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Standard modifiable cardiovascular risk factors and coronary artery disease severity in adults with myocardial infarction ≤ 35

Si-qi Tang [a,1], Xin-long Zhao [b,1], Quan Li [c], Yan-bo Liu [d], Yi-tao Han [b], Yu-xiong Chen [a], Jin-yan Lei [b], Ya-kun Zhao [a], Zhong-jie Fan [b,2,*], Yan-ping Ruan [e,2,**]

[a] Department of Internal Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China
[b] Department of Cardiology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China
[c] Center for Coronary Heart Disease, Beijing Anzhen Hospital, Capital Medical University, Beijing, China
[d] Department of International Medical Services, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China
[e] Department of Echocardiography, Beijing Anzhen Hospital, Capital Medical University, Beijing, China

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ABSTRACT

Background: Myocardial infarction (MI) in individuals ≤35 years is poorly characterized. The prevalence of standard modifiable cardiovascular risk factors (SMuRFs) and their associations with CAD severity at the index presentation and with post-index outcomes remain unclear.
Aims: We profiled SMuRFs in MI patients ≤35 years and assessed their association with CAD severity at the index MI and post-index outcomes.
Methods: This retrospective, two-center cohort study included index MI patients aged ≤35 years admitted to Beijing Anzhen Hospital and Peking Union Medical College Hospital between December 2011 and December 2021, and followed through February 2024. SMuRFs included hypertension, diabetes, hypercholesterolemia, and smoking. CAD severity was defined by the count of epicardial vessels with ≥50 % stenosis. Post-index event was major adverse cardiovascular and cerebrovascular events (MACCE).
Results: Among 776 patients (median age 33 years; 94 % male), 10 % had no SMuRFs, and 54 % had ≥2 SMuRFs. Smoking (74 %) and hypercholesterolemia (41 %) were most prevalent. Angiography revealed single-vessel disease in 47 %, two-vessel disease in 129 (17 %), and three-vessel disease in 194 (25 %); 11 % had no obstructive lesion. Each additional SMuRF increased the adjusted odds of more extensive CAD by 1.66-fold (95 % CI, 1.43–1.94). Diabetes, hypercholesterolemia, and hypertension were independently associated with multi-vessel disease, whereas smoking was not. Over a median follow-up of 5.6 years, 22.4 % experienced post-index MACCE, with higher incidence among patients with ≥3 SMuRFs.
Conclusions: Very young MI patients carry a high burden of SMuRFs, which correlate with greater CAD severity at the index presentation and worse post-index outcomes.

1. Introduction

Myocardial infarction (MI) remains a substantial cause of premature cardiovascular death worldwide [1]. Despite advances in preventive strategies, younger individuals have experienced a slower decline in MI incidence and mortality than elder populations [2]. The Atherosclerosis Risk in Communities Surveillance study showed an increase in the proportion of MI patients aged 35 to 54 years, rising from 27 % to 32 % between 1995 and 2014 [3]. Similarly, a Chinese cohort observed a 57 % increase in MI cases among individuals under 45 years old between 2010 and 2014 in Beijing [4].

Recent studies have predominantly defined premature MI as a first MI occurring before age 45 or 50 [5]. However, very young MI (≤35

* Corresponding authors. Department of Cardiology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, No.1 Shuaifuyuan, Wangfujing, Dongcheng District, Beijing 100730, China.
** Department of Echocardiography, Beijing Anzhen Hospital, Capital Medical University, No. 2 Anzhen Road, Chaoyang District, Beijing, 100029, China.
E-mail addresses: Fanzhongjie@pumch.cn (Z.-j. Fan), yanping.ruan@163.com (Y.-p. Ruan).
[1] These two authors contributed equally to this work.
[2] These two authors are co-corresponding authors.

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Glossary

Abbreviation/Acronym	Expanded Form
ACE inhibitor	Angiotensin-Converting Enzyme Inhibitor
AFIJI	Appraisal of Risk Factors in Young Ischemic Patients Justifying Aggressive Intervention
ARB	Angiotensin Receptor Blocker
BMI	Body mass index
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
DDCD	Duke Databank for Cardiovascular Disease
eGFR	Estimated glomerular filtration rate
GRS	Genetic Risk Score
HDL-C	High-density lipoprotein cholesterol
LAD	Left anterior descending artery
LCX	Left circumflex artery
LDL-C	Low-density lipoprotein cholesterol
LVEF	Left ventricular ejection fraction
LVEDd	Left ventricular end-diastolic diameter
MACCE	Major adverse cardiovascular and cerebrovascular events
MI	Myocardial infarction
NSTEMI	Non–ST-segment elevation myocardial infarction
PCI	Percutaneous coronary intervention
PCSK9-i	Proprotein convertase subtilisin/kexin type 9 inhibitor
PDAY	Pathobiological Determinants of Atherosclerosis in Youth
SBP	Systolic blood pressure
SMuRF	Standard Modifiable Risk Factor
STEMI	ST-segment elevation myocardial infarction

years), comprising <20 % of the cases, remains underrepresented in the literature. These patients develop coronary artery disease (CAD) two to three decades earlier than typical MI patients and may exhibit distinct risk profiles. In the Duke Databank for Cardiovascular Disease (DDCD), which enrolled 239 patients ≤35 years, individuals had a higher body mass index (BMI) but fewer traditional cardiovascular risk factors than those aged 35–45 [6]. Similarly, the Partners YOUNG-MI Registry compared 431 patients under 40 with 1666 patients aged 41–50, revealing lower hypertension rates and higher substance abuse rates in the younger group [7].

Substantial gaps remain in the understanding of MI pathogenesis in very young patients. The rising incidence of premature MI is primarily driven by the growing prevalence of traditional modifiable risk factors [8]. Standard modifiable cardiovascular risk factors (SMuRFs), including hypertension, diabetes, hypercholesterolemia, and smoking, remain central targets for preventive interventions [9]. In the GENESIS-PRAXY cohort which enrolled acute coronary syndrome (ACS) patients ≤55 years, positive family history and an elevated polygenic risk score were associated with increased angiographic CAD severity [10]. However, the relationship between SMuRF burden and angiographic CAD severity at presentation in very young MI patients has not been investigated.

Current primary and secondary prevention guidelines are predominantly age-dependent, often underestimating CAD risk in younger patients [11]. Notably, the 10-year Atherosclerotic Cardiovascular Disease risk calculator does not apply to individuals under 40. The DDCD study found that less than half of MI patients under 55 were eligible for statins before their index MI, with only 1/4 meeting the criteria for the very-high-risk population [12]. Risk-factor control also remains suboptimal among younger MI patients, with up to 30 % continuing to smoke and fewer than 20 % achieving recommended lipid targets [2,6]. Understanding the association between SMuRF and CAD severity may enhance early risk stratification and targeted preventive strategies in this young cohort with longer life expectancy.

