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Authors

Gong, Wei
Yan, Yan
Liu, Jing
et al.

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ORIGINAL RESEARCH

In-Hospital Mortality and Treatment in Patients With Acute Coronary Syndrome With and Without Standard Modifiable Cardiovascular Risk Factors: Findings From the CCC-ACS Project

Wei Gong, MD, PhD*; Yan Yan, MD*; Jing Liu, MD, PhD; Xiao Wang, MD; Wen Zheng, MD; Bin Que, MD; Hui Ai, MD; Sidney C. Smith Jr, MD; Gregg C. Fonarow, MD; Louise Morgan, MSN; Dong Zhao, MD, PhD; Changsheng Ma, MD; Yaling Han, MD, PhD; Shaoping Nie, MD, PhD; on behalf of the CCC-ACS Investigators

BACKGROUND: Patients with acute coronary syndrome without standard modifiable cardiovascular risk factors (SMuRFs; hypertension, smoking, dyslipidemia, diabetes) have not been well studied, with little known about their characteristics, quality of care, or outcomes. We sought to systematically analyze patients with ACS without SMuRFs, especially to evaluate the effectiveness of guideline-directed medical therapy for these patients.

METHODS AND RESULTS: In the CCC-ACS (Improving Care for Cardiovascular Disease in China-Acute Coronary Syndrome) project (2014–2019), we examined the presence and absence of SMuRFs and features among 89 462 patients with initial acute coronary syndrome. The main outcome was in-hospital all-cause mortality. Among eligible patients, 11.0% had none of the SMuRFs (SMuRF-less). SMuRF-less patients had higher in-hospital mortality (unadjusted hazard ratio [HR], 1.49 [95% CI, 1.19–1.87]). After adjustment for clinical characteristics and treatments, the associations between SMuRF status and in-hospital mortality persisted (adjusted HR, 1.35 [95% CI, 1.07–1.70]). Guideline-directed optimal medical therapy (receiving angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β-blockers, and statins) was not associated with lower mortality (adjusted HR, 0.98 [95% CI, 0.58–1.67]) in SMuRF-less patients, unlike the association in patients with SMuRFs (adjusted HR, 0.80 [95% CI, 0.66–0.98]). Sensitivity analyses were consistent with these results.

CONCLUSIONS: SMuRF-less patients were associated with an increased risk of in-hospital mortality. Guideline-directed medical therapy was less effective in SMuRF-less patients than in patients with SMuRFs. Dedicated studies are needed to confirm the optimal therapy for SMuRF-less patients.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02306616.

Key Words: acute coronary syndrome ■ guideline-directed medical therapy ■ in-hospital mortality ■ standard modifiable cardiovascular risk factors

Correspondence to: Shaoping Nie, MD, PhD, Center for Coronary Artery Disease, Division of Cardiology, Beijing Anzhen Hospital, Capital Medical University, No. 2 Anzhen Road, Chaoyang District, 100029 Beijing, China. Email: spnie@ccmu.edu.cn and Yaling Han, MD, PhD, Cardiovascular Research Institute and Department of Cardiology, General Hospital of Northern Theater Command, No. 83 Wenhua Road, Shenyang 110016, China. Email: hanyaling@263.net

*W. Gong and Y. Yan contributed equally.

A complete list of the CCC-ACS Investigators can be found in the Supplemental Material.

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CLINICAL PERSPECTIVE

What Is New?

- Little is known about the quality of care or clinical outcomes of patients with acute coronary syndrome without standard modifiable cardiovascular risk factors (SMuRFs). In this nationwide cohort study of 89 462 patients with initial acute coronary syndrome, >1 in 10 were without SMuRFs, and these patients experienced an increased risk of in-hospital mortality.
- Guideline-directed medical therapy was not associated with lower mortality in patients without SMuRFs, unlike the association in patients with at least 1 SMuRF.

What Are the Clinical Implications?

- SMuRF-less patients represent a clinically significant special population; the absence of identified standard risk factors exposure should not be viewed as being associated with favorable prognosis.
- Guideline-directed medical therapy was less effective in SMuRF-less patients than in patients with SMuRFs; dedicated studies are needed to narrow SMuRF-related differences in treatments and outcomes.

Nonstandard Abbreviations and Acronyms

CCC-ACS	Improving Care for Cardiovascular Disease in China–Acute Coronary Syndrome
DAPT	dual antiplatelet therapy
IPTW	inverse probability of treatment weighting
OMT	optimal medical therapy
SMuRF	standard modifiable cardiovascular risk factor

Acute coronary syndrome (ACS) remains one of the leading causes of death worldwide.[1–3] The standard modifiable cardiovascular risk factors (SMuRFs), including dyslipidemia, hypertension, diabetes, and smoking, have been widely recognized at a population level. They have been the target of high-efficiency primary and secondary prevention strategies for ACS and the basis for guideline-directed medical therapy.[4–7] However, there is a considerable proportion of patients presenting with ACS in the absence of SMuRFs (SMuRF-less). These patients are easily overlooked in current guidelines and clinical studies.[8] Conversely, ACS without SMuRFs is not a benign condition.[9–11] Recent studies have reported a paradoxical finding on the effect of SMuRFs on outcomes following acute myocardial infarction, with mortality rate being higher in patients without SMuRFs than in patients with at least 1 SMuRF.[9–11] Nonetheless, little is known about the quality of care or clinical outcomes of patients with ACS without SMuRFs. Moreover, data documenting the effectiveness of guideline-directed medical therapy for patients without SMuRFs are still limited, and the underlying mechanisms for the increased mortality rate among this group of patients are not clear. Filling in these information gaps could help identify the particularity of SMuRF-less patients, optimize the treatment, and may improve the outcomes of patients with ACS.

