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Long-term outcomes in patients with acute coronary syndrome undergoing percutaneous coronary intervention without standard modifiable cardiovascular risk factors: findings from the OPT-CAD cohort

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Abstract

Background Acute coronary syndrome (ACS) patients without standard modifiable cardiovascular risk factors (SMuRFs) have a higher risk of early mortality. However, little is known about their long-term outcomes, especially for patients undergoing percutaneous coronary intervention (PCI). This study aims to explore the long-term outcomes and identify independent factors associated with adverse clinical outcomes in patients with ACS undergoing PCI without SMuRFs.

Methods This study used data from *O*ptimal anti*P*latelet *T*herapy for Chinese patients with *C*oronary *A*rtery *D*isease (OPT-CAD) registry study. Clinical characteristics and outcomes of patients with and without SMuRFs were examined. The primary outcomes were major adverse cardia-cerebrovascular events (MACCE). The long-term (5 years) outcomes were compared between the without and with SMuRFs group in such cohort. An exploratory Cox proportional hazards regression was performed to identify the independent demographic and clinical predictors of the adverse clinical outcomes in the SMuRFs-absent cohort.

Results Among 5688 patients with ACS undergoing PCI, 392 (6.9%) were in the absence of SMuRFs and 5296 (93.1%) were in the presence of SMuRFs. There were no significant differences in MACCE rates between the two cohorts (9.44% vs. 9.76%, log-rank $P=0.90$). Cox proportional hazards regression indicated that age (HR, 1.06; 95% CI, 1.03–1.10; $P=0.001$) and thrombus lesions (HR, 2.58; 95% CI, 1.24–5.40; $P=0.011$) were independently associated with MACCE in the SMuRFs-absent cohort.

Conclusions Among patients with ACS undergoing PCI, SMuRFs-absent patients had similar MACCE rates when compared with those with one or more SMuRFs at 5 years.

This suggests that effective intervention strategies and updated risk assessment models are urgently needed in the SMuRFs-absent cohort.

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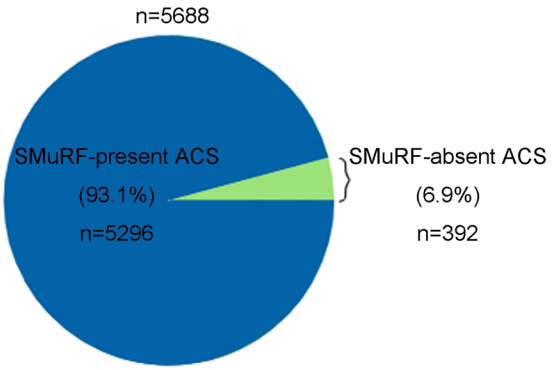
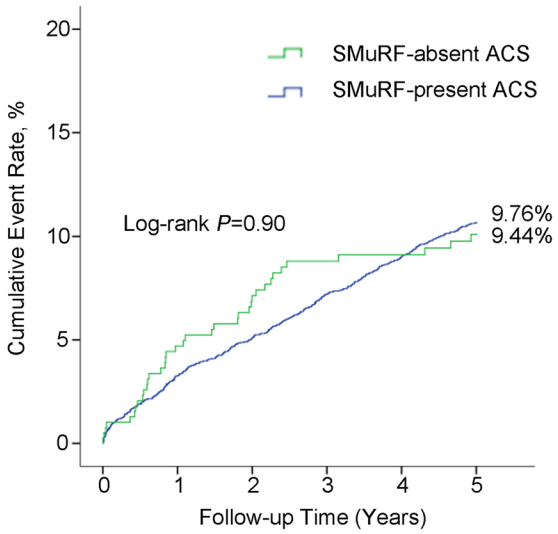
Keywords Cardiovascular risk factors, Acute coronary syndrome, Percutaneous coronary intervention, Age

Graphical Abstract

Among patients with ACS undergoing PCI, 6.9% patients did not have standard modifiable cardiovascular risk factors (SMuRFs).
The SMuRF-absent patients had a similar MACCE rates when compared with those with one or more SMuRF at 5 years.
Age and thrombus lesions were independent prognostic factors in the SMuRF-absent cohort.



