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ORIGINAL RESEARCH

Absence of Standard Modifiable Risk Factors in Middle Eastern Patients with Atherosclerotic Cardiovascular Disease. The Jordan Absence of Standard Modifiable Risk Factors (SMuRF-Less) Study

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Background: A growing number of individuals develop atherosclerotic cardiovascular disease (ASCVD) despite the absence of the standard modifiable risk factors (hypertension, diabetes, dyslipidemia, and cigarette smoking) (SMuRF-less patients). Prevalence of SMuRF-less patients in the Middle East has not been studied. This study investigates the prevalence, clinical profiles and outcomes of SMuRF-less patients compared with those who have SMuRFs.

Methods: We analyzed data from 6 published registries and from the Jordan SMuRF-less patients study, including baseline demographic features, cardiovascular risk factors, comorbid diseases, utilization of secondary prevention pharmacotherapy and one year outcome in SMuRF-less patients, those with 1–2 SMuRFs and with 3–4 SMuRFs. Results. A total of f 5540 ASCVD patients were enrolled. Mean age was 57.5 ± 11.6 years, and 1333 (24.1%) were women. Of the whole group, 214 (3.9%) were SMuRF-less, 3014 (54.4%) had 1–2 SMuRFs and 2312 (41.7%) had 3–4 SMuRFs. Compared with the SMuRFs groups, SMuRF-less group were younger, more likely to be men, and had lower prevalence of obesity, physical inactivity, metabolic syndrome, heart failure and chronic kidney disease. SMuRF-less patients were less likely to receive secondary prevention cardiovascular medications (antiplatelet agents, statins, renin angiotensin blockers and beta blockers); all $p < 0.001$. One year survival in the SMuRF-less patients was significantly lower than that in the SMuRFs groups (97.7% vs.98.4% vs.98.3%, respectively, $p = 0.01$). Multivariate analysis showed that young age, absence of heart failure and utilization of secondary preventive medications were associated with better one year outcome.

Conclusion: In this cohort of ME patients with ASCVD, nearly four in 100 were SMuRF-less. This rate is lower than that reported by most of published studies, mainly due to the high prevalence of the 4 SMuRFs. SMuRF-less patients were younger, had less comorbid disease, received less secondary prevention pharmacotherapy and had higher rate of one year mortality than those with SMuRFs.

Clinical Trials: The study is registered with ClinicalTrials.gov, unique identifier number NCT06199869.

Keywords: atherosclerotic cardiovascular disease, standard modifiable risk factors, SMuRF-less patients, Middle Eastern patients

Introduction

Atherosclerotic cardiovascular disease (ASCVD) claims the lives of millions of individuals annually on a global level, including the Middle East.[1,2] The major burden of ASCVD-related mortality is attributed to four standard modifiable risk

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factors (SMuRFs); hypertension (HTN), type 2 diabetes (T2D), elevated serum levels of low-density lipoprotein cholesterol (LDL-C) and cigarette smoking.[3,4] Hence, controlling the ASCVD epidemic relies heavily on early detection and management of these risk factors.[1–5] Presence of at least one SMuRF is considered to be key driver of coronary artery disease (CAD) syndromes including acute coronary syndrome (ACS), carotid artery disease and stroke, and peripheral arterial disease (PAD). SMuRFs constitute the central elements of the Framingham risk score and other validated algorithms, thereby, driving evidence-based guideline recommendations for cardiovascular disease prevention in clinical practice, and designing targeted strategies against SMuRFs.[6]

In the last few years, a growing numbers of individuals have been described who constitute a distinct subset of ASCVD patients but do not have any of the standard risk factors (SMuRF-less patients).[7] These patients account for about 1.5% to 26% of the ASCVD population.[8,9] A recent study found that almost 1 in 5 patients were SMuRF-less, and documented the presence of temporal and dynamic changes in the prevalence of SMuRF-less patients with time, with an increasing trend in the prevalence of this unique group over a period of approximately two decades from 14% in 1999 to 23% in 2017.[10]

Prognosis of SMuRF-less individuals was reported to be worse,[11] similar or more favorable than that in SMuRFs patients.[12–14] The significant heterogeneity of SMuRF-less populations has made it difficult to have guidelines. Published studies from the Middle East focused on evaluating traditional risk factors[15,16] with no existing data on SMuRF-less patients.

