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Ethnic variations in female vulnerability after an acute coronary event

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Objective: To determine the ethnic variation of short and long term female vulnerability after an acute coronary event in a population of Chinese, Indians, and Malays.

Design: Population based registry.

Patients: Residents of Singapore between the ages of 20–64 years with coronary events. Case identification and classification procedures were modified from the MONICA (monitoring trends and determinants in cardiovascular disease) project.

Main outcome measures: Adjusted 28 day case fatality and long term mortality.

Results: From 1991 to 1999, there were 16 320 acute coronary events, including 3497 women. Age adjusted 28 day case fatality was greater in women (51.5% v 38.6%, $p < 0.001$), with a larger sex difference evident among younger Malay patients. This inequality between the sexes was observed in both the pre-hospitalisation and post-admission periods. Among hospitalised patients, women were older, were less likely to have suffered from a previous Q wave or anterior wall myocardial infarction, and had lower peak creatine kinase concentrations. Case fatality was higher among women, with adjusted hazard ratios of 1.64 (95% confidence interval (CI) 1.43 to 1.88) and 1.50 (95% CI 1.37 to 1.64) for 28 day and mean four year follow up periods. There were significant interactions of sex and age with ethnic group ($p = 0.017$). The adjusted hazards for mortality among Chinese, Indian, and Malay women versus men were 1.30, 1.71, and 1.96, respectively. The excess mortality among women diminished with age.

Conclusion: In this multiethnic population, both pre-hospitalisation and post-admission case fatality rates were substantially higher among women. The sex discrepancy in long term mortality was greatest among Malays and in the younger age groups.

While acute myocardial infarction (MI) occurs more commonly among men, several studies have shown that short term mortality after the event is higher among women.^{1–2} A review of 27 studies concluded that the reasons for increased early mortality among women were older age and the presence of other unfavourable baseline clinical characteristics.³ Long term survival was shown to be better for women after adjusting for differences in age and other covariates in large MI population registries.³ Subsequent investigators found an interaction between sex and age,^{4–7} with a female excess of mortality among younger patients (< 50 years of age) that diminished with age. Survival was similar between the sexes among the elderly (> 70 years of age).

The higher early mortality among hospitalised women may also be attributed to a difference in survival pattern after an acute coronary event. Among those who died within 28 days in the Scottish MONICA (monitoring trends and determinants in cardiovascular disease) population of Glasgow,⁸ men were more likely to die out of hospital (74.3% v 67.8%; $p = 0.0004$). After hospitalisation, women were more likely to die, resulting in a similar 28 day case fatality rate between men (49.8%) and women (48.5%). However, in the MONICA project of 37 populations in 21 countries, the association between sex and MI outcome was inconsistent,⁹ varying between populations. We have shown strong ethnic differences both in the incidence of MI and in case fatality in Singapore.¹⁰ There may also be ethnic differences in the degree of sex discrepancy in mortality after MI in the context of a health care system that enables equal access to all Singapore citizens. Therefore, we compared short and long term coronary case fatality between men and women among Chinese, Indians, and Malays to determine the relation

between excess female mortality after an acute coronary event.

METHODS

Case identification and determination

The method adopted by the Singapore Myocardial Infarction Register (SMIR) has been described.¹¹ Briefly, it is a comprehensive population based register for all Singapore residents aged 20–64 years. Potential cases of MI, both in and out of hospital, were identified from discharge listings from all hospitals in Singapore (based on the *International classification of diseases*, 9th revision, codes 410 to 414), creatine kinase (CK) listings, the Registry of Births and Deaths, and postmortem reports. All pathology laboratories in Singapore submitted a quarterly listing of patients with CK ≥ 400 IU/l. It is a statutory requirement for all deaths to be reported within 24 hours of occurrence. All patients who were certified to have died of acute MI (usually out of hospital) were identified from the Registry of Births and Deaths. Necropsy reports were obtained where available. A structured questionnaire was also sent to the physician who certified out of hospital death to determine the events, symptoms, and signs before death. Trained investigators then rigorously evaluated all the reports of potential cases.

