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ORIGINAL RESEARCH

Characteristics, Treatment, and In-Hospital Outcomes of Older Patients With STEMI Without Standard Modifiable Risk Factors

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ABSTRACT

BACKGROUND Strategies targeting standard modifiable cardiovascular risk factors (SMuRFs), including hypertension, diabetes, hypercholesterolemia, and smoking, have been well established to prevent coronary heart disease. However, few studies have evaluated the management and outcomes of older patients without SMuRFs after myocardial infarction.

OBJECTIVES The authors sought to evaluate the profile of patients with ST-segment elevation myocardial infarction (STEMI) aged ≥75 years without SMuRFs.

METHODS This study is based on the CCC-ACS (Improving Care for Cardiovascular Disease in China-Acute Coronary Syndrome) project. Patients aged ≥75 years with a first presentation of STEMI were enrolled in this study between November 2014 and December 2019. Modified Poisson regression was used to evaluate the association between SMuRF-less and in-hospital outcomes.

RESULTS Among 10,775 patients with STEMI aged ≥75 years, 1,633 (15.16%) had no SMuRFs. Compared with those with SMuRF, SMuRF-less patients received less evidence-based treatment. In-hospital mortality was similar among patients with and without SMuRFs (5.44% vs 5.14%; $P = 0.630$). However, after adjustment for patient characteristics and treatment, being SMuRF-less was significantly associated with a reduced risk of mortality (RR: 0.80; 95% CI: 0.65-0.99; $P = 0.043$). SMuRF-less patients also had a significantly reduced risk of in-hospital death when only adjusting for in-hospital treatment (RR: 0.78; 95% CI: 0.63-0.98; $P = 0.030$), regardless of patient characteristics.

CONCLUSIONS Approximately 1 in 7 STEMI patients in China ≥75 years old had no SMuRFs. The similar mortality in patients with and without SMuRF can be partially explained by the inadequate in-hospital treatment of SMuRF-less patients. The quality of care for older patients without SMuRF should be improved. (CCC Project-Acture Coronary Syndrome; NCT02306616) (JACC: Asia 2024;4:73-83) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ACEI = angiotensin-converting enzyme inhibitor

ACS = acute coronary syndrome(s)

ARB = angiotensin receptor blocker

CHD = coronary heart disease

DAPT = dual antiplatelet therapy

FBG = fasting blood glucose

LDL-C = low-density lipoprotein-cholesterol

MACE = major adverse cardiovascular event(s)

OGTT = oral glucose tolerance test

PCI = percutaneous coronary intervention

SMuRF = standard modifiable cardiovascular risk factor

STEMI = ST-segment-elevation myocardial infarction

Since the Framingham Heart Study first reported the risk factors for coronary heart disease (CHD),[1] a growing body of research has explored and validated these risk factors.[2-5] Hypertension, diabetes, hypercholesterolemia, and smoking have been well recognized as standard modifiable cardiovascular risk factors (SMuRFs)[6,7]; subsequently, strategies targeting SMuRFs to prevent and treat CHD have been well established.[8-13] However, patients with CHD without SMuRFs (defined as SMuRFs-less) are often overlooked in clinical trials, usually being neither presented as a separate group nor evaluated for treatment efficacy.[14] Consequently, little is known about the best approach to management and secondary prevention strategies in these patients.

Several studies have evaluated the proportion and outcomes of SMuRFs-less patients presenting with CHD. A meta-analysis including 15 studies (n = 1,285,722) reported that 11.56% of patients with acute coronary syndrome had no SMuRFs, with proportions of 7.44% among patients with non-ST-segment elevation acute coronary syndrome and 12.87% among patients with ST-segment elevation myocardial infarction (STEMI), indicating that patients with STEMI had a higher proportion of SMuRFs-less than did patients with non-ST-segment elevation acute coronary syndrome.[15] Based on 2 Australian STEMI cohorts (n = 3,081), it found that the proportion of SMuRFs-less increased from 14%-27% between 1999 and 2017.[16] Unexpectedly, these studies found that patients without SMuRFs even have a significantly increased risk of mortality compared with those with SMuRF, partially explained by undertreatment.[7,15,17] But questions remain: is this true for the older patients as well? Is there a higher risk of mortality on the occurrence of STEMI if a person has always been SMuRFs-less? Few studies have specifically evaluated the impact of SMuRFs-less among older patients with STEMI. Therefore, in this study, we sought to comprehensively evaluate the profile of SMuRFs-less STEMI patients aged ≥75 years, including their characteristics, treatment, and in-hospital outcomes.

METHODS

STUDY DESIGN. The CCS-ACS (Improving Care for Cardiovascular Disease in China-Acute Coronary Syndrome) Project is a large nationwide registry and quality improvement study focusing on quality of ACS care, launched in 2014 as a collaborative initiative of the American Heart Association and the Chinese Society of Cardiology. The quality improvement tools, including monthly hospital quality reports, annual hospital recognition, regional workshops, and online educational materials, were developed and applied to help cardiologists improve their adherence to guideline recommendations for patients with ACS in daily clinical practice. Details of the design and methodology of the CCC-ACS project have been published.[18] In brief, 158 tertiary hospitals and 82 secondary hospitals were included across China between November 2014 and December 2019. Each month, the first 20-30 and 10-20 consecutive patients with ACS were recruited to the study from tertiary and secondary hospitals, respectively. Patients with STEMI were enrolled based on the principal discharge diagnosis by reviewing the inpatient list. A standard web-based data-collection platform (Oracle Clinical Remote Data Capture, Oracle) was used in this study.[19]

This study was performed in compliance with the Declaration of Helsinki. Institutional Review Board approval was granted for this research by the Ethics Committee of Beijing Anzhen Hospital, Capital Medical University. No informed consent was required. This study is registered at www.ClinicalTrials.gov (NCT02306616).