This study is the first that evaluates the prevalence of SMuRF-less patients in a large cohort of ASCVD patients in a Middle Eastern country, and compares their demographic and clinical profiles, other traditional and novel, nontraditional risk factors, comorbid diseases, use of guideline-recommended secondary cardiovascular medications, and one year survival compared with SMuRFs patients.

Methods

Study Design

The data presented in this study was drawn from two sources. The first source was a cohort of consecutive adult patients (age ≥ 18 years) diagnosed with ASCVD who were enrolled prospectively in the Jordan SMuRF-less Study (ClinicalTrials.gov, identifier number NCT06199869) from January 10, 2024 through August 20, 2024 in three community hospitals and six tertiary care centers that included 3 ministry of Health hospitals, two university hospitals, and one teaching private hospital) in Jordan. The second source of the data was a post hoc analysis of patients with ASCVD enrolled in six Middle Eastern registries.[15–20] These registries are the First Jordan Percutaneous Coronary Intervention Registry (ClinicalTrials.gov identifier NCT01841346),[15] the Atherosclerotic Cardiovascular Disease Novel and Classical Risk Factors in Young Middle Eastern Women Study (NCT04975503),[16] Surviving a Decade or More after Coronary Revascularization in a Middle Eastern Population Study (NCT03491722),[17] the Jordan Atrial Fibrillation Study (NCT03917992,[18] Statin Eligibility Among Middle Eastern Patients Presenting with Acute Myocardial Infarction (NCT03485742)[19] and the Jordan Covid-19 Pandemic Acute Cardiovascular events Study (NCT04368637).[20] Data were collected by trained coordinators using standardized case report forms. Demographic and anthropometric features, medical history, standard modifiable and non-modifiable and novel, nontraditional risk factors, comorbidities, utilization of pharmacotherapy for secondary cardiovascular prevention and one year survival after the first cardiovascular event were documented.

Inclusion Criteria and Definition of Exposures

Patients with ASCVD included those with coronary artery disease (CAD), stroke, carotid artery disease and peripheral arterial disease. CAD patient included those with acute coronary syndrome (ACS) (ST-segment elevation myocardial infarction [STEMI] and non-ST-segment-elevation ACS), chronic coronary angina (CSA) and CAD diagnosed by coronary computed coronary tomography angiography (CCTA). Three groups of patients were studied; patients who were SMuRF-less, those with 1–2 SMuRFs, and those with 3–4 SMuRFs.

Definitions of SMuRFs

The SMuRFs were all defined as binary variables. Criteria of the diagnosis of HTN, T2D, elevated serum LDL-C levels, and cigarette smoking was similar to those adopted by published studies.[3,7–10] HTN diagnosis was defined as having a previous diagnosis by a treating physician, use of antihypertensive medications, or a new diagnosis during hospitalization with repeated measurements of systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg. T2D was defined as a previous diagnosis, use of glucose-lowering medications, or serum level of hemoglobin A1c ≥6.5%. Dyslipidemia was inferred by a prior diagnosis of a treating physician, use of lipid-lowering agents, or elevated serum levels of LDL-C above the recommended target levels. A study participant was considered a current cigarette smoker in the presence of regular smoking within the past one year before enrollment.

Definitions of Other Traditional Risk Factors

Three other traditional risk factors were included in the analysis. Physical inactivity was defined as absence of regular physical activity of at least 30 minutes, 3 times per week. Obesity was defined based on a body mass index ≥30 kg/m^2. Positive family history of premature ASCVD was defined as the presence of a cardiovascular event in a first degree relative aged ≤55 years (male) or ≤65 year (female). Metabolic syndrome diagnosis was confirmed by the presence of at least 3 of the following criteria: HTN, obesity, serum level of high-density lipoprotein cholesterol (HDL-C) <40 mg/dl in men and <50 mg/dl in women, and serum level of triglycerides >150 mg/dl.