In this contemporary, two-center Chinese cohort of very young MI patients (≤35 years), we aimed to characterize the prevalence and patterns of SMuRFs, evaluate the association between SMuRFs and index angiographic CAD severity, and assess the impact of SMuRFs on post-index clinical outcomes.

2. Methods

2.1. Study population

This two-center, retrospective cohort study was conducted at Beijing Anzhen Hospital, Capital Medical University, and Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, two tertiary medical centers in Beijing, China. We consecutively included patients diagnosed with MI before the age of 35 years from 1 December 2011 to 1 December 2021. Patients were identified by ICD-10 discharge codes I21-I22. All cases were confirmed by two cardiologists according to the Fourth Universal Definition of Myocardial Infarction (2018) [13]. Patients with coexisting cardiomyopathy, myocarditis, missing laboratory records or coronary angiography, or a follow-up duration of less than one year were excluded. All data were collected anonymously. The Institutional Ethics Committee of Beijing Anzhen Hospital, Capital Medical University, and Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, approved this study. All subjects provided original consent for the research use of their data, and re-consent was waived. The study was registered with the Chinese Clinical Trial Registry (URL: http://www.chictr.org.cn; Unique identifier: ChiCTR2400085600).

2.2. Data collection

Data were extracted from the electronic medical record systems of both hospitals. All baseline variables and angiographic findings were obtained at the index MI admission. Clinical characteristics included residency, presenting features, cardiovascular risk factors, comorbid conditions, laboratory and echocardiographic findings, angiographic findings, and medications. Residency was categorized into three groups based on the patient's reported index residence: local (residing in Beijing), non-local urban (residing in urban areas outside Beijing), and non-local rural (residing in rural areas). Obesity was defined as a BMI ≥28kg/m^2 according to Guidelines for the Diagnosis and Treatment of Obesity (2024) in China [14]. A family history of premature CAD was defined as a first-degree relative hospitalised due to MI or angina with coronary revascularization before 55 years of age in men and 65 years in women. Left ventricular ejection fraction (LVEF) was measured using the biplane Simpson method with echocardiography. Medication use was abstracted at two time points. At admission, we recorded antiplatelet therapy, lipid-lowering agents, antihypertensive therapy, and glucose-lowering agents. At discharge, we recorded the prescribed regimen, including antiplatelet therapy, β-blockers, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), and lipid-lowering therapy.

2.3. Definition of SMuRFs

SMuRFs included hypertension, diabetes, hypercholesterolemia, and current smoking. The definitions of SMuRFs were made according to Figtree et al. [15,16] Hypertension was defined as a previous diagnosis, or use of antihypertensive medications ("pre-index diagnosed"); or a new diagnosis during the index admission ("newly diagnosed at index"). Hypercholesterolemia was defined by a previous diagnosis, use of low-density lipoprotein cholesterol (LDL-C)-lowering therapy

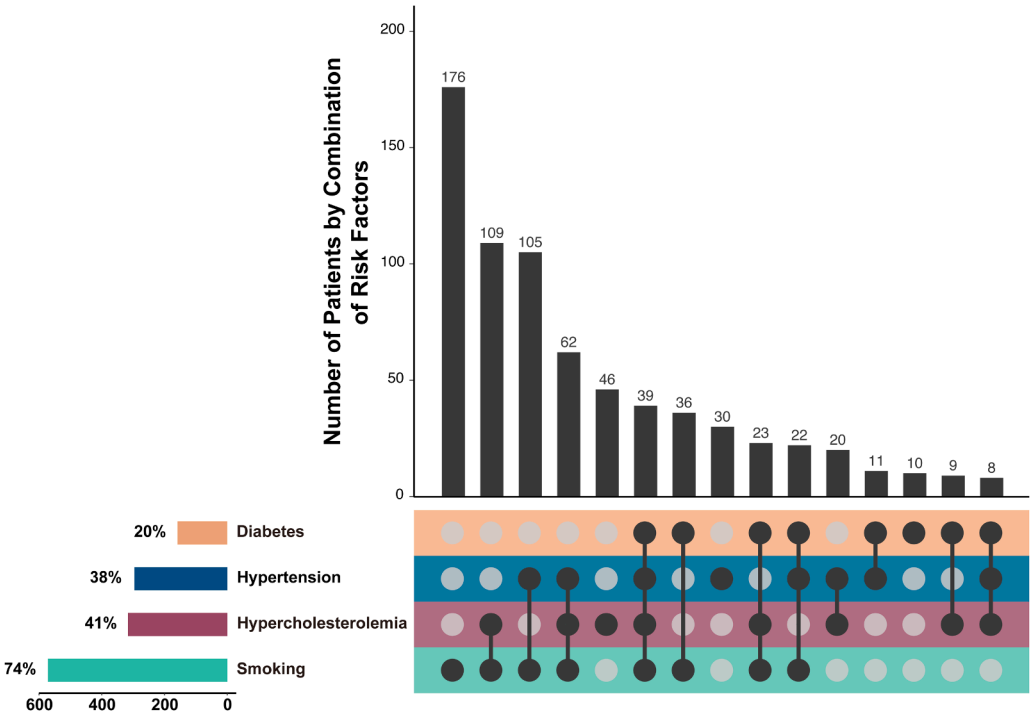


Fig. 1.

("pre-index diagnosed"); or an LDL-C level greater than 3.5 mmol/L, or a total cholesterol level greater than 5.5 mmol/L during the index admission in the absence of pre-index documentation or medication ("newly diagnosed at index"). Diabetes was defined as a previous diagnosis, or use of glucose-lowering medications ("pre-index diagnosed"); or a new diagnosis during the index admission, or HbA1c $\geq$ 6.5 % measured during the index admission in the absence of pre-index documentation or medication ("newly diagnosed at index"). Smoking was defined as smoking more than one cigarette per day within 30 days. Those with a history of smoking were classified as former smokers. All the patients had complete SMuRF data extracted from structured electronic medical records.

2.4. CAD severity

All angiograms were reviewed for the number and location of epicardial vessels with $\geq$50 % stenosis. Intravascular ultrasound or optical coherence tomography assisted in determining the possible pathogenesis of MI. CAD severity was defined by the sum of the epicardial coronary arteries established to have significant stenosis (range 0–3), i.e., left anterior descending artery (LAD), left circumflex artery (LCX), and right coronary artery (RCA). Left main (LM) stenosis $\geq$50 % was treated as equivalent to three-vessel disease. Multivessel disease was defined as $\geq$2 epicardial coronary arteries with $\geq$50 % stenosis. Revascularization strategies were recorded, including percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), and intravenous thrombolysis.

2.5. Follow-up and post-index events definition

Follow-up information was obtained from recommended clinical visit records at 1 month, 3 months, 6 months, 12 months, and annually thereafter. Additional data were collected through phone interviews for all patients between 1 September 2023 and 29 February 2024, with follow-ups censored on 29 February 2024, regardless of event occurrence. Follow-up for post-index information included the occurrence of MACCE, self-reported angina, new occurrences of diabetes, smoking status, and current medications. The study timeline is shown in Supplement Fig. 1.