STUDY POPULATION. During the study period, a total of 11,539 patients aged ≥75 years old with a definite principal diagnosis of STEMI were included in this study. STEMI was defined according to the guidelines issued by the Chinese Society of Cardiology for the diagnosis and management of patients with STEMI.[8] After exclusion of patients with previously diagnosed myocardial infarction or undergoing percutaneous coronary intervention (PCI) or coronary artery bypass grafting (n = 764), 10,775 older patients with the first occurrence of STEMI were included in this study.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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STUDY VARIABLES. **SMuRFs.** Patients with SMuRFs were defined as having at least one of the following variables: hypertension, diabetes, hypercholesterolemia, or current smoking. Hypertension was defined as having a previous diagnosis of hypertension, using antihypertensive drugs before this hospitalization, or having hypertension listed in the medical records as the secondary discharge diagnosis. Diabetes was defined as having a previous diagnosis of diabetes, using glucose-lowering drugs before this hospitalization, glycated hemoglobin A1c (HbA1c) concentration ≥6.5% during this admission, or having diabetes listed in the medical records as the secondary discharge diagnosis. Considering both blood pressure and fasting blood glucose could be influenced by neurohormonal response to myocardial infarction at acute phase, these were not incorporated in the definitions of hypertension and diabetes, respectively.[7] Hypercholesterolemia was defined as having a previous diagnosis of hypercholesterolemia, prehospital low-density lipoprotein-cholesterol (LDL-C) lowering treatment, an LDL-C concentration ≥3.4 mmol/L, or a total cholesterol concentration ≥5.2 mmol/L during the current admission.[20] Current smoking was defined as smoking within 1 year preceding the current hospitalization episode.[21] Patients without any of these SMuRFs were defined as SMuRFs-less.

Prehospital and in-hospital treatment. Prehospital treatments, including aspirin, $P2Y_{12}$ inhibitors, statins, β-blockers, and angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB), were defined as in-use if the patient used the drug within 2 weeks before the hospitalization. In-hospital treatments (including dual antiplatelet therapy [DAPT], statins, β-blockers, and ACEI/ARB) and PCI were defined as in-use if the patient took drugs within 24 h of admission or received PCI during the current hospitalization, according to the original medical records. In-hospital DAPT was defined by the use of both aspirin and any type of $P2Y_{12}$ inhibitor.

In-hospital outcomes. The primary outcome of this study was all-cause mortality during hospitalization. The secondary outcomes were in-hospital major adverse cardiovascular events (MACEs), defined as the composite of all-cause death, re-myocardial infarction, stent thrombosis, and stroke occurring during hospitalization. Detailed definitions of other variables are presented in Supplemental Methods.

STATISTICAL ANALYSIS. Continuous variables with normal distribution were shown as mean ± SD and differences between groups were compared using *t*-tests; continuous variables with a skewed distribution were presented as median (IQR); categorical variables were displayed as the number (percentage) and compared using the chi-square test. Multivariable logistic regression was applied to evaluate the association between SMuRFs-less and in-hospital treatment. OR (95% CI) were reported.

To determine the association between SMuRFs-less and in-hospital outcomes, modified Poisson regression was performed to estimate the risk ratios (RRs) and robust standard errors to estimate the 95% CIs.[22] Univariate analysis was performed first. We then performed a characteristic-adjusted model (Model 1) that included age (continuous), sex (male/female), systolic blood pressure (continuous), heart rate (continuous), estimated glomerular filtration rate (<30/30-59/60-89/≥90 mL/min/1.73 m^2), history of stroke (no/yes), Killip class at admission (I/I-III/IV), and cardiac arrest at admission (no/yes). In Model 2, prehospital treatments, including aspirin, $P2Y_{12}$ inhibitors, and β-blockers were added, based on Model 1. In Model 3, further adjustment was made for in-hospital treatment, including DAPT, statins, β-blockers, ACEI/ARB use within 24 h of admission, and PCI during hospitalization.

We further conducted subgroup analysis between males and females. Because SMuRFs are also risk factors for stroke, we excluded patients with a stroke history from the sensitivity analysis. Additionally, because patients with STEMI are not routinely administered an oral glucose tolerance test (OGTT) during hospitalization, the SMuRFs-less patients may have included those with diabetes only detectable using OGTT,[23] particularly among those with impaired fasting glucose and stress hyperglycemia after STEMI. Thus, we further excluded SMuRFs-less patients with fasting blood glucose ≥7.0 mmol/L from the sensitivity analysis.

In addition, we conducted a series of post-hoc mediation analyses to examine the degree to which specific in-hospital treatment might contribute to mortality in SMuRFs-less patients presenting with STEMI, as Figtree et al[7] conducted previously. The criteria for mediators were as follows: 1) associated with the factor of interest (interpreted as SMuRF-less status); 2) associated with the outcome; and 3) adjustment for it results in a reduced effect compared with unadjusted analysis. We compared RRs for the effect of SMuRFs-less status on mortality from an unadjusted model vs a model adjusted for each element of in-hospital treatment, and a model with all treatments.