Definitions of Novel, Nontraditional, Risk Factors

Nine nontraditional, women reproductive life-related risk factors were analyzed in the subgroup of young women (18–50 years of age) and were defined according to standard criteria.[20] Preterm delivery was defined as a live delivery before 37 weeks and after 20 weeks of gestation. Hypertensive disorders of pregnancy (HDP) were defined as the presence of gestational HTN taking place after 20 weeks of gestation, chronic HTN diagnosed as a preexisting disease before the 20th week of gestation, pre-eclampsia defined as HTN after the 20th week of gestation and proteinuria, and eclampsia defined as seizures not attributable to other causes in the presence of preeclampsia. Gestational DM was diagnosed if one or more of the following criteria were met: fasting plasma glucose ≥ 126 mg/ dl, 2-h plasma glucose ≥ 200 mg/dl following a 75 g oral glucose load, and random plasma glucose ≥ 200 mg/ dl in the presence of diabetes symptoms. Polycystic ovary syndrome (PCOS) was defined by the presence of two clinical or biochemical hyperandrogenism features, ovulatory dysfunction, or polycystic ovaries. Premature menopause was defined as oligo-amenorrhea of more than 12 months associated with serial elevated gonadotropins on three occasions measured 4–6 weeks apart in women under the age of 40 years. Radiation for breast cancer was documented by reviewing medical charts or patient self-reporting.

Other studied variables included presence of autoimmune connective tissue disease, depression and social determinants of health (place of residence (urban vs nonurban), level of education and presence of health insurance).

This non-interventional study was performed in accordance with the Declaration of Helsinki. The study received proper ethical oversight and Institutional Review Board approval from the participating institutions (Institutional Review Board/Independent Ethics Committee Istishari Hospital, Amman, Jordan). Each patient signed a written informed consent. The study is registered with ClinicalTrials.gov (NCT06199869).

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 24. Descriptive statistics were performed using means and standard deviation (SD) to describe the continuous variables and proportions were used to describe the categorical variables. Independent *t*-test was used to compare means and chi-square test was used to compare percentages of the variables in the three groups of patients according to the number of SMuRFs. A Forest plot was used to display odds ratio and 95% confidence interval of the use of the pharmacological medications across the three groups of patients. Binary logistic regression analysis was conducted to determine factors associated with better one-year survival in the whole cohort. A p-value of less than 0.05 was considered statistically significant.

Results

The analysis involved a total of 5540 patients, of those, 214 (3.9%) were SMuRF-less, 3014 (54.4%) had 1–2 SMuRFs and 2312 (41.7%) had 3–4 SMuRFs. Their mean age of the whole cohort was 57.5 ± 11.6 years, there were 866 (15.6%) young people (≤45 years of age), and 1333 (24.1%) were women. The diagnosis of ASCVD in the whole cohort included 4635 (83.7%) ACS patients, 144 (2.6%) CSA patients, 651 (11.8%) patients diagnosed by CCTA, 96 (1.7%) stroke and carotid disease patients, and 14 (0.3%) PAD patients. Overall, the most common SMuRF was dyslipidemia in 4053 (73.2%) patients, followed by HTN in 3197 (57.7%) patients, T2D in 2840 (51.3%) patients, and current cigarette smoking in 2350 (42.4%) patients.

Table 1 depicts comparison of clinical profiles, risk factors, serum lipoprotein levels and comorbid diseases in the three groups of patients. Compared with patients who have SMuRFs, SMuRF-less patients were younger, more likely to be men, and have lower prevalence of obesity, and family history of premature ASCVD. Prevalence of four comorbid diseases (heart failure, chronic kidney disease, metabolic syndrome and sleep apnea) was significantly lower among the SMuRF-less than the SMuRFs patients. Figure 1 shows the number of SMuRFs in three age strata. Around 60% of

Table 1 Clinical Features, Cardiovascular Risk Factors and Serum Lipoprotein Levels in SMuRF-Less and SMuRFs Patients