Data from the CCC-ACS (Improving Care for Cardiovascular Disease in China–Acute Coronary Syndrome) project, a real-word registry across China, provide an opportunity to explore the impact of being SMuRF-less on ACS treatment and in-hospital outcomes. In the present study, we systematically analyzed data from patients with ACS to examine the clinical characteristics of patients without SMuRFs and compared outcomes and management with their counterparts with at least 1 SMuRF.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Patient Selection

Data from the CCC-ACS database were used in the study. Launched in 2014, the CCC-ACS project (https://clinicaltrial.gov; NCT 02306616) is a nationwide registry involving 241 hospitals across China. The registry is a collaborative program of the American Heart Association and the Chinese Society of Cardiology, focusing on quality improvement efforts for ACS care. Details of the rationale and design of the CCC-ACS project have been reported previously.[12] Briefly, in every month, the first 20 to 30 consecutive patients with ACS were recruited in tertiary and 10 to 20 patients in secondary hospitals. Patient were eligible for enrollment with a principal discharge diagnosis of ACS, including ST-segment–elevation myocardial infarction (STEMI) and non–ST-segment–elevation acute coronary syndrome. Institutional review board approval was granted for this research with a waiver for informed consent by the ethics committee of Beijing Anzhen Hospital, Capital Medical University. The protocol was approved by the ethics committee of Beijing Anzhen Hospital, Capital Medical University (2014018).

Information on participants was compiled by trained abstractors via an electronic data capture platform and was collected according to standardized definitions in the operations manual. To ensure the accuracy and completeness of the data, several approaches were adopted, including online automatic checks for invalid values, face-to-face training workshops, on-site quality control, monitoring of data completeness, and third-party audits.

All eligible patients with confirmed ACS diagnosis at discharge between November 1, 2014 and December 31, 2019 were included in this study. Patients who had a history of coronary artery disease, including prior myocardial infarction, prior percutaneous coronary intervention, or coronary artery bypass grafting were excluded from the analysis. In addition, this study excluded patients who died during hospitalization on the day of or day after arrival, patients with cardiogenic shock at admission, and patients with contraindication for guideline-directed medical therapy (angiotensin-converting enzyme inhibitors [ACEIs]/angiotensin receptor blockers [ARBs], β-blockers, and statins).

Definitions of SMuRFs and Study Variables

The exposure variable was defined as having at least 1 of the following SMuRFs: hypertension, diabetes, dyslipidemia, or current smoker status. Definitions of SMuRFs were based on electronic medical records (*International Classification of Diseases* (*ICD-9 and ICD-10*) codes), hospital findings, and patient self-report on smoking at admission. Hypertension was defined as having a history of hypertension or receiving antihypertensive pharmacotherapy, or a new diagnosis of hypertension during the index admission. Diabetes was defined as having a history of diabetes or receiving glucose-lowering pharmacotherapy, or a new diagnosis of diabetes during the index admission. Dyslipidemia was defined as a history of dyslipidemia, previous or ongoing cholesterol lowering treatment, low-density lipoprotein cholesterol ≥3.5 mmol/L, or total cholesterol ≥5.5 mmol/L during the index admission. A patient was defined as a current smoker if they had smoked within the preceding 1 year before the index hospitalization. SMuRF-less patients were defined as patients without SMuRFs.

In accordance with the guidelines for the management of ACS, we calculated the proportion of acute treatments and medical therapies for secondary prevention. Acute treatment measures for patients with ACS included dual antiplatelet therapy (DAPT), guideline-directed medical therapy (ACEIs/ARBs, β-blockers, or statins) within 24 hours of arrival, and acute reperfusion therapy. Guideline-directed optimal medical therapy (OMT) was defined as receiving ACEIs/ARBs, β-blockers, and statins within 24 hours of arrival. For patients with non–ST-segment–elevation acute coronary syndrome, acute reperfusion therapy included timely percutaneous coronary intervention for eligible patients following guideline recommendation (within 2, 24, and 72 hours of admission for groups with very high risk, high risk, and moderate risk, respectively).[13] Medical therapies for secondary prevention were recorded in discharge medical documents including medicine prescriptions of DAPT, ACEIs/ARBs, β-blockers, or statins, and smoking cessation and cardiac rehabilitation counseling.

End Points

The primary end point was in-hospital all-cause mortality. The secondary end point was major adverse cardiovascular events, defined as any occurrence of cardiovascular death, myocardial infarction, stent thrombosis, or stroke during hospitalization. Major bleeding was defined as any of the following events: fatal bleeding, intracranial bleeding, retroperitoneal bleeding, drop in hemoglobin ≥40 g/L during hospitalization, transfusion with overt bleeding, or bleeding requiring surgical intervention. Stent thrombosis was defined as an acute/subacute thrombotic occlusion of a coronary stent after the procedure. Myocardial infarction as an in-hospital event refers to a reinfarction during hospitalization for the index myocardial infarction. Stroke was defined as a new neurologic deficit during the index event hospitalization. Cardiac arrest was the sudden cessation of cardiac mechanical activity, requiring prompt provision of cardiopulmonary resuscitation and defibrillation. All end points were reported by clinical doctors and documented in medical records during hospitalization.

Statistical Analysis

Clinical characteristics of enrolled patients are described. Continuous variables are presented as mean±SD if a normal distribution and as median and interquartile range if skewed. Categorical variables are presented as frequency and percentage. The *t* test or Kruskal-Wallis test for continuous variables and χ^2 test for categorical variables were used to test for statistically significant differences between the SMuRF-less and SMuRF ≥1 groups. Kaplan-Meier methods were used to estimate the 15-day event rates for in-hospital outcomes. Comparisons between the study groups were performed using the log-rank test. Censoring was assumed in patients who had a nonfatal outcome at the time of a given outcome.