For variables with a missing rate of <15%, we imputed missing values using the sequential regression multiple imputation method implemented by

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TABLE 1 Characteristics and Prehospital Treatment of Patients With and Without SMuRFs

	SMuRFs-Less (n = 1,633)	≥1 SMuRF (n = 9,142)	*P* Value
Age, y	80.69 ± 4.25	80.29 ± 4.16	<0.001
Age group			<0.001
<80 y	754 (46.17)	4,766 (52.13)	
80-84 y	603 (36.93)	2,987 (32.67)	
≥85 y	276 (16.90)	1,389 (15.19)	
Sex			0.001
Male	1,009 (61.79)	5,247 (57.47)	
Female	624 (38.21)	3,888 (42.53)	
SMuRFs			
Hypertension	–	6,572 (71.89)	–
Diabetes mellitus	–	2,947 (32.24)	–
Hypercholesterolemia	–	3,701 (40.48)	–
Current smoking	–	2,496 (27.30)	–
Vital signs			
SBP levels, mm Hg	122.10 ± 22.98	130.0 ± 25.23	<0.001
DBP levels, mm Hg	72.61 ± 13.62	75.17 ± 14.72	<0.001
Heart rates, beats/min	77.78 ± 18.55	78.88 ± 18.45	0.026
Laboratory measurement			
TC, mmol/L	3.95 (3.41-4.45)	4.38 (3.65-5.21)	<0.001
LDL-C, mmol/L	2.33 (1.90-2.75)	2.67 (2.09-3.32)	<0.001
LDL-C ≥1.8 mmol/L	1,302 (79.73)	7,747 (84.74)	<0.001
HDL-C, mmol/L	1.10 (0.90-1.32)	1.10 (0.91-1.33)	0.672
HDL-C <1.0 mmol/L	589 (36.07)	3,221 (35.23)	0.515
TG, mmol/L	1.00 (0.75-1.40)	1.20 (0.88-1.70)	<0.001
TG ≥2.3 mmol/L	118 (7.23)	1,096 (11.99)	<0.001
RC, mmol/L	0.46 (0.26-0.71)	0.54 (0.30-0.83)	<0.001
FBG, mmol/L	5.87 (5.00-7.20)	6.40 (5.26-8.39)	<0.001
FBG ≥7.0 mmol/L	457 (27.99)	3,729 (40.79)	<0.001
eGFR, mL/min/1.73 m^2	71.16 (53.56-84.46)	67.27 (49.54-83.07)	<0.001
eGFR			<0.001
<30 mL/min/1.73 m^2	170 (10.41)	714 (7.81)	
30-59 mL/min/1.73 m^2	900 (55.11)	4,828 (52.81)	
60-89 mL/min/1.73 m^2	487 (29.82)	2,924 (31.98)	
≥90 mL/min/1.73 m^2	76 (4.65)	676 (7.39)	
LVEF			0.224
<40%	147 (13.28)	1,032 (15.01)	
41%-49%	255 (23.04)	1,630 (23.7)	
≥50%	705 (63.69)	4,215 (61.29)	

Continued on the next page

IVEware software version 0.2 (Survey Research Center, University of Michigan) in the total ACS population of the CCC-ACS project.[24]

Statistical analyses were performed using SAS 9.4 (SAS Institute). Two-tailed *P* values of <0.05 were considered statistically significant.

RESULTS

CHARACTERISTICS AND PREHOSPITAL TREATMENT OF PATIENTS WITH AND WITHOUT SMuRFs. Of 10,775 patients with STEMI aged ≥75 years, 1,633 (15.16%) had no documented SmuRFs before or during this hospitalization. Compared with patients with SMuRFs, SMuRFs-less patients had a slightly higher average age (80.69 ± 4.25 years vs 80.29 ± 4.16 years; $P = 0.001$) and a higher proportion of age ≥80 years (Table 1). In addition, a higher proportion of male patients were observed among those who were SMuRFs-less (61.79% vs 57.47%; $P = 0.001$).

In these older patients with SmuRFs, the most common SMuRF was hypertension (71.89%), followed by hypercholesterolemia (40.48%), diabetes (32.24%), and current smoking (27.30%). SMuRFs-less patients had significantly lower average levels of systolic blood pressure (122.10 ± 22.98 mm Hg vs 130.00 ± 25.23 mm Hg; $P < 0.001$), diastolic blood pressure (72.61 ± 13.62 mm Hg vs 75.17 ± 14.72 mm Hg; $P < 0.001$), and heart rates (77.78 ± 18.55 beats/min vs 78.88 ± 18.45 beats/min; $P = 0.026$) than did patients with SMuRFs. Meanwhile, the median concentrations of total cholesterol (3.95 [IQR: 3.41-4.45] mmol/L vs 4.38 [IQR: 3.65-5.21] mmol/L; $P < 0.001$), LDL-C (2.33 [IQR: 1.90-2.75] mmol/L vs 2.67 [IQR: 2.09-3.32] mmol/L; $P < 0.001$), triglyceride (1.00 [IQR: 0.75-1.40] mmol/L vs 1.20 [IQR: 0.88-1.70] mmol/L; $P < 0.001$), remnant cholesterol (0.46 [IQR: 0.26-0.71] vs 0.54 [IQR: 0.30-83]; $P < 0.001$), fasting blood glucose (FBG) (5.87 [IQR: 5.00-7.20] vs 6.40 [IQR: 5.26-8.39]; $P < 0.001$), and estimated glomerular filtration rate (71.16 [IQR: 53.56-84.46] vs 67.27 [IQR: 49.54-83.07]; $P < 0.001$) were also lower in patients without SMuRFs (Table 1). However, there was a large proportion (80%) of SMuRFs-less patients with LDL-C ≥1.8 mmol/L at admission.

