

## ORIGINAL ARTICLE

# Mortality After ST-Segment–Elevated Myocardial Infarction Among Patients With and Without Standard Modifiable Cardiovascular Risk Factors in China

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**BACKGROUND:** Patients without standard modifiable cardiovascular risk factors (SMuRF) have an associated increased mortality with ST-segment–elevation myocardial infarction. This study aims to provide insight into the clinical features, treatments, and outcomes of SMuRF-less patients.

**METHODS:** This nationwide, multicenter cohort study utilized data from the Chinese Cardiovascular Association Database–Chest Pain Center, a national registry derived from electronic medical records of accredited chest pain centers across China. We included adults aged ≥18 years with ST-segment–elevation myocardial infarction admitted between January 1, 2017, and December 31, 2021. The index date was the date of hospital admission. SMuRF included hypertension, diabetes, hyperlipidemia, or smoking, ascertained from medical records at admission. SMuRF-less status was defined as the absence of all 4 risk factors. Outcomes included all-cause mortality at 0 to 30 days and 31 to 365 days. Multivariable Cox regression and landmark analysis were used to assess associations between SMuRF status and mortality.

**RESULTS:** Of 379 811 ST-segment–elevation myocardial infarction patients, 87 830 (23.1%) were SMuRF-less. The 30-day all-cause mortality was higher in SMuRF-less patients than in those with SMuRF (10.7% versus 6.7%). After multivariable adjustment, SMuRF-less status remained independently associated with increased 30-day mortality (adjusted hazard ratio, 1.22 [95% CI, 1.19–1.25]). In the 31- to 365-day follow-up period, the mortality rate was numerically higher in the SMuRF-less group (3.8% versus 3.2%), but there was no significance after covariate adjustment (adjusted hazard ratio, 1.00 [95% CI, 0.95–1.04]). The elevated 30-day mortality associated with SMuRF-less status was consistent across most subgroups but significantly more pronounced in men than in women ( $P$  for interaction  $<0.001$ ).

**CONCLUSIONS:** In this nationwide analysis, nearly one-quarter of ST-segment–elevation myocardial infarction cases were SMuRF-less. Compared with patients with SMuRF, the mortality excess in SMuRF-less patients was confined to the first 30 days, and mortality did not differ subsequently.

**Key Words:** acute coronary syndrome ■ cardiovascular diseases ■ China ■ myocardial infarction ■ risk factors

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## WHAT IS KNOWN

- A substantial number of patients with ST-segment-elevation myocardial infarction present without any standard modifiable risk factors (SMuRF), and international studies indicate this SMuRF-less subgroup experiences unexpectedly higher in-hospital mortality despite their seemingly lower-risk profile.
- Although this early survival disadvantage in SMuRF-less patients is well-documented in Western registries, the mortality gap compared with SMuRF patients has been observed to diminish over longer-term follow-up.

## WHAT THE STUDY ADDS

- This large Chinese national study confirms SMuRF-less ST-segment-elevation myocardial infarction is independently associated with significantly higher 30-day mortality, a risk that persists despite adjustment for clinical characteristics and receipt of guideline-directed treatments.
- Crucially, the excess mortality risk entirely disappears after 30 days, and the early disadvantage is particularly pronounced in male patients, suggesting distinct sex-specific pathophysiological mechanisms or care disparities.
- Guideline-directed therapy and primary percutaneous coronary intervention did not fully mitigate the excess early risk in SMuRF-less patients.

CVD.<sup>2</sup> Hypertension, hyperlipidemia, diabetes, and smoking are well-established modifiable cardiovascular risk factors (SMuRF) commonly linked to CVD and routinely used to assess acute myocardial infarction (AMI) risk in patients.<sup>3</sup> Harmonized individual-level data from a global cohort showed that 22.2% and 19.1% of deaths from any cause among women and men, respectively, may be attributable to 5 modifiable risk factors.<sup>4</sup>

However, a substantial proportion of ST-segment-elevation myocardial infarction (STEMI) patients present without these traditional risk factors, known as SMuRF-less patients.<sup>5</sup> In Western populations, studies have shown that SMuRF-less patients tend to have higher early mortality and worse short-term outcomes, despite being perceived as low-risk due to the absence of modifiable risk factors.<sup>6</sup> These patients often experience delays in diagnosis, treatment initiation, and lower adherence to guideline-directed therapies, which contribute to their adverse outcomes.<sup>6,7</sup> Similar findings have been observed in several countries, including Canadian and US cohorts, where SMuRF-less patients exhibit higher in-hospital mortality and poorer prognoses.<sup>8,9</sup>

Studies from developing countries are scarce, with China having only 1 study based on data from 2014.<sup>10</sup> However, research on this population remains limited, and there is a lack of large-scale, nationwide studies examining their clinical characteristics, treatment disparities, and outcomes. Previous studies have identified underutilization of evidence-based therapies, particularly among women, contributing to the increased mortality observed in this group.<sup>6,11</sup> Despite this, most research in the world has been hospital-based, with few exploring long-term outcomes or addressing the impact of sex and treatment delays on survival, and there is relatively less data from China.

This present study aims to provide a comprehensive analysis of the clinical features, treatment patterns, 0- to 30-day and 31- to 365-day mortality of SMuRF-less patients with STEMI, using data from the China Chest Pain Center database, one of the largest national registries in the country. By comparing SMuRF-less and SMuRF patients, we sought to highlight the critical need for timely interventions and improved adherence to guideline-directed therapies, particularly for vulnerable subgroups like women, to improve overall clinical outcomes.

## Nonstandard Abbreviations and Acronyms

<b>ACE</b>	angiotensin-converting enzyme
<b>ACS</b>	acute coronary syndrome
<b>AMI</b>	acute myocardial infarction
<b>CCA</b>	Chinese Cardiovascular Association
<b>CHD</b>	coronary heart disease
<b>CVD</b>	cardiovascular disease
<b>FMC</b>	first medical contact
<b>GDMT</b>	guideline-directed medical therapy
<b>PCI</b>	percutaneous coronary intervention
<b>SMuRF</b>	standard modifiable cardiovascular risk factors
<b>STEMI</b>	ST-segment-elevation myocardial infarction
<b>TIMI</b>	Thrombolysis in Myocardial Infarction

The past 30 years have witnessed a rapid increase in cardiovascular disease (CVD) incidence, posing significant challenges to global healthcare systems.<sup>1</sup> The 2022 Report on Cardiovascular Health and Diseases in China highlights the ongoing rise in CVD prevalence and mortality, estimating 330 million individuals currently affected and attributing 2 out of 5 deaths to

## METHODS

### Data Availability

The data analyzed in this study were based on the Chinese Cardiovascular Association (CCA) database. Individual-level data in the registers can only be accessed through secure servers, and only the export of aggregated data, as presented in research articles, is allowed as per law. Permission to access

data can be made only after fulfilling specific requirements to safeguard the anonymity of the study participants. For these reasons, data cannot be made generally available.

