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Interactions of ST-elevation myocardial infarction, age, and sex and the risk of major adverse cardiovascular events among Chinese adults: a secondary analysis of a single-centre prospective cohort

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ABSTRACT

Objectives This study aimed to evaluate the interactions of ST-elevation myocardial infarction (STEMI), ageing and sex with respect to the incidence of major adverse cardiovascular events (MACE) among Chinese adults.

Design Secondary analysis of a single-centre prospective cohort.

Setting Patients who were admitted to cardiology clinics of the Affiliated Hospital of Jiangsu University due to acute myocardial infarction (MI) from June 2017 to November 2019 were eligible for inclusion in the study. This research only examined in-hospital cases.

Participants Patients aged <18 years or confirmed dead within 24 hours from admission were excluded. A total of 843 adults were included in the analysis.

Primary and secondary outcome measures MACE was defined as any occurrence of cardiovascular mortality, MI recurrence, cardiogenic shock or heart failure. The relative excess risk due to interaction (RERI), attributable proportion (AP) and the synergy index were computed to quantify the interactions. Men without STEMI and adults without STEMI aged <60 years were the reference groups when examining the risk of MACE.

Results The female participants with STEMI showed a statistically higher risk of MACE compared with the male participants without STEMI (relative risk (RR): 2.713, CI: 1.350 to 5.426, p=0.005). A 3.327 times higher risk of MACE was detected in the older adults with STEMI (aged ≥60 years) compared with the adults without STEMI aged <60 years (RR: 3.327, CI: 1.414 to 8.955, p=0.01). Older female patients also had an increased risk of MACE (RR: 3.033, CI: 1.432 to 6.777, p=0.005). A positive additive interaction was detected between STEMI and age (RERI: 1.917, CI: 0.196 to 3.637; AP: 0.576, CI: 0.174 to 0.979). STEMI and sex also indicated an additive interaction (AP: 0.459, CI: 0.018 to 0.899).

Conclusion In this Chinese population with MI, the risk of MACE was increased by about 2.7 times in women with STEMI compared with men without STEMI. MACE incidence increased by about 3.3 times in older patients with STEMI compared with younger patients without STEMI. STEMI and age, and STEMI and sex, may have a positive additive interaction.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The additive and multiplicative interactions were quantified.
⇒ Missing data were filled using multiple imputation to retain the maximum sample size.
⇒ Limitations of this study included limited generalisability for other ethnic groups and potential confounding variables in the complex process of major adverse cardiovascular event progression.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death worldwide, resulting in 18.6 million global deaths in 2019, according to the American Heart Association.[1] In China, CVD accounts for more than 40% of mortality. Furthermore, the prevalence increases substantially, approximately 14.7%, from 1991 to 2016 in China.[2] Associating with substantial physiological and economic burdens, CVD has led to a vast research endeavour. Major adverse cardiovascular events (MACE), composed of multiple severe cardiovascular endpoints, is widely used as research outcomes in cardiovascular studies.

Numerous studies are designated to explore approaches to prevent and manage MACE, and several risk factors have been identified, such as smoking, physical activity, nutritional intake, weight status, high blood pressure, metabolic syndrome, blood cholesterol and lipid profile, kidney disease, etc.[1] Age and sex are two conventional risk factors associated with cardiovascular conditions. The risk of cardiovascular conditions is higher in

adult women than adult men, which may be attributed to the disparities in sex steroid hormones.[1 3] The incidence of MACE increases progressively during the ageing process due to the declined physiological and biological functions.[4–6]

Myocardial infarction (MI), commonly known as heart attack, is the cardiac myocytes injury caused by the blockage of the arteries.[7] As the most severe manifestation of coronary artery disease, MI affects more than 7 million people worldwide. There are two types of MI, ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (non-STEMI), mainly distinguished by the difference in an ECG. As a precursor of STEMI, ST-segment elevation is strongly related to the occurrence of MACE,[8] the monitoring of which is essential to predict recurrent myocardial ischaemia following MI.[9] Therefore, accurately identifying and distinguishing the morphological variations of the ST segment have clinical significance.

Interaction refers to the effect of one exposure on an outcome change when another exposure is present. Although the individual risk factor of cardiovascular conditions has been well established, the joint interactions among MACE risk factors are understudied and remain an assumption in the Chinese population. Thus, the objective of this study is to evaluate the interactions of STEMI, ageing and sex on the incidence of MACE among Chinese adults.

METHODS

Study design

This prospective cohort study pooled data of patients who were admitted to cardiology clinics of the Affiliated Hospital of Jiangsu University due to acute MI from June 2017 to November 2019. Patients who were <18 years or confirmed dead within 24 hours from admission were excluded. Data from 843 adults were included in the final analysis of this study. This study only examined inpatient cases, and follow-ups were performed during the treatment. Furthermore, cardiovascular death and hospital remission were considered endpoints of the study. Therefore, no loss to follow-up occurred in the analysis. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013. The original data of this study were included in the Improving Care for Cardiovascular Disease in China (CCC) Project. All data were stored and managed by the main centre (Beijing Anzhen Hospital) of the CCC Project. This study used de-identified data sent and approved by the Beijing Anzhen Hospital Ethics Committee.