We assessed the associations between the SMuRF-status and study outcomes using Cox proportional hazards regression models, with calculation of hazard ratios (HRs) and 95% CIs, presented in the tables. Six

models were used to analyze the effects of SMuRF status on study outcomes: (1) an unadjusted model; (2) an adjusted model with age, sex, and type of ACS; (3) a further adjusted model, controlling prespecified variables with an impact of in-hospital mortality (medical insurance, previous cerebrovascular disease, medical history of heart failure, peripheral artery disease, family history of early coronary artery disease, acute heart failure at admission, cardiac arrest at admission, heart rate, systolic blood pressure, renal insufficiency, hemoglobin at admission, left ventricular ejection fraction <40%, and hospital level); (4) a further adjusted model, controlling DAPT at arrival; (5) a further adjusted model, considering acute reperfusion therapy; and (6) in patients with ACS, we adjusted for OMT within 24 hours of arrival. Imputation was performed for variables with missing data with the sequential regression multiple imputation method by IVEware software version 0.2 (Survey Research Center, University of Michigan, Ann Arbor, MI).

We also did a further analysis assessing the association between the use of OMT and study outcomes in SMuRF-less patients. To consolidate the findings, inverse probability of treatment weighting (IPTW) using the propensity score method was performed to compare differences between the OMT and no-OMT groups among the SMuRF-less patients. A logistic regression was performed to estimate propensity score, adjusting for the following variables: age, sex, previous disease history (renal failure history, heart failure history, peripheral artery disease, and previous cerebrovascular disease), heart rate, and systolic blood pressure. IPTW was calculated by each individual based on propensity score. Each case from the OMT group was given a weight of Pt/propensity score, and each case from the no-OMT group was given a weight of (1−Pt)/(1−propensity score), where Pt refers to the proportion of patients receiving OMT among the whole cohort. By this means we obtained a stabilized weight for each case of the study cohort, avoiding any extreme values that may result in unreliable outcomes. Three models were applied to explore the association between OMT use and each of the end points: (1) an unadjusted model, (2) an adjusted Cox proportional hazard model controlling prespecified variables with impact of in-hospital outcomes (age, sex, and type of ACS, medical insurance, previous cerebrovascular disease, medical history of heart failure, peripheral artery disease, family history of early coronary artery disease, acute heart failure at admission, cardiac arrest at admission, heart rate, systolic blood pressure, renal insufficiency, hemoglobin at admission, left ventricular ejection fraction <40%, hospital level, DAPT at arrival, and acute reperfusion therapy), and (3) an IPTW model. No OMT was used as the reference in these further analyses.

All tests were 2-sided, and a P value of <0.05 was considered to indicate statistical significance. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

A total of 113 650 patients were enrolled in the CCC-ACS project up to December 31, 2019. After excluding patients with a suspected ACS at admission or a history of coronary artery disease, 98 910 patients were selected (Figure). Based on the medical history, laboratory test, concomitant medicine, and discharge diagnosis, 10 964 patients were identified as SMuRF-less (Figure). Patients without SMuRFs were more unstable at admission at a higher rate of cardiogenic shock (3.2% versus 2.4%, P<0.001) (Table S1). This may affect the acute treatment of patients without SMuRFs.

To avoid the impact of the patient's clinical status at admission on treatment and prognosis, we further excluded patients who died during hospitalization on the day of or day after arrival, patients with cardiogenic shock at admission, and patients with contraindication for guideline-directed medical therapy (ACEIs/ARBs, β-blockers, or statins), and 89 462 patients were included for analysis. There were 9852 (11.0%) patients classified as SMuRF-less (Figure). Patient's baseline characteristics at admission are shown in Table 1. More SMuRF-less patients were women, had a higher rate of STEMI, on average were older, and were less likely to have comorbidities. They had lower levels of systolic blood pressure and lower rate of renal insufficiency.

Differences in Management Between Groups

Differences in acute management and medical therapies for secondary prevention between groups are shown in Table 2. Compared with the ≥1 SMuRF group, the SMuRF-less group was less frequently treated with guideline-directed medical therapy (ACEIs/ARBs, β-blockers, statins, or OMT) within 24 hours of arrival. Among patients with STEMI, patients without SMuRFs were less likely to receive acute reperfusion therapy than patients with ≥1 SMuRF (61.5% versus 64.6%, P<0.001). Additionally, medical therapies for secondary prevention were described less for the patients without SMuRFs than those with at least 1 SMuRF (Table 2).

Clinical Outcomes and Association With SMuRF Status

SMuRF-less patients had significantly higher unadjusted rates of in-hospital all-cause mortality (89 [0.9%]