The post-index event was a composite of major adverse cardiovascular and cerebrovascular events (MACCE), including all-cause death, recurrent MI, ischemia-driven revascularization, and ischemic stroke. Recurrent MI was defined according to the Fourth Universal Definition of MI, which includes evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia [17]. Ischemia-driven revascularization included any PCI or CABG performed due to documented myocardial ischemia. Ischemic stroke was defined as an acute episode of focal or global neurological dysfunction caused by cerebral infarction, in line with the American Heart Association/American Stroke Association guidelines. The study timeline is shown in Supplement Fig. 1.

2.6. Statistical analysis

Baseline characteristics were compared using independent *t*-tests for normally distributed continuous variables (mean $\pm$ standard deviation, SD), Mann-Whitney U tests for skewed variables (median [interquartile range, IQR]), and χ^2 or Fisher's exact tests for categorical variables. SMuRF distributions and combinations were visualized with an UpSet plot.

Kendall's τ assessed the monotonic association between SMuRF count and CAD severity. Proportional-odds logistic regression quantified the graded association in unadjusted models and models adjusted for age, sex, BMI, established inflammatory disease, and family history of premature CAD. Associations of individual SMuRFs and SMuRF pairs with multivessel CAD were evaluated using univariable and multivariable logistic regression with the same clinical covariates. In sensitivity analyses, pre-index diagnosed SMuRFs were analyzed and adjusted by the same model, also were further adjusted for admission medications: aspirin, any lipid-lowering therapy, antihypertensive therapy, and glucose-lowering therapy. Results are presented as odds ratios (ORs) with 95 % confidence intervals (CIs). MACCE incidence was expressed per 100 person-years. Kaplan-Meier curves stratified by SMuRF count estimated cumulative event-free survival, and compared across groups

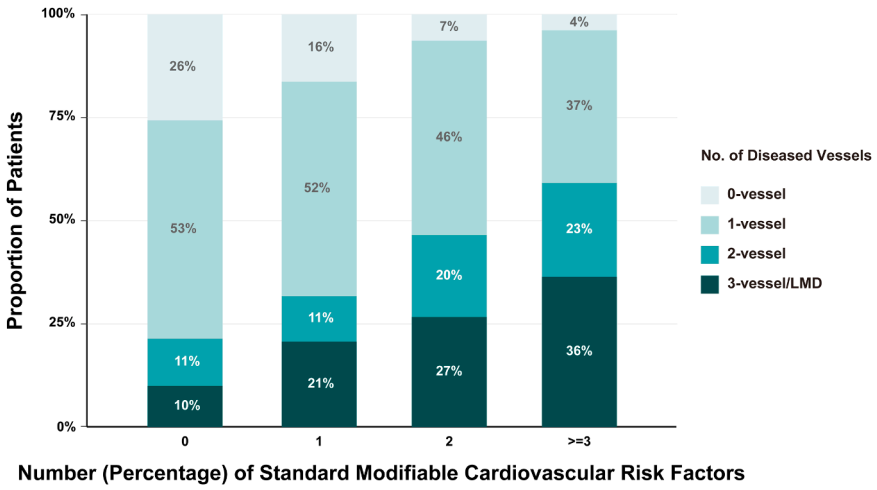


Fig. 2.

with overall and pairwise log-rank tests. Subgroup analyses were performed by MI subtype. We performed time-to-event models for post-index MACCE landmarked at discharge. Cox proportional hazards models assessed the association between SMuRF burden and post-index MACCE in unadjusted models and discharge medication-adjusted models. The discharge medication-adjusted model controlled for discharge antiplatelet therapy, β-blockers, ACE inhibitors or ARBs, lipid-lowering therapy, age, sex, BMI, established inflammatory disease, and family history of premature CAD. In addition, the intervention-adjusted model included index interventions (PCI/CABG), healthcare utilization (residency), age, sex, BMI, established inflammatory disease, and family history of premature CAD. Because the age range in this cohort was relatively narrow, we repeated the model without age adjustment. Results are presented as hazard ratios (HRs) with 95 % CIs.

The significance level was $P < 0.05$, and all tests were two-sided. All statistical analyses were performed using R statistical software (version 4.3.0).

3. Results

3.1. Baseline characteristics and outcome

Of the 934 patients initially identified with MI, three were re-diagnosed as myocarditis or cardiomyopathy, 57 lacked complete angiography, and 98 were lost to follow-up (Supplement Fig. 2). The final cohort comprised 776 patients (median age, 33 years [IQR, 30–34]; 94 % male). ST-segment elevation MI (STEMI) accounted for 61 % of index presentations. Revascularization was performed via PCI in 74 % and CABG in 3 % of patients.

3.2. SMuRF distribution and clinical profile

Overall, only 70 patients (9 %) presented without SMuRFs (SMuRF-less), 33 % ($n = 258$) had one SMuRF, 38 % ($n = 296$) had two, 15 % ($n = 116$) had three, and 5 % ($n = 40$) had all four. Current smoker was most prevalent (74 %), followed by hypercholesterolemia (41 %), hypertension (38 %), and diabetes mellitus (20 %). Additionally, 15 patients (2 %) were former smokers. The most common SMuRF combinations were 'smoking + hypercholesterolemia' (15 %), 'smoking + hypertension'