SMuRFs-less patients were less likely to have a history of heart failure (0.98% vs 1.78%; $P = 0.019$), stroke (6.06% vs 12.91%; $P < 0.001$), and renal failure (0.61% vs 2.10%; $P < 0.001$), but had a similar proportion of atrial fibrillation, peripheral artery disease, and chronic obstructive pulmonary disease as did patients with SMuRFs (Table 1).

Although SMuRFs-less patients had a higher proportion of being classified as Killip class I (57.38% vs 53.82%) at admission, they had a higher likelihood of presenting with cardiac arrest than did patients with SMuRFs (3.00% vs 2.17%; $P = 0.038$) (Table 1). Because SMuRFs-less patients had fewer traditional risk factors as well as less history of heart failure, stroke, and renal failure, they had a lower rate of prehospital treatments than patients with SMuRFs (Table 1).

IN-HOSPITAL TREATMENT OF PATIENTS WITH AND WITHOUT SMuRFs. The evidence-based core treatments of STEMI, including drugs and PCI, were compared between patients with and without SMuRFs. SMuRFs-less patients had significantly lower use rates of DAPT (92.84% vs 94.21%;

$P = 0.031$), statins (89.77% vs 93.26%; $P < 0.001$), β-blockers (42.38% vs 46.66%; $P = 0.001$), ACEI/ARB (30.56% vs 46.27%; $P < 0.001$), as well as PCI (63.44% vs 66.25%; $P = 0.027$), compared with patients with SMuRFs (**Figure 1A**), no matter in males or females (Supplemental Figure 1). In addition, the rate of primary PCI was also slightly lower among SMuRFs-less patients (46.97% vs 48.75%; $P = 0.184$), although without statistical significance. And among those without PCI, the proportion of thrombolysis was only 4.4%.

We further calculated the ORs of receiving these treatments of SMuRFs-less patients, using patients with 3 or more SMuRFs as the reference group. We found a "dose-response relationship" between the number of SMuRFs and the likelihood of receiving treatment; the lower the number of SMuRFs, the lower the probability of receiving evidence-based treatment (**Figure 1B**).

IN-HOSPITAL OUTCOMES AMONG SMuRFs-LESS PATIENTS. The median length-of-stay of patients with STEMI aged ≥75 years in this study was 10 (IQR: 7-14) days and a total of 581 (5.39%) patients died during hospitalization. The incidence of all-cause mortality was similar among patients with and without SMuRFs (5.44% vs 5.14%; $P = 0.630$) (Supplemental Table 1). We used different models to further explore the association between being SMuRFs-less and in-hospital all-cause mortality. In the univariate analysis, SMuRFs-less patients had a 5% reduced risk of all-cause mortality, but without statistical significance (RR: 0.95; 95% CI: 0.76-1.19; $P = 0.630$). After adjustment for patient characteristics, the risk of all-cause mortality was reduced among SMuRFs-less patients, but the difference remained nonsignificant (RR: 0.84; 95% CI: 0.68-1.05; $P = 0.136$). The RR for SMuRFs-less patients was almost unchanged after adjusting for prehospital treatment (RR: 0.83; 95% CI: 0.67-1.04; $P = 0.100$). After further adjustment for in-hospital treatment, being SMuRFs-less was significantly associated with a 20% reduced risk of mortality (RR: 0.80; 95% CI: 0.65-0.99; $P = 0.043$) (**Table 2**).

In further subgroup analysis by sex, SMuRFs-less was associated with reduced risk of mortality among both males (RR: 0.82; 95% CI: 0.62-1.08) and females (RR: 0.74; 95% CI: 0.54-1.03; P for interaction = 0.570).

After excluding patients with stroke history, being SMuRFs-less was significantly associated with reduced risk of in-hospital mortality in all 3 multivariate-adjusted models (**Table 2**). After excluding SMuRFs-less patients with FBG ≥7.0 mmol/L, in both the univariate and multivariate-adjusted analyses, being SMuRFs-less was associated with a significantly reduced risk of mortality (**Table 2**).

TABLE 1 Continued

	SMuRFs-Less (n = 1,633)	≥1 SMuRF (n = 9,142)	*P* Value
History of diseases			
Heart failure	16 (0.98)	163 (1.78)	0.019
Atrial fibrillation	49 (3.00)	294 (3.22)	0.648
Stroke	99 (6.06)	1,180 (12.91)	<0.001
PAD	12 (0.73)	81 (0.89)	0.543
Renal failure	10 (0.61)	192 (2.10)	<0.001
COPD	56 (3.43)	309 (3.38)	0.919
Cardiac condition at admission			
Killip class			0.011
I	947 (57.38)	4,920 (53.82)	
II-III	530 (32.46)	3,319 (36.30)	
IV	166 (10.17)	903 (9.88)	
Cardiac arrest	49 (3.00)	198 (2.17)	0.038
Prehospital treatment			
Aspirin	109 (6.67)	1,413 (15.46)	<0.001
$P2Y_{12}$ inhibitors	90 (5.51)	1,050 (11.49)	<0.001
Statins	–	1,087 (11.89)	–
β-blockers	11 (0.67)	487 (5.33)	<0.001
ACEI/ARB	–	785 (8.59)	–