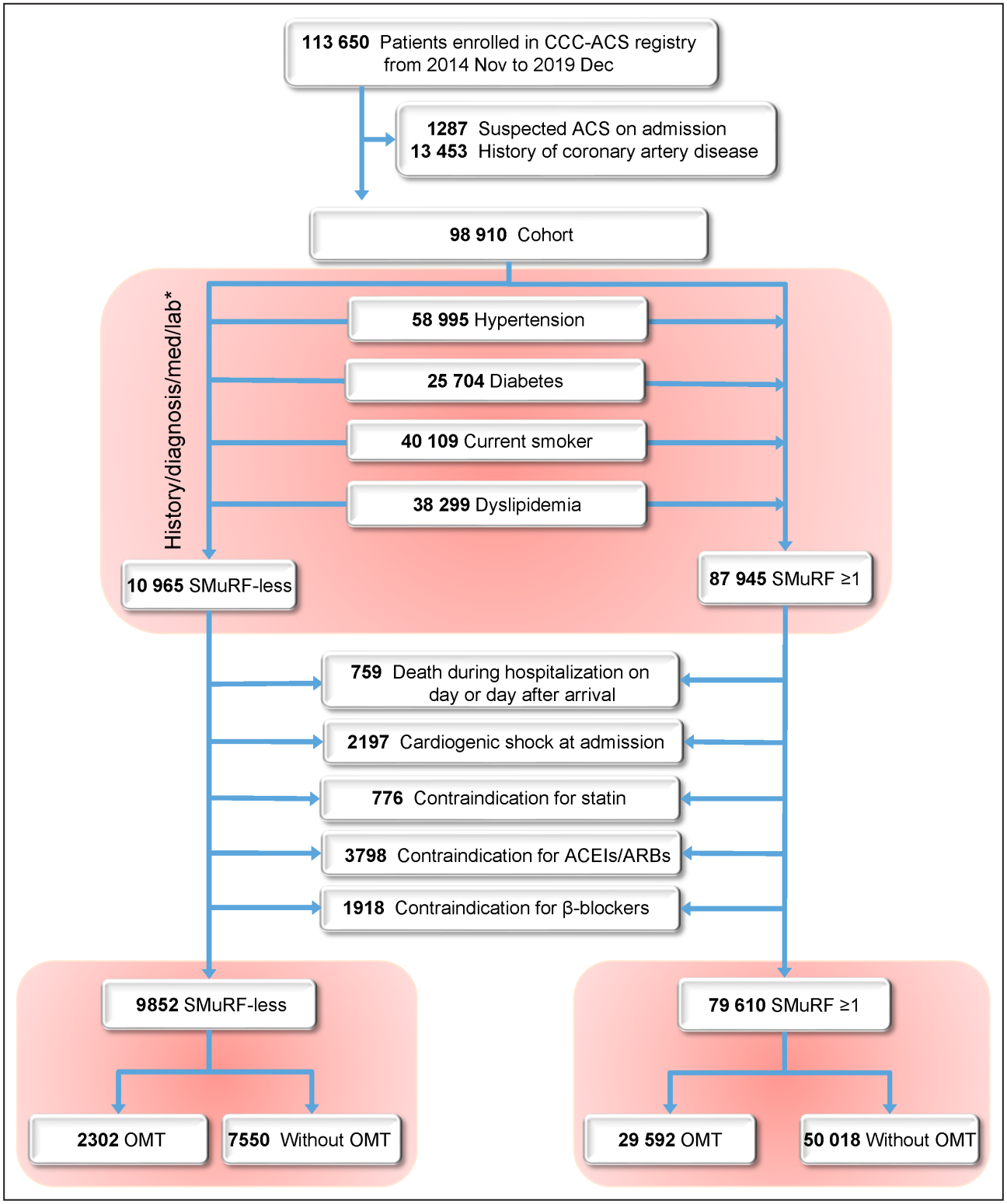

Figure. Patient selection flowchart.
*Definitions of SMuRFs were based on medical history, diagnosis, medication, or laboratory data. ACEIs/ARBs indicates angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; ACS, acute coronary syndrome; CCC-ACS, Improving Care for Cardiovascular Disease in China–Acute Coronary Syndrome; OMT, optimal medical therapy; and SMuRF, standard modifiable cardiovascular risk factor.

Table 1. Baseline Characteristics

Characteristics	SMuRF-less (n=9852)	≥1 SMuRF (n=79610)	*P* value
Sociodemographic			
Age, y	64.3±12.8	62.4±12.3	<0.001
Age ≥65 y	4959 (50.3)	34639 (43.5)	<0.001
Women	3190 (32.4)	20461 (25.7)	<0.001
ACS type			
STEMI	6179 (62.7)	47497 (59.7)	<0.001
NSTE-ACS	3673 (37.3)	32113 (40.3)	<0.001
Medical insurance			
Urban insurance	4847 (49.2)	43234 (54.3)	<0.001
Rural insurance	2880 (29.2)	18591 (23.4)	
Other insurance	950 (9.6)	7830 (9.8)	
Self-paid	1175 (11.9)	9955 (12.5)	
SMuRF reported at admission			
Hypertension	0 (0)	46058 (57.9)	<0.001
Dyslipidemia	0 (0)	5860 (7.4)	<0.001
Diabetes	0 (0)	18321 (23.0)	<0.001
Current smoker	0 (0)	36890 (46.3)	<0.001
Medical history			
Heart failure history	71 (0.7)	859 (1.1)	<0.001
Peripheral artery disease	48 (0.5)	579 (0.7)	0.007
Hemorrhagic stroke	31 (0.3)	597 (0.7)	<0.001
Ischemic stroke	361 (3.7)	5925 (7.4)	<0.001
Family history of early CAD	19 (0.2)	407 (0.5)	<0.001
Clinical status at admission			
Heart failure	363 (3.7)	3339 (4.2)	0.0166
Cardiac arrest	68 (0.7)	512 (0.6)	0.58
Heart rate, bpm	76.7±15.5	77.5±15.3	<0.001
Systolic blood pressure, mm Hg	124.2±19.6	132.8±23.1	<0.001
Laboratory and echocardiogram variables			
Hemoglobin, g/L	133.4±20.4	137.61±20.0	<0.001
Renal insufficiency	1076 (10.9)	10200 (12.8)	<0.001
Glucose, mmol/L	6.1±2.0	6.9±3.0	<0.001
LDL-C, mmol/L	2.4±0.6	2.8±1.0	<0.001
TC, mmol/L	4.0±0.8	4.6±1.3	<0.001
LVEF, %	55.8±10.0	56.2±26.3	0.14
Duration of hospitalization, d	9 (7–12)	9 (7–12)	0.55