	Hazard ratio	95% CI	*P*-value
Age	1.06	1.03-1.10	0.001
Thrombus lesions	2.58	1.24-5.40	0.011



Background

Acute coronary syndrome (ACS) is a global public health concern and is largely explained by a set of standard modifiable cardiovascular risk factors (SMuRFs), such as smoking, hypertension, diabetes, and dyslipidemia. However, some individuals have ACS despite a paucity of SMuRFs. A meta-analysis of 14 clinical trials with 1,285,722 participants found that 11.56% of patients with ACS did not have SMuRFs [1]. More importantly, patients without SMuRFs have a higher risk of early mortality during hospitalization or 30 days after discharge [1–6].

Previous studies have primarily focused on short-term outcomes (limited to mortality) in SMuRFs-absent patients presenting with ACS [2–6]. However, there is limited evidence regarding their long-term outcomes, particularly in patients undergoing percutaneous coronary intervention (PCI), as well as outcomes including myocardial infarction and stroke, while the long-term outcomes of SMuRFs-absent patients in the Chinese cohort have also not been reported. Additionally, the current strategy of categorizing patients into SMuRFs and SMuRFs-absent based on indicators is not the most ideal, such as smoking is only indicated as current smoking status (ex-smokers excluded), dyslipidemia only included elevation of total cholesterol and low-density lipoprotein cholesterol levels (high-density lipoprotein cholesterol levels excluded). Therefore, further investigations are needed with a stricter definition of SMuRFs-absent status, more coronary revascularization with PCI, and longer follow-up times to better determine the prognosis of patients with ACS without SMuRFs.

The *O*ptimal anti*P*latelet *T*herapy for Chinese patients with *C*oronary *A*rtery *D*isease (OPT-CAD) was a large-scale, multicenter, prospective, real-world practice observational registry study designed to develop a predictive model, derive a prognostic score, estimate the risk of ischemic events in individual patients, and guide the management for antiplatelet therapy [7]. One strength of the OPT-CAD registry is the availability of complete in-hospital treatments and long-term follow-up data. All the patients were discharged with PCI with a follow-up of 5 years. This study provides an opportunity to investigate the long-term outcomes of patients with ACS without SMuRFs. Utilizing this robust database, we aimed to examine the long-term (5 years) outcomes, while we also identify independent prognostic

factors associated with adverse clinical outcomes in the SMuRFs-absent cohort.

Methods

Study design and population

The OPT-CAD study was registered at *ClinicalTrials.gov*(NCT01735305). Details of the OPT-CAD study have been published previously [7]. This study included 14,032 consecutive patients with CAD who survived until hospital discharge between January 2012 and March 2014 at 107 centers in China. We selected patients with ACS from the OPT-CAD registry who underwent percutaneous coronary intervention (PCI) and completed a 5-year follow-up. The patients diagnosed with ACS which range from ST-elevation myocardial infarction (STEMI) to NSTEMI and unstable angina (UA) had at least one of the following: electrocardiographic changes consistent, serial increases in levels of biochemical markers of cardiac necrosis (troponin or creatine kinase MB fraction, creatine phosphokinase) [7]. Patients with a known medical history of ischemic disease (myocardial infarction, stroke, or peripheral arterial disease) or coronary revascularization (either PCI or coronary artery bypass grafting (CABG)) were excluded, because we have no information on the use of lipid-lowering drugs before admission in our database. These patients have been receiving lipid-lowering drugs for secondary prevention. In this way, we could eliminate almost the impact of lipid-lowering drug therapy on lipid levels.

Data collection and follow-up

Baseline and follow-up data were collected by the investigators and recorded using internet-based electronic case reports. Patients consulted with the hospital at 12, 24, 36, 48, and 60 months after discharge via telephone, rehospitalization, or outpatient visits. Adverse clinical events and medication statuses were recorded for each protocol during each visit. A regular phone call follow-up did not provide any advice on antiplatelet or other cardiovascular treatments, except when the patients were in an urgent situation. An independent clinical events committee adjudicated all the endpoint events.

Outcomes

The primary outcomes were MACCE, defined as a composite of all-cause death, nonfatal myocardial infarction (MI), and nonfatal stroke at 5 years. Secondary outcomes were major (BARC3-5) bleedings.