## Study Design and Population

The National Chest Pain Centers Program is a large-scale, multifaceted initiative focused on continuous quality improvement for managing acute chest pain. In October 2019, the National Health Commission launched the China Alliance of Chest Pain Centers to enhance accreditation standards and expand the establishment of chest pain centers nationwide. The program operates through a centralized, web-based registry, the CCA Database–Chest Pain Center, where hospitals independently collect and submit case data. These data, extracted from medical records, cover patient demographics, prehospital interventions, presenting symptoms, in-hospital treatments (including medication and reperfusion), and discharge outcomes.<sup>12,13</sup> By the end of 2021, 5107 hospitals participated in the accreditation project, with 2096 achieving accreditation—1047 under the standard model and 1049 under the basic model.

We analyzed all patient records from the CCA Database–Chest Pain Centers, covering admissions from January 1, 2017, to December 31, 2021. Eligible patients for this analysis were adults aged  $\geq 18$  years who presented with suspected acute coronary syndrome (ACS) and were diagnosed with STEMI. Exclusion criteria included a history of revascularization procedures (such as percutaneous coronary intervention [PCI], coronary artery bypass grafting, or myocardial infarction) and unclear SMuRF group assignments (Figure 1).

The data were processed to remove all information that could reveal patients' identities. Anonymized data are available through a formal application process and after review by the

Data Management Committee of the CCA Database–Chest Pain Center. The study protocol was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the institutional review board at the Tianjin Medical University General Hospital (IRB2022-WZ-145). Informed consent was waived due to the retrospective nature of the study.

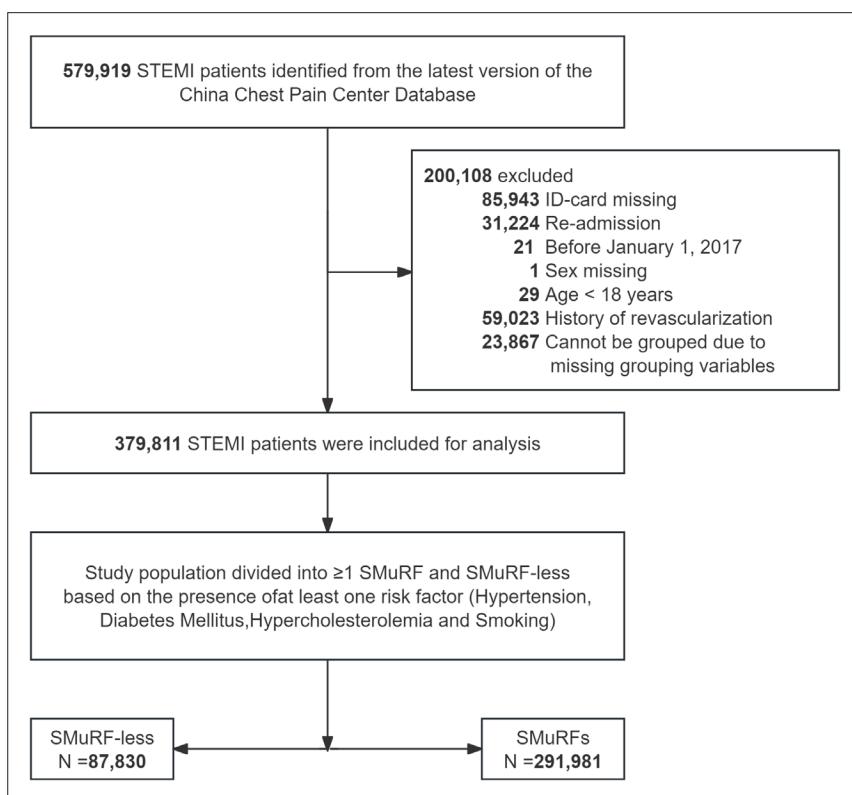
Individual-level data in the registers can only be accessed through secure servers, and only the export of aggregated data, as presented in research articles, is allowed as per law. Permission to access data can be made only after fulfilling specific requirements to safeguard the anonymity of the study participants. For these reasons, data cannot be made generally available.

## Definition of SMuRF

The exposure variable was defined as the presence of 1 or more SMuRF: a history of hypertension, diabetes, hyperlipidemia, or smoking. Hypertension, diabetes, and hyperlipidemia histories were classified based on diagnoses from the hospital. A history of smoking was defined as regular smoking ( $\geq 1$  cigarette per day) before the index hospitalization. SMuRF patients were defined as having at least 1 of the aforementioned risk factors, whereas SMuRF-less patients had no documented SMuRF in their admission medical records.

## Study Variables

Reperfusion therapy was defined as the reopening of the occluded coronary vessel and included thrombolysis, primary PCI, transport PCI, and coronary artery bypass grafting. Indicators of STEMI patients' access to care include time from



**Figure 1. Flowchart of patients included in the study.**

ID indicates identity document; STEMI, ST-segment–elevation myocardial infarction; and SMuRF, standard modifiable cardiovascular risk factors.

symptom onset to first medical contact, time from first medical contact to wire crossing in primary PCI patients, and time from first medical contact to needle initiation in patients receiving thrombolytic therapy. They also include metrics of effective reperfusion, such as successful thrombolysis or achieving a TIMI (Thrombolysis in Myocardial Infarction) flow grade of 3, and timely reperfusion, defined as time from first medical contact to needle initiation <30 minutes or time from first medical contact to wire crossing <120 minutes. We also included data on patients' admission blood pressure, heart rate, Killip classification, in-hospital treatments (including reperfusion), and emergency medications administered at admission.

The primary outcome was all-cause mortality assessed at 2 landmark periods: 0 to 30 days and 31 to 365 days, defined as death within the specified time from the index date or period start. The secondary outcome was cardiac mortality. The study utilized unique national IDs to link patient data with the China National Death Registration System,<sup>14</sup> ensuring accurate vital status tracking for all patients in the China Alliance of Chest Pain Center database.