Values are presented as mean±SD, median (interquartile rang), or number (percentage). Percentages may not sum to100 due to rounding. ACS indicates acute coronary syndrome; CAD, coronary artery disease; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; NSTE-ACS, non–ST-segment–elevation acute coronary syndrome; STEMI, ST-segment–elevation myocardial infarction; SMuRF, standard modifiable cardiovascular risk factor; and TC, total cholesterol.

patients versus 488 [0.6%] patients, *P*<0.001), cardiovascular death (87 [0.9%] patients versus 480 [0.6%] patients, *P*<0.001), cardiogenic shock (107 [1.1%] patients versus 603 [0.8%] patients, *P*<0.001), cardiac arrest (103 [1.1%] patients versus 538 [0.7%] patients, *P*<0.001), and combined major adverse cardiovascular events (153 [1.6%] patients versus 984 [1.2%] patients, *P*=0.01) (Table 3). There was no difference between the 2 groups in major bleeding (168 [1.7%] versus 1547 [1.9%], *P*=0.1) (Table 3).

After adjustment for age, sex, type of ACS, and other clinical characteristics, SMuRF-less patients were associated with an increased risk of in-hospital mortality (adjusted HR, 1.38 [95% CI, 1.10–1.75]) (Table 3). To evaluate whether the SMuRF status difference in mortality could be explained by disparities in the acute management of ACS, we further adjusted for the use of DAPT, acute reperfusion therapy, and guideline-directed OMT within 24 hours of arrival. After additional adjustment for acute treatments, the associations between SMuRF-status and in-hospital mortality remained statistically significant in patients with ACS (adjusted HR, 1.35 [95% CI, 1.07–1.70]) (Table 3). Sensitivity analyses, excluding patients who did not have urban insurance, produced consistent results for in-hospital mortality (Table S2).

Table 2. Differences in Acute Management and Medical Therapies for Secondary Prevention

Characteristics	SMuRF-less (n=9852)	≥1 SMuRF (n=79610)	*P* value
Acute treatment			
DAPT at arrival	8709 (89.1)	73684 (93.2)	<0.001
ACEIs/ARBs	3225 (32.7)	41063 (51.6)	<0.001
β-Blockers	5015 (50.9)	47364 (59.5)	<0.001
Statins	8867 (90.0)	75364 (94.7)	<0.001
OMT	2302 (23.4)	29592 (37.2)	<0.001
Acute reperfusion therapy for STEMI	3803 (61.5)	30684 (64.6)	<0.001
Primary PCI	3354 (54.3)	27008 (56.9)	<0.001
Fibrinolysis	348 (5.6)	2712 (5.7)	
Fibrinolysis + PCI	101 (1.6)	964 (2.0)	
DTB within 90 min for primary PCI	1656 (79.9)	13235 (80.4)	0.59
Timely PCI for eligible NSTE-ACS	514 (27.0)	5322 (27.9)	0.41
Medical therapies for secondary prevention			
DAPT at discharge	8166 (82.9)	69885 (87.8)	<0.001
ACEIs/ARBs at discharge	3695 (37.5)	44312 (55.7)	<0.001
β-Blockers at discharge	5821 (59.1)	53633 (67.4)	<0.001
Statins at discharge	8726 (88.6)	73894 (92.8)	<0.001
Cardiac rehabilitation counseling	3282 (33.3)	27643 (34.7)	0.006

Values are presented as number (percentage). ACEIs/ARBs indicates angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; DAPT, dual antiplatelet therapy; DTB, door-to-balloon time; NSTE-ACS, non–ST-segment–elevation acute coronary syndrome; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; SMuRF, standard modifiable cardiovascular risk factor; and STEMI, ST-segment–elevation myocardial infarction.

Table 3. Associations Between SMuRF Status and In-Hospital Outcomes Analyzed With Cox Proportional Hazard Models in Patients With ACS

Variable	SMuRFs-less (n=9852)/events, n (%)	≥1 SMuRF (n=79 610)/ events, n (%)	*P* value	Unadjusted	Adjusted for clinical characteristics		Adjusted for clinical characteristics and treatment		
					Model 1	Model 2	Model 3	Model 4	Model 5
				HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Death	89 (0.9)	488 (0.61)	<0.001	1.49 (1.19–1.87)	1.30 (1.04–1.64)	1.38 (1.10–1.75)	1.38 (1.09–1.74)	1.38 (1.09–1.73)	1.35 (1.07–1.70)
Cardiovascular death	87 (0.88)	480 (0.6)	<0.001	1.48 (1.18–1.86)	1.30 (1.03–1.63)	1.38 (1.09–1.74)	1.38 (1.09–1.74)	1.37 (1.08–1.73)	1.34 (1.06–1.70)
Cardiac shock	107 (1.09)	603 (0.76)	<0.001	1.44 (1.17–1.77)	1.30 (1.06–1.60)	1.22 (0.99–1.51)	1.24 (1.00–1.53)	1.24 (1.00–1.53)	1.22 (0.98–1.50)
Cardiac arrest	103 (1.05)	538 (0.68)	<0.001	1.55 (1.26–1.92)	1.40 (1.13–1.73)	1.39 (1.12–1.73)	1.43 (1.15–1.77)	1.43 (1.15–1.77)	1.42 (1.14–1.76)
MI	31 (0.31)	202 (0.25)	0.26	1.25 (0.85–1.82)	1.20 (0.82–1.75)	1.29 (0.87–1.90)	1.27 (0.86–1.87)	1.26 (0.85–1.87)	1.25 (0.84–1.86)
Stent thrombosis	9 (0.09)	92 (0.12)	0.5	0.79 (0.40–1.57)	0.77 (0.39–1.53)	0.83 (0.42–1.66)	0.85 (0.43–1.71)	0.86 (0.43–1.72)	0.88 (0.44–1.76)
Stroke	38 (0.39)	289 (0.36)	0.72	1.06 (0.76–1.49)	1.01 (0.72–1.41)	1.07 (0.76–1.52)	1.03 (0.72–1.46)	1.03 (0.72–1.45)	0.99 (0.69–1.40)
Major bleeding	168 (1.71)	1547 (1.94)	0.1	0.88 (0.75–1.03)	0.84 (0.72–0.99)	0.94 (0.80–1.11)	0.92 (0.78–1.08)	0.92 (0.78–1.08)	0.91 (0.78–1.07)
MACE	153 (1.55)	984 (1.24)	0.01	1.26 (1.06–1.49)	1.16 (0.98–1.37)	1.23 (1.03–1.47)	1.21 (1.02–1.45)	1.21 (1.02–1.44)	1.19 (1.00–1.41)