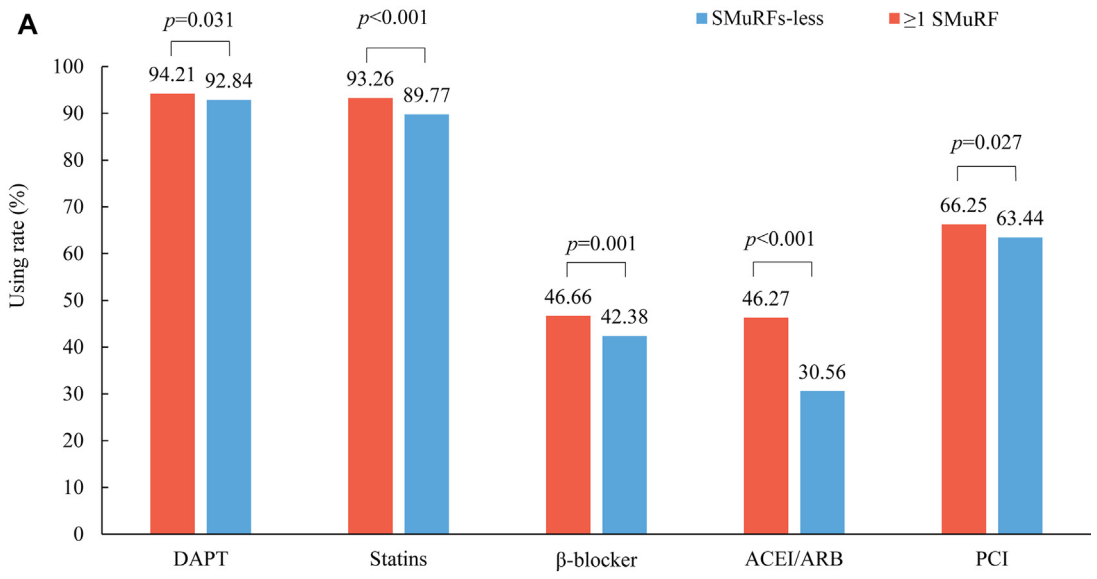
Values are mean ± SD, n (%), or median (IQR).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; COPD = chronic obstructive pulmonary disease; DBP = diastolic blood pressure; HDL-C = high-density lipoprotein-cholesterol; eGFR = estimated glomerular filtration rate; FBG = fasting blood glucose; LDL-C = low-density lipoprotein-cholesterol; LVEF = left ventricular ejection fraction; PAD = peripheral arterial disease; RC = residual cholesterol; SBP = systolic blood pressure; SMuRF = standard modifiable cardiovascular risk factor; TC = total cholesterol; TG = triglyceride.

In total, 695 (6.45%) of the study population had MACE during hospitalization. The incidence of MACE was also similar among patients with and without SMuRFs (6.49% vs 6.25%; $P = 0.716$) (Supplemental Table 1). After multivariate adjustment for characteristics, prehospital treatment, and in-hospital treatment, being SMuRFs-less was associated with 17% reduced risk of in-hospital MACE (RR: 0.65; 95% CI: 0.66-1.07; $P = 0.152$), but without statistical significance.

SMuRFs-LESS, IN-HOSPITAL TREATMENT, AND ALL-CAUSE MORTALITY. To further examine whether the lower use of evidence-based treatment among SMuRFs-less patients could partially explain their higher short-term mortality, we conducted post-hoc mediation analyses (**Table 3**). Compared with the unadjusted model, the effect of SMuRFs-less status on mortality was slightly reduced when each treatment was adjusted independently. However, after coadjustment for the 5 core treatment measures, SMuRFs-less patients had a statistically significant reduced risk of mortality (RR: 0.78; 95% CI: 0.63-0.98; $P = 0.030$),

FIGURE 1 In-Hospital Treatment



(A) Rate of in-hospital treatment. (B) OR of in-hospital treatment (reference group: ≥3 SMuRFs). ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; DAPT = dual antiplatelet therapy; PCI = percutaneous coronary intervention; SMuRF = standard modifiable cardiovascular risk factor.

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with a RR similar to that in the fully adjusted model (Model 3) (**Central Illustration**).

We further evaluated the association between the number of in-hospital treatment and all-cause mortality among SMuRFs-less patients. Compared with patients with 0-1 evidence-based treatment, those with 2, 3, 4, or all 5 of the treatments had an incremental relative risk reduction, no matter in univariate or multivariate analysis (**Table 4**).

DISCHARGE TREATMENT OF PATIENTS WITH AND WITHOUT SMuRFs. Among the 10,194 patients who survived STEMI, SMuRFs-less patients also had a lower prescription of drugs at discharge, especially for β-blockers and ACEI/ARB (aspirin: 86.96% vs 88.19%; $P = 0.170$; $P2Y_{12}$ inhibitors: 89.15% vs 90.92%; $P = 0.028$; statins: 88.19% vs 90.51%; $P = 0.005$; β-blockers: 51.52% vs 58.16%; $P < 0.001$; ACEI/ARB: 37.06% vs 52.39%; $P < 0.001$), compared with patients with SMuRFs.

DISCUSSION

Using CCC-ACS data from 2014-2019, we comprehensively compared characteristics, in-hospital management, and outcomes of patients aged ≥75 years with first-presentation STEMI with and without SMuRFs. Compared with those with SMuRFs, SMuRFs-less patients were older, with a higher proportion of males, lower levels of blood pressure, blood lipids and blood glucose, and less history of cardiovascular diseases, and they received less evidence-based therapy during hospitalization. Although SMuRFs-less patients had a similar incidence of mortality to patients with SMuRFs, they had a significantly lower risk of mortality after adjustment for evidence-based therapy.