Patient and public involvement

Patients were not directly involved in this research. De-identified data were used for analysis in this study.

Outcomes

Currently, no consensus definition of MACE has been established. Various endpoints have been used in previous studies.[10 11] The primary outcome of this study was the occurrence of the MACE, defined as the occurrence of cardiovascular mortality, MI recurrence, cardiogenic shock, or heart failure. Participants were categorized into the MACE group if any of the conditions appeared. STEMI and non-STEMI were diagnosed according to the guidelines developed by the China Society of Cardiology of Chinese Medical Association 2020 and 2012, respectively.[12 13] The presence of cardiogenic shock was determined based on the European Society of Cardiology definition.[14] Heart failure was defined according to the Chinese guidelines for the diagnosis and treatment of heart failure.[15]

Potential covariates

Demographic characteristics, including age, sex and education level, were collected in the clinical records on admission. Heart rate, blood pressure, weight, and height were measured and recorded in the clinical records. Body mass index (BMI) was calculated using body weight and height (kg/m^2). Since the history of angina, MI, percutaneous coronary intervention (PCI), coronary artery bypass graft, atrial fibrillation, chronic heart failure, hypertension, diabetes, stroke, peripheral vascular disease, chronic obstructive pulmonary disease, renal insufficiency, smoking, and alcohol consumption were associated or coexisted with the MACE, they were extracted from the medical history records and investigated in this research.

Laboratory indicators

Creatine kinase-MB (CKMB), an isoenzyme of creatine kinase found in the heart muscle cells,[16] is a cardiac marker to assess acute MI. Another protein that regulates the heart muscle contraction and indicates the progression of MI is troponin.[17] Brain natriuretic peptide (BNP) is a cardiac hormone secreted from the cardiomyocytes to maintain normal cardiorenal function. Therefore, serum creatinine, troponin and BNP were evaluated in this research. Since hepatic diseases are linked with cardiac diseases bidirectionally,[18] liver enzymes, alanine aminotransferase (ALT) and aspartate transaminase (AST) were analysed. Total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) were also examined because lipid profile is strongly associated with CVD.[19]

Statistical analysis

All analyses were two-tailed tests. SAS V.9.4 (SAS Institute) was used to perform multivariable analysis. R (V.4.0.3) was applied to create forest plots (https://CRAN.R-project.org/package=forestplot) and analyse possible interactions. Multiple imputation was completed by R CRAN-Package mice (r-project.org).[20] Alpha=0.05 was used to determine the significance of the analysis. The

Table 1 Multiple imputation and sensitive analysis

Variable	Missing data, n (%)	Before (n=843)	After (n=843)	P value
Height, cm, mean±SD	40 (4.74)	166.49±7.48	166.57±7.51	0.826
Weight, kg, mean±SD	132 (15.68)	67.82±12.17	68.50±12.24	0.276
Troponin, M (Q_1, Q_3)	9 (1.07)	4.67 (0.57, 16.10)	4.48 (0.56, 15.60)	0.864
CKMB, M (Q_1, Q_3)	12 (1.43)	21.50 (4.90, 56.70)	21.05 (4.85, 56.70)	0.985
ALT, M (Q_1, Q_3)	1 (0.12)	33.00 (21.00, 55.00)	33.00 (21.00, 54.70)	0.969
AST, M (Q_1, Q_3)	1 (0.12)	72.70 (31.70, 168.60)	72.60 (31.70, 167.50)	0.982
FPG, M (Q_1, Q_3)	2 (2.37)	5.99 (5.12, 8.12)	5.99 (5.12, 8.12)	1.000
TC, mean±SD	9 (1.07)	4.57±1.14	4.57±1.14	0.962
TG, M (Q_1, Q_3)	9 (1.07)	1.60 (1.12, 2.21)	1.61 (1.12, 2.22)	0.931
HDL, mean±SD	9 (1.07)	1.01±0.29	1.01±0.29	0.946
LDL, M (Q_1, Q_3)	9 (1.07)	2.53 (2.01, 3.19)	2.53 (2.02, 3.19)	0.946
INR, M (Q_1, Q_3)	22 (2.61)	0.97 (0.92, 1.03)	0.97 (0.92, 1.03)	0.820
BNP, M (Q_1, Q_3)	16 (1.90)	137.00 (38.30, 476.00)	137.00 (38.20, 475.00)	0.962

ALT, alanine aminotransferase; AST, aspartate transaminase; BNP, brain natriuretic peptide; CKMB, creatine kinase-MB; FPG, fasting plasma glucose; HDL, high-density lipoprotein; INR, international normalised ratio; LDL, low-density lipoprotein; M, median; Q, quartile; TC, total cholesterol; TG, triglyceride.

distribution of variables was tested for normality by the Shapiro normality test. Normally distributed continuous variables were expressed in means and SDs (mean±SD), while non-normally distributed variables were displayed in medians and IQRs (M (Q_1, Q_3)). Intergroup comparisons were conducted by the independent t-test or the Mann-Whitney test when appropriate. Categorical variables were shown as numbers and percentages (n (%)) and compared by the X^2 test or Fisher's exact test.