## Statistical Analysis

Categorical variables were summarized as frequencies and percentages. Numerical variables were summarized as the mean (SD) or the median (interquartile range), depending on data distribution. To explore differences in characteristics, in-hospital findings, and management between SMuRF-less patients and patients with SMuRF, categorical variables were analyzed using the  $\chi^2$  test, and continuous variables using Student *t* tests. Associations between the exposure variable and study outcomes were assessed using multivariable Cox regression models to estimate hazard ratios (HR) and 95% CIs. Cumulative mortality risk, stratified by SMuRF-less status, was constructed using the Kaplan-Meier method. The proportional hazards assumption was tested using the Schoenfeld residuals test. Due to violation of the proportional hazard assumption, Kaplan-Meier curves were compiled in the context of a landmark analysis with a 30-day threshold to assess at 0- to 30-day and 31- to 365-day periods, defined as death within the specified time from the index date or period start.<sup>15</sup> Covariates for adjustment included: sex, age, pulse, respiration rate, blood pressure on admission, previous medical history, Killip class, reperfusion therapy, and initial in-hospital medications. We applied multiple imputations using chained equations across 5 data sets to impute missing values for these clinical variables.

We evaluated the association with SMuRF status on 0- to 30-day and 31- to 365-day mortality, considering sex-specific treatment differences in patients with STEMI. In addition, we analyzed the characteristics and outcomes of SMuRF versus SMuRF-less patients in both men and women.

All analyses were done with STATA software (version 17.0) and R software (version 4.2.0). A 2-sided *P* value of <0.05 was considered to indicate statistical significance.

## RESULTS

From January 1, 2017, to December 31, 2021, 579 901 adult patients with STEMI were identified in the CCA database. After excluding individuals with a history of myocardial infarction or revascularization, the remaining

379 811 patients constituted the study population. Of the 379 811 patients, 87 830 (23.1%) were SMuRF-less, and 291 981 (76.9%) had ≥1 SMuRF before hospitalization (Figure 1).

Baseline demographics, distribution of SMuRF, and in-hospital treatments are presented in the Table. The median age of the study population was 64 years. Compared with SMuRF patients, those without SMuRF were older at the onset of STEMI. Of these patients, 24.4% were women. Patients with SMuRF had a lower proportion of women. Among patients with SMuRF, the most common condition was hypertension (185 982 [63.7%]), followed by smoking (137 210 [47.0%]), diabetes (79 927 [28.3%]), and hyperlipidemia (76 365 [26.2%]). SMuRF-less patients were less likely to have histories of conditions, such as obesity, coronary heart disease (CHD), family history of premature CHD, heart failure, peripheral artery disease, and chronic kidney disease.

On presentation of STEMI, SMuRF-less patients had significantly lower systolic blood pressure and heart rate compared with those with SMuRF, and the cardiac function classification at admission was worse. The time from symptom onset to first medical contact and the time from first medical contact to needle initiation were significantly shorter in patients with SMuRF. However, there was no significant difference in time from first medical contact to wire crossing between SMuRF-less patients and patients with SMuRF. Patients with SMuRF were more likely to achieve effective reperfusion (85.3% versus 79.0%).

In terms of emergency medication therapy, SMuRF-less patients were less likely to receive guideline-directed medical therapy (GDMT), including antiplatelet drugs (91.5% versus 94.0%), statins (76.9% versus 80.4%), and  $\beta$ -blockers (32.4% versus 36.7%). Furthermore, SMuRF-less patients were less likely to undergo reperfusion therapy (81.1% versus 85.6%) and primary PCI (53.5% versus 62.7%).

## Zero- to 30-Day and 31- to 365-Day Mortality

During the 1-year follow-up, a total of 40 689 patients died, including 12 365 (14.1%) in the SMuRF-less group and 28 324 (9.7%) in the SMuRF group. The curves diverged from the initial day of STEMI presentation. The cumulative mortality risk is depicted in Figure 2A.

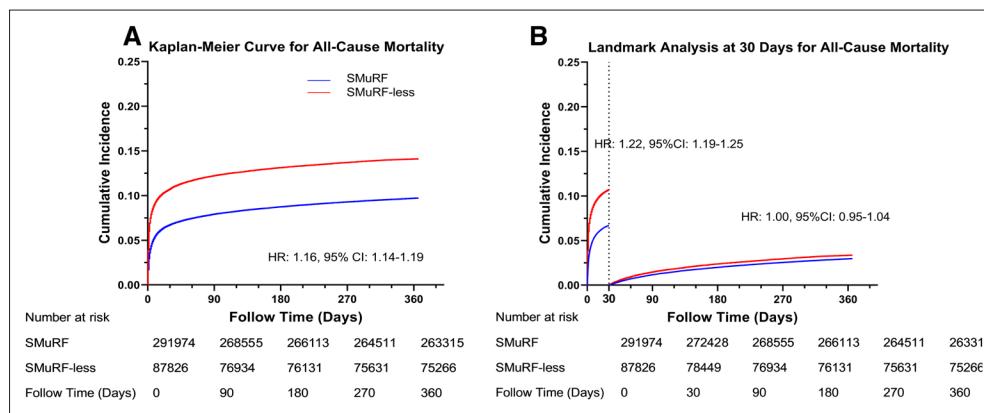
For 30-day mortality (Figure 2B; Figure 3; Table S1), 9377 out of 87 626 patients (10.7%) in the SMuRF-less group died, compared with 19 546 out of 291 571 patients (6.7%) in the SMuRF group. SMuRF-less status was associated with a higher risk of death in the crude analysis (HR, 1.64 [95% CI, 1.59–1.67]) and in the multivariable-adjusted analysis (HR, 1.22 [95% CI, 1.19–1.25]).