Demographic characteristics and clinical presentation were documented. However, this information was not available for a substantial number of patients who died out of hospital. Patient ethnicity was obtained from the source of

Abbreviations: CI, confidence interval; MI, myocardial infarction; MONICA, monitoring trends and determinants in cardiovascular disease; NRM-2, National Registry of Myocardial Infarction 2; SMIR, Singapore Myocardial Infarction Register

Table 1 Acute coronary events and 28 day case fatality by age and sex

Age (years)	Men		Women	
	Events	Deaths	Events	Deaths
20–24	14	5 (35.7%)	5	3 (60.0%)
25–29	45	16 (35.6%)	4	2 (50.0%)
30–34	232	72 (31.0%)	20	10 (50.0%)
35–39	628	182 (29.0%)	40	20 (50.0%)
40–44	1311	348 (26.5%)	127	62 (48.8%)
45–49	1874	533 (28.4%)	301	142 (47.2%)
50–54	2300	764 (33.2%)	485	234 (48.2%)
55–59	2888	1188 (41.1%)	992	503 (50.7%)
60–64	3531	1838 (52.1%)	1523	881 (57.8%)
All	12823	4946 (38.6%)	3497	1857 (53.1%)*
Mean (SD)	53.0 (8.3)	38.6%†	56.8 (6.7)*	51.5%†

* $p < 0.001$; †age adjusted to overall Singapore male event distribution.

notification. Offspring follow the ethnic group of the father. There are three major ethnic groups in Singapore: Chinese, Malays, and Indians, who are descendants of immigrants from China, the Malaysian Archipelago, and the Indian subcontinent, respectively. While intermarriage between ethnic groups was infrequent, the practice is becoming more common. Other ethnic groups, including Eurasians, are small (1.5%) and were excluded from analysis. Symptoms were classified as typical if chest pain, or a similar description, was the principal symptom of MI lasting for ≥ 20 minutes. A history of MI was obtained from the patient history or medical records. ECGs were read according to the Minnesota criteria.¹² Information on history and ECG was not available for patients who died before hospitalisation.

Patients were classified according to a local modification of the MONICA algorithm¹³ under one of nine diagnostic categories, as previously reported.¹¹ While the SMIR was restricted only to those with definite MI, the present study included patients with diagnostic categories of definite acute MI (MONICA NF1 category) or clinical acute MI, and death from MI with or without necropsy (MONICA F1, F2, and F9 categories). This paper reports the findings for the period from 1991 to 1999.

Invasive cardiac procedures

The Central Claims and Processing System of the Ministry of Health was established in 1990 for payment of hospital charges, including surgical procedure fees. For almost all residents, part of the payment is derived from a compulsory savings scheme and it is routinely audited to ensure accuracy of data collection. Specific charge codes were designed to capture the use of each invasive cardiac procedure—namely, coronary angiography, coronary angioplasty, and coronary artery bypass grafting. The date of the procedure was also entered. To determine whether and when the patient had undergone an invasive cardiac procedure, the SMIR was linked to this system until 31 December 2000.

Linkage to the registry of births and deaths

Besides providing a source for identification of cases, the SMIR is linked to the Registry of Births and Deaths to determine the vital status of each patient. Previous studies have documented the completeness of this information source.¹⁴ The last date of follow up for this report was 31 December 2000.

Statistical analysis

SPSS for Windows version 10 (SPSS Inc, Chicago, Illinois, USA) was used for data management and analysis. Several internal checks were set up in the database to ensure information quality.

χ^2 Tests were used to analyse differences in categorical variables and analysis of variance for continuous variables. Age was analysed as a continuous variable and was stratified into two groups: 20–54 years and 55–64 years. Kaplan-Meier estimates were performed for long term survival, with the log rank test for comparison between groups. Cox regression analysis was applied to predict survival outcomes by sex, age, and ethnic groups. Among hospitalised patients, the following covariates were used to adjust for the sex difference estimate in the Cox model: age, symptoms, peak CK concentration, history of previous MI, Q wave MI, and use of revascularisation procedures within 28 days. Interactions between either sex or age and ethnic groups were tested by introduction of product terms.

