

Influence of Ethnicity, Age, and Time on Sex Disparities in Long-Term Cause-Specific Mortality After Acute Myocardial Infarction

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Background—We examined the influence of sex, ethnicity, and time on competing cardiovascular and noncardiovascular causes of death following acute myocardial infarction in a multiethnic Asian cohort.

Methods and Results—For 12 years, we followed a prospective nationwide cohort of 15 151 patients (aged 22–101 years, median age 63 years; 72.3% male; 66.7% Chinese, 19.8% Malay, 13.5% Indian) who were hospitalized for acute myocardial infarction between 2000 and 2005. There were 6463 deaths (4534 cardiovascular, 1929 noncardiovascular). Compared with men, women had a higher risk of cardiovascular death (age-adjusted hazard ratio [HR] 1.3, 95% CI 1.2–1.4) but a similar risk of noncardiovascular death (HR 0.9, 95% CI 0.8–1.0). Sex differences in cardiovascular death varied by ethnicity, age, and time. Compared with Chinese women, Malay women had the greatest increased hazard of cardiovascular death (HR 1.4, 95% CI 1.2–1.6) and a marked imbalance in death due to heart failure or cardiomyopathy (HR 3.4 [95% CI 1.9–6.0] versus HR 1.5 [95% CI 0.6–3.6] for Indian women). Compared with same-age Malay men, Malay women aged 22 to 49 years had a 2.5-fold (95% CI 1.6–3.8) increased hazard of cardiovascular death. Sex disparities in cardiovascular death tapered over time, least among Chinese patients and most among Indian patients; the HR comparing cardiovascular death of Indian women and men decreased from 1.9 (95% CI 1.5–2.4) at 30 days to 0.9 (95% CI 0.5–1.6) at 10 years.

Conclusion—Age, ethnicity, and time strongly influence the association between sex and specific cardiovascular causes of mortality, suggesting that health care policy to reduce sex disparities in acute myocardial infarction outcomes must consider the complex interplay of these 3 major modifying factors. (*J Am Heart Assoc.* 2016;5:e003760 doi: 10.1161/JAHA.116.003760)

Key Words: acute myocardial infarction • age • ethnicity • sex disparity • time

Studies have identified that women have higher all-cause mortality than men following acute myocardial infarction (AMI).^{1–6} These studies have consistently shown that women are, on average, 10 years older at presentation; have a higher burden of comorbidities; and are less likely to receive up-to-date treatment, including reperfusion therapy, than men.⁷ Accounting for age differences often attenuates the observed sex differences in all-cause mortality, suggesting that age-associated comorbidity accounts for the excess risk in women.^{2,3}

Few data compare the actual causes of death following AMI in men and women. Such studies may expose disparities in cardiovascular outcomes that are not otherwise revealed when deaths from a single cause are considered.^{8,9} We hypothesized that women with AMI, being older than men with AMI, would have more age-associated noncardiovascular mortality.

Singapore is an ethnically diverse city-state comprising 3 major Asian populations that broadly represent large parts of Asia—Chinese (74.1%), Malay (13.4%), Indian (9.2%)—and

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other ethnicities (3.3%).¹⁰ Having previously shown that disparities in cardiovascular and noncardiovascular mortality exist among Chinese, Indian, and Malay ethnic groups,¹¹ we further postulated that sex disparities in the specific causes of cardiovascular mortality after AMI would differ among ethnic groups. Finally, we sought to quantify the interactive effects of ethnicity, age, and time on the association between sex and long-term cardiovascular death outcomes.

Methods

Patient Population

With a population of 5.5 million, Singapore's health care is readily accessible and affordable. The public health care system provides universal access for all Singapore citizens and permanent residents through 3 interdependent government-led financing programs—Medisave, Medishield, and Medifund—thereby minimizing treatment disparities.^{12,13} The public health care system manages 96% of AMI cases across the nation,¹⁴ and for those aged ≥ 21 years, clinical and follow-up details are recorded by the national Singapore Myocardial Infarction Registry.

Diagnosis at hospital admission is based on the World Health Organization Multinational MONItoring of trends and determinants in Cardiovascular disease (WHO-MONICA) criteria and includes ST-segment and non-ST-segment elevation myocardial infarction.¹⁵ Discharge details are recorded using the International Classification of Diseases, Ninth Revision (ICD-9) codes 410.00 to 414.19 and/or postmortem reports. Following the introduction of the universal definition of AMI in 2000, the troponin and creatine phosphokinase-MB results of all patients were further reviewed. A total of 87.3% had troponin or creatine phosphokinase-MB levels >99 th percentile of each hospital laboratory's reference population, and a diagnosis of AMI was made in these patients if there was accompanying ischemia. The remaining 12.7% did not have sufficient cardiac biomarker data to make a diagnosis based on the universal definition. Their diagnosis was based on the original WHO-MONICA criteria at admission.

The study was conducted according to the Declaration of Helsinki, and the National Healthcare Group Domain Specific Review Board approved the data analysis and collection in all 6 publicly funded hospitals in Singapore. The requirement for written informed consent was waived.

Clinical Variables

Data collection and site monitoring were performed by the Singapore Cardiac Databank (SCDB). All clinical chemistry laboratories in Singapore submit a quarterly listing of patients with elevated cardiac troponin, creatine phosphokinase-MB,

and creatine phosphokinase results to the SCDB. Data regarding demographics, medical history, severity of AMI at admission, and early medical and acute reperfusion therapies after admission were recorded for all patients through medical record review. Ethnicity was ascertained at hospital admission from state-issued identification that specifies self-designated race, which is recorded using only one of the following categories: Chinese, Malay, Indian, and "other."

Follow-up and Death Ascertainment

Date and details of cause of death were ascertained through record linkage with the Singapore National Registry of Births and Deaths. The ICD-9 and ICD-10 were used to code and classify mortality data from death certificates. It is a statutory requirement that deaths be registered within 24 hours of occurrence. The last date of follow-up for the study was March 1, 2012.