Definition

The SMuRFs were defined as diabetes, hypertension, dyslipidemia, and smoking. Diabetes mellitus was defined as a previous history of disease, use of diet, insulin, oral antidiabetic drugs, or fasting plasma glucose levels > 7 mmol/L on two occasions in previously untreated patients. Hypertension was defined as systolic arterial pressure ≥ 140 mmHg and/or diastolic arterial pressure ≥ 90 mmHg, or if the patient was prescribed blood pressure medication due to a medical history of hypertension.

This study used two definitions of dyslipidemia for the analysis. Definition I [8]: Dyslipidemia was defined as fasting total serum cholesterol levels ≥ 6.2 mmol/l, low-density lipoprotein cholesterol (LDL-C) levels ≥ 4.1 mmol/l, high-density lipoprotein cholesterol (HDL-C) levels < 1.0 mmol/l, or a known history of dyslipidemia with current use of lipid-lowering drugs. Since this study aimed to provide a more stringent control over various risk factors, it also developed a more rigorous definition of dyslipidemia in addition to the standard definition. Definition II: Dyslipidemia was defined as fasting total serum cholesterol levels ≥ 5.2 mmol/l, LDL-C levels ≥ 3.4 mmol/l, HDL-C levels < 1.0 mmol/l, or a known history of dyslipidemia with current use of lipid-lowering drugs. Thrombus lesions are defined as the presence of thrombus formation observed during coronary angiography in patients with ACS. Smoking was defined as prior or current smoking according to the OPT-CAD study. MI was defined according to the Fourth Universal Definition [9]. Stroke was defined as a local or systemic loss of neurological function caused by an ischemic event, with residual symptoms lasting at least 24 h. The specific details of other definitions can be found in Additional file 1.

Statistical analysis

Quantitative data are expressed as mean ± standard deviation, and qualitative data are presented as frequencies (percentages). Independent two-sample *t*-tests were used to compare the cohorts. Chi-squared or Fisher's exact tests were used to compare categorical variables. A Cox model was used to evaluate associations between patient characteristics and MACCE, adjusting for baseline characteristics with $P < 0.10$ in the univariable analysis. Kaplan–Meier analysis was used to estimate survival status, with log-rank tests to compare distributions. An exploratory multivariable Cox proportional hazards regression analysis was performed to identify the independent demographic and clinical predictors of the endpoints. Statistical significance was set at two-sided $p < 0.05$. Statistical analysis was performed with SPSS version 23.0 (IBM Corp., Armonk, N.Y., USA).

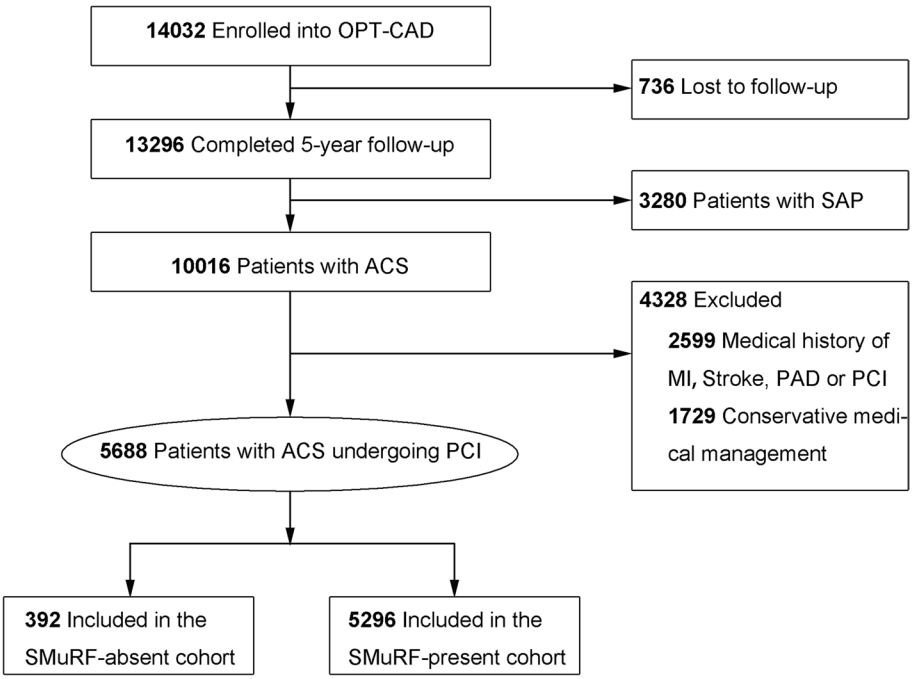


Fig. 1 Flow chart of the study population. SAP, stable angina pectoris; ACS, acute coronary syndrome; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; SMuRFs, standard modifiable cardiovascular risk factors