RESULTS

There were 16 320 acute coronary events, of which 12 823 (78.6%) occurred in men. Table 1 shows the distribution of acute coronary event and case fatality by age and sex. Women were older than men (56.8 v 53.0 years, $p < 0.001$). The number of events was 10-fold higher in men than in women between the ages of 20–34 years but this difference declined to about twofold for those between 60–64 years. Overall, the 28 day age adjusted case fatality rate was higher for women (51.5% v 38.6%, $p < 0.001$, odds ratio 1.81, 95% confidence

Table 2 Twenty eight day case fatality occurring before or after hospitalisation by ethnic group and sex

Timing of death	Chinese			Indians			Malays		
	Men	Women	OR (95% CI)	Men	Women	OR (95% CI)	Men	Women	OR (95% CI)
Before hospitalisation	28.9% (2317/8028)	36.6% (753/2055)	1.43 (1.29 to 1.58)	26.2% (597/2282)	35.5% (205/577)	1.56 (1.28 to 1.89)	29.2% (670/2294)	50.6% (410/811)	2.48 (2.10 to 2.92)
After hospitalisation	14.3% (816/5711)	21.6% (281/1302)	1.65 (1.42 to 1.92)	14.0% (236/1685)	22.3% (83/372)	1.76 (1.33 to 2.33)	14.3% (232/1624)	24.7% (99/401)	1.97 (1.51 to 2.57)
Total	39.0% (3133/8028)	50.3% (1034/2055)	1.58 (1.44 to 1.74)	37.3% (833/2282)	49.9% (288/577)	1.73 (1.44 to 2.08)	39.3% (902/2294)	62.8% (509/811)	2.60 (2.20 to 3.07)

CI, confidence interval; OR, odds ratio.

Figure 1 Kaplan-Meier plots showing long term survival after onset of an acute coronary event in the community for men and women between the ages of (A) 20–54 years ($p < 0.0001$) and (B) 55–64 years ($p < 0.0001$).

interval (CI) 1.67 to 1.95). The patients comprised 10 083 Chinese (61.8%), 3105 Malays (19.0%), and 2859 Indians (17.5%); 273 patients (1.7%) who belonged to other ethnic groups were excluded from subsequent analysis.

Twenty eight day case fatality from symptom onset: before and after admission to hospital

Overall, there was little difference between the two sexes in the proportion of deaths that took place before hospitalisation (73.6% in men and 74.7% in women, $p = 0.38$) (table 2). For men, this rate was similar among the three ethnic groups ($p = 0.37$). However, the proportion of deaths that occurred before hospitalisation among Malay women (80.6%) was higher than among Chinese (72.8%) and Indian women (71.2%) ($p = 0.001$). Regardless of ethnic group, 28 day case fatality among women was consistently higher than among men during both the pre-hospitalisation and post-admission

periods. There was also significant ethnic variation in the degree of female excess in case fatality, with the Malays having the largest sex gap.

Long term case fatality from symptom onset

After a mean (SE) follow up period of 987 (9) days, the case fatality rate remained higher among women (fig 1A). The overall age-ethnic adjusted hazard ratio for the female excess in long term case fatality was 1.31 (95% CI 1.24 to 1.37, $p < 0.001$). There were also significant interactions between age, sex, and ethnic group ($p = 0.001$). The degree of sex difference in survival diminished with age (fig 1B). Malays had the largest gap (table 3). Young Malay patients had the greatest sex discrepancy in long term case fatality.

Hospitalised MI patients

The following analyses are restricted to patients who survived until hospital admission.

Baseline characteristics

Women admitted for MI were older, were less likely to have had a previous Q wave or anterior wall MI, and had lower peak CK concentrations (table 4). They were less likely to undergo coronary angiography within 28 days of the event, but the rate of coronary revascularisation was comparable between the two sexes.