PROPORTION OF SMuRFs-LESS AMONG OLDER PATIENTS WITH STEMI. Although increasing numbers of studies have examined the problems of SMuRFs-less patients, few studies have focused on this issue in the older population. In this study, we found that 15% of patients with STEMI ≥75 years old could be identified as SMuRFs-less, which was similar to the proportion (14.9%) reported by the SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) registry study, in which patients with STEMI had a median age of 68 (IQR: 59-78) years.[7] A recently published meta-analysis

FIGURE 1 Continued

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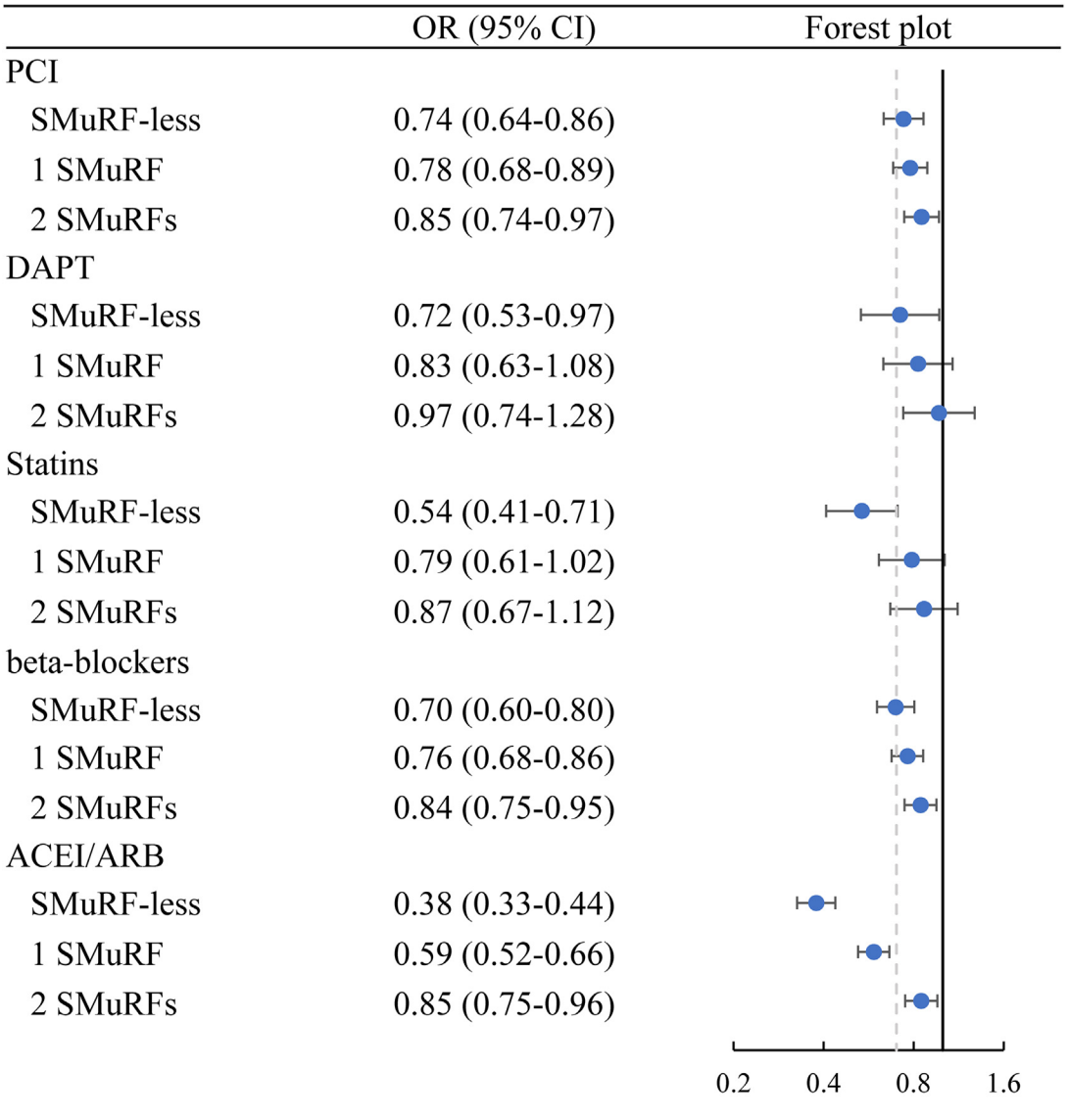

based on 15 studies (n = 1,285,722) reported that the pooled proportion of SMuRFs-less patients was 12.87% among patients with STEMI.[15] The seemingly higher proportion of SMuRFs-less among the older could be explained to some extent by "survival bias"; that is, patients with multiple risk factors generally had a shorter lifespan, and STEMI occurs later in the SMuRFs-less population. We can expect an increasing absolute number of SMuRFs-less patients with STEMI with the accelerating aging of the population.

CHARACTERISTICS OF SMuRFs-LESS PATIENTS PRESENTED WITH STEMI. Although SMuRFs-less patients had a slightly higher average age, they had a 6% higher proportion of age ≥80 years. The much lower proportion of prior events observed among SMuRFs-less patients indicates that lifetime avoidance of these risk factors could resist some of the pathophysiological changes brought by aging.