Each death was attributed to the primary cause exclusively, which was categorized as either cardiovascular or noncardiovascular. The cardiovascular causes were subclassified as coronary heart disease, stroke, diabetes mellitus complications, heart failure or cardiomyopathy, and other cardiovascular. Noncardiovascular causes were malignancy, infection, renal failure, and other noncardiovascular. These classifications were made separately by 2 independent clinicians (C.S.P.L. and M.Y.Y.C.) to enhance quality control of the data. Any disagreement in classification was resolved by consensus.

Statistical Methods

Patient characteristics were compared by the 2-sample *t* test or χ^2 test, as appropriate. Survival time was calculated from the index hospital admission for AMI to the date of the specific cause of death or date of censor.

To study the extent to which the risk of noncardiovascular death competed with the risk of cardiovascular death, these 2 broad categories were compared within each sex-ethnicity group. The data augmentation method of Lunn and McNeil¹⁶ was applied to the Cox regression models. This approach enabled direct comparison of cardiovascular and noncardiovascular deaths by hazard ratio (HR), which quantifies their relative contributions to overall mortality.

The cumulative incident death rates in the presence of competing events were estimated using the delta method.¹⁷ To assess the effects of sex and ethnicity, we used the Fine and Gray¹⁸ regression model, which is a modification of the Cox model and permits analysis of a particular cause of death to suitably account for the remaining and thus competing causes. This model can also be extended to include multiple risk factors under investigation, including the possibility of their interaction, and calculates the corresponding adjusted

HR. To investigate the possibility of changing HR for sex over time after AMI, we included a time-varying covariate defined by the product of sex (coded 0 or 1) and the patient's survival time.

For cardiovascular and noncardiovascular deaths, the first model within each ethnic group included sex as an explanatory variable. We then sequentially added age and the interaction of sex by age to determine the extent to which age modified the estimated HR for sex. With respect to cardiovascular mortality, we further used a series of Fine and Gray regression models to assess the potential effect modifications by groups of variables on the associations of sex and risk of death with age. Four groups of variables were used separately: (1) diabetes mellitus; (2) hypertension; (3) diabetes mellitus, hypertension, renal failure, AMI category, and Killip class; and (4) reperfusion therapy and medical therapy.

Univariate models were used to compare Malay and Indian patients with Chinese patients for cardiovascular and noncardiovascular death by sex. The potential effect modifications were assessed with 3 groups of covariates: (1) age; (2) age, reperfusion therapy, and medical therapy; and (3) age, diabetes mellitus, hypertension, renal failure, AMI category, and Killip class.

Age was modeled as a categorical variable (22–49, 50–59, 60–69, 70–79, and 80–101 years) because a significant departure from linear trend was found. All analyses and figures were obtained using Stata version 13 (StataCorp).¹⁹ A *P* value of <0.05 was considered statistically significant.

Results

Presenting Characteristics and In-Hospital Treatment

Of a total of 15 151 unique patients hospitalized nationwide in Singapore for AMI from 2000 to 2005, 6 were excluded for the following reasons: Cause of death was unknown for 5, and death was recorded as occurring prior to admission for 1. Of the remaining 15 145 patients, the majority were men (72.3%), and their ages ranged from 22 to 101 years (median 63 years). There were 10 097 (66.7%) Chinese, 3003 (19.8%) Malay, and 2045 (13.5%) Indian patients, suggesting relatively fewer Chinese patients in our cohort than in the population at large and relatively more Malay and Indian patients. We observed sex and ethnic differences in baseline characteristics and treatment at presentation. Compared with men, women in each ethnic group were older, had a greater burden of comorbidities, and presented with a higher Killip class but received less revascularization or evidence-based therapy during hospitalization (Table 1). Compared with Chinese patients, Malay and Indian patients were younger, but the prevalence of diabetes mellitus in women was higher in Malay

(61.5%) and Indian (70.4%) patients compared with Chinese patients (47.7%). Malay men received more revascularization therapy but less evidence-based drug therapy during hospitalization than Chinese men, whereas Indian women received more revascularization and more evidence-based drug therapy than Chinese women.

Cardiovascular Versus Noncardiovascular Causes of Death

A total of 6463 deaths occurred during a median follow-up of 7.3 years (maximum 12.2 years). Among patients who died, 4534 (70.2%) deaths were from cardiovascular causes and 1929 (29.8%) were noncardiovascular (Table 2). The most common cause of cardiovascular death was coronary heart disease (80.5%) followed by stroke (8.3%), whereas heart failure, complications of diabetes mellitus, and other cardiovascular causes each accounted for similar proportions (3.5%). The principal cause of noncardiovascular death was infection (41.6%) followed by malignancy (37.4%), renal failure (7.1%), and other noncardiovascular causes (14.0%), of which chronic obstructive pulmonary disease was the most common.

The 30-day and 10-year all-cause mortality rates were 11.6% and 44.6%, respectively, after AMI (Figure S1). Mortality rates differed by cause of death: The cardiovascular-related mortality rate was 10.3% at 30 days and increased 3-fold to 31.0% at 10 years, with a predominance of coronary heart disease deaths (Figure S2). Noncardiovascular mortality rates were lower, at 1.3%, by 30 days but increased 10-fold to 13.6% at 10 years. There was a greater proportion of cardiovascular deaths in the early (≤ 30 days) versus late (> 30 days) period (88.7% versus 63.2%, $P < 0.0001$) and a 2-fold greater risk of cardiovascular than noncardiovascular death over 12 years of follow-up (HR 2.4, 95% CI 2.2–2.5, $P < 0.0001$).

Sex and Ethnicity

At 10 years, the all-cause mortality rates were 37.5% and 62.9% for men and women, respectively, and 44.7%, 48.9%, and 37.8% for Chinese, Malay, and Indian patients, respectively. For cardiovascular mortality, the 10-year rates were 23.2% for Chinese men, 43.3% for Chinese women; 29.3% for Malay men, 51.2% for Malay women, 24.3% for Indian men, and 35.3% for Indian women (Figure 1). For noncardiovascular mortality, the 10-year rates were 12.5% for Chinese men, 17.6% for Chinese women, 9.9% for Malay men, 14.3% for Malay women, 7.8% for Indian men, and 13.4% for Indian women (Figure 1). In all sex–ethnicity groups, the risk of cardiovascular death was greater than the risk of noncardiovascular death, with HRs of cardiovascular versus noncardiovascular death ranging from 1.9 for Chinese men to 3.6 for Malay women (Table 2).