Case fatality rates after admission

Overall, the age adjusted 28 day and one year case fatality rates were higher for women (table 4). The adjusted hazard ratios for 28 day and one year case fatality were 1.64 (95% CI 1.43 to 1.88) and 1.56 (95% CI 1.39 to 1.75), respectively. Interaction between sex and ethnicity was not significant. After a mean (SE) follow up period of 1428 (10) days, the excess female case fatality persisted (adjusted hazard ratio 1.50, 95% CI 1.37 to 1.64). However, there were significant interactions between age, sex, and ethnic group ($p = 0.017$). The sex gap in long term case fatality diminished with age (fig 2). When only 28 day survivors were analysed, the long term mortality gap between men and women persisted (adjusted hazard ratio 1.40, 95% CI 1.24 to 1.57).

Case fatality was generally similar among the three ethnic groups for men but differed for women, with the highest mortality among Malay women, an intermediate rate among Indian women, and the lowest rate among Chinese women. With increasing duration of follow up, the sex difference appeared to narrow for Chinese but to widen for Malays (table 5). Eventually, Malays had the largest sex discrepancy with women being almost twice as likely to die as men.

Table 3 Long term coronary mortality according to sex, ethnicity, and age group

Age group (years)	Chinese		Indians		Malays	
	Men	Women	Men	Women	Men	Women
20–54	37.2% (1434/3859)	52.0% (291/560)	37.3% (466/1248)	63.8% (113/177)	40.4% (481/1190)	71.7% (167/233)
HR†	1.48 (1.30 to 1.68)***		1.93 (1.57 to 2.37)***		2.09 (1.75 to 2.50)***	
55–64	58.4% (2434/4169)	64.7% (968/1495)	56.0% (579/1034)	62.8% (251/400)	61.4% (678/1104)	79.9% (462/578)
HR†	1.14 (1.05 to 1.22)**		1.63 (1.27 to 2.10)*		1.50 (1.33 to 1.69)***	
20–64	48.2% (3868/8028)	61.3% (1259/2055)	45.8% (1045/2282)	63.1% (364/577)	50.5% (1159/2294)	77.6% (629/811)
Age adjusted HR†	1.19 (1.12 to 1.27)***		1.35 (1.20 to 1.53)***		1.62 (1.47 to 1.79)***	

†Cox regression (95% CI).

* $p = 0.041$; ** $p = 0.001$; *** $p < 0.001$.

HR, hazard ratio.

Table 4 Characteristics of patients treated in hospital for myocardial infarction

Characteristic	Men (n = 9016)	Women (n = 2074)	Age adjusted rates for women*
Age (years)†	53 (46, 59)	58 (53, 62)‡	
Ethnic group			
Chinese	5710 (63.3%)	1302 (62.8%)	
Indian	1624 (18.0%)	401 (19.3%)	
Malay	1682 (18.7%)	371 (17.9%)§	
Typical symptoms	6768 (75.1%)	1315 (63.4%)	64.4%‡
Previous MI	1048 (11.6%)	198 (9.5%)	8.1%‡
Q wave MI	6706 (74.4%)	1314 (63.4%)	63.1%‡
Anterior Q wave MI	3387 (37.6%)	680 (32.8%)	33.6%‡
CK (U/l)†	1189 (617, 2569)	878 (479, 1737)‡	
Angiography within 28 days	3434 (38.1%)	634 (30.6%)	33.1%‡
Revascularisation within 28 days	1385 (15.4%)	288 (13.9%)	15.0%§
28 day case fatality	1284 (14.2%)	463 (22.3%)	22.0%‡
1 year case fatality	1666 (18.5%)	604 (29.1%)	28.0%‡

*Adjustment based on male age structure; †median (25th and 75th centile); ‡p<0.001; §not significant for sex comparison.

CK, creatine kinase, MI, myocardial infarction.

DISCUSSION

We found that the acute coronary event case fatality rate was consistently higher for women than for men, during the periods both before and after hospitalisation and among 28 day survivors. The sex disparity persisted after a mean follow up period of 2.7 years. Despite an upper age limit of 64 years, there was evidence for a diminishing strength of association with age. With an increasing number of older women having an MI, the sex discrepancy is expected to reduce further. We also found a significant interaction between ethnic group, age, and sex for long term survival. The sex discrepancy was particularly evident for younger patients and smallest among Chinese patients.