Meanwhile, it is worth noting the potential for undetected risk factors among patients defined as

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TABLE 2 The Association Between SMuRFs-Less and In-Hospital All-Cause Death

	Whole Study Population (N = 10,775)		Sensitivity Analysis 1[a] (n = 9,496)		Sensitivity Analysis 2[b] (n = 10,316)	
	RR (95% CI)[c]	*P* Value	RR (95% CI)[c]	*P* Value	RR (95% CI)[c]	*P* Value
No. of events	581				538	
Unadjusted	0.95 (0.76-1.19)	0.582	0.90 (0.71-1.16)	0.445	0.64 (0.47-0.87)	0.005
Model 1	0.84 (0.68-1.05)	0.136	0.77 (0.61-0.97)	0.029	0.63 (0.47-0.84)	0.002
Model 2	0.83 (0.67-1.04)	0.100	0.76 (0.60-0.96)	0.022	0.61 (0.46-0.83)	0.001
Model 3	0.80 (0.65-0.99)	0.043	0.74 (0.59-0.92)	0.008	0.60 (0.45-0.80)	0.001

Model 1: characteristics adjusted, including age, sex, SBP, heart rate, LVEF, eGFR, history of stroke, Killip class at admission, cardiac arrest at admission; Model 2: model 1 + prehospital treatment, including aspirin, $P2Y_{12}$ inhibitors, and β-blockers; Model 3: model 2 + in-hospital treatment, including DAPT, statins, β-blockers, ACEI/ARB, and PCI. [a]Sensitivity analysis 1: excluding patients with stroke history. [b]Sensitivity analysis 2: excluding SMuRFs-less patients with fasting blood glucose ≥7.0 mmol/L. [c]Reference group: patients with SMuRFs.

DAPT = dual antiplatelet therapy; PCI = percutaneous coronary intervention; RR = relative risk; other abbreviations as in Table 1.

SMuRFs-less, because risk factors are always defined using diagnostic thresholds despite risk being a continuum. In this study, we found that 80% of SMuRFs-less patients had LDL-C ≥1.8 mmol/L, which is an important threshold for secondary prevention of CHD. In addition, as only 60% of patients tested HbA1c and OGTT during hospitalization, there may have been missed diagnoses of diabetes among patients classified as SMuRFs-less. However, this subset of patients tends to have a much higher risk resulting from their long-term unrecognized and uncontrolled risk factors, raising the average risk of SMuRFs-less patients. After excluding those with FBG ≥7.0 mmol/L among SMuRFs-less patients, SMuRFs-less was associated with significantly reduced risk of in-hospital mortality in this study.

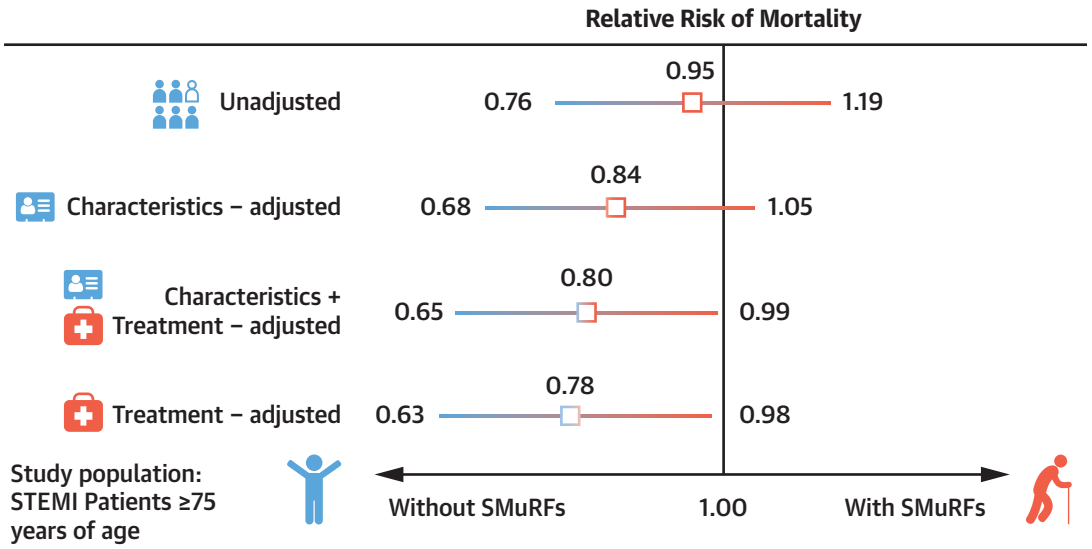
TABLE 3 SMuRFs-Less, In-Hospital Treatment, and All-Cause Mortality

Model	Variable	RR (95% CI)[a]	*P* Value
SMuRFs-less	SMuRFs-less	0.95 (0.76-1.19)	0.582
SMuRFs-less + DAPT	SMuRFs-less	0.93 (0.74-1.16)	0.497
	DAPT	0.36 (0.29-0.44)	<0.001
SMuRFs-less + statins	SMuRFs-less	0.87 (0.70-1.09)	0.230
	Statins	0.26 (0.21-0.31)	<0.001
SMuRFs-less + β-blockers	SMuRFs-less	0.92 (0.73-1.15)	0.456
	β-blockers	0.47 (0.39-0.56)	<0.001
SMuRFs-less + ACEI/ARB	SMuRFs-less	0.83 (0.67-1.05)	0.115
	ACEI/ARB	0.39 (0.32-0.47)	<0.001
SMuRFs-less + PCI	SMuRFs-less	0.92 (0.73-1.15)	0.441
	PCI	0.44 (0.38-0.52)	<0.001
SMuRFs-less + all above treatments	SMuRFs-less	0.78 (0.63-0.98)	0.030
	DAPT	0.85 (0.67-1.09)	0.201
	Statins	0.39 (0.32-0.48)	<0.001
	β-blockers	0.69 (0.57-0.82)	<0.001
	ACEI/ARB	0.52 (0.43-0.63)	<0.001
	PCI	0.52 (0.44-0.61)	<0.001

[a]Reference group: patients with SMuRFs and patients without corresponding treatment.
Abbreviations as in Tables 1 and 2.