Results

Baseline characteristics

In this study, 5688 patients with ACS undergoing PCI (Fig. 1), 392 (6.9%) were SMuRFs-absent cohort and 5296 (93.1%) were at least one SMuRFs cohort. The patient demographics and clinical data according to Definition I are shown in Table 1. Baseline parameters such as age (59.68 ± 10.81 vs. 61.90 ± 11.07, $P < 0.001$), sex (4064 (76.74%) vs. 235 (59.95%), $P < 0.001$), body mass index (24.61 ± 2.94 vs. 23.37 ± 3.13, $P < 0.001$), family history (612 (11.56%) vs. 20 (5.10%), $P < 0.001$), and type of CAD, smoking, and HDL-C (1.05 ± 0.34 vs. 1.30 ± 0.30, $P < 0.001$) were significantly different between the two cohorts. The patient demographics and clinical data according to Definition II are shown in Additional file 1: Table S1**.** The patient characteristics of medical therapy at discharge are shown in Table 1. Utilization rates of β-blocker (4048 (76.44%) vs. 281 (71.68%), $P = 0.033$) and angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blockade (ARB) at discharge were lower (3773 (71.24%) vs. 211 (53.83%), $P < 0.001$), while use of statins was higher in the SMuRFs-absent cohort (5116 (96.60%) vs. 388 (98.98%), $P = 0.010$). Patient characteristics of medical therapy at discharge according to Definition II are shown in Additional file 1: Table S1.

Angiographic and interventional therapy characteristics

The angiographic and interventional therapy characteristics according to Definition I are shown in Table 2. Patients with SMuRFs exhibited considerably increased target vessels, number of stents (1.63 ± 0.90 vs. 1.50 ± 0.78, $P = 0.003$), longer stent length (41.19 ± 26.13 vs. 37.11 ± 22.74, $P = 0.001$), and proportion of left circumflex artery (LCX) (1298 (24.51%) vs. 70 (17.86%), $P = 0.003$) and diffuse lesions (1995 (37.67%) vs. 126 (32.14%), $P = 0.029$), compared with those without SMuRFs. The angiographic and interventional therapy characteristics according to Definition II are shown in Additional file 1: Table S2.

Clinical events in 5-year follow-up

At 5 years, there were no significant differences in the rate of MACCE between the without and with SMuRFs cohorts (Table 3 and Fig. 2). There were also no significant differences in the rate of BARC types 3–5 bleeding (Table 3). Comparison of the data based on Definitions II also revealed no significant differences in the 5-year prognosis between the two cohorts (Additional file 1: Table S3). The adverse clinical outcomes for STEMI, NSTEMI, and UA patients are detailed in Additional file 1: Table S4. There were no differences in MACCE and BARC bleeding between the two patient groups across various subpopulations.