Clinical Features	SMuRF-less (N=214)	1–2 SMuRFs (N=3014)	3–4 SMuRFs (N=2312)	p-value
Age and sex				
Mean age ± SD	55.3 ± 12.8	56.7 ± 12.1	58.7 ± 10.6	<0.001
Age group				
18–45 years	44 (20.6%)	547 (18.2%)	275 (11.9%)	<0.001
46–65 years	124 (57.9%)	1756 (58.3%)	1432 (61.9%)	
>65 years	46 (21.5%)	711 (23.6%)	605 (26.2%)	
Gender:				
Male	165 (77.1%)	2324 (77.1%)	1718 (74.3%)	0.056
Female	49 (22.9%)	690 (22.9%)	594 (25.7%)	
ASCVDs				
CAD:				
ACS	172 (80.37%)	2557 (84.84%)	1906 (82.44%)	0.0305
CAD by CCTA	2 (0.93%)	67 (2.22%)	75 (3.24%)	
Chronic stable angina	29 (13.55%)	329 (10.92%)	293 (12.67%)	
CVA	10 (4.67%)	56 (1.86%)	30 (1.30%)	0.0010
PVD	1 (0.47%)	5 (0.17%)	8 (0.35%)	0.3517
Standard modifiable risk factors (SMuRFs)				
Hypertension	0 (0%)	1141 (37.9%)	2056 (88.9%)	<0.001
Dyslipidemia	0 (0%)	1866 (61.9%)	2187 (94.6%)	<0.001
Cigarette smoker	0 (0%)	1101 (36.5%)	1249 (54.0%)	<0.001
Type 2 diabetes	0 (0%)	862 (28.6%)	1962 (84.9%)	<0.001

(*Continued*)

Table 1 (Continued).

Clinical Features	SMuRF-less (N=214)	1–2 SMuRFs (N=3014)	3–4 SMuRFs (N=2312)	p-value
Other traditional risk factors				
BMI ≥ 30 kg/m2	43 (26.9%)	626 (34.3%)	673 (41.6%)	<0.001
BMI (mean±SD)	27.0 ± 3.9	28.1 ± 4.8	29.0 ± 4.9	<0.001
Family history of premature CVD	48 (23.3%)	903 (31.1%)	908 (41.0%)	<0.001
Physical inactivity	31 (68.9%)	356 (64.3%)	389 (74.4%)	0.0015
Novel risk factors (women 18–50 years)				
Preterm delivery	5 (20.0%)	43 (27.0%)	17 (28.3%)	0.720
Hypertensive disease of pregnancy	9 (36.0%)	41 (25.8%)	18 (30.0%)	0.525
Gestational diabetes	4 (16.0%)	23 (14.5%)	13 (21.7%)	0.441
Weight gain after pregnancy	7 (28.0%)	27 (17.0%)	7 (11.7%)	0.186
Premature menopause	1 (4.0%)	18 (11.3%)	8 (13.3%)	0.454
Radiation for breast cancer	0 (0.0%)	2 (1.3%)	0 (0.0%)	0.589
Polycystic ovary syndrome	1 (4.0%)	11 (6.8%)	6 (10.0%)	0.581
Social determinants of health				
Education				
No school, school, or diploma	28 (63.6%)	339 (64.2%)	348 (71.5%)	0.056
Bachelor and postgraduate	16 (36.4%)	189 (35.8%)	139 (28.5%)	
Residence				
Urban residence	34 (75.6%)	411 (77.1%)	385 (78.9%)	0.736
Non-urban residence	11 (24.4%)	122 (22.9%)	103 (21.1%)	
Lack of health insurance	22 (48.9%)	131 (24.6%)	86 (17.6%)	<0.001
Depression	3 (9.1%)	28 (11.6%)	10 (7.6%)	0.469
Comorbid conditions				
Chronic kidney disease	6 (3.2%)	141 (5.9%)	169 (8.7%)	0.0001
Heart failure	27 (13.0%)	362 (14.1%)	350 (17.5%)	0.004
Metabolic syndrome	1 (2.2%)	143 (28.3%)	290 (62.2%)	0.000
Autoimmune disease	0 (0.0%)	15 (7.3%)	4 (4.0%)	0.184
Obstructive sleep apnea	3 (5.6%)	52 (8.4%)	104 (18.5%)	<0.001
Serum lipoproteins (mg/dL)				
Total cholesterol				
Mean ± SD)	162.4 ± 42.3	181.90 ± 50.6	178.23 ± 53.8	0.007
Median (IQR))	161 (178–138)	176 (209–147)	170 (206.5–142)	0.0004

(*Continued*)

Table 1 (Continued).