INSUFFICIENT TREATMENT AND "CORRECTABLE RISK" OF DEATH AMONG SMuRFs-LESS PATIENTS. Despite having lower levels of risk factors and less history of diseases, SMuRFs-less patients have been reported to have a 1.6-fold increased risk of in-hospital mortality[15]; in this study, we observed a similar mortality rate among those with and without SMuRFs. Some previous studies have found that insufficient drug therapy could be a contributor.[7] In the present study, we also found that SMuRFs-less patients received less evidence-based treatment than did those with SMuRFs. In the step-adjusted multivariate analysis, being SMuRFs-less was significantly associated with a lower risk of in-hospital mortality after adjustment for evidence-based treatment. We further conducted a post-hoc mediation study to explore the impact of treatment, and found a significant association between SMuRFs-less status and reduced mortality after simultaneously adjusting for multiple treatment factors. Comparison of the 2 models shows that treatment is the most important factor in reducing the risk of in-hospital death in patients, regardless of adjustment for patient characteristics. This finding is supported by the results from the SWEDEHEART study, which found that increased early mortality rates are attenuated after adjustment for use of guideline-indicated treatments.[7] In fact, drugs like statins and ACEIs/ARBs actually have broader efficacy in addition to their ability to lower blood lipids and blood pressure, especially in the acute phase, such as anti-inflammatory effects, reduction of neurohormonal activation and infarct size, and an increase in regional wall motion and collateral coronary flow.[25-29] Therefore, the findings from this study not only shed light on why SMuRFs-less patients did not have a lower mortality rate, but also have important implications for clinical practice, readdressing the importance of early provision of

CENTRAL ILLUSTRATION **The Association Between SMURFs-Less and In-Hospital Mortality**



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SMuRFs-less was significantly associated with a reduced risk of in-hospital mortality in both the characteristics + treatment-adjusted model and the only treatment-adjusted model, and the point estimates of relative risk were similar in both models, indicating that in-hospital treatment is an important influencing factor on in-hospital mortality in SMuRFs-less patients. SMuRF = standard modifiable cardiovascular risk factor; STEMI = ST-segment elevation myocardial infarction.

evidence-based treatment for older patients with STEMI, irrespective of risk factor status. So far, few ACS guidelines have specially addressed the management of patients without traditional risk factors, resulting in an invisibility of SMuRFs-less patients for clinicians. Future guidelines should specially design clinical pathways for these vulnerable patients and studies to improve quality of care should specially measure the clinical treatment of these patients.

STUDY STRENGTHS AND LIMITATIONS. This is the first study to comprehensively evaluate the absence of SMuRFs among patients ≥75 years with first-presentation STEMI based on a nationally representative registry with large sample size. To explore the independent association between SMuRFs-less status and in-hospital outcomes, we comprehensively adjusted for patient characteristics and prehospital and in-hospital treatment.

There were also several limitations to this study. First, because OGTT is rarely performed and not all patients undergo HbA1c testing during hospitalization, there may be pre-existing diabetes among some patients defined as SMuRFs-less. To avoid the potential impact of this bias, we performed a sensitivity analysis. Second, SMuRFs were defined as categorical based on clinical diagnosis and accepted cutoff values; however, the risk of death due to blood pressure, FBG, and blood lipids is usually linear. In addition, it should be noted that only two thirds of older patients with STEMI either took PCI or thrombolytic therapy, and not more than one-half of them took primary PCI in this study, no matter whether among those with or without SMuRFs. This phenomenon has also been reported by other studies,[30-32] indicating a low rate of revascularization was a universal problem for the older population. How to

TABLE 4 **The Association Between the Number of In-Hospital Treatments and All-Cause Mortality Among SMuRFs-Less Patients**

	Univariate Analysis		Multivariate Analysis[a]	
No. of Treatments	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value
0-1	Reference	-	Reference	-
2	0.50 (0.29-0.86)	0.012	0.75 (0.44-1.25)	0.267
3	0.22 (0.13-0.39)	<0.001	0.52 (0.31-0.87)	0.013
4	0.13 (0.06-0.27)	<0.001	0.45 (0.21-0.93)	0.032
5	0.10 (0.04-0.29)	<0.001	0.39 (0.13-1.19)	0.097

[a]Adjusted variables included: age, sex, SBP, heart rate, LVEF, eGFR, history of stroke, Killip class at admission, and cardiac arrest at admission.

Abbreviations as in Tables 1 and 2.

improve revascularization rates in the older population is a priority for quality-of-care improvement research in the future. Also, long-term follow-up information was not available for this study. Therefore, we could not assess the long-term impact of SMuRFs-less status after the occurrence of STEMI. Inevitably, because this is an observational study, unmeasured confounding may have accounted for the association between being SMuRFs-less and in-hospital outcomes.

CONCLUSIONS

Approximately 1 in 7 patients with STEMI ≥75 years old in China had no SMuRFs. Although lower absolute mortality was not observed among older patients with STEMI without SMuRFs, the risk was significantly reduced after adjustment for in-hospital treatment, indicating that lifetime risk factor control could still alleviate the harm from STEMI, and older patients without SMuRFs still benefit from evidence-based treatment. Quality of care for older patients without SMuRFs should be improved.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients without SMuRFs are not under-represented among older patients with STEMI in clinical practice. SMuRFs-less patients could benefit from current core treatment after the occurrence of STEMI.

TRANSLATIONAL OUTLOOK: Evidence-based treatment should also be provided to older patients with STEMI without SMuRFs. More studies are needed for this group of patients.

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KEY WORDS mortality, older, risk factor, ST-segment elevation myocardial infarction, treatment

APPENDIX For supplemental methods, a table, and a figure, please see the online version of this paper.