For mortality from 31 to 365 days (Figure 2B; Figure 3; Table S2), 2988 out of 78 249 patients (3.8%) in the SMuRF-less group died, compared with 8778 out of 272 025 patients (3.2%) in the SMuRF group. In crude

**Table. Patient Characteristics**

Characteristics	Total; N=379811	SMuRF-less; n=87830	SMuRF; n=291981	P value
Admission characteristics				
Age, y, median (IQR)	64.0 (53.0–72.0)	65.0 (54.0–74.0)	63.0 (53.0–72.0)	<0.001
Women, n (%)	93 949 (24.7)	25 815 (29.4)	68 134 (23.3)	<0.001
SMuRF, n (%)				
Hypertension	185 982 (49.0)	0 (0.0)	185 982 (63.7)	<0.001
Hyperlipidemia	76 365 (20.1)	0 (0.0)	76 365 (26.2)	<0.001
Diabetes	79 927 (21.6)	0 (0.0)	79 927 (28.3)	<0.001
Smoking history	137 210 (36.1)	0 (0.0)	137 210 (47.0)	<0.001
Clinical characteristics				
SBP, mean (SD)	132.2 (26.9)	126.9 (25.5)	133.9 (27.1)	<0.001
Consciousness, sober (%)	374 610 (98.7)	86 313 (98.3)	288 297 (98.8)	<0.001
Respiratory rate, median (IQR)	20 (18–20)	20 (18–20)	20 (18–20)	<0.001
Heart rate, median (IQR)	77 (65–90)	76 (64–89)	77 (65–90)	<0.001
Killip I class, n (%)	270 705 (74.7)	61 803 (73.5)	208 902 (75.1)	<0.001
Killip IV class, n (%)	21 823 (6.0)	5849 (7.0)	15 974 (5.7)	<0.001
Previous history, n (%)				
Family history of premature CHD	9908 (2.6)	1676 (1.9)	8232 (2.8)	<0.001
Obesity	24 219 (6.4)	1860 (2.1)	22 359 (7.7)	<0.001
Coronary heart disease	122 419 (32.2)	23 263 (26.5)	99 156 (34.0)	<0.001
Atrial fibrillation	14 473 (3.8)	3098 (3.5)	11 375 (3.9)	<0.001
Heart failure	20 652 (6.0)	4076 (5.0)	16 576 (6.3)	<0.001
Valvular heart disease	4623 (1.2)	982 (1.1)	3641 (1.2)	0.002
Peripheral artery disease	12 813 (3.5)	1756 (2.0)	11 057 (3.9)	<0.001
COPD	7362 (2.0)	1413 (1.6)	5949 (1.0)	<0.001
CKD	11 759 (3.2)	1389 (1.6)	10 370 (3.7)	<0.001
Anemia	9398 (2.5)	2056 (2.3)	7342 (2.6)	<0.001
Peptic ulcer	6688 (1.8)	1238 (1.4)	5450 (1.9)	<0.001
Thyroid dysfunction	5810 (1.6)	945 (1.1)	4865 (1.7)	<0.001
Cancer	3945 (1.1)	951 (1.1)	2994 (1.1)	0.54
Emergency medication, n (%)				
Antiplatelet	338 650 (93.4)	77 025 (91.5)	261 625 (94.0)	<0.001
Statin	273 822 (79.6)	61 495 (76.9)	212 327 (80.4)	<0.001
β-Blocker	119 819 (35.7)	25 327 (32.4)	94 492 (36.7)	<0.001
In-hospital management, n (%)				
S-to-FMC	372 882	86 059	286 823	NA
Median (IQR), min	167 (69–547)	173 (70–578)	165 (68–540)	<0.001
FMC-to-W	184 194	36 580	147 614	NA
Median (IQR), min	93 (70–151)	93 (70–153)	93 (70–151)	0.55
FMC-to-N	46 878	11 995	34 883	NA
Median (IQR), min	34 (25–62)	33 (24–60)	35 (25–63)	<0.001
Effective reperfusion	184 342 (83.9)	37 354 (79.0)	146 988 (85.3)	<0.001
Timely reperfusion	141 272 (64.2)	29 321 (63.1)	111 951 (64.4)	<0.001
Reperfusion therapy	306 862 (84.6)	68 263 (81.1)	238 599 (85.6)	<0.001
Primary PCI	219 391 (60.6)	44 993 (53.5)	174 398 (62.7)	<0.001
Thrombolysis	38 351 (10.6)	10 324 (12.3)	28 027 (10.1)	<0.001

Consciousness: evaluated using the Alert, Voice, Pain, Unresponsive scale at the initial hospital presentation (alert, responsive to verbal stimuli, pain-responsive, unresponsive). The figures in the table represent the proportion of alert. CHD indicates coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; FMC-to-N, time from first medical contact to needle initiation; NA, not applicable; FMC-to-W, time from first medical contact to wire crossing; IQR, interquartile range; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; SMuRF, standard modifiable cardiovascular risk factors; and S-to-FMC, time from symptom onset to first medical contact.



**Figure 2. Kaplan-Meier survival curves for all-cause mortality up to 1 year.**

**A**, The Kaplan-Meier curve for all-cause mortality within 1 year in the overall population. **B**, The landmark analysis curve for all-cause mortality within 1 year in the overall population. SMuRF indicates standard modifiable cardiovascular risk factors.

analysis without covariate adjustment, patients without SMuRF had a higher mortality risk (HR, 1.19 [95% CI, 1.14–1.23]). However, in the multivariable-adjusted analysis, SMuRF-less status was not associated with increased mortality (HR, 1.00 [95% CI, 0.95–1.04]).

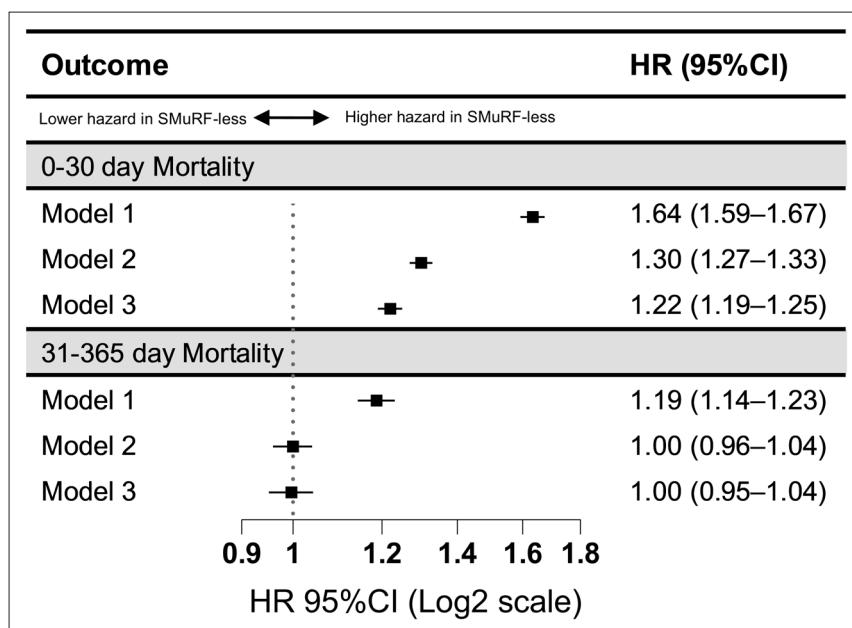
In the secondary outcome analysis, within 0 to 30 days of admission, cardiac death accounted for 80.4% (23209/28,923) of all causes of death, and at 31- to 365-day follow-up, cardiac death accounted for 78.3% (31846/40,689) of all causes of death. The results for cardiac death were similar to those for all-cause mortality (Figures S1 and S5).