Missing data and outliers

If missing data constituted for less than 25% of the variable dataset, multiple imputation was used to fill the missing data. Multiple imputation is a well-established statistical technique commonly used in clinical and epidemiological studies to prevent bias from excluding participants with incomplete records.[21 22] Since the missing data were replaced by plausible values, a sensitivity analysis was conducted to evaluate the validity of estimated values. Values that were three times greater than the 75th percentile of each variable dataset were considered as outliers and were therefore replaced by the maximum value calculated using multiple imputation. The missing frequency plot (online supplemental file 1) and correlation table (online supplemental file 2) were uploaded. Since the missing variables were not significantly correlated with other variables, the majority of missing data were missing at random.

Interactions

Multivariable logistic regression analyses were performed to investigate the influence of age, sex and STEMI on the risk of MACE. Three regression models were constructed when investigating the individual effect of age, sex and STEMI on MACE risk. Model 1 (unadjusted model) was the crude model, not adjusting any variables. Model 2 (clinically adjusted model) controlled for BMI, heart rate and diastolic blood pressure (DBP). Model 3 (clinical and laboratory parameter-adjusted model) controlled for BMI, DBP, heart rate, troponin I, creatinine and BNP.

Similarly, three models were implemented when examining the impact of potential interactions on MACE risk. Furthermore, the effect of the interactions of the three variables—age, sex and STEMI—in MACE incidence was also examined using logistic regression analysis. Three interactions were analysed: STEMI and sex, STEMI and age, and sex and age. Model 1 was the unadjusted model. Model 2 adjusted for BMI, heart rate, DBP with STEMI–sex interaction further controlled for age, STEMI–age interaction further controlled for sex and sex–age interaction further controlled for STEMI. Model 3 controlled for troponin I, creatinine and BNP, in addition to the effects adjusted in model 2. The relative risk (RR) and the 95% CI were obtained.

The relative excess risk due to interaction (RERI) and attributable proportion (AP) were computed to quantify the additive effect of the interactions, which were commonly used in epidemiological studies.[23] The RERI was defined as RERI=RR11−RR10−RR01+1, where RR was combined with two exposure statuses (1=exposed; 0=unexposed).[24] The (AP)=RERI/RR11 calculated the proportion of disease in the exposed group that can be attributed to the exposure. An additive effect existed if the CI of RERI or AP did not contain 0. The magnitude of multiplicative interaction was assessed by the synergy index (S), where (S)=RR11/(RR10×RR01).[25] A multiplicative interaction was significant if the CI did not include 1.