Model 1: adjusted for age, sex, and type of ACS. Model 2: adjusted for variables in Model 1 plus medical insurance, previous cerebrovascular disease, medical history of heart failure, peripheral artery disease, family history of early coronary artery disease, acute heart failure at admission, cardiac arrest at admission, heart rate, systolic blood pressure, renal insufficiency, hemoglobin at admission, LVEF <40%, and hospital level. Model 3: adjusted for variables in Model 2 plus DAPT at arrival. Model 4: adjusted for variables in Model 3 plus acute reperfusion therapy. Model 5: adjusted for variables in Model 4 plus OMT (receiving ACEIs/ARBs, β-blockers, and statins) within 24 h of arrival. ACEIs/ARBs indicates angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; ACS, acute coronary disease; DAPT, dual antiplatelet therapy; HR, hazard ratio; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; MI, myocardial infarction; OMT, optimal medical therapy; and SMuRF, standard modifiable cardiovascular risk factor.

Impact of Early Guideline-Directed OMT on In-Hospital Outcomes of SMuRF-Less Patients

To evaluate whether the SMuRF status difference in mortality could be associated with differences in the use of guideline-directed medical therapy at the acute phase, we further analyzed the association between guideline-directed OMT and SMuRF status (Table 4 and Table S3). For patients without SMuRFs, the rate of all-cause death was 18 (0.78%) for 2302 individuals with OMT and 71 (0.94%) for 7550 individuals treated without OMT (unadjusted HR, 0.83 [95% CI, 0.50–1.39]). For patients with at least 1 SMuRF, the rate of all-cause death was 144 (0.49%) for 29 592 individuals with OMT and 344 (0.69%) for 50 018 individuals without OMT (unadjusted HR, 0.71 [95% CI, 0.58–0.86]) (Table 4). After adjusting for potential confounders of baseline characteristic, DAPT at arrival, and acute reperfusion therapy, no significant association remained between the OMT status and mortality for patients without SMuRFs (adjusted HR, 0.98 [95% CI, 0.58–1.67]), but with significance for those with at least 1 SMuRF (adjusted HR, 0.80 [95% CI, 0.66–0.98]) (Table 4 and Figure S1). Similar results were also found in the Cox model based on IPTW population (Table 4 and Table S4).

To consolidate the findings, we conducted a sensitivity analysis by excluding SMuRF-less patients who had not received DAPT or acute reperfusion therapy. In total, we identified 3769 SMuRF-less patients, of whom 1012 were classified as receiving OMT (Figure S2). Patients receiving OMT were on average younger, fewer women, with higher heart rate and systolic blood pressure. After adjustment using the IPTW methods, baseline characteristics were well balanced (Table S5). In-hospital mortality before discharge was not different in patients with OMT compared with no OMT, with an adjusted HR of 0.57 (95% CI, 0.22–1.50). Similar results were found in the IPTW population (adjusted HR, 0.60 [95% CI, 0.24–1.50]) (Table S6).

DISCUSSION

This large-scale national study emphasized the particularity and importance of patients with ACS without SMuRFs. Among nearly 90 000 patients with ACS in the CCC-ACS registry who were analyzed in this study, not having SMuRFs was associated with increased in-hospital mortality. After adjustment for clinical characteristics and treatments, the associations between SMuRF status and in-hospital mortality persisted. Furthermore, this study showed that guideline-directed medical therapy was not associated with lower mortality in patients without SMuRFs, unlike the association in patients with at least 1 SMuRF.

Table 4. Unadjusted and Cox Adjusted Hazard Ratios for In-Hospital Outcomes in Patients With or Without OMT Stratified by SMuRF Status