Table 1 Patient demographics and clinical data according to Definition I

	SMuRFs-present ACS ($n=5296$)	SMuRFs-absent ACS ($n=392$)	*P*-value
Age, years	59.68 ± 10.81	61.90 ± 11.07	< 0.001
Male	4064 (76.74%)	235 (59.95%)	< 0.001
BMI, kg/m^2	24.61 ± 2.94	23.37 ± 3.13	< 0.001
Family history of CAD	612 (11.56%)	20 (5.10%)	< 0.001
Anemia	510 (9.79%)	48 (12.34%)	0.105
Type of CAD	-	-	0.022
STEMI	1910 (36.06%)	167 (42.60%)	-
NSTEMI	664(12.54%)	38(9.69%)	-
UA	2722 (51.40%)	187 (47.70%)	-
Smoking	-	-	< 0.001
None	2298 (43.39%)	392 (100.00%)	-
Current	2576 (48.64%)	0 (0.00%)	-
Former	422 (7.97%)	0 (0.00%)	-
eGFR, mL/min/1.73m^2	112.91 ± 40.25	111.57 ± 35.42	0.477
TC, mmol/L	4.46 ± 1.21	4.49 ± 0.86	0.538
LDL-C, mmol/L	2.61 ± 1.04	2.60 ± 0.77	0.838
HDL-C, mmol/L	1.05 ± 0.34	1.30 ± 0.30	< 0.001
LVEF, %	60.31 ± 8.72	60.06 ± 8.49	0.582
Medical therapy at discharge			
Aspirin	5228 (98.72%)	385 (98.21%)	0.401
Clopidogrel	5208 (98.34%)	383 (97.70%)	0.349
β-blocker	4048 (76.44%)	281 (71.68%)	0.033
ACEI/ARB	3773 (71.24%)	211 (53.83%)	< 0.001
Statin	5116 (96.60%)	388 (98.98%)	0.010
PPI	2039 (38.50%)	139 (35.46%)	0.232

Data are presented as *n* (%) or mean ± SD

SMuRFs standard modifiable cardiovascular risk factors, *BMI* body mass index, *CAD* coronary artery disease, *STEMI* ST-elevation myocardial infarction, *NSTEMI* non-ST-elevation myocardial infarction, *UA* unstable angina, *TC* total cholesterol, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *eGFR* estimated glomerular filtration rate, *LVEF* left ventricular ejection fraction, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blockade, *PPI* proton pump inhibitor

Table 2 Angiographic and interventional therapy characteristics according to Definition I

	SMuRFs-present ACS ($n=5296$)	SMuRFs-absent ACS ($n=392$)	*P*-value
No. of target vessel	-	-	0.036
1	4092 (78.03%)	312 (81.46%)	-
2	837 (15.96%)	43 (11.23%)	-
3	315 (6.01%)	28 (7.31%)	-
Target vessel location	-	-	-
LM	201 (3.80%)	21 (5.36%)	0.123
LAD	3146 (59.40%)	245 (62.50%)	0.228
LCX	1298 (24.51%)	70 (17.86%)	0.003
RCA	1846 (34.86%)	121 (30.87%)	0.109
Complex lesions	-	-	-
Total occlusion	207 (3.91%)	9 (2.30%)	0.107
Bifurcation	244 (4.61%)	22 (5.61%)	0.363
Diffuse lesion	1995 (37.67%)	126 (32.14%)	0.029
Small vessel	311 (5.87%)	23 (5.87%)	0.997
Thrombus	570 (10.76%)	54 (13.78%)	0.066
No. of stents	1.63 ± 0.90	1.50 ± 0.78	0.003
RVD	3.04 ± 0.45	3.05 ± 0.48	0.603
Total length of stents, mm	41.19 ± 26.13	37.11 ± 22.74	0.001

Data are presented as *n* (%) or mean ± SD

SMuRFs standard modifiable cardiovascular risk factors, *LM* left main coronary artery, *LAD* left anterior descending coronary artery, *LCX* left circumflex coronary artery, *RCA* right coronary artery, *RVD* reference vessel diameter

Table 3 Adverse clinical outcomes in 5-year follow-up according to Definition I

	SMuRFs-present ACS ($n=5296$)	SMuRFs-absent ACS ($n=392$)	*P*-value
MACCE	517 (9.76%)	37 (9.44%)	0.835
All-cause mortality	303 (5.72%)	19 (4.85%)	0.470
MI	122 (2.30%)	6 (1.53%)	0.319
Stroke	143 (2.70%)	14 (3.57%)	0.310
BARC types 3–5 bleeding	79 (1.49%)	9 (2.30%)	0.213

Data are presented as *n* (%)

SMuRFs standard modifiable cardiovascular risk factors, *MACCE* major adverse cardia-cerebrovascular events, *MI* myocardial infarction, *BARC* Bleeding Academic Research Consortium

To explore prognostic factors in patients without SMuRFs, a Cox proportional hazards regression was performed. Interestingly, the analysis indicated that age (hazard ratio, 1.06 (1.03–1.10); $P=0.001$) and thrombus (hazard ratio, 2.58 (1.24–5.40); $P=0.011$) lesions were independently associated with MACCE in such patients according to Definition I (Table 4).