Table 2 Intergroup comparison of baseline characteristics

Variables	Total (n=843)	Non-MACE (n=736)	MACE (n=107)	P value
Demographic characteristics				0.007
Education level, n (%)				
Middle school	268 (31.79)	240 (32.61)	28 (26.17)	
College/university and above	67 (7.95)	60 (8.15)	7 (6.54)	
Elementary school and below	364 (43.18)	302 (41.03)	62 (57.94)	
Technical secondary school	144 (17.08)	134 (18.21)	10 (9.35)	
Sex, n (%)				<0.001
Male	623 (73.90)	558 (75.82)	65 (60.75)	
Female	220 (26.10)	178 (24.18)	42 (39.25)	
Age, years, mean±SD	66.20±13.12	65.06±12.83	74.05±12.44	<0.001
BMI, kg/m^2, mean±SD	24.42±3.56	24.40±3.54	24.54±3.68	0.710
Heart rate, count, mean±SD	80.21±16.05	79.20±15.31	87.19±19.10	<0.001
SBP, mm Hg, mean±SD	130.21±22.17	130.58±21.74	127.65±24.92	0.251
DBP, mm Hg, mean±SD	76.89±13.97	77.45±13.70	73.06±15.23	0.002
Medical history				
Angina (yes), n (%)	155 (18.39)	136 (18.48)	19 (17.76)	0.857
MI (yes), n (%)	48 (5.69)	38 (5.16)	10 (9.35)	0.081
PCI (yes), n (%)	90 (10.68)	77 (10.46)	13 (12.15)	0.597
CABG (yes), n (%)	6 (0.71)	4 (0.54)	2 (1.87)	0.170
Atrial fibrillation (yes), n (%)	19 (2.25)	16 (2.17)	3 (2.80)	0.723
Chronic heart failure (yes), n (%)	11 (1.30)	7 (0.95)	4 (3.74)	0.040
Hypertension (yes), n (%)	563 (66.79)	481 (65.35)	82 (76.64)	0.021
Diabetes (yes), n (%)	218 (25.86)	178 (24.18)	40 (37.38)	0.004
Stroke (yes), n (%)	77 (9.13)	56 (7.61)	21 (19.63)	<0.001
Peripheral vascular disease (yes), n (%)	3 (0.36)	1 (0.14)	2 (1.87)	0.044
COPD (yes), n (%)	18 (2.14)	13 (1.77)	5 (4.67)	0.066
Renal insufficiency (yes), n (%)	14 (1.66)	9 (1.22)	5 (4.67)	0.023
History of smoking, n (%)				0.023
Never smoked	522 (61.92)	440 (59.78)	82 (76.64)	
Quit smoking	39 (4.63)	36 (4.89)	3 (2.80)	
Currently smoking	282 (33.45)	260 (35.33)	22 (20.56)	
Drinking alcohol (yes), n (%)	65 (7.71)	62 (8.42)	3 (2.80)	0.042
Laboratory indicators				
Troponin (ng/mL), M (Q_1, Q_3)	4.52 (0.56, 16.30)	3.97 (0.51, 14.25)	8.69 (2.22, 21.40)	<0.001
CKMB (ng/mL), M (Q_1, Q_3)	21.10 (4.80, 57.00)	20.90 (4.60, 56.10)	23.70 (7.30, 67.60)	0.142
Haematocrit (%), M (Q_1, Q_3)	41.30 (37.20, 44.90)	41.75 (37.80, 45.10)	38.00 (34.50, 42.50)	<0.001
Platelet count (10^9/L), mean±SD	201.74±63.76	200.60±64.03	209.58±61.64	0.174
Creatinine (μmol/L), M (Q_1, Q_3)	70.90 (58.90, 89.70)	70.10 (58.50, 86.25)	84.20 (65.80, 119.40)	<0.001
ALT (μ/L), M (Q_1, Q_3)	33.00 (21.00, 55.00)	33.00 (21.45, 53.40)	35.00 (17.90, 68.70)	0.515
AST (μ/L), M (Q_1, Q_3)	72.50 (31.70, 167.50)	72.70 (31.70, 165.75)	72.00 (31.00, 196.60)	0.610
FPG (mmol/L), M (Q_1, Q_3)	5.99 (5.11, 8.12)	5.87 (5.05, 7.79)	7.23 (5.65, 10.35)	<0.001
TC (mmol/L), mean±SD	4.57±1.14	4.56±1.09	4.64±1.44	0.566
TG (mmol/L), M (Q_1, Q_3)	1.60 (1.12, 2.21)	1.62 (1.13, 2.27)	1.37 (1.09, 1.84)	0.012
HDL (mmol/L), mean±SD	1.01±0.29	1.01±0.29	1.04±0.31	0.405

Continued

Table 2 Continued

Variables	Total (n=843)	Non-MACE (n=736)	MACE (n=107)	P value
LDL, mmol/L, M (Q_1, Q_3)	2.53 (2.02, 3.19)	2.53 (2.04, 3.17)	2.55 (1.91, 3.27)	0.778
INR, M (Q_1, Q_3)	0.97 (0.92, 1.03)	0.97 (0.92, 1.02)	1.02 (0.95, 1.09)	<0.001
BNP, pg/mL, M (Q_1, Q_3)	134.00 (37.00, 468.00)	112.00 (31.35, 342.00)	777.00 (286.00, 1780.00)	<0.001
ECG				
ST-elevation (yes), n (%)	356 (42.23)	301 (40.90)	55 (51.40)	0.040

ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; BNP, brain natriuretic peptide; CABG, coronary artery bypass graft; CKMB, creatine kinase-MB; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL, high-density lipoprotein; INR, international normalised ratio; LDL, low-density lipoprotein; M, median; MACE, major adverse cardiovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; Q, quartile; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

RESULT

Multiple imputation

As summarised in table 1, multiple imputation was performed to fill missing data in 13 variable datasets, including height, weight, troponin, CKMB, ALT, AST, fasting plasma glucose (FPG), TC, TG, HDL, LDL, international normalised ratio (INR) and BNP. Except for weight, missing data consisted of less than 10% of each variable dataset. A total of five imputation sets were created. Further sensitivity analysis of the multiple imputation was conducted. The plausible values filled by multiple imputation did not significantly impact the original dataset since no statistical differences were detected before and after multiple imputation.

Intergroup comparisons

The average follow-up time was 10.45±5.04 days, with a median being 10 (7, 12) days. Baseline characteristics were compared between the MACE and non-MACE groups (table 2). For demographic and anthropometric characteristics, age, sex, education level, heart rate and blood pressure were significantly different between groups. A considerably higher percentage of the study participants in the MACE group reported having a history of chronic heart failure, hypertension, diabetes, stroke, peripheral vascular disease and renal insufficiency compared with the non-MACE group. A lower percentage of people were smokers or alcohol consumers in the MACE group compared with the non-MACE group. When examining the laboratory biomarkers, troponin, haematocrit, serum creatinine, FPG, TG, INR and BNP were significantly different between the MACE and non-MACE groups. The ECG revealed a higher proportion of participants having STEMI in the MACE group than the non-MACE group (51.4% vs 40.90%, p=0.04).