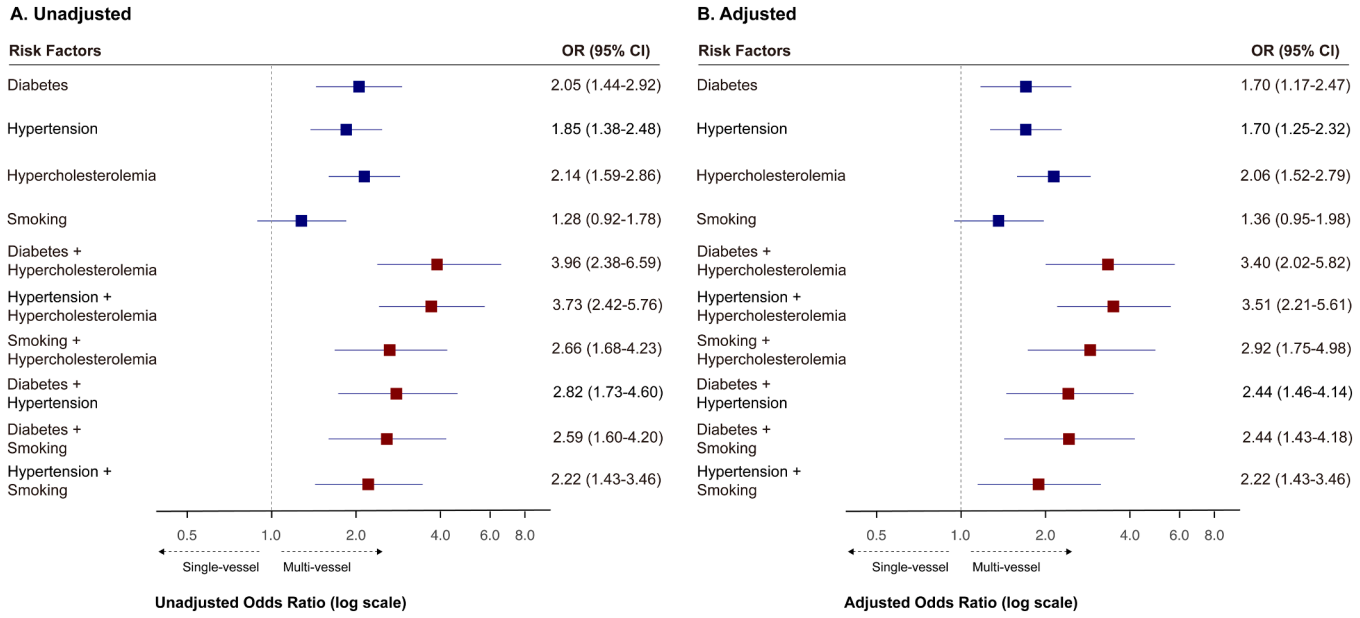


Fig. 3.

Table 1
Baseline patient characteristics according to with and without SMuRFs.

	Total Population ($N = 776$)	SMuRF-less ($N = 70$)	≥1 SMuRF ($N = 706$)	*P* Value
Age, median (IQR), yrs	33 (30, 34)	32 (28, 34)	33 (30, 34)	0.005
Male	732 (94)	55 (79)	677 (96)	< 0.001
Residency				0.454
Local	358 (46)	28 (40)	330 (47)	
Non-local urban	344 (44)	36 (51)	308 (44)	
Non-local rural	74 (10)	6 (9)	68 (10)	
Previous MI	52 (7)	5 (7)	47 (7)	0.803
Index presentation				0.590
NSTEMI	306 (39)	25 (36)	281 (40)	
STEMI	470 (61)	45 (64)	425 (60)	
Killip class 3–4	22 (3)	3 (4)	19 (3)	0.458
SBP, median (IQR), mmHg	121 (111, 133)	118 (107, 129)	121 (112, 134)	0.009
DBP, median (IQR), mmHg	75 (69, 84)	70 (64, 75)	76 (70, 85)	< 0.001
Heart rate, median (IQR), bpm	75 (66, 83)	76 (67, 84)	74 (66, 83)	0.392
Cardiac Arrest	16 (2)	2 (3)	14 (2)	0.648
Cardiogenic Shock	19 (2)	2 (3)	17 (2)	0.686
Non-SMuRFs				
BMI, mean (SD), kg/m^2	28.1 (3.6)	25.6 (3.5)	28.3 (3.5)	< 0.001
Obesity	334 (43)	15 (21)	319 (45)	< 0.001
Chronic kidney disease	12 (2)	1 (1)	11 (2)	1.000
Inflammatory diseases	26 (3)	9 (13)	17 (2)	< 0.001
Peripheral vascular disease	30 (4)	2 (3)	28 (4)	1.000
Cerebrovascular disease	3 (0.4)	0 (0)	3 (0.4)	1.000
Family History	159 (20)	8 (11)	151 (21)	0.070
Laboratory Results				
eGFR, median (IQR), mL/min	115.4 (104.3, 121.4)	116.9 (109.7, 122.3)	115.2 (104.1, 120.9)	0.093
Total cholesterol (IQR), mg/dL	176.0 (142.7, 209.2)	143.7 (122.4, 164.3)	180.2 (145.0, 211.9)	< 0.001
LDL-C, median (IQR), mg/dL	109.8 (84.7, 140.2)	88.0 (76.2, 100.5)	112.9 (85.5, 143.9)	< 0.001
HDL-C, median (IQR), mg/dL	33.6 (29.0, 38.7)	35.6 (29.7, 41.0)	33.3 (29.0, 38.3)	0.084
Triglycerides, median (IQR), mg/dL	170.9 (118.7, 256.0)	124.0 (84.1, 170.9)	175.3 (123.1, 261.3)	< 0.001
Lipoprotein(a), median (IQR), mg/dL	9.9 (4, 20.8)	9 (4.8, 17.3)	10.0 (4.0, 21.2)	0.744
LVEF, mean (SD), %	57.2 (8.6)	57.5 (9.6)	57.2 (8.5)	0.813
LVEDd, mean (SD), mm	49.8 (5.4)	49.9 (4.9)	49.8 (5.4)	0.897
Regional Wall Motion Abnormality	454 (59)	42 (60)	412 (58)	0.889
Angiographic findings				
No. of diseased vessels				< 0.001
0	86 (11)	18 (26)	68 (10)	
1	367 (47)	37 (53)	330 (47)	
2	129 (17)	8 (11)	121 (17)	
3 or Left main ≥ 50 %	194 (25)	7 (10)	187 (26)	
Left main ≥ 50 %	20 (3)	3 (4)	17 (2)	0.414
Left anterior descending ≥ 50 %	502 (65)	38 (54)	464 (66)	0.075
Left circumflex ≥ 50 %	312 (40)	15 (21)	297 (42)	0.002
Right coronary artery ≥ 50 %	363 (47)	15 (21)	348 (49)	< 0.001
PCI	576 (74)	35 (50)	541 (77)	< 0.001
CABG	27 (3)	1 (1)	26 (4)	0.503
Thrombolysis	63 (8)	4 (6)	59 (8)	0.587
Medications at admission				
Antiplatelet therapy	44 (6)	3 (4)	41 (6)	0.789
Lipid-lowering agents	85 (11)	0 (0)	72 (10)	< 0.001
Antihypertensive therapy	164 (21)	0 (0)	164 (23)	< 0.001
Glucose-lowering agents	72 (9)	0 (0)	72 (10)	< 0.001
Medications at discharge				
Aspirin	764 (98)	69 (93)	695 (99)	0.003
Clopidogrel	478 (62)	43 (58)	435 (62)	0.601
Ticagrelor	257 (33)	14 (19)	243 (35)	0.009
Other anti-platelet agents	7 (1)	1 (1)	6 (1)	0.506
β Blockers	674 (87)	59 (80)	615 (88)	0.084
ACE inhibitors/ARBs	512 (66)	32 (43)	480 (68)	< 0.001
Statin	762 (98)	68 (92)	694 (99)	< 0.001
PCSK9-i	9 (1)	0 (0)	9 (1)	1.000

Data are given as number (percentage), unless otherwise indicated. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; LVEDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; PCSK9-i, proprotein convertase subtilisin/kexin type 9 inhibitor; SBP, systolic blood pressure; SD, standard deviation; SMuRF, standard modifiable cardiovascular risk factor; and STEMI, ST-segment–elevation myocardial infarction.