Pre-hospitalisation and post-admission deaths

An earlier study of 5542 patients in the Glasgow MONICA centre attributed the female excess in coronary mortality among hospitalised patients⁸ to a higher proportion of men dying suddenly before hospitalisation, with the less vulnerable men surviving to be admitted. After hospital admission, more women died than men, resulting in a similar overall 28 day case fatality. Results from MONICA population registries for ages 35–64 years were conflicting.⁹ Among 29 populations studied, 28 day case fatality was higher among women in 13 (45%). When the studies were taken together, women were still more likely to die with an age adjusted ratio of 1.07 and of 1.24 for hospitalised patients. In contrast with the Scottish MONICA, our study found that women were more likely to die both before and after hospitalisation, although the disparity was greater after hospitalisation. These differences persisted after adjusting for age and ethnicity in our population. While the response to reperfusion treatment was similar between the two sexes,¹⁵ the adjusted 30–35 day mortality was still higher among women in two large international trials comprising more than 77 000 patients.^{7 16}

Hospitalised patients

The magnitude of the 28 day case fatality rate was consistent with most of the MONICA populations.⁹ Several studies have reported that long term mortality among survivors of MI are similar or lower among women,^{17–19} especially among older patients.²⁰ In a study of hospitalised MI survivors in the USA,⁶ two year mortality was higher among women < 60 years, whereas women ≥ 80 years old were less likely to die. We found that one year and four year case fatality rates of hospitalised patients were greater among younger women and that the extent of the sex difference in long term

mortality diminished with age. Of concern was that the sex disparity in long term mortality after MI persisted among 28 day survivors. The reasons for the excess mortality are uncertain and have been attributed to adverse baseline characteristics.²⁰ However, other investigators⁶ reported that the higher mortality among younger women persisted after controlling for inequalities in clinical condition and severity of MI. Coronary artery disease occurs less frequently among women.²¹ For MI to develop in young women, there must be substantial loss of protection, which might also have resulted in poorer outcome.²²

Figure 2 Kaplan-Meier plots showing long term survival after admission for a myocardial infarction event in men and women between the ages of (A) 20–54 years ($p < 0.0001$) and (B) 55–64 years ($p < 0.0001$).

Table 5 Case fatality rates among hospitalised patients according to sex and ethnic group

Case fatality	Chinese		Indians		Malays	
	Men (n=5710)	Women (n=1302)	Men (n=1682)	Women (n=371)	Men (n=1624)	Women (n=401)
28 days*	816 (14.3%)	281 (21.6%)	236 (14.0%)	83 (22.4%)	232 (14.3%)	99 (24.7%)
Adjusted† HR	1.59 (1.33 to 1.89)		1.67 (1.20 to 2.32)		1.75 (1.29 to 2.38)	
1 year**	1041 (18.2%)	352 (27.0%)	305 (18.1%)	110 (29.6%)	320 (19.7%)	142 (35.4%)
Adjusted† HR	1.46 (1.26 to 1.70)		1.69 (1.28 to 2.21)		1.71 (1.34 to 2.18)	
Long term***	1551 (27.2%)	506 (38.9%)	448 (26.6%)	159 (42.9%)	489 (30.1%)	219 (54.6%)
Adjusted† HR	1.30 (1.15 to 1.46)		1.71 (1.38 to 2.12)		1.96 (1.62 to 2.35)	

p Value for sex-ethnic group interaction *0.58, **0.11, ***0.017.

†The variables that were adjusted for in the Cox model were age, typical symptoms, history of previous MI, peak CK concentration, Q wave MI, and use of revascularisation procedures within 28 days.

95% CI in parentheses.