### Subgroup Analysis

However, interactions were observed only for age and sex with respect to 30-day mortality. During the 0 to 30

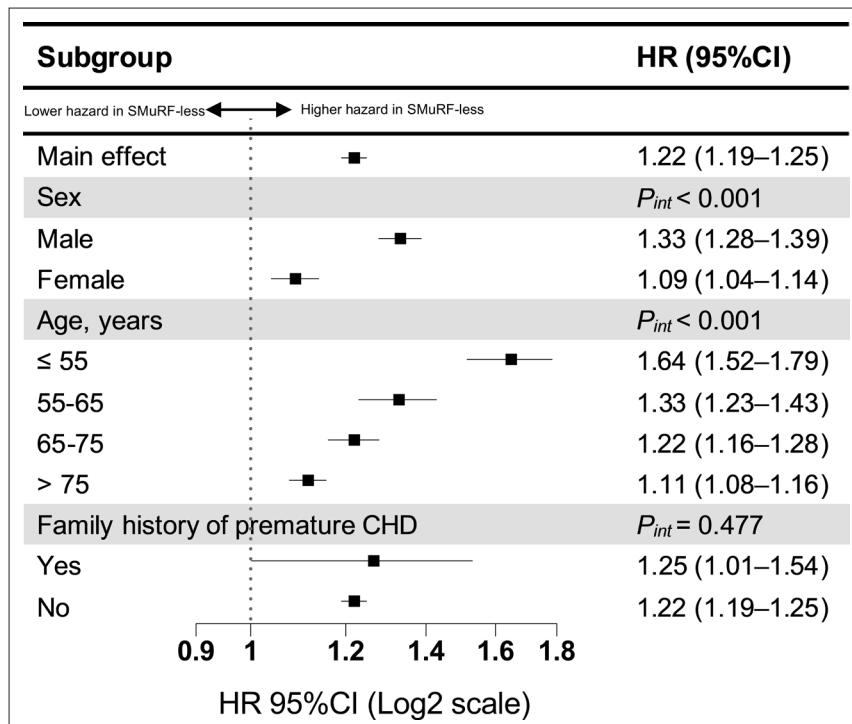
days follow-up period, we observed that while mortality increased with age, the association with SMuRF-less status on mortality gradually diminished ( $P$  for interaction  $<0.001$ ). By the 31- to 365-day follow-up, the mortality difference between the SMuRF and SMuRF-less groups disappeared. Among patients with a family history of premature CHD, the impact of SMuRF-less status on mortality was no longer observed, either within 30 days or between 31 and 365 days (Figure 4).

Notably, among male patients, after adjusting for covariates, those without SMuRF had significantly higher mortality risk (HR, 1.33 [95% CI, 1.28–1.39]). The outcomes in women were similar, though the influence was weaker: after adjustment, a significant difference in mortality was observed for patients without SMuRF (HR, 1.09 [95% CI, 1.04–1.14];  $P$  for interaction  $<0.001$ ; Figure 4). Surprisingly, the association with SMuRF-less



**Figure 3. Hazard ratios (HRs) for all-cause mortality between standard modifiable cardiovascular risk factor (SMuRF)-less patients and patients with SMuRF within 0 to 30 days and 31 to 365 days.**

Point estimates and 95% CIs are presented from Cox regression analyses in the total population. Cox regression models, Model 1: Unadjusted; Model 2: Model adjusted for admission sign (age, sex, respiratory rate, heart rate, awareness, and Killip classification on admission); Model 3: Model adjusted for admission sign, past history (coronary heart disease [CHD], family history of premature CHD, atrial fibrillation, heart failure, valvular heart disease, peripheral artery disease, chronic obstructive pulmonary disease, chronic kidney disease, anemia peptic ulcer, thyroid dysfunction, and cancer) and treatment measures (statins,  $\beta$ -blocker, antiplatelet, reperfusion therapy, and symptom onset to first medical contact).



**Figure 4. Subgroup analysis of hazard ratios (HRs) for primary outcome between standard modifiable cardiovascular risk factor (SMuRF)-less patients and patients with SMuRF with 30 days.**

The subgroup analysis of point estimates and 95% CIs derived from Cox regression analyses for all-cause mortality within 30 days in the total population. Cox regression analyses, model: model adjusted for admission sign, past history, and treatment measures. CHD indicates coronary heart disease.

status on 31- to 365-day mortality was no longer evident in either male or female patients with STEMI after excluding those who died within 30 days (Figures S3). Baseline demographics, SMuRF distribution, and in-hospital treatments, stratified by sex and SMuRF status, are shown in Table S3. Crude and adjusted all-cause and cardiac mortality differences between the SMuRF-less and SMuRF groups are presented in Figure 5 and Figure S1.