Three models were constructed when investigating the individual impact of age, sex and STEMI on the risk of MACE (table 3 and figure 1). In the unadjusted model, age (<0.001), sex (0.001) and STEMI (0.041) were all

Table 3 Individual effect of age, sex and STEMI on the risk of MACE

	Unadjusted model*		Clinically adjusted model†		Clinical and laboratory parameter-adjusted model‡	
Variables	RR (95% CI)	P value	RR (95% CI)	P value	RR (95% CI)	P value
Age						
Age <60	Reference					
Age ≥60	3.810 (2.167 to 7.258)	<0.001	3.668 (2.004 to 7.218)	<0.001	2.453 (1.290 to 4.980)	0.009
Sex						
Male	Reference					
Female	2.026 (1.320 to 3.083)	0.001	1.581 (1.010 to 2.468)	0.045	1.302 (0.779 to 2.147)	0.307
STEMI						
No	Reference					
Yes	1.529 (1.018 to 2.299)	0.041	1.481 (0.965 to 2.275)	0.072	1.940 (1.188 to 3.200)	0.009

*Model 1 (unadjusted model): the unadjusted crude model.
†Model 2 (clinically adjusted model): adjusted for body mass index, diastolic blood pressure and heart rate.
‡Model 3 (clinical and laboratory parameter-adjusted model): adjusted for body mass index, diastolic blood pressure, heart rate, troponin I, creatinine and brain natriuretic peptide.
MACE, major adverse cardiovascular events; RR, relative risk; STEMI, ST-elevation myocardial infarction.

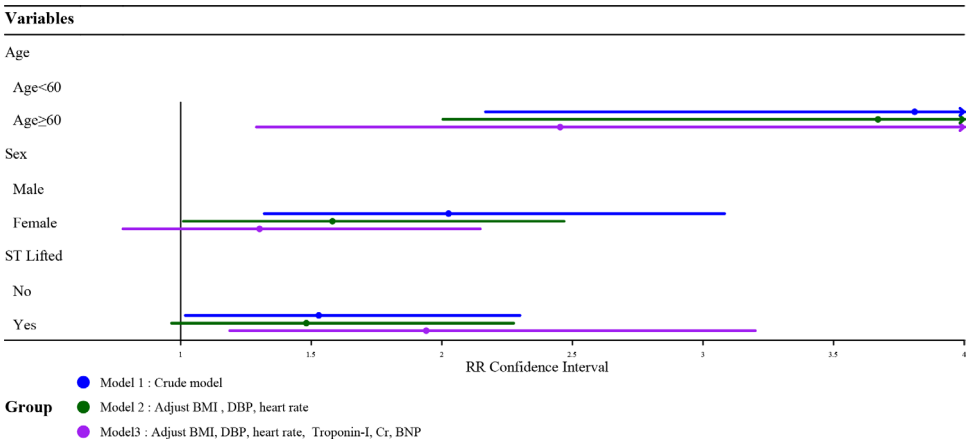

Figure 1 Multivariable logistic regression analysis: the influence of single variable on MACE risk. Model 1 (unadjusted model) was the crude model; model 2 (clinically adjusted model) adjusted for body mass index (BMI), diastolic blood pressure (DBP) and heart rate; model 3 (clinical and laboratory parameter-adjusted model) controlled for BMI, DBP, heart rate, troponin I, creatinine (Cr) and brain natriuretic peptide (BNP). MACE, major adverse cardiovascular events; RR, relative risk.

associated with MACE risk. In the clinically adjusted model, the risk of MACE increased 3.668 times in participants aged ≥60 years compared with participants aged <60 years (RR: 3.668, CI: 2.004 to 7.218, p<0.001). Women showed a significantly higher risk of MACE than men (RR: 1.581, CI: 1.010 to 2.468, p=0.045). When further controlling for laboratory biomarkers in the clinical and laboratory parameter-adjusted model, MACE incidence was 2.453 times higher in older adults than adults (RR: 2.453, CI: 1.290 to 4.980, p=0.009). Compared with the non-STEMI group, a significantly higher risk of MACE was observed in the STEMI group (RR: 1.940, CI: 1.188 to 3.20, p=0.009).

Interactions

Three interactions, STEMI and sex, STEMI and age, and age and sex, were analysed in table 4 and figure 2. Men without STEMI, younger adults without STEMI (<60 years) and younger men aged <60 years were set as the three reference groups since the risk of cardiovascular events is higher in women, older adults and patients with STEMI.