Sex, age, and ethnicity

While an earlier review,³ based largely on hospitalised patients, concluded that early mortality among women was not substantially increased after adjusting for baseline characteristics, reports based on large databases showed that women were at a higher risk of dying after MI,^{5, 23} especially younger patients. Similar mortality was observed between men and women among those ≥ 75 years in the National Registry of Myocardial Infarction 2 (NRFMI-2)⁵ and among patients ≥ 65 years in Medicare's cooperative cardiovascular project.²⁴ Recently, the Swedish national acute myocardial infarction register²⁰ reported that 28 day case fatality was higher among women < 50 years old (odds ratio 1.31, 95% CI 1.18 to 1.46). Similarly, we found that the age-sex interaction in case fatality was operative in a population registry and that the effect persisted during follow up. In addition, our population based registry had wide disparities in the female excess in coronary mortality among the three ethnic groups. While the age-sex relation was preserved in each ethnic group, Malays consistently had the greatest difference. In addition, we have found a significant interaction between sex and ethnicity on long term follow up. Of the three ethnic groups, the sex difference in long term case fatality was largest among Malays followed by Indians and then Chinese. These sex differences across ethnic groups were predominantly caused by inequalities in female survival, whereas ethnic differences in male case fatality were modest. The explanations for these discrepancies are unclear. It is likely that other factors, such as cultural, psychosocial, socioeconomic, and possibly other biological factors,²⁵ are operating for the sex difference to continue to diverge among hospitalised Malay patients. Our registry lacked data on risk and prognostic factors such as diabetes, which has been consistently associated with poorer outcome.²⁶ Nonetheless, our national health survey from 1998²⁷ provides some insight. The sex difference in prevalence of diabetes was greatest for Malays (14.3% v 8.2%) compared with Chinese (8.4% v 7.7%) and Indians (14.9% v 16.7%). Another reason may relate to the more frequent atypical presentation of MI among women than men (35.6% v 24.9% in the SMIR), which may have delayed seeking medical attention and prolonged the time to receiving life saving treatments,²⁸ particularly among young Malay women. Willingness to seek medical attention²⁹ and undergo procedures that may potentially improve long term outcome may also partly explain the disparity. In the USA, African Americans were less inclined to undergo cardiac procedures in the coronary care unit³⁰ or to consent to percutaneous coronary intervention³¹ and coronary artery bypass grafting.³² In Finland, the incidences of MI and 28 day and one year case fatality were significantly higher among those in the lower income groups and with only secondary education.³³ Similarly, male patients with little education were more likely to die suddenly after MI.³⁴ From 1990 to

2000, the proportion with tertiary education rose from 5.3% to 19.6% among Indians, from 9.2% to 19.6% among Chinese, and from only 1.5% to 4.9% for Malays in Singapore.³⁵

For several years, extensive public education programmes on heart attack have been conducted throughout the country. The annual healthy lifestyle campaign is a nationwide event designed to promote healthy living and eating habits among Singaporeans. Several strong disincentives have been established to curb tobacco abuse. Risk factors for atherosclerosis and the clinical manifestations of MI are even taught to young school children. Despite these efforts, wide sex and ethnic disparities persist in a relatively close knit and affluent society with a freely accessible health care system. The impact of adverse behavioural patterns, psychosocial and biological factors, and socioeconomic and educational status requires further study.

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IMAGES IN CARDIOLOGY

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Cardiac haematoma after coronary angioplasty

A 65 year old man presented with chest discomfort accompanied by ST elevation in leads V1-V5 on an ECG. Coronary angiography revealed severe stenosis in the mid portion of the left anterior descending artery (panel A, arrowhead). During percutaneous coronary intervention, a 0.014 inch guidewire was inserted into the septal perforator branch, leading to persistent extravasation of contrast media (panel B). Prolonged balloon inflation in the septal perforator and a reversal of anticoagulation resulted in a haemostasis with difficulty. Subsequent echocardiography showed a newly developed homogenous bulge proceeding from the septal wall (panels C and D: LA, left atrium; LV, left ventricle), with no accumulation of pericardial fluid. Fortunately, neither haemodynamic deteriorations nor elevations of cardiac enzymes occurred during the clinical course of this unfavourable complication. The huge haematoma in his heart was gradually resorbed and disappeared completely several weeks later.

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