Variable	SMuRF-less					≥1 SMuRFs					
	OMT (n=2302)/ events, n (%)	No OMT (n=7550)/ events, n (%)	*P* value	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	OMT (n=29592)/ events, n (%)	No OMT (n=50018)/ events, n (%)	*P* value	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Death	18 (0.78)	71 (0.94)	0.48	0.83 (0.50–1.39)	0.98 (0.58–1.67)	0.85 (0.51–1.41)	144 (0.49)	344 (0.69)	<0.001	0.71 (0.58–0.86)	0.80 (0.66–0.98)	0.72 (0.59–0.87)
Cardiovascular death	17 (0.74)	70 (0.93)	0.40	0.80 (0.47–1.35)	0.94 (0.55–1.63)	0.82 (0.49–1.38)	143 (0.48)	337 (0.67)	<0.001	0.72 (0.59–0.87)	0.81 (0.66–1.00)	0.72 (0.59–0.88)
Cardiogenic shock	25 (1.09)	82 (1.09)	1.00	1.00 (0.64–1.56)	1.01 (0.64–1.60)	0.94 (0.60–1.48)	173 (0.58)	430 (0.86)	<0.001	0.68 (0.57–0.81)	0.80 (0.66–0.95)	0.71 (0.59–0.85)
Cardiac arrest	25 (1.09)	78 (1.03)	0.83	1.05 (0.67–1.65)	1.11 (0.69–1.77)	1.05 (0.67–1.64)	166 (0.56)	372 (0.74)	0.0024	0.76 (0.63–0.91)	0.86 (0.71–1.03)	0.76 (0.63–0.91)
MI	7 (0.30)	24 (0.32)	0.92	0.96 (0.41–2.22)	1.06 (0.44–2.56)	1.03 (0.46–2.30)	73 (0.25)	129 (0.26)	0.76	0.96 (0.72–1.29)	0.93 (0.69–1.26)	0.92 (0.69–1.23)
Stent thrombosis	2 (0.09)	7 (0.09)	0.94	0.94 (0.19–4.51)	0.80 (0.16–3.95)	0.70 (0.13–3.70)	43 (0.15)	49 (0.10)	0.06	1.48 (0.98–2.23)	1.33 (0.87–2.03)	1.45 (0.96–2.20)
Stroke	7 (0.30)	31 (0.41)	0.47	0.74 (0.33–1.68)	0.75 (0.32–1.73)	0.72 (0.33–1.61)	76 (0.26)	213 (0.43)	<0.001	0.60 (0.46–0.78)	0.63 (0.48–0.83)	0.60 (0.46–0.77)
Major bleeding	33 (1.43)	135 (1.79)	0.25	0.80 (0.55–1.17)	0.76 (0.52–1.13)	0.74 (0.51–1.09)	538 (1.82)	1009 (2.02)	0.05	0.90 (0.81–1.00)	0.89 (0.80–0.99)	0.85 (0.76–0.94)
MACE	29 (1.26)	124 (1.64)	0.19	0.77 (0.51–1.15)	0.82 (0.54–1.25)	0.74 (0.50–1.11)	312 (1.05)	672 (1.34)	<0.001	0.78 (0.69–0.90)	0.82 (0.72–0.95)	0.78 (0.68–0.89)

Model 1: adjusted by age, sex, type of ACS, medical insurance, previous cerebrovascular disease, medical history of heart failure, peripheral artery disease, family history of early coronary artery disease, acute heart failure at admission, cardiac arrest at admission, heart rate, systolic blood pressure, renal insufficiency, hemoglobin at admission, LVEF <40%, hospital level, DAPT at arrival, and acute reperfusion therapy. Model 2: adjusted by type of ACS and LVEF in an IPTW sample (matching specifications were shown in Table S4). ACS indicates acute coronary disease; DAPT, dual antiplatelet therapy; HR, hazard ratio; IPTW, inverse probability of treatment weighting; LVEF, left ventricle ejection fraction; MACE, major adverse cardiovascular events; MI, myocardial infarction; OMT, optimal drug therapy; and SMuRF, standard modifiable cardiovascular risk factor.

Several previous studies have consistently observed a significant proportion of patients with acute myocardial infarction without SMuRFs.[9–11] The National Registry of Myocardial Infarction for 542008 patients reported that 14.4% of patients with acute myocardial infarction had no SMuRFs, a proportion similar to the 14.9% that was reported by The Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) registry.[9,10] However, these studies were limited to acute myocardial infarction and therefore may not be generalizable to the overall ACS population. To our knowledge, this analysis represents the largest study to date examining the relationship of SMuRFs and mortality after initial ACS in contemporary practice. Our study found that 11.0% of patients with ACS had no SMuRFs. Another study reported that the proportion of SMuRF-less patients was increasing.[11] There may be several potential explanations for this increase. One potential reason may be that successful management of SMuRFs in primary care effectively increases the relative proportion of patients with other risk factors that have not been well recognized. Another potential explanation that is plausible is that some unknown factors, such as heavy metal exposure levels, obstructive sleep apnea, drug taking, and air particulate matter, may be leading to atherosclerotic events or nonatherosclerotic coronary events (such as spontaneous coronary artery dissection or coronary artery spasm) in SMuRF-less patients.[1,14–16] The increasing proportion of patients who are SMuRF-less highlights the importance of establishing evidence for them.

The association of SMuRF-less status with increased mortality suggests that these patients are a special population of ACS requiring a call to action. The SWEDEHEART registry reported that SMuRF-less patients with STEMI have an almost 50% higher 30-day mortality rate than their counterparts with SMuRFs.[9] In this study, we observed that SMuRF-less patients were associated with an increased risk of in-hospital mortality. The paradox of SMuRFs has given prominence to the particularity of SMuRF-less patients and the necessity of studying the internal causes.