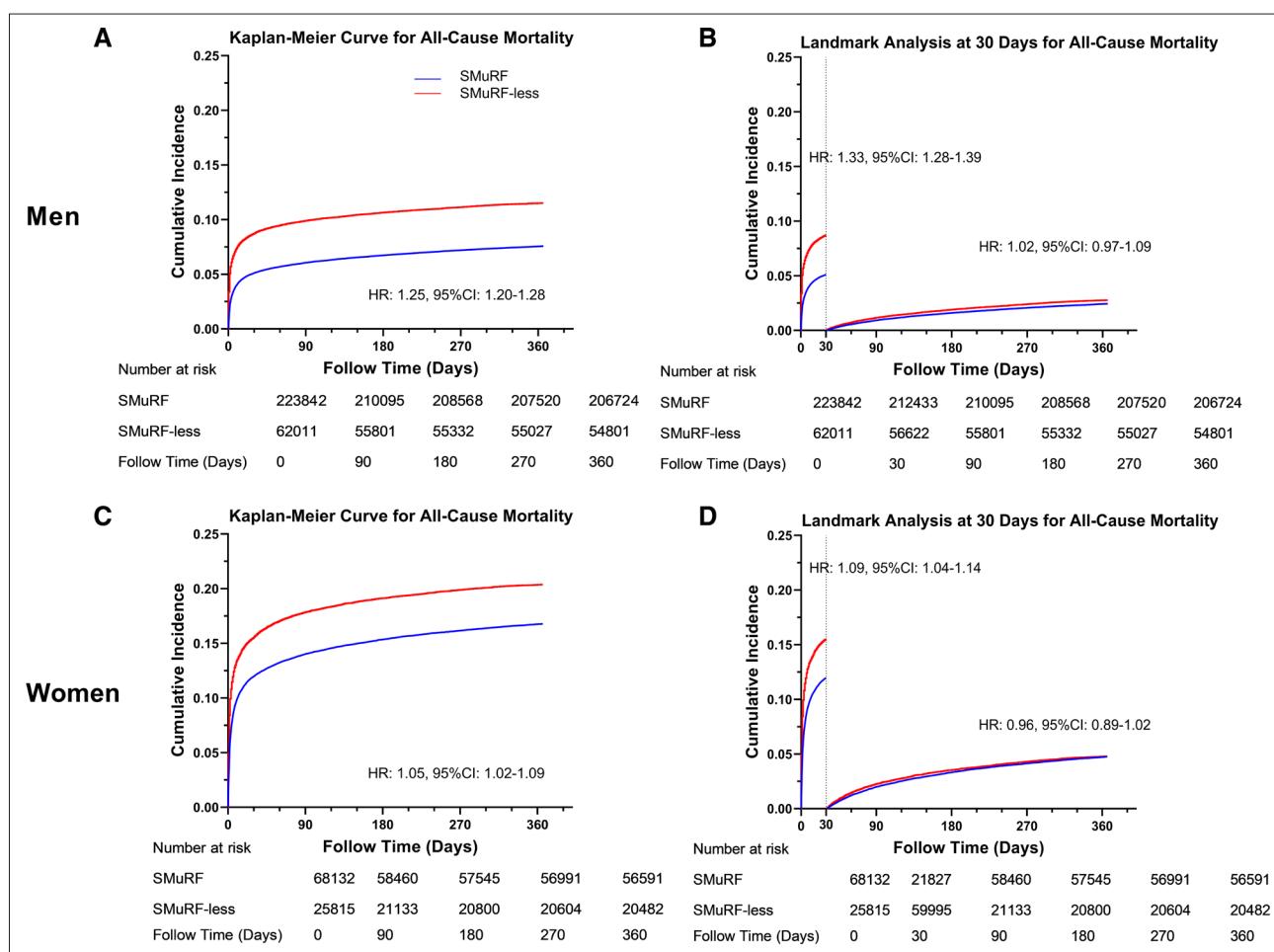
Subgroup analyses revealed critical variations in mortality risk by revascularization status, GDMT timing, and sex. Regardless of early GDMT administration, SMuRF-less patients exhibited persistently elevated 0- to 30-day mortality (early GDMT: HR, 1.11 [95% CI, 1.04–1.18]; nonearly GDMT: HR, 1.24 [95% CI, 1.20–1.28];  $P_{int}=0.070$ ), with GDMT failing to modify this early risk. Beyond 30 days, mortality converged irrespective of GDMT status (early GDMT: HR, 0.99 [95% CI, 0.94–1.04]; nonearly GDMT: HR, 0.98 [95% CI, 0.90–1.06];  $P_{int}=0.903$ ). This pattern was particularly pronounced in men, where SMuRF-less status consistently increased 0- to 30-day mortality regardless of early GDMT (early GDMT: HR, 1.26 [95% CI, 1.16–1.36]; nonearly GDMT: HR, 1.34 [95% CI, 1.29–1.39];  $P_{int}=0.512$ ). In contrast, early GDMT completely abolished the elevated mortality risk in SMuRF-less patients (nonearly GDMT: HR, 1.12 [95% CI, 1.07–1.17]; early GDMT: HR, 0.97 [95% CI, 0.88–1.07];  $P_{int}=0.047$ ; Figure S4). Primary PCI status further modified outcomes: whereas 0 to 30 day mortality remained elevated in SMuRF-less patients regardless of PCI (PCI: HR, 1.21 [95% CI, 1.14–1.28]; non-PCI: HR, 1.39 [95% CI, 1.33–1.46]), the 1-year mortality disparity

was eliminated in PCI-treated patients (HR, 1.00 [95% CI, 0.93–1.07]) but persisted without PCI (HR, 1.16 [95% CI, 1.05–1.27]; Figure S5).

## DISCUSSION

By utilizing the CCA data set from 2017 to 2021, which includes >300 000 patients with STEMI from >2000 centers across China, this nationwide, multicenter retrospective cohort study revealed the following findings. First, SMuRF-less patients experienced delays in treatment and were less likely to receive reperfusion therapy compared with those with SMuRF. Second, although SMuRF-less status was associated with increased mortality during 0 to 30 days, this association did not persist during 31 to 365 days. Third, the detrimental impact of SMuRF-less status appeared more pronounced in men and showed age-dependent attenuation. These findings highlight the complexity of SMuRF-less patients, particularly in relation to sex-specific treatment disparities and the evolving impact of SMuRF-less status over time.

In our cohort, 23.1% of patients were SMuRF-less, consistent with previous studies where the proportion of SMuRF-less patients in STEMI populations ranged from 11.0% to 26.2%.<sup>6,7,16–19</sup> In addition, the proportion of SMuRF-less patients has been steadily increasing in studies from certain countries.<sup>5,7</sup> Across all studies, SMuRF-less patients were older, had more comorbidities, initiated treatment later, and were less likely to receive treatment. In both the overall AMI patient population and various AMI subtypes, the proportion of females in the SMuRF-less group typically ranges from 20% to 40%.



**Figure 5. Sex subgroup analysis of Kaplan-Meier survival curves for 1-year all-cause mortality.**

**A**, The Kaplan-Meier curve for all-cause mortality within 1 year in the male patient population. **B**, The landmark analysis curve for all-cause mortality within 1 year in the male patient population. **C**, The Kaplan-Meier curve for all-cause mortality within 1 year in the female patient population. **D**, The landmark analysis curve for all-cause mortality within 1 year in the female patient population. HR indicates hazard ratio; and SMuRF, standard modifiable cardiovascular risk factors.