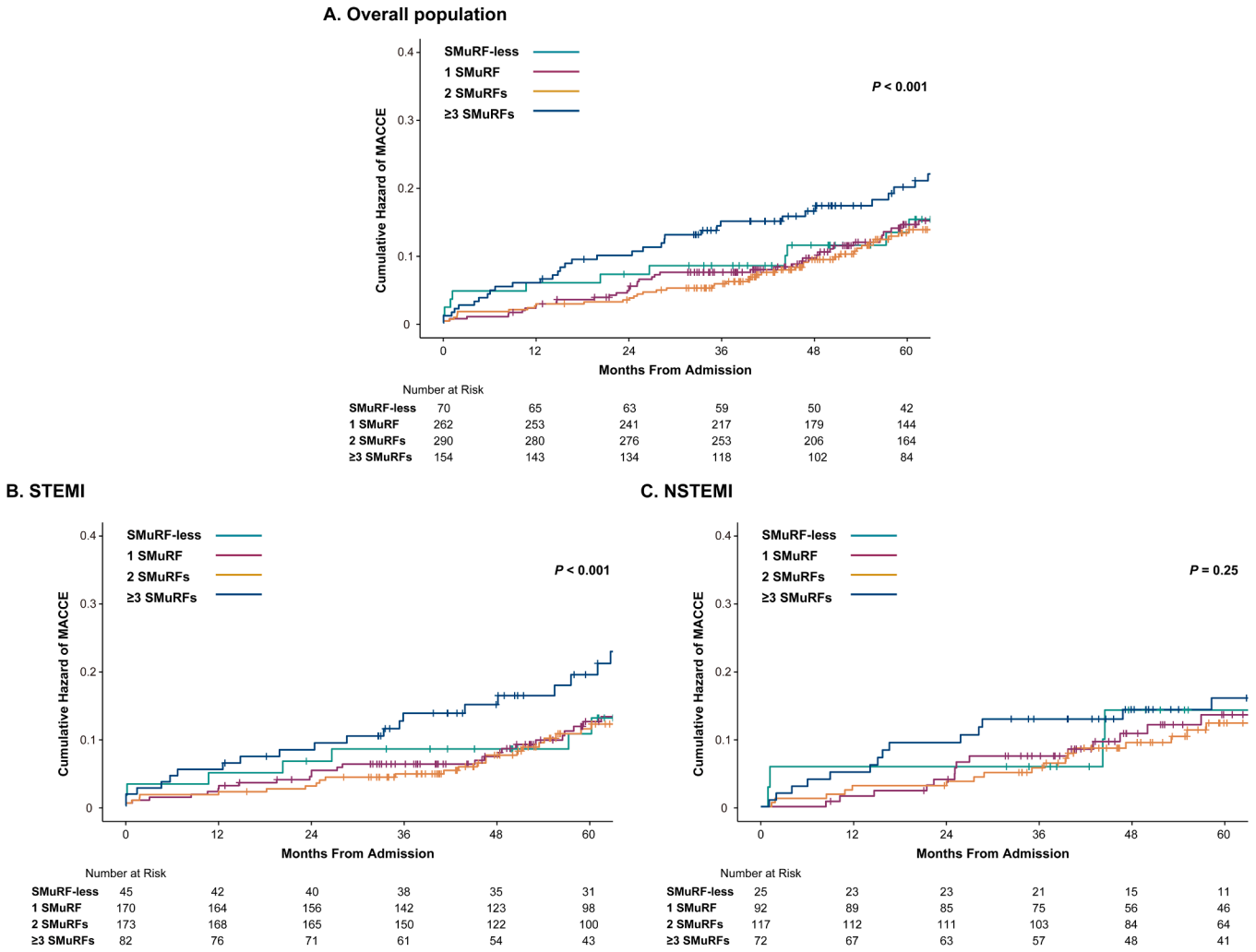


Fig. 4.

(15 %), and 'smoking + hypertension + hypercholesterolemia' (10 %) (Fig. 1). When considering only pre-index diagnoses, 117 patients (15 %) were SMuRF-less, 370 patients (48 %) had one SMuRF, 228 patients (29 %) had two, 43 patients (6 %) had three, and 18 patients (2 %) had all four SMuRFs. The prevalence of pre-index diagnosed hypercholesterolemia, hypertension, and diabetes mellitus was 14 %, 35 %, and 9 %, respectively (Supplement Fig. 3).

Patients who were SMuRF-less were younger (32 years [IQR, 28–34] vs. 33 years [IQR, 30–34]; $P = 0.005$), more frequently female (21 % vs. 4 %; $P < 0.001$), and had a lower prevalence of obesity (21 % vs. 45 %; $P < 0.001$), with a significantly lower mean BMI (25.6 ± 3.5 kg/m^2 vs. 28.3 ± 3.5 kg/m^2; $P < 0.001$). A family history of premature CAD was similar between SMuRF-less and SMuRF patients (11 % vs. 21 %; $P = 0.070$), whereas established inflammatory diseases were more common in the SMuRF-less group (13 % vs. 2 %; $P < 0.001$) (Table 1). The diagnosis and ICD-10 codes are listed in Supplement Table 1.

3.3. SMuRFs burden and CAD severity

Patients without epicardial vessel stenosis ≥50 % on the index angiogram (0-vessel stenosis) accounted for 86 patients (11 %). Single-vessel disease was the most frequent angiographic finding, identified in 367 patients (47 %), followed by three-vessel disease or LM disease in 194 (25 %), and two-vessel disease in 129 (17 %). The LM was involved in 20 patients (3 %).

SMuRF-less patients exhibited less extensive disease, with fewer stenoses in the LCX (21 % vs. 42 %; $P = 0.001$) and RCA (21 % vs. 49 %; $P < 0.001$). Few SMuRF-less patients underwent PCI (50 % vs. 77 %; $P < 0.001$). SMuRF-less patients less frequently received aspirin (93 % vs. 99 %; $P = 0.002$), ticagrelor (20 % vs. 34 %; $P = 0.021$), statins (91 % vs. 99 %; $P < 0.001$), and ACE inhibitors/ARBs (44 % vs. 68 %; $P < 0.001$) at discharge (Table 1).

A graded association between the number of SMuRF and CAD severity was observed (Kendall's $\tau = 0.227$; $z = 7.35$; $P < 0.001$) (Fig. 2). In unadjusted ordinal logistic regression, each additional SMuRF was associated with a 70 % higher odds of more extensive coronary involvement (OR, 1.70 [95 % CI, 1.47–1.96]; $P < 0.001$). After adjustment for age, sex, BMI, family history of premature CAD, and inflammatory disease, diabetes, the association remained significant (adjusted OR, 1.66 [95 % CI, 1.43–1.94]; $P < 0.001$).