Discussion

This extensive multicenter study highlights a subgroup of patients who present with ACS, despite not having SMuRFs, which is often overlooked. Using data from a large, comprehensive Chinese ACS registry of over 5000 individuals, we observed that those without SMuRFs had similar MACCE rates when compared to those with SMuRFs. The absence of SMuRFs is conventionally considered a reliable indicator of low risk for cardiovascular events, namely better outcomes than those who possess conventional risk factors. However, we identified similar rates of cardio-cerebrovascular events between the groups without and with SMuRFs, with nearly 10% of the

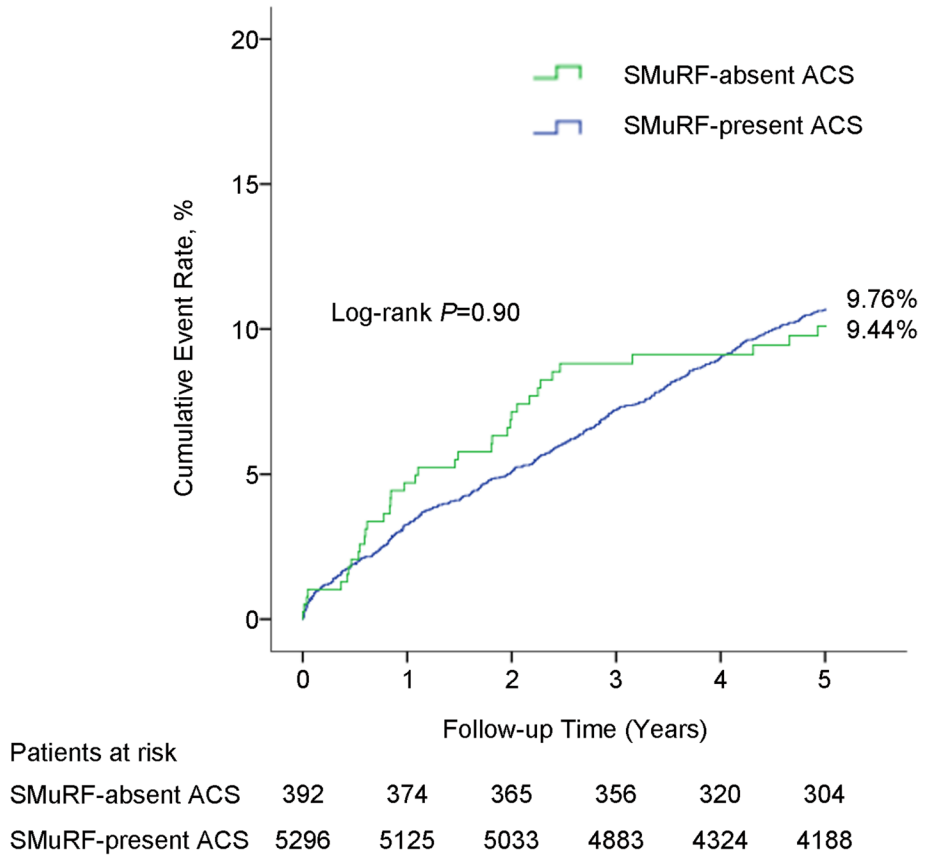


Fig. 2 Kaplan–Meier analysis for cumulative events in the 5-year follow-up between the SMuRF-absent and SMuRF-present patients. SMuRFs, standard modifiable cardiovascular risk factors

Table 4 A multivariate Cox regression analysis in the SMuRFs-absent cohort according to Definition I

	Hazard ratio	95% CI	*P*-value
Age	1.06	1.03–1.10	0.001
Thrombus lesions	2.58	1.24–5.40	0.011

CI confidence interval, *SMuRFs* standard modifiable cardiovascular risk factors, *MACCE* major adverse cardia-cerebrovascular events

patients suffering from MACCE, as summarized in the Central Illustration.