When examining the synergistic effect of STEMI and sex on MACE risk, male participants without STEMI were the reference group. The female participants with STEMI showed a statistically higher risk of MACE compared with the reference group (RR: 2.476, CI: 1.320 to 4.595, p=0.004). The risk further increased in the clinical and laboratory parameter-adjusted model (RR: 2.713, CI: 1.350 to 5.426, p=0.005). For the interaction between STEMI and age, adults aged <60 years without STEMI were the reference. The risk of MACE increased in older adults without STEMI aged ≥60 years in the clinically adjusted model (RR: 2.714, CI: 1.219 to 6.924, p=0.022). However, the risk remained the highest in older adults with STEMI (RR: 4.36, CI: 1.953 to 11.162, p<0.001). In the clinical and laboratory parameter-adjusted model, only older adults with STEMI displayed a higher risk of MACE (RR: 3.327, CI: 1.414 to 8.955, p=0.01). In sex and age interaction, younger men aged <60 years were the reference group. In the clinically adjusted model, younger women aged <60 years were associated with a 3.155 times higher risk of MACE. Nevertheless, the MACE risk increased significantly in older women aged ≥60 years (RR: 5.364, CI: 2.706 to 11.351, p<0.001). Similarly, older women aged ≥60 years showed the most significant increase of MACE risk when compared with the reference group (RR: 3.033, CI: 1.432 to 6.777, p=0.005).

Table 4 also demonstrated the quantified measures of each interaction. STEMI and sex generated a significant additive effect since the CI of AP did not include 0 (AP=0.459, CI: 0.018 to 0.899). Similarly, an additive effect has also been observed between STEMI and age since the CI of both AP and RERI did not contain 0 (AP=0.576, CI: 0.174 to 0.979; RERI=1.917, CI: 0.196 to 3.637). No additive nor multiplicative interactions were found between sex and age.

DISCUSSION

Main findings

Our study investigated the risk of MACE when STEMI, age and sex jointly interacted with each other in the Chinese population. When examining the individual risk factors, age and STEMI are associated with 2.453 times and 1.940 times higher risk of MACE, respectively. Sex was not linked to the incidence of MACE in the individual analysis. However, the RR of MACE increased when examining the potential interactions among the three variables. The incidence of MACE increased 2.713 times in women with STEMI compared with men without STEMI. Among older adults with STEMI, MACE incidence increased 3.327 times comparing younger adults without STEMI. Older women showed a 3.033 times higher occurrence of MACE than younger men.

When quantitating the interactions, STEMI and sex showed a positive additive interaction with AP=0.459, implying 45.9% of the MACE incidence may be attributed

Table 4 Quantitative measures of potential interactions

Interactions	Unadjusted model		Clinically adjusted model†		Clinical and laboratory parameter-adjusted model‡	
	RR (95% CI)	P value	RR (95% CI)	P value	RR (95% CI)	P value
STEMI and sex		LR§=0.003		LR=0.027		LR=0.007
STEMI (no) and sex (male)	Reference					
STEMI (no) and sex (female)	1.832 (0.999 to 3.362)	0.05	1.306 (0.685 to 2.430)	0.406	0.918 (0.429 to 1.895)	0.82
STEMI (yes) and sex (male)	1.414 (0.844 to 2.368)	0.187	1.284 (0.748 to 2.199)	0.361	1.550 (0.855 to 2.829)	0.149
STEMI (yes) and sex (female)	3.118 (1.728 to 5.623)	<0.001	2.476 (1.320 to 4.595)	0.004	2.713 (1.350 to 5.426)	0.005
STEMI and age		LR<0.001		LR<0.001		LR=0.001
STEMI (no) and age (<60)	Reference					
STEMI (no) and age (≥60)	3.542 (1.731 to 7.247)	0.001	2.714 (1.219 to 6.924)	0.022	1.494 (0.623 to 4.044)	0.394
STEMI (yes) and age (<60)	1.772 (0.755 to 4.157)	0.188	0.894 (0.275 to 2.819)	0.847	0.916 (0.273 to 3.01)	0.884
STEMI (yes) and age (≥60)	5.392 (2.620 to 11.099)	<0.001	4.362 (1.953 to 11.162)	<0.001	3.327 (1.414 to 8.955)	0.01
Sex and age		LR<0.001		LR<0.001		LR=0.096
Sex (male) and age (<60)						
Sex (male) and age (≥60)	0.647 (0.081 to 5.164)	0.68	0.574 (0.031 to 3.193)	0.605	0.573 (0.030 to 3.298)	0.608
Sex (female) and age (<60)	2.984 (1.558 to 5.716)	0.001	3.158 (1.647 to 6.476)	<0.001	2.183 (1.101 to 4.625)	0.032
Sex (female) and age (≥60)	5.159 (2.622 to 10.151)	<0.001	5.364 (2.706 to 11.351)	<0.001	3.033 (1.432 to 6.777)	0.005

Interactions	RERI	AP	S	P value
STEMI and sex	1.245 (–0.414 to 2.904)	0.459 (0.018 to 0.899)¶	1.907 (0.725 to 5.108)	0.194
STEMI and age	1.917 (0.196 to 3.637)¶	0.576 (0.174 to 0.979)¶	2.431 (0.679 to 8.904)	0.17
Sex and age	1.276 (–0.600 to 3.152)	0.421 (–0.125 to 0.967)	2.422 (0.388 to 47.565)	0.427