Table 1. Patient Demographics, Medical History, Clinical Features, and In-Hospital Therapy by Sex and Ethnicity

Characteristic	Chinese		Malay		Indian		All Patients	
	Men	Women	Men	Women	Men	Women	Men	Women
Patients, n	7171	2926	2206	797	1575	470	10 952	4193
Age, y, mean (range)	60.7 (22–101)	72.2 (27–100)*	58.8 (22–94) [†]	65.9 (31–95)* [†]	57.3 (22–101) [†]	65.4 (27–91) [†] *	59.8 (22–101)	70.3 (27–100)*
Current smoker	46.5	11.3*	54.0 [†]	4.7 [†]	46.1	2.6 [†]	47.9	9.0*
Medical history								
Prior MI	10.4	11.0	10.7	11.3	15.5 [†]	12.5	11.2	11.2
Prior CABG	2.7	2.7	2.0	1.5	4.6 [†]	4.9 [†]	2.9	2.7
Diabetes mellitus	29.2	47.7*	35.0 [†]	61.5 [†]	45.3 [†]	70.4 [†]	32.7	52.9*
Hypertension	55.6	72.6*	48.6 [†]	73.8*	49.5 [†]	70.6*	53.3	72.6*
Hyperlipidemia	49.6	49.7	44.9 [†]	50.2**	52.1	51.6	49.1	50.0
Renal failure	5.1	9.6*	5.8	11.0*	3.7 [†]	5.9** [†]	5.1	9.4*
Clinical characteristics								
STEMI	48.3	38.2*	47.0	36.0*	48.3	38.1*	48.0	37.8*
Killip class I	71.1	56.9*	70.0	53.7*	70.9 [†]	56.8*	70.9	56.3*
Killip class II	16.7	23.7	18.9	23.8	19.1	24.0	17.5	23.8
Killip class III	7.1	10.7	6.4	13.2	6.0	11.7	6.8	11.3
Killip class IV	5.1	8.7	4.7	9.3	4.0	7.5	4.9	8.6
In-hospital therapy								
Reperfusion therapy								
Primary and salvage PCI or emergency CABG	42.7	23.7*	43.3	22.8*	44.6	29.6 [†]	43.1	24.2*
Intra-aortic balloon counter pulsation	4.2	3.1**	3.9	3.1	3.8	3.8	4.1	3.2**
Medical therapy								
Aspirin	88.3	80.8*	90.5 [†]	83.9 [†]	91.4 [†]	86.8** [†]	89.2	82.1*
Beta blocker	74.7	64.2*	72.0 [†]	62.0*	75.9	67.9*	74.3	64.2*
Thienopyridine	57.3	44.0*	50.1 [†]	42.5*	55.9	50.3** [†]	55.6	44.4*
Lipid-lowering therapy	75.8	64.4*	78.2 [†]	70.4 [†]	78.4 [†]	71.9** [†]	76.7	66.4*
ACE inhibitors	61.9	58.0*	65.5 [†]	63.6 [†]	63.8	67.5 [†]	62.9	60.2**
Glycoprotein IIb/IIIa inhibitors	7.8	5.2*	6.1 [†]	4.5	7.9	7.7 [†]	7.5	5.4*

ACE indicates angiotensin-converting enzyme; CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

* $P < 0.0001$ compared with men of the same ethnic group.

** $P < 0.05$ compared with men of the same ethnic group.

[†] $P < 0.0001$ compared with Chinese patients of the same sex.

[‡] $P < 0.05$ compared with Chinese patients of the same sex.

Table 2. The Number of Cardiovascular and Noncardiovascular Deaths Within the Corresponding Subcategories, HRs Comparing Cardiovascular and Noncardiovascular Mortality Classified by Sex and Ethnicity, and the HRs for Women Versus Men for Cardiovascular and Noncardiovascular Mortality Within the 3 Ethnic Groups

	Chinese		Malay		Indian		All Patients	
	Men	Women	Men	Women	Men	Women	Men	Women
Patients, n	7171	2926	2206	797	1575	470	10 952	4193
Cardiovascular	1663	1268	646	408	383	166	2692	1842
CHD	1365 (82.1)	1006 (79.3)	526 (81.4)	290 (71.1)*	324 (84.6)	137 (82.5)	2215 (82.3)	1433 (77.8)*
Stroke	130 (7.8)	129 (10.2)**	39 (6.0)	49 (12.0)**	19 (5.0)	9 (5.4)	188 (7.0)	187 (10.2)*
Diabetes mellitus complications	61 (3.7)	63 (5.0)	28 (4.3)	27 (6.6)	10 (2.6)	8 (4.8)	99 (3.7)	98 (5.3)**
HF/cardiomyopathy	60 (3.6)	25 (2.0)**	29 (4.5)	23 (5.6)	14 (3.7)	6 (3.6)	103 (3.8)	54 (2.9)
Other cardiovascular	47 (2.8)	45 (3.6)	24 (3.7)	19 (4.7)	16 (4.2)	6 (3.6)	87 (3.2)	70 (3.8)
Noncardiovascular	897	515	218	114	122	63	1237	692
Infection	302 (33.7)	255 (49.5)*	90 (41.3)	64 (56.1)**	59 (48.4)	32 (50.8)	451 (36.5)	351 (50.7)*
Malignancy	396 (44.2)	162 (31.5)*	83 (38.1)	26 (22.8)**	41 (33.6)	13 (20.6)	520 (42.0)	201 (29.1)*
Renal failure	53 (5.9)	37 (7.2)*	16 (7.3)	17 (14.9)**	5 (4.1)	8 (12.7)**	74 (6.0)	62 (9.0)**
Other noncardiovascular	146 (16.3)	61 (11.8)**	29 (13.3)	7 (6.1)	17 (13.9)	10 (15.9)	192 (15.5)	78 (11.3)**
HR for cardiovascular vs noncardiovascular causes	1.9 (1.7–2.0)	2.5 (2.2–2.7)	3.0 (2.5–3.5)	3.6 (2.9–4.4)	3.1 (2.6–3.9)	2.6 (2.0–3.5)	2.2 (2.0–2.3)	2.7 (2.4–2.9)
HR for women vs men, cardiovascular mortality								
Unadjusted	1	2.2 (2.0–2.3)	1	2.1 (1.8–2.4)	1	1.6 (1.3–1.9)	1	2.1 (1.9–2.2)
Adjusted for age	1	1.2 (1.1–1.3)	1	1.6 (1.4–1.8)	1	1.2 (1.0–1.4)	1	1.3 (1.2–1.4)
HR for women vs men, noncardiovascular mortality								
Unadjusted	1	1.5 (1.3–1.6)	1	1.5 (1.2–1.9)	1	1.8 (1.3–2.4)	1	1.5 (1.4–1.7)
Adjusted for age	1	0.8 (0.7–0.9)	1	1.04 (0.8–1.3)	1	1.2 (0.8–1.6)	1	0.9 (0.8–1.0)