In our study, 6.9% of ACS patients were classified as SMuRFs-absent. In contrast, a global meta-analysis reported that 11.56% were SMuRFs-less [1], and the CCC-ACS project, a real-world registry across China, found this proportion to be 11.0% [2]. Several factors may explain the discrepancy. First, definitions of SMuRFs-absent status vary across studies. Our criteria included ex-smokers and HDL-C levels, which differ from other studies. Additionally, prior literature has shown significant geographical variation in SMuRFs-absent prevalence among ACS patients, with the lowest rates observed in Asia (7.52%) [1]. Ethnic differences in risk factor profiles may further contribute to the discrepancy. Timely PCI, as a key component of invasive strategies, has significantly reduced ischemic risk in patients with ACS [10]. A composite endpoint of all-cause death, nonfatal myocardial infarction, and stroke may provide a more comprehensive assessment of ischemic risk in ACS patients with or without SMuRFs. However, prior studies have predominantly focused on all-cause mortality as the primary long-term outcome [5, 6, 11]. Furthermore, standardized definitions for long-term outcomes, particularly major bleeding were not reported across all studies [1]. PCI with concomitant antithrombotic drugs, is also associated with an increased bleeding risk, which affects prognosis at least as much as ischemic complications and is associated with impaired survival [10]. However, there were no significant differences in rates of BARC bleeding between the two patient groups in our study. Therefore, antithrombotic drugs may be safely administered in SMuRFs-absent ACS patients. Moreover,

intensive antithrombotic therapy in such patients could potentially mitigate thrombotic risk without exacerbating bleeding complications.

We demonstrated an independent association between age and MACCE in individuals without SMuRFs. These results support the notion that age alone, in the absence of known traditional modifiable SMuRFs, may be sufficient to drive atherosclerotic development in humans. Age is well established as the most significant risk factor for cardiovascular events [12]. This association is likely related to longer exposure to various atherosclerotic risk determinants over time as well as other aging-associated phenomena, including increased nucleic acid damage, apoptosis, and reduced regenerative capacity [13]. Our study also found that the presence of thrombus lesions identified during angiography in patients with ACS was highly correlated with a worse prognosis and an increased risk of MACCE. The underlying mechanism is that unstable atherosclerotic plaques rupture and form thrombi, which is the pathogenesis of ACS. The presence of unstable plaques suggests a more severe condition, which leads to a higher incidence of MACCE. This finding is consistent with the current understanding of ACS pathophysiology in which plaque disruption and subsequent thrombus formation play crucial roles in the development of acute coronary events [14]. The presence of thrombus lesions on angiography is a direct manifestation of this process and indicates a high risk of adverse outcomes. Previous studies have also demonstrated a strong association between angiographic evidence of thrombus and an increased risk of adverse events in patients with ACS [15].

The data indicate an unmet need for new biomarkers to identify patients at risk of adverse clinical outcomes. This could provide opportunities to effectively target pharmacotherapy. In our previous study, we assessed the occurrence and prognostic significance of clonal hematopoiesis of indeterminate potential (CHIP), which is a common age-related phenomenon defined as acquired somatic mutations in the driver genes of known hematologic malignancies driver genes [16], in patients with ACS in the absence of SMuRFs [17]. The presence of *DNMT3A/TET2/ASXL1*-CHIP driver mutations was significantly associated with a poor prognosis in patients with ACS undergoing PCI without SMuRFs [17]. Interestingly, human genetics study has indicated heightened expression of several inflammatory cytokines as the consequence of CHIP mutations. Humans with *TET2*mutations are reported to have elevated levels of circulating IL-1β and IL-6 [18]. *DNMT3A*mutations show modestly increased levels of circulating IL-6 [18]. The level of circulating IL-6 has also been found to be increased in carriers of *ASXL1*mutations [18]. Although we acknowledge that the connection between CHIP and the present findings is indirect, further research is necessary to evaluate its role in ACS. Thus, while the concept of CHIP holds potential as a future biomarker, its relevance to the present study is more speculative and requires confirmation in larger, focused cohorts.