3.4. SMuRFs and the risk of multivessel diseases

In univariable analyses, diabetes, hypercholesterolemia, and hypertension were significantly associated with higher odds of multivessel disease, whereas smoking was not (Fig. 3A). After adjustment for age, sex, BMI, family history of premature CAD, and inflammatory disease, diabetes (adjusted OR, 1.70 [95 % CI, 1.17–2.47]; $P = 0.005$), hypercholesterolemia (adjusted OR, 2.06 [95 % CI, 1.52–2.79]; $P < 0.001$), and hypertension (adjusted OR, 1.70 [95 % CI, 1.25–2.32]; $P < 0.001$) remained significantly associated with multivessel involvement, while smoking did not (adjusted OR, 1.36 [95 % CI, 0.95–1.98]; $P = 0.096$).

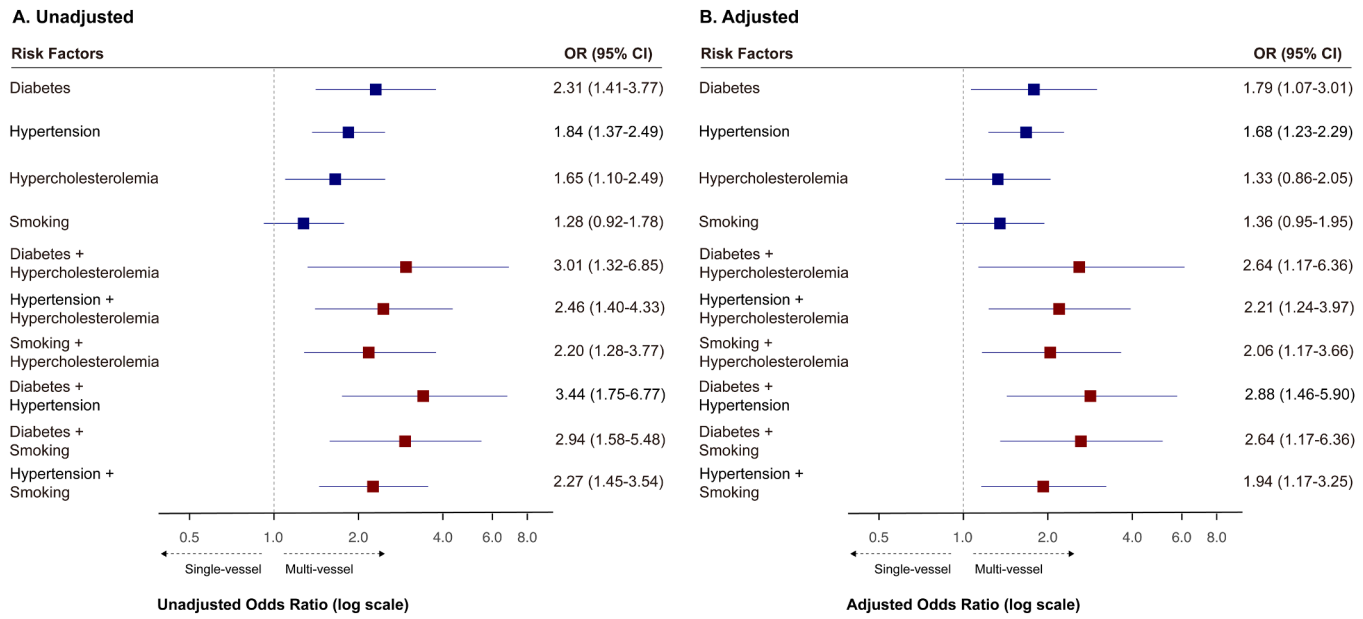


Fig. 5.

The combination of hypertension and hypercholesterolemia was linked to the highest risk (adjusted OR, 3.51 [95 % CI, 2.21–5.61]; $P < 0.001$) (Fig. 3B). No significant interactions among SMuRFs were detected among individual SMuRFs (Supplement Table 2).

3.5. Association of SMuRFs with post-index MACCE

During a median follow-up of 5.6 years (IQR, 3.6–8.0), 174 patients (22.4 %) experienced MACCE, with an overall incidence of 3.88 events per 100 patient-years (95 % CI, 3.33–4.47). Recurrent MI was the most frequent event, occurring in 75 patients (1.61 events per 100 patient-years, 95 % CI: 1.27–1.98), followed by ischemia-driven revascularization in 62 patients (1.30 events per 100 patient-years, 95 % CI: 0.99–1.64), all-cause death in 29 patients (0.59 events per 100 patient-years, 95 % CI: 0.39–0.81), and stroke in 8 patients (0.16 events per 100 patient-years, 95 % CI: 0.06–0.29). Details of medications used during follow-up are provided in Supplement Table 3, which shows lower rates of antiplatelet therapy, β-blockers, ACE inhibitors/ARBs, statins, and PCSK9 inhibitors among SMuRF-less patients.

Incidence rates were comparable among SMuRF-less patients and those with 1 or 2 SMuRFs (3.17 [95 % CI, 2.99–3.34], 3.25 [95 % CI, 3.16–3.34], and 3.24 [95 % CI, 3.15–3.33] events per 100 patient-years, respectively) but higher in those with ≥3 SMuRFs (6.70 events per 100 patient-years; 95 % CI, 6.52–6.87). Pairwise log-rank tests validated that only patients with ≥3 SMuRF had a significantly higher MACCE rate than those with 0–2 SMuRFs (vs. 0 SMuRFs, $P = 0.024$; vs. 1 SMuRF, $P = 0.005$; vs. 2 SMuRFs, $P < 0.001$) (Fig. 4A). In subgroup analyses, the relationship between SMuRF count and MACCE persisted in STEMI patients (Fig. 4B), but was not statistically significant among those with non-ST-segment elevation MI (NSTEMI) (Fig. 4C). Short-term outcomes (≤12 months) were comparable across groups, whereas patients with ≥3 SMuRFs showed worse outcomes beyond 12 months (Supplement Fig. 4). When individual post-index MACCE events were analyzed, only ischemia-driven revascularization was significantly associated with SMuRF count (Supplement Fig. 5).