CHD indicates coronary heart disease; HF, heart failure; HR, hazard ratio.

* $P < 0.0001$ compared to men of the same ethnic group.

** $P < 0.05$ compared to men of the same ethnic group.

Women had a higher unadjusted risk of both cardiovascular mortality (HR 2.1, 95% CI 1.9–2.2, $P < 0.0001$) and noncardiovascular mortality (HR 1.5, 95% CI 1.4–1.7, $P < 0.0001$). After adjusting for age, the increased risk for women remained significant for cardiovascular mortality but was no longer significant for noncardiovascular mortality (Table 2).

Interactions of Ethnicity and Age With Sex

There was a significant sex-by-ethnicity interaction for cardiovascular mortality ($P = 0.010$ for interaction) but not for noncardiovascular mortality ($P = 0.51$ for interaction) (Table 3). After adjustment for all covariates, Malay men and women had a greater risk (HR 1.4) of cardiovascular mortality than same-sex Chinese patients. The interaction analysis further revealed sex-specific ethnic differences in cause-specific mortality; compared with Chinese women, Malay women had a 3.4-fold greater risk of death due to heart failure or

cardiomyopathy, whereas Indian women did not have a significantly greater risk of death due to heart failure or cardiomyopathy. Among men, the ethnic disparity in heart failure or cardiomyopathy mortality outcomes was far less pronounced (Malay men versus Chinese men: HR 1.6, 95% CI 1.0–2.5).

We further observed an interaction between sex and age for mortality in Chinese patients ($P = 0.014$ for interaction) and Malay patients ($P = 0.0040$ for interaction) but not in Indian patients ($P = 0.70$ for interaction) (Figure S3). After adjusting for diabetes mellitus, hypertension, renal failure, AMI category, and Killip class, the sex–age interaction remained significant in the Malay patients ($P = 0.026$ for interaction); notably, Malay women aged 22 to 49 years displayed a striking excess of cardiovascular mortality risk compared with Malay men of similar age (HR 2.5, 95% CI 1.6–3.8; $P < 0.0001$). Additional adjustment for in-hospital therapy did not change these associations materially.

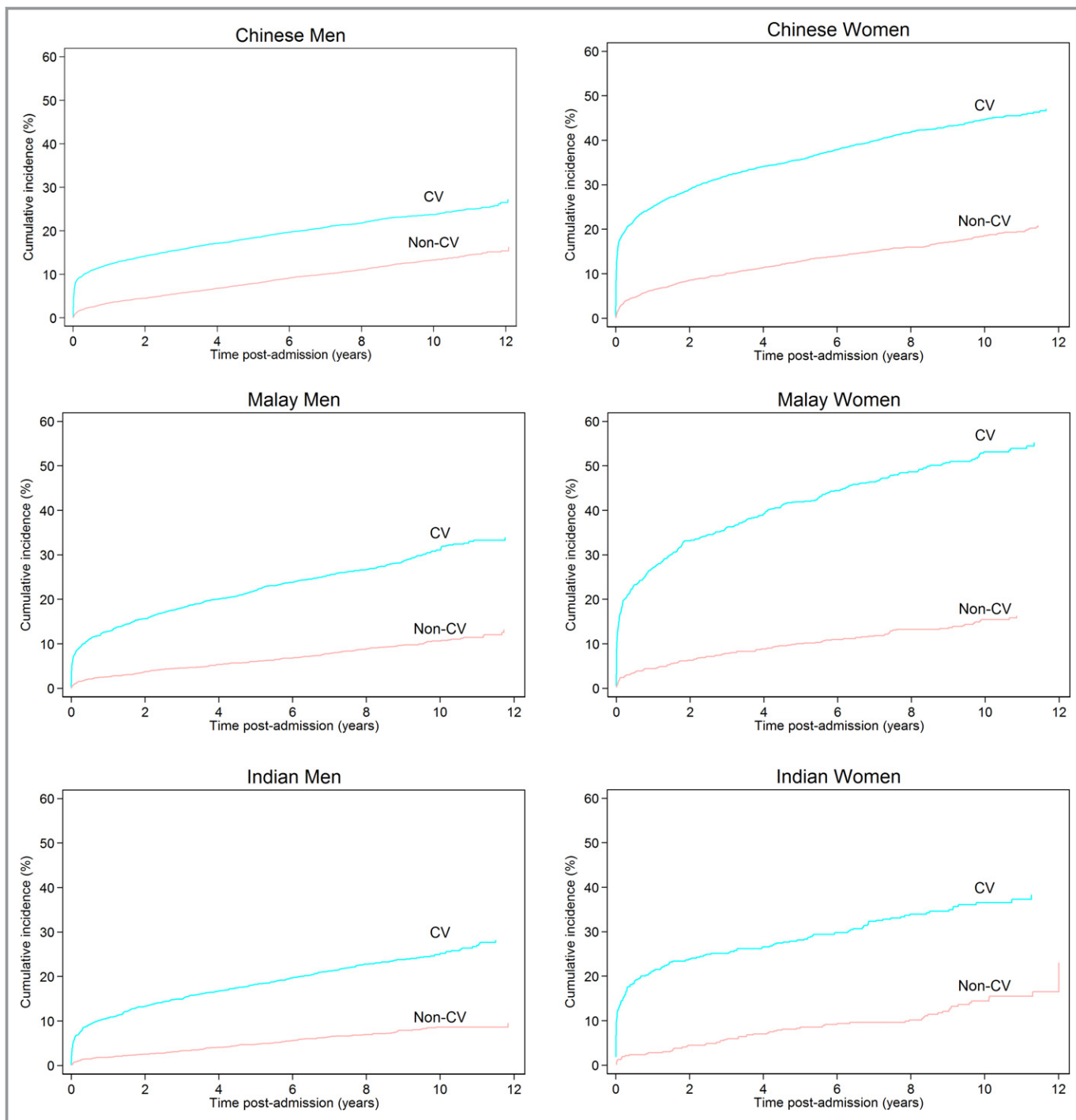


Figure 1. Competing cumulative incidences of cardiovascular and noncardiovascular death after acute myocardial infarction in men and women of Chinese, Malay, and Indian ethnicity.