Clinical Features	SMuRF-less (N=214)	1–2 SMuRFs (N=3014)	3–4 SMuRFs (N=2312)	p-value
LDL-C				
Mean ± SD)	95.2 ± 31.9	114.1 ± 45.2	109.1 ± 45.5	0.0002
Median (IQR))	92 (106–75)	110 (139–84)	102 (135–77)	0.0001
LDL-C > 190	1 (0.5%)	91 (3.0%)	76 (3.3%)	0.342
LDL-C ≤ 55	158 (73.83%)	1513 (50.20%)	957 (41.39%)	0.052
HDL-C				
Mean ± SD)	41.7 ± 11.5	39.6 ± 11.9	37.9 ± 16.9	0.003
Median(IQR))	41.5 ($^{51-34}$)	38 ($^{46-31}$)	35 ($^{43-30}$)	0.0001
HDL-C < 50 (females)	7 (58.3%)	225 (67.6%)	265 (77.5%)	0.009
HDL < 40 (males)	22 (52.4%)	664 (63.1%)	708 (71.5%)	0.000
Triglycerides				
Mean ± SD)	152.4 ± 110.3	169.8 ± 112.7	201.7 ± 159.7	0.0000
Median (IQR))	123.5 (161.5–86)	145 (202–105)	164 (239–116)	0.0001

Abbreviations: SD, standard deviation; IQR, interquartile range; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SMuRFs; ACS, acute coronary syndrome; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CVA, cerebrovascular disease; PAD, peripheral arterial disease.

SMuRF-less patients were 46–65 years of age. Unlike those older than 65 years of age, the young group (18–45 years of age) were more likely to be SMuRF-less.

There were 367 young women (age 18 to 50 years) enrolled in the study (6.6% of the whole cohort, and 27.5% of all women). Of these young women, 28 (7.6%) were SMuRF-less, and there were no significant differences in the prevalence rates of any of the novel, nontraditional risk factors in the SMuRF-less compared with SMuRFs. Of the social determinants of health studied, a higher level of education with borderline significance and lack of health insurance were more prevalent in SMuRF-less patients. Serum lipoproteins profile was more favorable among the SMuRF-less group with lower total cholesterol, LDL-C and triglycerides levels, and higher HDL-C levels. Furthermore, optimal low levels of LDL-C (≤55 mg/dL) were observed more in the SMuRF-less group compared with the SMuRFs patients.

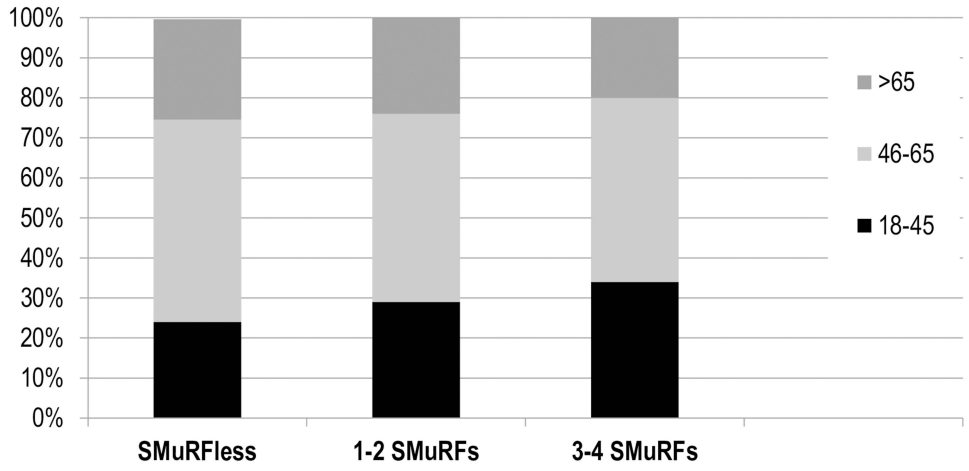

Figure 1 Age strata (years) of the participating patients according to the number of the standard modifiable risk factors.
Abbreviation: SMuRFs, standard modifiable risk factors.

