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 7,8
Bias	9	Describe any efforts to address potential sources of bias	Page 16
Study size	10	Explain how the study size was arrived at	Page 11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 7,8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 9,10
		(*b*) Describe any methods used to examine subgroups and interactions	n/a
		(*c*) Explain how missing data were addressed	n/a
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 11
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1,2
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount)	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 3,4

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 4
		(*b*) Report category boundaries when continuous variables were categorized	Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page 9,10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 16,17
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 16,17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 18

*Give information separately for exposed and unexposed groups.

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