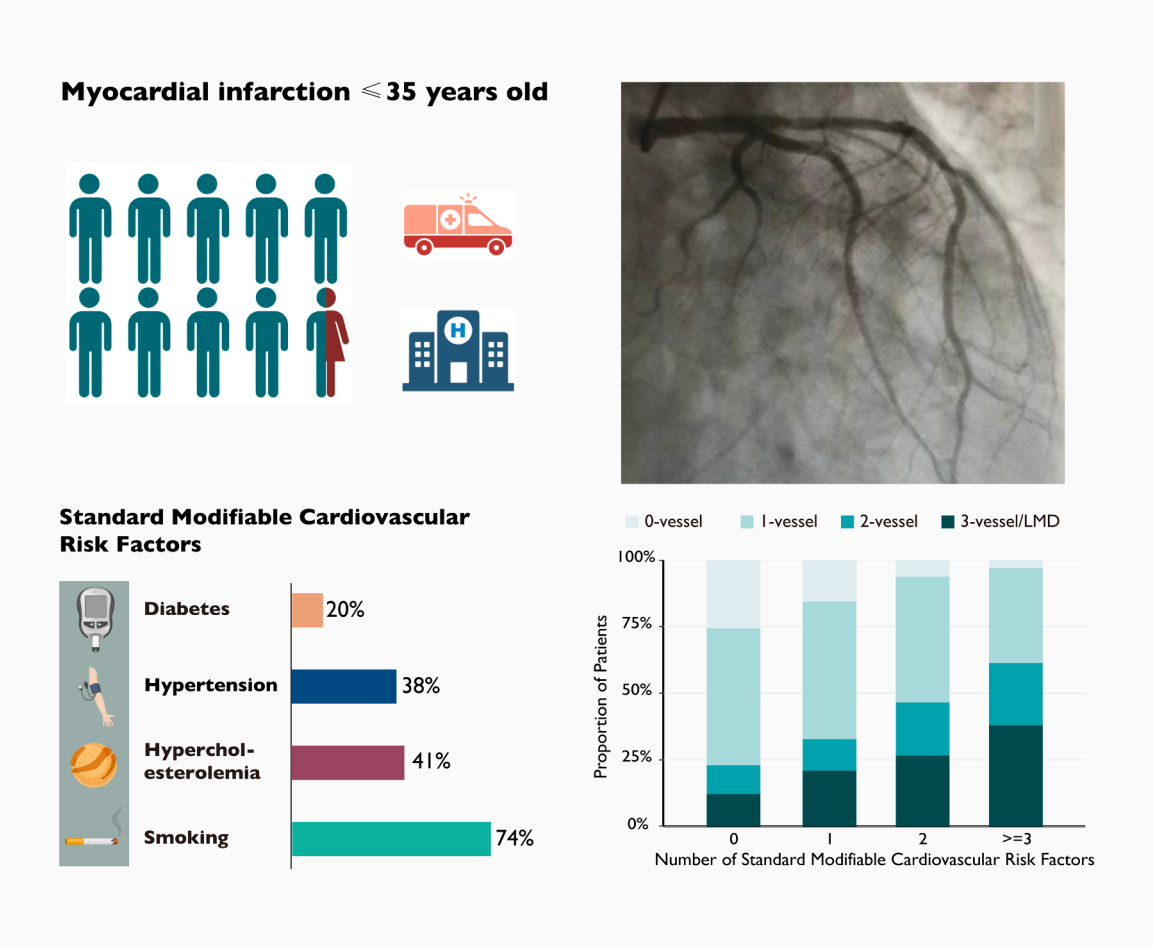
In the unadjusted Cox regression model, the HR for the number of SMuRFs was 1.34 (95 % CI [1.15–1.56]). After adjusting for discharge medication and interventions, the association between the number of SMuRFs and MACCE remained significant, with HRs of 1.30 (95 % CI [1.10–1.53]; $P = 0.002$) and 1.31 (95 % CI [1.11–1.54]; $P = 0.001$) in the respective models (Supplement Tables 4 and 5). When further adjusted for diseased vessels, the association remained significant (HR, 1.18 [95 % CI, 1.01–1.39]; $P = 0.041$) (Supplement Tables 6).

3.6. Sensitivity analysis

A graded association was observed between the number of pre-index diagnosed SMuRFs and CAD severity (Kendall's $\tau = 0.158$; $z = 5.076$; $P < 0.001$). In unadjusted ordinal logistic regression, each additional pre-index diagnosed SMuRF was associated with a 47 % higher odds of more extensive coronary involvement (OR, 1.47 [95 % CI, 1.26–1.70]; $P < 0.001$). This association remained significant after adjustment for age, sex, BMI, family history of premature CAD, and inflammatory disease (adjusted OR, 1.41 [95 % CI, 1.20–1.65]; $P < 0.001$). Further adjustment for antiplatelet therapy, lipid-lowering agents, antihypertensive therapy, and glucose-lowering agents at admission did not affect the significance of the association (adjusted OR, 1.58 [95 % CI, 1.25–1.98]; $P < 0.001$).

In sensitivity analyses for multivessel disease, we used pre-index diagnosed diabetes, hypercholesterolemia, hypertension, and smoking status (smoker vs. never smoker). Fifteen patients were classified as former smokers, resulting in a total of 66 SMuRF-less patients and 710 patients with SMuRFs. In univariable analyses, pre-index diagnosed diabetes, hypercholesterolemia, and hypertension were significantly associated with higher odds of multivessel disease, whereas smoking was not significantly associated (Fig. 5A). After adjustment for age, sex, BMI, family history of premature CAD, and inflammatory disease, pre-index diagnosed hypercholesterolemia was no longer significantly associated with multivessel disease (adjusted OR, 1.33 [95 % CI, 0.86–2.04]; $P = 0.196$), and smoking remained non-significant (adjusted OR, 1.36 [95 % CI, 0.95–1.95]; $P = 0.099$). Diabetes (adjusted OR, 1.79 [95 % CI, 1.07–3.01]; $P = 0.027$) and hypertension (adjusted OR, 1.68 [95 % CI, 1.23–2.29]; $P = 0.001$) were significantly associated with multivessel involvement. The combination of diabetes and hypertension was related to the highest risk (OR, 2.88 [95 % CI, 1.46–5.90]; $P = 0.003$) (Fig. 5B).

Given that 94 % of participants were male, we also excluded sex from the adjusted model for all SMuRFs, and results remained consistent after adjustment for age, BMI, family history of premature CAD, and inflammatory disease (Supplement Figure 6).



Central Illustration.

4. Discussion

Among 776 very young MI patients, 90 % had at least one SMuRF, with a notably high prevalence of smoking. We observed a graded relationship where each additional SMuRF increased the odds of multivessel disease by 70 %. Diabetes, hypercholesterolemia, and hypertension were individually associated with multivessel disease, while smoking was not independently predictive. Patients with three or more SMuRFs experienced significantly worse post-index outcomes, which was evident among patients with STEMI but was not among NSTEMI. We contributed to the understanding of the burden of SMuRF in relation to CAD severity among MI patients aged ≤35 years. The high prevalence and cumulative impact of traditional risk factors in this population highlight the importance of refining prevention and risk-stratification strategies for younger MI patients.

Traditional modifiable cardiovascular risk factors are pivotal in the pathogenesis of premature MI [2]. The INTERHEART study attributed 94 % of MI risk in those <60 years to modifiable factors [18]. In individuals aged 15–34, the Pathobiological Determinants of Atherosclerosis in Youth risk score, which integrated serum lipoproteins, smoking status, blood pressure, obesity and hyperglycemia, showed that each one-unit increment was linked to an 18 % higher odds of advanced coronary lesions [19]. In the Framingham Offspring Study, early-adult exposure (ages 20–39 years) to diastolic blood pressure >90 mm Hg and LDL-*C* > 160 mg/dL conferred 3.6-fold and 2.4-fold higher hazards of coronary heart disease, respectively, independent of later-life exposures [20]. Our findings extended this knowledge by showing that the accumulation of four conventional modifiable risk factors during youth or early adulthood is linked to greater CAD severity in later life.