Patients without SMuRFs had a lower utilization of ACEI/ARB than those with SMuRFs. The absence of traditional risk factors may influence physicians' clinical judgment regarding disease severity and subsequent therapeutic decisions. A typical example is the lower prescription rate of ACEI/ARB in non-hypertensive patients, despite potential benefits beyond blood pressure control. However, it also highlights the ongoing opportunity to narrow the care gap and improve outcomes in future practices. SMuRFs have been widely used for many years to assess the occurrence, severity, and prognosis of CAD, and are supported by substantial evidence-based medical data. Populations with SMuRFs tended to have a higher incidence of CAD, more severe disease, and poorer outcomes than those without SMuRFs. However, our study showed that in a relatively large sample population, there was no significant difference in the 5-year prognosis between patients without and with SMuRFs. This suggests that the influence and patterns of how patients without SMuRFs develop to CAD and progress to MACCE are still not fully understood. Therefore, a thorough investigation of nontraditional modifiable risk factors has important clinical significance. For patients in this category, a more comprehensive risk assessment should be conducted, and targeted interventions, such as standardized management of underlying conditions and maintaining good psychological health, should be implemented to improve prognosis. To study and improve the potential utility and scalability of the SMuRFs-absent CAD clinical pathway, a multicenter, prospective, observational patient registry has been established (ACTRN12622000452796) [19]. All patients receiving care in the SMuRFs-absent CAD clinics across international sites will be invited to participate.

Limitations

This study had some limitations. First, as a post hoc analysis of an observational study, the inclusion and exclusion criteria were broader with greater extrapolation potential compared to randomized controlled trials, making the results prone to potential bias. Second, the sample size may have been underpowered to detect differences in major clinical events between patients with and without SMuRFs. Therefore, the results should be interpreted with caution. Furthermore, less commonly used risk factors such as lipoprotein-a,

high-sensitivity C-reactive protein, and genetic risk scores were unavailable for assessment. Third, the OPT-CAD database does not include data on Door to Balloon time and Angina to Balloon time. The Door to Balloon time is a crucial indicator in assessing the response speed of healthcare systems for patients with ACS undergoing PCI. The absence of this information may limit our ability to fully evaluate the factors influencing a patient's prognosis, thereby impacting the interpretation of the results. Fourth, the OPT-CAD database does not include comprehensive data on the use of lipid-lowering drugs prior to admission for patients without a known history of dyslipidemia. While we accounted for lipid-lowering drug use in patients with a prior diagnosis of dyslipidemia, this limitation may impact the comprehensive assessment of all patients' pre-admission treatment and its influence on the study outcomes, particularly for those newly diagnosed with dyslipidemia during hospitalization. Finally, we did not evaluate potential genetic contributions to disease development independent of SMuRFs, which could play an important role.

Conclusions

ACS patients without SMuRFs undergoing PCI had a similar risk of cardiovascular events when compared with those with one or more SMuRFs at 5 years. Age and thrombus lesions may have prognostic value in predicting cardiovascular events in patients without SMuRFs. Future studies are required to reproduce our findings in larger cohorts. Discovery of novel biomarkers/makers of ACS beyond SMuRFs may identify high-risk individuals and provide valuable preventative strategies among SMuRFs-absent patients with ACS.

Abbreviations

ACS	Acute coronary syndrome
SMuRFs	Standard modifiable cardiovascular risk factors
PCI	Percutaneous coronary intervention
MACCE	Major adverse cardia-cerebrovascular events
STEMI	ST-elevation myocardial infarction
UA	Unstable angina
CABG	Coronary artery bypass grafting
LDL-C	Low-density lipoprotein cholesterol
HDL-C	High-density lipoprotein cholesterol
LCX	Left circumflex artery
CHIP	Clonal hematopoiesis of indeterminate potential

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-03933-2.

Additional File 1: Tables S1-S4. Table S1. Patient demographics and clinical data according to Definition II. Table S2. Angiographic and interventional therapy characteristics according to Definition II. Table S3. Adverse clinical outcomes in 5-year follow up according to Definition II. Table S4. Subgroup analyses in each patient categories separately.

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Authors' contribution

YLH, ZXJ and HWL designed the work, and ZXJ drafted the manuscript. MHQ acquired and analyzed the data. JL, WZ, DHZ, DSL and KN assisted with the design of the work. YLH and YL supervised the work and critically revised the manuscript. All the authors gave final approval and agreed to be accountable for all the aspects of work ensuring integrity and accuracy.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate.

This study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in a priori approval from the institution's human research committee. This study was also approved by the Research Ethics Committee of the General Hospital of Northern Theater Command, China. Informed consent was obtained from all patients.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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