Table 2 Pharmacotherapy Across the Three Groups of Patients According to the Number of SMuRFs

Medications	SMuRF-less (N=214)	1–2 SMuRFs (N=3014)	3–4 SMuRFs (N=2312)	P-value
Aspirin	173 (81.2%)	2695 (89.9%)	2135 (92.4%)	<0.001
Clopidogrel	122 (57.3%)	1623 (54.2%)	1343 (58.2%)	0.0137
Ticagrelor/Prasugrel	18 (8.5%)	429 (14.3%)	347 (15.0%)	0.032
Dual antiplatelet therapy	132 (62.0%)	1928 (64.3%)	1605 (69.5%)	0.0002
Statins	145 (67.8%)	2696 (89.5%)	2180 (94.3%)	<0.001
Renin angiotensin system blockers inhibitors	83 (38.8%)	1499 (49.7%)	1470 (63.6%)	<0.001
Beta blockers	146 (68.2%)	2142 (71.1%)	1772 (76.6%)	<0.001
Oral hypoglycemic agents	10 (5.0%)	334 (13.6%)	633 (33.3%)	<0.001
Insulin	6 (3.0%)	297 (12.1%)	587 (30.8%)	<0.001

Abbreviation: SMuRFs, standard modifiable risk factors.

Overall, there was a near universal prescription of aspirin (90.6%) and statins (90.6%). Beta blockers were prescribed for 73.3%, dual oral antiplatelet agents for two-thirds (66.2%) and renin angiotensin blockers for more than half (55.1%) of the patients. A significantly lower percentage of SMuRF-less patients received these medications compared with the SMuRFs patients (Table 2 and Figure 2). Moreover, SMuRF-less patients were more likely to receive clopidogrel than the more potent antiplatelet agents ticagrelor and prasugrel compared with the SMuRFs patients.

There were 3094 (55.8%) patients who had a cardiovascular event at least one year prior to enrollment in the study, and the other 2446 (44.2%) were enrolled before the passage of one year since the cardiovascular event. Of the former group, 52 (1.7%) died in the first year and 3042 (98.3%) survived one year after enrollment. One-year all-cause mortality was 2.3%, in the SMuRF-less patients, 1.6% in the group with 1–2 SMRFs, and 1.7% in the group with 3–4SMuRFs (p = 0.01). In the univariate analysis that examined 16 clinical and pharmacological variables (Supplementary Table S1), there were seven clinical variables (young age, male sex, absence of hypertension, smoking, heart failure and chronic kidney