Time-Varying Changes

The magnitude of the relative influence of sex and ethnicity on cardiovascular mortality varied substantially as the time after AMI increased. The higher risk of death among women was greatest in the immediate period after hospitalization and

gradually tapered off thereafter with longer follow-up in all ethnic groups compared with men (Figure 2). This tapering of sex disparity in cardiovascular outcomes over time was most pronounced for Indian patients; beyond 10 years from the index AMI, Indian women actually had a lower risk of cardiovascular death compared with Indian men (HR 0.9, 95% CI 0.5–1.6).

Table 3. Hazard Ratio Comparisons of the Malay and Indian Patients With Chinese Patients for Cardiovascular (and the Corresponding Subcategory) and Noncardiovascular Causes for Each Sex

	Men		Women		P Value for Sex–Ethnicity Interaction
	Malay	Indian	Malay	Indian	
Unadjusted					
Cardiovascular	1.3 (1.2–1.4)	1.0 (0.9–1.2)	1.2 (1.1–1.4)	0.8 (0.6–0.9)	0.010
CHD	1.3 (1.1–1.4)	1.1 (0.9–1.2)	1.1 (0.9–1.2)	0.8 (0.7–1.0)	
Stroke	1.0 (0.7–1.4)	0.7 (0.4–1.1)	1.4 (1.0–2.0)	0.4 (0.2–0.8)	
Diabetes mellitus complications	1.5 (1.0–2.3)	0.7 (0.4–1.5)	1.6 (1.0–2.5)	0.8 (0.4–1.6)	
HF/cardiomyopathy	1.6 (1.0–2.5)	1.1 (0.6–1.9)	3.4 (1.9–6.0)	1.5 (0.6–3.6)	
Other cardiovascular	1.7 (1.0–2.7)	1.5 (0.9–2.7)	1.6 (0.9–2.7)	0.8 (0.4–1.9)	
Noncardiovascular	0.8 (0.7–0.9)	0.6 (0.5–0.7)	0.8 (0.6–1.0)	0.7 (0.6–0.9)	0.51
Adjusted for age					
Cardiovascular	1.4 (1.3–1.5)	1.2 (1.0–1.3)	1.6 (1.4–1.8)	1.0 (0.8–1.2)	
Noncardiovascular	0.8 (0.7–1.0)	0.7 (0.6–0.8)	1.0 (0.8–1.2)	0.9 (0.7–1.2)	
Adjusted for age and in-hospital therapy					
Cardiovascular	1.3 (1.2–1.5)	1.2 (1.0–1.3)	1.5 (1.4–1.7)	1.1 (0.9–1.2)	
Noncardiovascular	0.8 (0.7–1.0)	0.7 (0.6–0.9)	0.9 (0.8–1.2)	0.9 (0.7–1.2)	
Adjusted for age, comorbidities, and clinical characteristics*					
Cardiovascular	1.4 (1.3–1.6)	1.1 (1.0–1.2)	1.4 (1.2–1.6)	0.9 (0.7–1.1)	
Noncardiovascular	0.8 (0.7–1.0)	0.7 (0.6–0.8)	0.9 (0.7–1.1)	0.9 (0.7–1.1)	

CHD indicates coronary heart disease; HF, heart failure.

*Age, diabetes mellitus, hypertension, renal failure, acute myocardial infarction category, and Killip class.

Discussion

We studied the individual causes of 6463 deaths arising in 15 151 patients aged 22 to 101 years who were hospitalized for AMI between the years 2000–2005 and followed for a maximum of 12 years. Prominent influences of ethnicity, age,

and time on the association between sex and specific cardiovascular causes of long-term mortality were observed. We showed >2-fold higher risk of death from cardiovascular versus noncardiovascular causes. Despite the younger ages of Malay and Indian patients, there were no differences in noncardiovascular death between men and women after adjusting for age. Age-adjusted cardiovascular death, however, was higher among women than men, with the largest sex disparity in cardiovascular death observed among Malay patients. The interaction analysis among sex, ethnicity, and age further revealed a much higher incidence of heart failure and cardiomyopathy as an underlying cause of cardiovascular death in Malay women compared with Chinese women. The sex disparity in cardiovascular death was most devastating when Malay women aged 22 to 49 years were compared with Malay men of similar age; these young Malay women had 2.5 times increased risk of cardiovascular death compared with same-age Malay men. Interestingly, the sex disparity in cardiovascular death tapered over time. This narrowing of the sex difference in cardiovascular death over time was most striking among Indian patients; indeed, Indian women had less cardiovascular death than Indian men beyond 10 years of follow-up. These findings have important public health

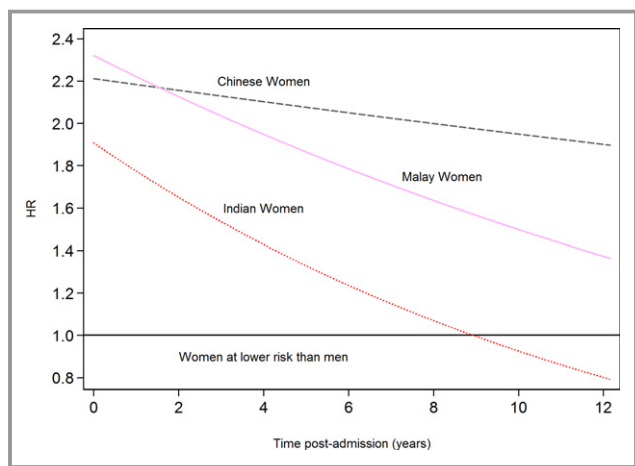


Figure 2. The decline in the time-varying hazard ratio (HR) profiles for cardiovascular mortality risk for Chinese, Malay, and Indian women relative to men of the same ethnic group.

implications for targeting planning of risk stratification and secondary prevention strategies in multiethnic communities.