The research findings regarding the disparity in the proportion of females between the SMuRF-less and SMuRF groups are inconsistent.<sup>6,7,16</sup> In the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart (SWEDHEART) study in Sweden, the proportion of females in the SMuRF-less group among patients with STEMI was lower than in the SMuRF group (23.5% versus 34.5%).<sup>6</sup> Similar trends were also observed in research from the United States and Australia.<sup>7,19</sup> Interestingly, our data showed that the proportion of SMuRF-less patients was higher in women, which is consistent with previous studies from China, South Korea, Japan, and Singapore.<sup>10,20,21</sup> This may be related to the lower smoking rates among Chinese women.<sup>22</sup>

Our results demonstrated a 22% higher 30-day mortality risk in the SMuRF-less group compared with the SMuRF group in patients with STEMI. Similar to most studies, AMI patients without traditional cardiovascular risk factors exhibited a significantly higher risk of mortality, a difference that remained after adjusting for

baseline characteristics.<sup>6,9,21</sup> A meta-analysis of 1.28 million patients with ACS found that the risk of in-hospital mortality was 1.57× higher in the SMuRF-less group compared with the SMuRF group.<sup>23</sup> However, some studies have reported no significant difference in mortality between the 2 groups, or even a lower risk of death in the SMuRF-less group. For instance, a Korean registry of 11 390 AMI patients treated with PCI found no difference in mortality between the groups.<sup>20</sup>

Our study's results were consistent with those of most studies, but the significant difference in mortality between the SMuRF-less and SMuRF groups appeared early, as indicated by the Kaplan-Meier curve. Subsequently, a landmark analysis was performed to categorize follow-up time into 2 periods: within 30 days after admission and between 31 and 365 days after admission. The results aligned with our expectations: mortality in the SMuRF-less group was significantly higher than in the SMuRF group within 30 days of admission, and this difference remained significant after adjusting for multiple

risk factors. However, between 31 and 365 days after admission, the mortality difference between the groups disappeared. This further supports the notion that the higher mortality in SMURF-less patients occurs early in the disease.

All studies showed an older age of onset in the SMURF-less group.<sup>6,16,23,24</sup> Age may directly influence the baseline risk of CHD, independent of other risk factors.<sup>25</sup> One possible explanation is that in patients without traditional risk factors, disease typically manifests at older ages, when the baseline risk has increased enough to precipitate the condition.<sup>26</sup> SMURF-less patients are more likely to develop cardiogenic shock, potentially due to the absence of risk factors such as hypertension and diabetes, which may result in a lack of myocardial ischemic preconditioning and reduced tolerance.<sup>24,27</sup> Cardiovascular magnetic resonance data from the Third DANish Study of Acute Treatment of Patients With ST-Segment Elevation Myocardial Infarction (DANAMI-3) substudy demonstrate significantly larger acute infarct sizes in SMURF-less versus SMURF-positive patients with STEMI (17% versus 13%;  $P=0.04$ ), indicating more severely impaired myocardial salvage capacity in this population.<sup>28</sup>

Studies have reported mixed results regarding delays in seeking care. Our study clearly shows that patients in the SMURF-less group experience significant delays in seeking medical attention, possibly due to a lack of preventive awareness. The SWEDEHEART study reported a shorter time from symptom onset to hospital admission in the SMURF-less group (3.0 hours versus 3.1 hours).<sup>6</sup> However, Swiss and Japanese studies did not find any difference in delay between the 2 groups.<sup>29,30</sup> Regarding in-hospital delays, the door-to-balloon time was longer for SMURF-less patients in the Japanese study (90 versus 82 minutes,  $P=0.04$ ).<sup>30,31</sup> Encouragingly, no in-hospital delay was observed in our study, and no significant difference in time from first medical contact to wire crossing was found between the 2 groups. Consistent with multinational studies,<sup>9,16</sup> in-hospital use of aspirin, statins, or  $\beta$ -blockers was less frequent in SMURF-less compared with SMURF groups. This disparity persists despite international guidelines,<sup>32,33</sup> recommending early administration unless contraindicated, while Chinese guidelines<sup>33</sup> specifically advise initiating oral  $\beta$ -blockers within 24 hours for all patients with STEMI without contraindications. This highlights implementation gaps in early clinical management and secondary prevention.

In our study, we found that SMURF-less status was associated with increased 30-day mortality in both male and female patients with STEMI. Interestingly, the 30-day mortality rate in female SMURF-less patients was nearly twice that of male SMURF-less patients; by contrast, the association was weaker in female patients. In line with previous studies, women, especially those without

traditional risk factors, should receive greater attention to guideline-recommended treatments.<sup>6,7,18</sup>

The differences in outcomes between men and women may be due to the varying impact of risk factors on each sex. Studies have shown that risk factors like hypertension, diabetes, and smoking are more strongly associated with cardiovascular disease in women.<sup>34,35</sup> In particular, smoking poses a higher risk for women, with female smokers having a 25% higher relative risk of CHD compared with male smokers, independent of other cardiovascular risk factors. Furthermore, the pooled relative risk reduction for women compared with men increased by 2% for each additional year of follow-up.<sup>36</sup> This may also explain why female patients in the SMURF-less group had a higher risk of death than those in the SMURF group in Western studies.

According to the CCC-ACS registry,<sup>37</sup> GDMT, including ACE (angiotensin-converting enzyme) inhibitor/angiotensin receptor blocker,  $\beta$ -blockers, and statins, failed to reduce mortality in SMURF-less patients (adjusted HR, 0.98 [95% CI, 0.58–1.67]), indicating limited efficacy in this subgroup. Our findings reveal a critical sex-specific divergence: among male patients, SMURF-less status consistently elevates 0- to 30-day mortality risk irrespective of early GDMT exposure, whereas in female patients, early GDMT abolishes the associated survival disadvantage. This contrast highlights that standard secondary prevention strategies fail to address the unique pathophysiology of SMURF-less atherosclerosis in men, requiring alternative therapeutic approaches to improve outcomes. At the same time, it confirms the critical importance of promptly initiating GDMT during the acute phase of STEMI to optimize survival in women.