There were several potential explanations for the increased mortality rate in SMuRF-less patients. First, some studies hypothesized that this finding may be explained by residual confounding caused by age, sex, and other clinical features in patients without SMuRFs, and the association persisted after multivariate adjustment.[10,17] Second, perceived low risk in ACS cases might have decreased prescriptions of guideline-directed treatments. The SWEDEHEART registry indicated that the increased mortality among patients with STEMI without SMuRFs could be explained by the suboptimal prescription rates of guideline-directed treatments.[9] Most recently, the China Acute Myocardial Infarction registry reported that the increased crude mortality

risk among SMuRF-less patients was caused by confounding factors related to unfavorable clinical characteristics and poor management. Even after multivariate adjustment, it has been concluded that a higher SMuRF risk is associated with poor prognosis in patients with STEMI.[18] A meta-analysis also highlights the impact of early guideline-directed treatments on poor prognosis in SMuRF-less patients.[19] However, these studies ignored the impact of the patient's clinical status at admission on treatment and prognosis. SMuRF-less patients had a higher likelihood of presenting with cardiogenic shock at admission than patients with SMuRFs.[10] Our study also found that patients without SMuRFs were more unstable at admission at a higher rate of cardiogenic shock (3.2% versus 2.4%, $P<0.001$). In this study, to avoid the impact of the patient's clinical status at admission on treatment and prognosis, we excluded patients who died during hospitalization on the day of or day after arrival, patients with cardiogenic shock at admission, and patients with contraindication for guideline-directed medical therapy. We found that the associations between SMuRF status and in-hospital mortality remained significant, even after adjustment for clinical characteristics and guideline-directed treatments. Interestingly, we observed that guideline-directed medical therapy was not associated with favorable prognosis in patients without SMuRFs, unlike the association in patients with at least 1 SMuRF. This study suggested that suboptimal prescription rates of guidelines-directed treatments may not explain the increased mortality rate in SMuRF-less patients. On the other hand, current guideline-directed treatments may not fully apply to SMuRF-less patients. It indicates the need for dedicated studies to explore and determine the optimal therapy for this specific patient subgroup.

The higher in-hospital mortality rate of SMuRF-less patients may reflect differing underlying pathophysiology. SMuRFs may be the tip of the iceberg of risk factors for ACS. Several previous large-scale genome-wide association studies have showed that the majority of genetic loci associated with coronary artery disease were not associated with identified standard risk factors.[20–22] Deloukas et al found that >66% of loci associated with coronary artery disease are not associated with identified standard risk factors. These data, highlighting the dramatic difference between high-risk patient identification and targeted prevention would suggest the need for more widely accessible novel risk factors for coronary artery disease, particularly relevant for these individuals. Advances in new technologies and data science, such as omics, multiomics, and single-cell analysis, have made it possible to identify unknown biological processes and networks.[23,24] Although it is absolutely necessary that we continue to identify and address the burden of standard risk factor for atherosclerosis in primary prevention, parallel efforts also should continue to reveal the potential mechanisms underlying disease in SMuRF-less patients. Targeted quality improvement programs are required to address SMuRF-related disparities in quality of care for patients with ACS.

The study has several strengths, including the use of a national registry, a large sample size, and comprehensive data collection. However, there are also limitations that need to be acknowledged. First, as with all observational studies, there is the potential for bias. To mitigate this, we included most confounding factors in the multivariate analysis. However, there may still be unmeasured or residual confounding that could have influenced our findings. Second, the group of SMuRF-less patients likely includes individuals with missed risk factors or multiple subthreshold risk factors, as well as those with increased susceptibility to atherosclerotic drivers. We addressed this concern by defining SMuRFs based on various criteria and conducting extensive adjusted analyses. Third, it is important to interpret the association between SMuRF-less patients and higher in-hospital mortality with caution, despite implementing multiple adjustments. Several potential factors could influence the results, including the patient's clinical status at admission (such as cardiogenic shock) and medical insurance coverage. To mitigate the impact of the patient's clinical status at admission on treatment and prognosis, our study excluded patients who died during hospitalization on the day of or day after arrival, those with cardiogenic shock at admission, and those with contraindication for guideline-directed medical therapy. Additionally, to account for any potential confounding effect of medical insurance, we conducted sensitivity analysis by excluding patients who did not have urban insurance. The results showed consistently that SMuRF-less patients were associated with an increased risk of in-hospital mortality in patients with urban insurance. Fourth, our study could not ascertain precisely the doctors' rationale for their treatment decisions, and there was a lack of long-term follow-up data. Improved visibility of SMuRF-less patients in future studies, especially those studies examining new risk factors. Despite all this, we believe that our main finding of association of SMuRF-less status with increased mortality on initial ACS is robust.

CONCLUSIONS

Among patients with ACS, >1 in 10 were without SMuRFs, and these patients experienced an increased risk of in-hospital mortality. The absence of identified standard risk factors exposure should not be viewed as being associated with favorable prognosis. Guideline-directed medical therapy was not associated with lower mortality in patients without SMuRFs, unlike the association in patients with at least 1 SMuRF. SMuRF-less patients represent a clinically significant special population,

requiring dedicated studies to narrow SMuRF-related differences in treatments and outcomes.

ARTICLE INFORMATION

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Affiliations

Center for Coronary Artery Disease, Division of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China (W.G., Y.Y., X.W., W.Z., B.Q., H.A., S.N.); National Clinical Research Center for Cardiovascular Diseases, Beijing, China (W.G., Y.Y., X.W., W.Z., B.Q., H.A., C.M., S.N.); Beijing Institute of Heart (W.G., Y.Y., X.W., W.Z., B.Q., H.A., C.M., S.N.), and Department of Epidemiology, Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart (J.L., D.Z.), Lung, and Blood Vessel Diseases, Beijing, China; Division of Cardiology, University of North Carolina, Chapel Hill, NC (S.C.S.); Division of Cardiology, Geffen School of Medicine at University of California, Los Angeles, CA (G.C.F.); International Quality Improvement Department, American Heart Association, Dallas, TX (L.M.); and Department of Cardiology, General Hospital of Northern Theater Command, Shenyang, China (Y.H.).

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Disclosures

None.

Supplemental Material

Data S1
Tables S1–S6
Figures S1–S2

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