A review of 39 studies²⁰ with follow-up ≥ 5 years concluded that sex differences in longer term mortality were largely explained by differences between men and women in age, comorbidities, and treatment. No studies, however, have accounted for the competing risk from individual causes of cardiovascular and noncardiovascular death. Substantial geographical disparities exist in the occurrence of and (relatively short-term) mortality from cardiovascular disease.²¹ In particular, South Asian (Indian) migrants, who are resident in several countries, are prone to suffer myocardial infarction or coronary death.^{22–26} In the United States, Indian (South Asian) persons tend to have earlier onset of coronary heart disease than those of Chinese or Japanese (East Asian) origin. Interestingly, compared with studies of primarily white populations, we observed a much higher prevalence of hypertension in women than men in our study; this likely reflects the much older age of the women and the striking age-specific increases in prevalence of hypertension in the Singapore population (age-specific prevalence increases from 36% in the group aged 50 to 59 years to 56% in the group aged 60 to 69 years in the general population). Even after adjusting for hypertension as an independent variable in the corresponding regression models (Figure S3C), sex differences in cardiovascular mortality persisted.

Although long-term post-AMI mortality from Singapore has been described,^{27–29} prior studies were performed in 1991–1999 and were confined to those aged <65 years. The current results extend these findings to a more contemporary cohort treated with current standards of AMI care, as shown by the significant use of primary percutaneous coronary intervention and the high use of evidence-based therapies (Table 1). Furthermore, prior studies did not account for competing risk from noncardiovascular death, and that may have exaggerated the cardiovascular mortality burden.³⁰ Our study is the first to carefully quantify the specific subcauses of cardiovascular and noncardiovascular death, to examine the time-varying influence of sex and ethnicity, and to parse the complexities of the interactions among ethnic groups, sex, and age at admission for AMI on mortality.

The interaction analysis revealed a complex influence of ethnicity on the association between sex and specific causes of cardiovascular death. We observed that among women with AMI, Malay women were at a far higher risk of cardiovascular death due to heart failure or cardiomyopathy. In contrast, among men, the ethnic disparities in heart failure or cardiomyopathy death were far less pronounced (Table 3). These differences could not be accounted for by the prevalent comorbidities (diabetes mellitus and hypertension) at presentation. Although there was evidence of sex disparities in in-hospital treatment of AMI, with markedly lower use of primary

percutaneous coronary intervention and evidence-based medications in women compared with men, use of these proven therapies was similar if not higher in Malay patients compared with Chinese patients of the same sex. Given the widening ethnic differences in cardiovascular death risk over time, we postulated that differences in access to health care or control of risk factors such as diabetes mellitus may have played a role. This possibility has important public health implications and suggests that Malay patients, and especially younger Malay women, should be targeted for intense secondary prevention measures following AMI. Further research is needed to better understand the underlying causes of this sex–ethnicity interaction in heart failure mortality outcomes. Health care policy might also consider greater use of renin–angiotensin system blockers and beta blockers for Malay women with AMI.

We further observed that the effect of sex–ethnicity interactions in cardiovascular mortality after AMI varied markedly with age. Sex disparities in cardiovascular mortality were greatest among young Malay women compared with Malay men of similar age (Figure S3). In our cohort, Malay women more frequently had a history of diabetes mellitus, hypertension, and renal failure at the time of hospital admission compared with Malay men of similar age. A common explanation for the greater mortality burden associated with young women is the potential sex disparity in treatment following AMI. Young Malay women in our study were less likely to be treated with aspirin, primary or salvage percutaneous coronary intervention, or emergency coronary artery bypass grafting. Nevertheless, careful adjustment for in-hospital therapy had a negligible effect on the sex estimates of mortality risk, suggesting that other factors may contribute to the greater mortality burden in young Malay women. It is unclear whether young Malay women have a unique biological factor or socioeconomic status (SES) that contributes to this heightened sex disparity in cardiovascular mortality. We and others have observed differential metabolism of clopidogrel among Chinese, Malay, and Indian patients, caused by underlying genetic differences in CYP2C19 polymorphisms.^{31–33} Chinese and Malay patients have a higher prevalence of CYP2C19 loss-of-function polymorphisms, leading to lower levels of the clopidogrel active metabolite and poorer inhibition of platelet aggregation. In contrast, Indian patients have a lower prevalence of the loss-of-function metabolite and a higher prevalence of the gain-of-function metabolite, leading to higher levels of the clopidogrel active metabolite and greater inhibition of platelet aggregation. Differences in SES have been cited as a key determinant of AMI outcomes.^{34,35} Ethnic inequalities in SES persist in modern-day Singapore, as shown in population census reports conducted in 2000 and 2010, at the beginning and end of our study period, respectively.¹⁰ Trends in SES identify Indian

persons as a privileged minority ethnic group whose high SES may contribute toward better long-term health outcomes, whereas the lower SES of Malay persons may in part explain their poorer long-term outcomes. Our findings suggest an urgent need to better understand the biological response and cultural attitudes pertaining to this vulnerable subgroup of women who are afflicted by AMI in the prime of life.

The influence of time on sex disparities in AMI outcomes was highly divergent among the 3 ethnicities. Among Indian men and women, the steep attenuation of relative risk and the unexpected finding of a reversal in relative risk of cardiovascular mortality beyond 10 years suggested longitudinal conditions that were unique to this ethnicity (Figure 2). In-depth profiling of sex-specific biological adaptations and cultural attitudes after AMI in Indian patients may yield valuable insights into how we can reduce sex disparities in cardiovascular outcomes in other ethnicities.