In line with prior studies, diabetes, dyslipidemia, and hypertension were each independently associated with multivessel disease [21–23]. Notably, patients with concurrent diabetes and hypercholesterolemia had a 3.6-fold higher odds of multivessel involvement. Current smoking showed a high rate in this cohort, and a trend of positive correlation with multivessel disease, but did not reach significance. While current smoking was prevalent in this cohort and showed a positive trend with multivessel disease, this did not reach statistical significance. Although not directly related to atherosclerotic burden, smoking has a significant thrombogenic effect through endothelial dysfunction, enhanced platelet and macrophage adhesion, and the activation of a procoagulant, inflammatory environment [24]. YOUNG-MI registry showed similar long-term mortality rates between never smokers and former smokers. However, smoking cessation within one year after MI is associated with more than a 50 % reduction in both all-cause and cardiovascular mortality [25]. Strict smoking control and cessation are therefore essential for young individuals.

Previous studies reported an approximately 10–20 % SMuRF-less in the typical ACS cohorts, a rate consistent with our very young MI population [16,26]. A global meta-analysis estimated that 11.6 % of ACS patients were SMuRF-less [27]. The Improving Care for Cardiovascular Disease in China-Acute Coronary Syndrome project (2014–2019) reported a similar rate of 11.0 % in China [28]. Among patients under 50 years, the YOUNG-MI registry found a higher SMuRF-less rate of 17 % [11]. Smoking is a major contributor to this burden, with China accounting for 44 % of global cigarette consumption in 2014, according to the WHO [29]. We found varying smoking prevalences across different

cohorts in the literature. In the DDCD study, 48.5 % of patients with a first diagnosis of obstructive CAD under 35 years were current smokers [6], while the International Survey of Acute Coronary Syndromes in Transitional Countries (ISACS-TC) registry reported 61.2 % of patients aged ≤45 were current smokers [30]. In the Bremen STEMI Registry, 82.3 % of MI patients younger than 45 years were current smokers [31]. A Japanese study involving 69 patients aged ≤40 receiving PCI reported an ever-smoking rate of 67.9 % [32]. With over half of the current smoking rate observed in young MI cohorts, these data further emphasize the significant global tobacco burden.

Two notable differences emerged when comparing patients with and without SMuRFs. First, SMuRF-less patients were younger, more often female, and had lower BMI, yet exhibited a higher prevalence of inflammatory diseases. This phenotype differs markedly from the classic atherosclerotic profile, emphasizing inflammation as an important non-conventional risk factor. Established inflammatory conditions, such as systemic lupus erythematosus and rheumatoid arthritis, are well-recognized CAD risk enhancers [33,34], possibly through autoantibody-mediated endothelial dysfunction, altered cytokine signalling, and enhanced leukocyte activation [35,36].

Second, the comparable prevalence of premature CAD family history suggests a similar underlying inherited risk between SMuRF-less and SMuRF-positive groups. Although genetic factors improve CAD risk prediction [37,38], their incremental predictive value beyond traditional risk factors remains moderate [39]. Notably, a pooled analysis of over 55,000 individuals demonstrated that adherence to a favorable lifestyle significantly reduced CAD risk by 46 % among those with the highest genetic risk, highlighting the importance of modifiable risk factors in disease prevention [40].

We found that SMuRF-less STEMI patients had outcomes comparable to those with one or two SMuRFs, but exhibited significantly better survival than patients with three or more SMuRFs. However, this divergence was not observed among NSTEMI patients. Previous studies also suggest that outcomes among SMuRF-less patients vary depending on the type of MI subtype. In STEMI populations, SMuRF-less patients exhibit increased early and long-term mortality [26,41]. For example, the SWEDEHEART registry reported a 47 % increase in 30-day mortality among SMuRF-less STEMI patients compared to those with SMuRFs, with excess deaths persisting up to eight years [16]. Conversely, NSTEMI patients without SMuRFs generally show comparable or even improved long-term survival [42,43]. Indeed, NSTEMI analysis of the SWEDEHEART registry reported lower long-term event rates in SMuRF-less patients despite an initially elevated 30-day mortality [44]. The mechanisms behind this subtype-specific disparity remain unclear, though less frequent use of ACE inhibitors, ARBs, and statins among SMuRF-less patients may play a role, consistent with findings from the SWEDEHEART registry [16]. Current consensus nonetheless recommends comprehensive secondary prevention for all MI survivors, regardless of SMuRF status [15].

5. Limitations

This study provides important insights into the characteristics and outcomes of very young MI patients within a contemporary Chinese cohort. However, several limitations warrant consideration.

First, the timing of index-admission measurements may have led to misclassification of SMuRFs. For example, lipid levels obtained during the acute MI may not reflect pre-MI physiology, and pre-index lipid panels were uncommon and not consistently recorded in this young population. To mitigate this, we distinguished pre-index documented SMuRFs from those newly recognized at index and performed sensitivity analyses restricted to pre-index documented cases. Second, the retrospective design precludes causal inference. While SMuRFs are likely antecedent to CAD, the analysis is cross-sectional at the index MI and does not establish temporality. Third, we lacked data on cumulative smoking exposure (e.g., pack-years), which limited evaluation of dose-response effects. Fourth, the study was conducted at two tertiary medical centers in Beijing, which may limit the generalizability of the findings to other populations. Validation in broader and more diverse geographic cohorts would strengthen external applicability. Fifth, the estimation of CAD severity was based on the number of vessels with ≥50 % stenosis, a simpler measure than lesion-level tools such as the SYNTAX score, which was not collected in this study. Sixth, cardiac magnetic resonance (CMR) was not routinely performed among patients without obstructive CAD, introducing residual diagnostic uncertainty in those classified as having 0-vessel disease. Finally, while our analyses focused on SMuRFs, other risk factors may also influence outcomes in young MI patients, and future studies should explore the contribution of non-SMuRF factors in this population.

6. Conclusion

Very young MI patients carried a high burden of SMuRFs, associated with greater CAD severity and worse long-term outcomes. Further studies should evaluate targeted prevention strategies in this young population.

CRediT authorship contribution statement

Si-qi Tang: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Xin-long Zhao:** Data curation. **Quan Li:** Resources, Investigation. **Yan-bo Liu:** Investigation, Funding acquisition, Data curation. **Yi-tao Han:** Software. **Yu-xiong Chen:** Data curation. **Jin-yan Lei:** Validation. **Ya-kun Zhao:** Visualization. **Zhong-jie Fan:** Writing – review & editing, Funding acquisition. **Yan-ping Ruan:** Writing – review & editing, Project administration, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2025.101334.

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