Finally, similar to the findings in the overall population, after excluding those who died within 30 days, no significant difference in 1-year mortality was observed between SMURF-less and SMURF groups, suggesting that the prognosis difference was primarily evident in the acute phase. This was consistent with findings from the SWEDEHEART study.<sup>6</sup> The long-tErm follow-uP of antithrombotic management patterns In acute CORonary syndrome patients (EPICOR) and EPICOR Asia registries cover 28 countries across Europe, Latin America, and Asia, and the included population is representative of the world.<sup>38</sup> We acknowledge key methodological distinctions: First, our cohort exclusively examined patients with STEMI whereas EPICOR enrolled postdischarge ACS survivors; second, we assessed 0- to 30-day and 31- to 365-day mortality versus their 2-year postdischarge end point; third, compared with our study, EPICOR included more patients without STEMI, greater intergroup age differences, racial diversity, lower female representation, and increased PCI utilization rates. Crucially, EPICOR's finding that SMURF absence did not confer reduced 2-year mortality aligns with our observations. This consistency reinforces the temporal pattern wherein SMURF

associations seem most pronounced during STEMI's acute phase, underscoring primary prevention's importance. Furthermore, EPICOR demonstrates that patients with combined SMuRF and prior CVD exhibit higher mortality regardless of sex. Due to our exclusion of revascularized patients, meaningful subgroup assessment of this specific population was precluded in our cohort.

Consistent with prior evidence, our findings demonstrate that SMuRF-less patients globally face substantially higher mortality risks during the early phase of STEMI. Consequently, implementing tailored primary prevention strategies for this specific population worldwide is critically important for future clinical management.

As cardiovascular risk factor management has improved, the incidence and mortality of CHD and AMI have decreased. The INTERHEART study reported that cardiovascular risk factors accounted for 90% of the population attributable risk of MI.<sup>39</sup> Although inflammation is recognized as a key factor in atherosclerosis, most studies show that SMuRF-less patients have lower or similar C-reactive protein levels compared with SMuRF patients, suggesting inflammation may not be a major driver in this group.<sup>6,20</sup> In addition to traditional risk factors, genetics play a crucial role in CHD. Although controlling traditional risk factors has reduced mortality, total population attributable risks remain below 100%, highlighting the need to identify new mechanisms and markers. Although polygenic risk scores have shown limited impact compared with traditional assessments,<sup>40</sup> they may support earlier CHD prevention in younger populations, particularly for those in the highest 20% of genetic risk.<sup>41</sup> Cardiovascular risk assessment is recommended for identifying high-risk individuals for lifestyle and pharmacological interventions per European Society of Cardiology and American College of Cardiology/American Heart Association guidelines.<sup>32,42</sup> The proportion of SMuRF-less patients varies across racial groups, likely due to genetic factors. In the Myocardial Infarction National Audit Project (MINAP) registry, White people were more likely to be SMuRF-less, while Asians were less likely (odds ratio, 0.53 [95% CI, 0.50–0.57]).<sup>43</sup>

Given growing interest in primary prevention of ACS, novel predictors operating across multiple biological levels show significant promise for identifying high-risk individuals missed by traditional models. These include genetic risk stratification using polygenic risk scores, plasma biomarkers such as lipoprotein(a) and multiomics-derived signatures, and direct atherosclerotic phenotyping through coronary artery calcium scoring via noncontrast computed tomography and coronary computed tomography angiography. Such approaches provide new screening pathways for reclassifying risk in SMuRF-less populations.<sup>44</sup>

Our study has several strengths, including its position as one of the largest investigations of SMuRF-less patients with STEMI in China. By integrating the Chinese

Center for Disease Control and Prevention database, we were able to follow-up on patient outcomes for 1 year. We included the largest cohort studied to date, along with multiple time-to-surgery variables, allowing for a comprehensive assessment of in-hospital delays in patients with STEMI. We identified significant treatment disparities among women between SMuRF and SMuRF-less, with insufficient preventive awareness emerging as a critical factor contributing to the differences in mortality between groups. These findings underscore the need for more aggressive reperfusion therapy in patients with STEMI, particularly women, regardless of the presence of traditional risk factors.

Despite its strengths, this study has limitations. First, as an observational study, although we adjusted for known confounders, unmeasured confounders may exist, and the causal link between SMuRF-less status and mortality remains unclear. Second, SMuRF classification was based on clinical diagnosis, which may involve omitted or absent prior disease history in some patients. In addition, some risk factors are continuous, which may create a risk gradient not fully captured.<sup>45</sup> Third, due to the limited variables in our database, certain factors influencing outcomes were excluded, potentially affecting result accuracy. For instance, although recent publications propose including obesity as a fifth SMuRF component,<sup>24,46</sup> the absence of body mass index data in our database prevented analysis of this modified SMuRF definition. Consequently, a sensitivity analysis using a SMuRF definition that includes obesity was not feasible in this study. Fourth, as our follow-up focused only on mortality, we lacked data on recurrent myocardial infarction, heart failure, readmissions, and other events, which is a limitation of our analysis. Finally, the inclusion of only certified chest pain centers may exclude hospitals with lower medical levels, introducing potential data bias.

## CONCLUSIONS

In conclusion, this multicenter analysis reveals that patients with STEMI presenting without conventional modifiable cardiovascular risk factors constitute a substantial proportion (23.1%) of STEMI cases. Notably, this SMuRF-less cohort demonstrated significantly elevated 30-day mortality rates compared with their risk factor-positive counterparts. This excess early mortality was especially pronounced among male patients. Beyond the 30-day window, mortality risk profiles between the groups converged.

## ARTICLE INFORMATION

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### Author Contributions

Dr Sun contributed to conceptualization, data curation, formal analysis, methodology, writing—original draft. Dr Liang contributed to conceptualization, supervision, validation, writing—original draft. Dr Sun contributed to conceptualization, supervision, writing—review and editing. Dr Aa contributed to data curation, methodology, and validation. Liang Zhao contributed to conceptualization and methodology. L. Li contributed to the investigation and writing—review and editing. P. Li contributed to data curation and methodology. Y. Li contributed to supervision, writing—original draft. Roger Dr Foo contributed to supervision, writing—original draft. Dr Chan contributed to supervision and writing—original draft. Dr Yang contributed to conceptualization, supervision, and writing—review and editing. Dr Zhou contributed to conceptualization, supervision, validation, and writing—review and editing.

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### Disclosures

None.

### Supplemental Material

Tables S1–S3

Figures S1–S5

STROBE Checklist

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