Our study has several limitations that require explanation. First, we were not able to study nonfatal cardiovascular outcomes in our analysis. Nonetheless, the focus on fatal outcomes allowed us to leverage fully curated mortality records with certified specific causes of death. Second, data regarding SES, education level, body mass index, and smoking were available in our study cohort but only for a limited number of study patients (<30%), making it difficult to draw any meaningful conclusions about the effects of these factors on women's health in long-term outcomes. These cardiovascular death risk factors may have influenced outcomes and warrant further study.³⁶ Third, other clinical measures such as lipids and insulin levels and adherence to medication or lifestyle factors were not collected in the registry; therefore, it was not possible to assess whether these factors could attenuate the observed sex disparities in the present study. Fourth, the inclusion of only Asian patients in this study limited our ability to generalize our findings to other populations. Finally, the effect of age could not be fully accounted for in a standard Cox regression analysis. In this regard, relative survival ratio and relative excess risk estimates have notable advantages compared with standard Cox survival analysis, as we have demonstrated in another analysis comparing all-cause mortality between younger and older patients with AMI.³⁷ We were unable to perform these estimates for cardiovascular mortality in the present study because there are no cause-specific cardiovascular mortality life tables in Singapore, and such tables are required for those estimates.

A major strength of this study lies in the unselected patients with AMI from a single health care system. Near complete ascertainment of deaths is possible in Singapore, where all citizens and permanent residents are linked to the Singapore National Registry of Births and Deaths through a unique state-issued identification number, regardless of age, sex, or ethnicity.

Conclusion

Age, ethnicity, and time strongly influence the association between sex and specific cardiovascular causes of mortality, suggesting that health care policy to reduce sex disparities in AMI outcomes must consider the complex interplay of these 3 major modifying factors. Such in-depth interaction analyses can provide valuable insights into future unmet needs in health care disparities research and direct resource redistribution in long-term cardiovascular secondary prevention policy.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Figure S1:

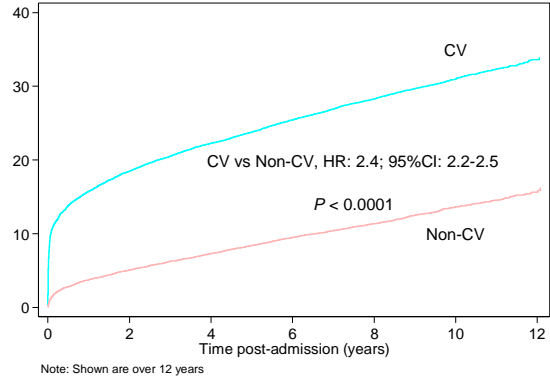
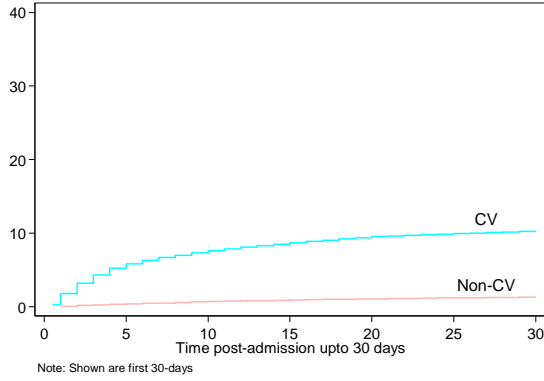


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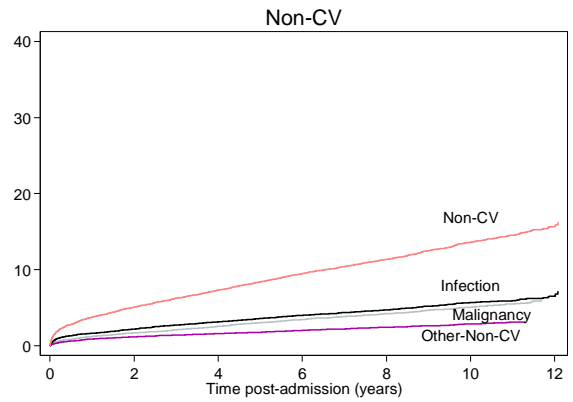
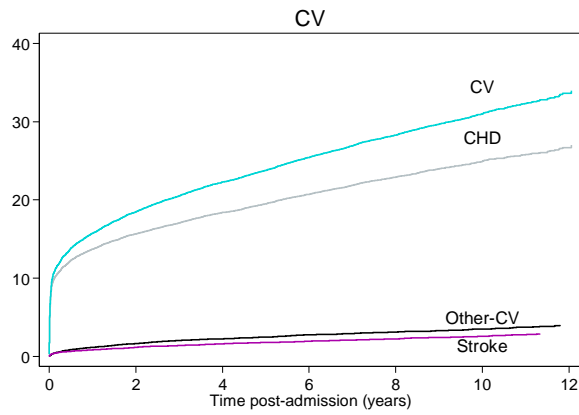
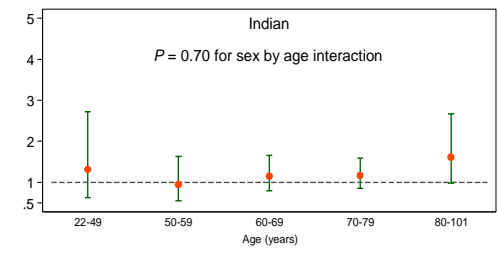
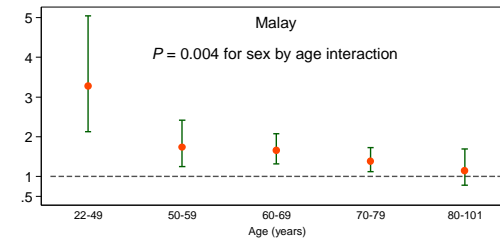
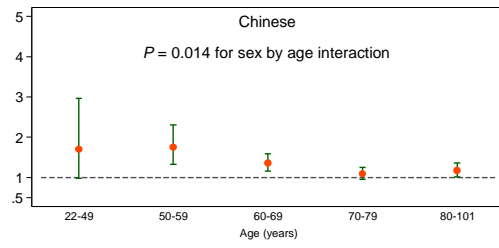
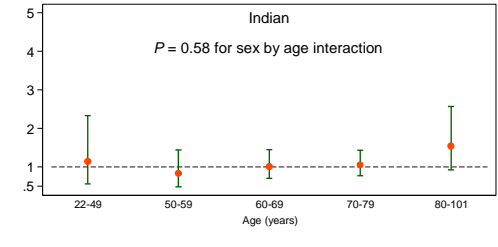
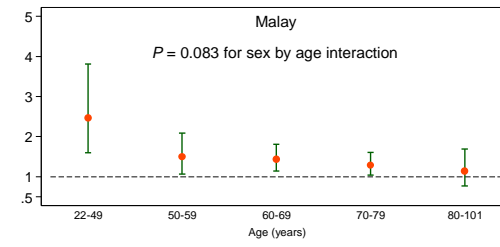
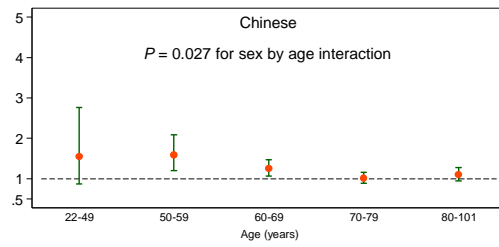