*Model 1 (unadjusted model): the unadjusted model.
†Model 2 (clinically adjusted model): adjusted for body mass index, diastolic blood pressure and heart rate. STEMI and sex further controlled for age; STEMI and age further controlled for sex; sex and age further controlled for STEMI.
‡Model 3 (clinical and laboratory parameter-adjusted model): adjusted for body mass index, diastolic blood pressure, heart rate, troponin I, creatinine and brain natriuretic peptide. STEMI and sex further controlled for age; STEMI and age further controlled for sex; sex and age further controlled for STEMI.
§LR: p value of the likelihood ratio test.
¶RERI and AP were significant when the CI does not include 0.
AP, attributable proportion; RERI, relative risk due to interaction; RR, relative risk; S, synergy index; STEMI, ST-elevation myocardial infarction.

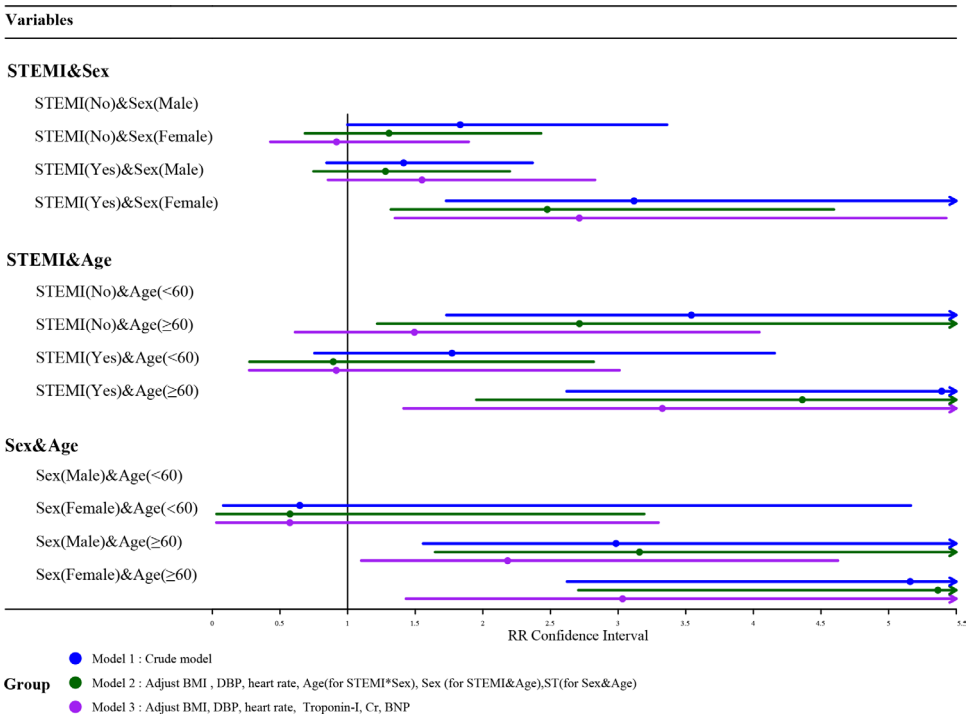

Figure 2 Multivariable logistic regression analysis: the influence of interactions on MACE risk. Model 1 (unadjusted model) was the unadjusted model; model 2 (clinically adjusted model) adjusted for body mass index (BMI), diastolic blood pressure (DBP) and heart rate. STEMI and sex further controlled for age; STEMI and age further controlled for sex; sex and age further controlled for STEMI. Model 3 (clinical and laboratory parameter-adjusted model): adjusted for BMI, DBP, heart rate, troponin I, creatinine (Cr) and brain natriuretic peptide (BNP). STEMI and sex further controlled for age; STEMI and age further controlled for sex; sex and age further controlled for STEMI. MACE, major adverse cardiovascular events; RR, relative risk; STEMI, ST-elevation myocardial infarction.

to the synergistic interaction between STEMI and sex. Additionally, a positive additive interaction was present between STEMI and age, with 57.6% of the MACE incidence being attributed to the interaction. The multivariable analysis also proved the potential interactions, with women with STEMI and older adults with STEMI indicating the greatest risk of MACE comparing with their reference groups. Using the RERI, AP and S, we were able to estimate the potential biological interactions instead of statistical interactions among the three variables.[26] Thus, the synergistic biological interactions detected in our study indicate that a combination of these factors poses a significantly greater risk of MACE than a single risk factor. The greater risk of these interactions may be attributed to biological, clinical and behavioural determinants.

Ageing

According to the China Country Assessment Report on Aging and Health developed by the WHO, the size of the elderly population is expanding at a much faster rate in China compared with other low/middle-income countries. The projected elderly population ageing 60 years or older will reach 28% by 2040.[27] Since ageing is the premier risk factor of developing cardiac diseases, the rising elderly population contributes to an increased lifetime risk of MACE. One consistent physiological change of cardiac ageing is a declined myocardial reserve capacity.[5 28] Decreased heart rate and variability and increased left ventricular (LV) mass are also associated with ageing.