Figure S3

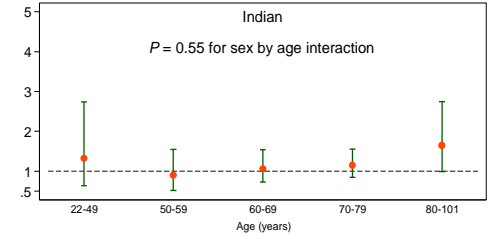
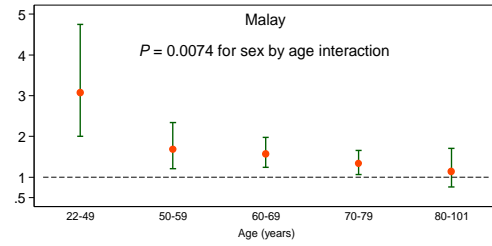
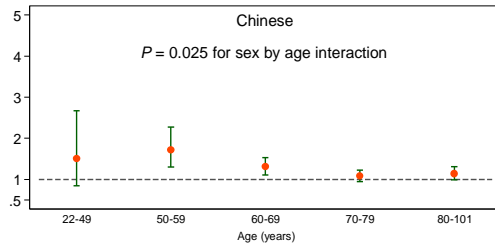
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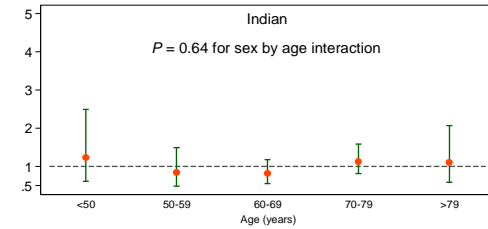
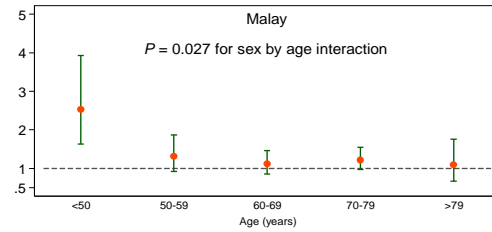
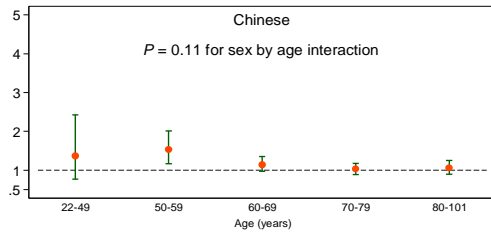
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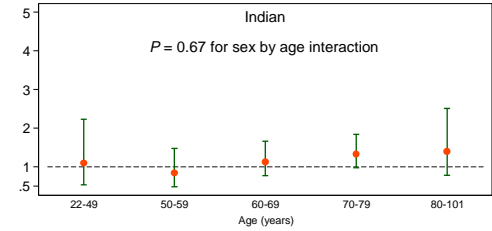
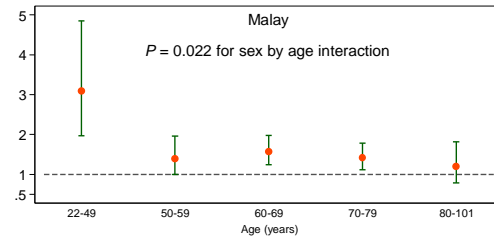
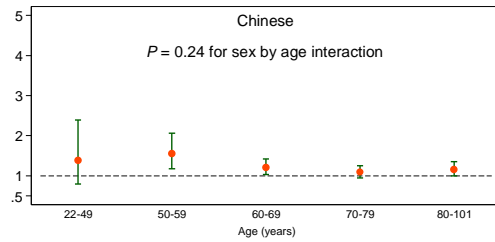
(c) Adjusted for hypertension



(d) Adjusted for comorbidities and clinical characteristics



(e) Adjusted for in-hospital therapy



* The unadjusted hazard ratios (HRs) (a) were derived from the model that included sex, age, interaction of sex by age. The adjusted HRs (d) were derived from the model that includes sex, age, interaction of sex by age, diabetes mellitus, hypertension, renal failure, AMI category, killip class. The adjusted HRs (e) were derived from the model that includes sex, age, interaction of sex by age, reperfusion therapy and medical therapy.

Supplemental Figure Legends:

Figure S1. Competing cumulative incidences of cardiovascular (CV) death and Non-CV death in the first 30 days and for upto 12 years post acute myocardial infarction (AMI)

Figure S2. Competing cumulative incidence of death from sub-causes within the cardiovascular (CV) deaths and sub-causes within the Non-CV deaths post acute myocardial infarction (AMI).
CHD, coronary heart disease.

Figure S3: Hazard ratio (HR) for cardiovascular mortality of women, as compared with men, with age at hospital admission for acute myocardial infarction (AMI) within the Chinese, Malay and Indian patients: (a) with no adjustment, after adjustment for (b) diabetes mellitus, (c) hypertension, (d) diabetes mellitus, hypertension, renal failure, AMI category and Killip class and (e) in-hospital therapy