The ageing process impacts the cardiac structure and function on a molecular and cellular level by modulating several pathways autophagy, increasing mitochondrial oxidative stress, telomere attrition, alterations in the insulin-like growth factor pathway, growth differentiation factor 11 and 5-AMP-activated protein kinase signalling pathways.[4 5] Various factors are involved in the heart's ageing process, such as collagen, matrix metalloproteinases, cardiac fibroblast cell physiology, cardiomyocyte cell physiology, cardiac macrophage physiology and myocardial endothelial cell physiology.[28] Furthermore, ageing is associated with the attenuation of autophagy, a strategy combating the age-associated accumulation of damaged cellular components, promoting the development of heart failure, hypertension, atherosclerosis and ischaemic heart disease.[29] The oxidative stress theory of ageing proposes that the reactive oxygen species (ROS) damage increases with age, resulting in the accumulation of macromolecular damage.[30] The presence of ROS is linked to LV dysfunction, arrhythmia and cardiac remodelling,[31] implying a higher risk of MACE in the elderly population.

Sex

Biological sex disparities in cardiac function were established by scientists in the early 20th century. In-hospital

mortality is higher in women than in men with STEMI.[1] In addition, a higher intrinsic heart rate, as well as lower heart rate variability, has been observed in women than men, possibly due to differences in ion channels and electrical activities.[32] In the ageing process, sex discrepancies in cardiac system change also exist, with women showing a more rapid increase in the LV wall thickness and higher prevalence of heart failure with preserved ejection fraction than men.[33] Such disparities may vary due to the differences in sex hormones, remodelling patterns and extracellular matrix components.[34] Although our interaction analysis did not reveal a significant synergistic effect between age and sex, the risk of MACE in older women increases approximately threefold compared with the reference, implying the importance of managing cardiovascular conditions in such population.

Clinically, women suffer from a higher risk of several cardiac conditions and greater complications. A 5-year retrospective study examined the sex disparity of post-PCI prognosis in patients with STEMI.[35] The findings demonstrated a higher incidence of in-hospital mortality and post-intervention complications in female participants than the male participants. Another study investigating patients with acute coronary syndrome revealed a higher risk of MACE in women after receiving PCI compared with men.[36]

Besides biological differences, behavioural factors may also increase the risk of MACE. The mortality rate of patients with STEMI is substantially lower, up to 51% reduction when medical intervention is performed within 60 min of the onset of symptoms.[37] Scientists have observed disparities in seeking medical care among patients with STEMI in northeastern China.[38] Older female patients showed a significantly greater extent of prehospital delays than younger male patients with STEMI, therefore, potentially increasing the risk of MACE. A more recent multicentre study yielded similar results.[39] Women and older patients with acute STEMI had longer pain-to-call delays than men and younger patients, which possibly explained the synergistic effect found in our study. Uneven distribution of medical resources, lack of socioeconomic support and low education level may contribute to such disparities.

Strengths and limitations

The prevalence of MACE varied from 9.1% to 15.8%, which is similar to the prevalence of our study, 12.7%, implying the representativeness of the study sample. In this research, we not only analysed each interaction as a risk factor but also provided quantitative measures of the interactions. RERI, AP and S were computed to estimate the measures of the interactions. Nevertheless, the shortcomings of our study need to be addressed. This research only examined in-hospital MACE patients, resulting in a short-term clinical outcome. The progression of MACE involved complex biological, environmental and socioeconomic factors, which may be the confounding factors in this study. However, we adjusted multiple significant anthropometric, behavioural and biochemical variables to minimise the influence of confounding variables. Another shortcoming of this study is the limited generalisability. The race of this research is limited to Chinese Asians, which may not be generalisable to other races. Furthermore, selection bias may exist since the sample collection was restricted to Jiangsu province, a developed, high-income province where medical resources are sufficient.

In China, the rate of hospital admission for STEMI has increased substantially, while the in-hospital mortality has not decreased,[40] reflecting the necessity of improving the understanding as well as management of such conditions. Our study uncovers more insights regarding MI by quantitatively assessing the interactions of STEMI, age and sex in affecting the risk of MACE in Chinese patients. The results of this study provide fundamental information to support future studies exploring the cause of disparities and addressing potentially modifiable risk factors, such as establishing health education programmes and intervention, and increasing the accessibility of medical care among certain groups.

CONCLUSION

In this Chinese population with MI, the risk of MACE was increased by about 2.7 times in women with STEMI compared with men without STEMI. MACE incidence was increased by about 3.3 times in older adults with STEMI compared with younger adults without STEMI. A positive additive interaction exists between STEMI and age, and STEMI and sex. No synergistic effect was observed between sex and age. Future studies with longer follow-up time are needed since our study only examined in-hospital MACE cases. The quantitated interactions revealed in our study support future studies to research the explanation of the interactions and develop possible solutions.

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Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by the Beijing Anzhen Hospital Ethics Committee (NCT02306616). Signed informed consent was obtained from all study participants or guardians.

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