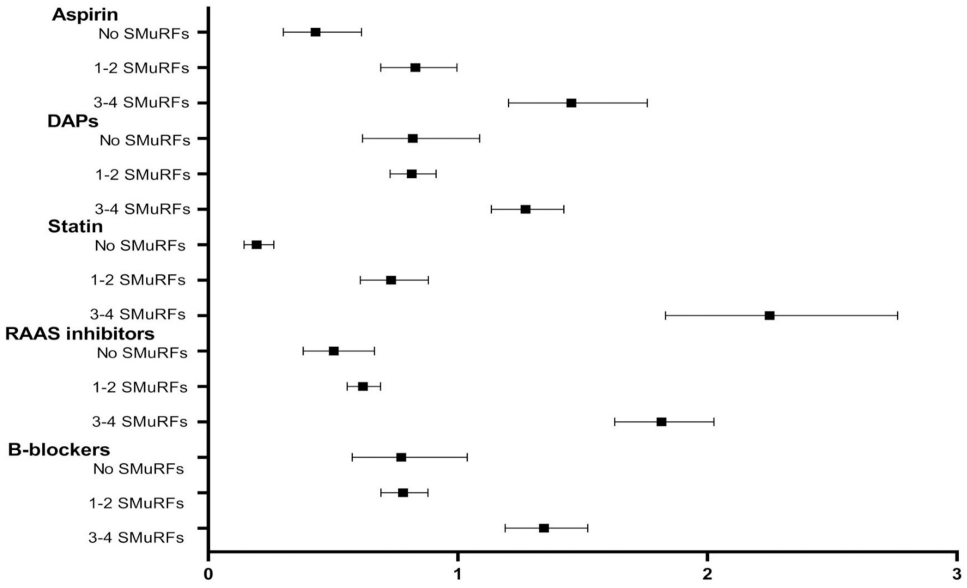

Figure 2 Forest plot showing the use of cardiovascular medications according to the number of the standard modifiable risk factors.
Abbreviations: DAPs, dual antiplatelet agents; RAAS, renin angiotensin aldosterone system; SMuRFs, standard modifiable risk factors.

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Table 3 Multivariate Analysis of Variables Associated with Better One year Survival

Variable	Odds Ratio	95% Confidence Interval	P value
Age ≤ 55 years	6.82	2.03–22.92	0.002
Absence of heart failure	2.67	1.43–4.98	0.002
Use of antiplatelet agents	5.24	2.48–11.09	<0.001
Use of statins	3.93	2.01–7.68	<0.001
Use of renin angiotensin system inhibitors	3.12	1.66–5.86	<0.001

disease, and clinical [rather than radiological] diagnosis of CAD), and use of three medication groups (antiplatelet agents, statins and renin angiotensin system blockers) were more prevalent in the patients who survived one year (Figure 2). Multivariable analysis showed that only young age, absence of heart failure and the use of the first three of the former medications were independently associated with ASCVD (Table 3).

Discussion

The key findings from this first large Middle Eastern study of SMuRF-less patients with ASCVD are (a) nearly one in 25 patients was SMuRF-less, (b) More than 5 in 10 of the patients had 1–2 SMuRFs, and 4 in 10 had all of the 4 SMuRFs, (c) compared with SMuRFs patients, SMuRF-less patients were younger, had less comorbid diseases, and had a lower one year survival rate.

The importance of early recognition and target interventions against the four SMuRFs (hypertension, T2D, dyslipidemia and cigarette smoking) in the pathogenesis and progression of ASCVD has been well recognized.[21] However, there is a certain proportion of ASCVD patients who lack these risk factors with an estimated annual number of about 30 million cases. This group of patients is underrepresented in clinical trials and guidelines, and the best approach to managing them has not been well-defined yet.[21,22]

The proportion of SMuRF-less ASCVD patients varies widely among published studies and registries. Prevalence of SMuRF-less patients as low as 1.5% was reported by a study from Japan on about 111,000 ACS patients,[22] and as high as 25.4% reported by a study from India on 2379 patients[23] and 26.6% by a study from USA on about 434,000 STEMI patients.[13] The current study, which is the first to address this issue in the Middle East, showed that the prevalence of 3.9% of SMuRF-less patients is among the lowest rates reported from various geographic areas. The discrepancies in the reported prevalence rates of SMuRF-less patients in different geographic areas are explained by regional variation in the prevalence of cardiovascular risk factors, age of the patients, clinical presentation of the ASCVD patients studied (ie, STEMI, NSTEMI, or chronic stable angina) and the period during which each study was conducted in (ie, in the 1990s vs 2000 and beyond). A temporal increase in the prevalence of SMuRF-less patients over time was demonstrated in large longitudinal studies from Australia that showed an increase in the prevalence of SMuRF-less patients from 11% in 2006 to 27% in 2014.[10,24]

A crucial issue in evaluating ASCVD SMuRF-less patients is how studies defined each of the four SMuRFs, and this in turn may have affected the prevalence and outcome of the SMuRF-less patients.[25] The current study adopted the standardized definitions to diagnose the SMuRFs.[9–12,21–26] Different cut-off levels have been used to define each SMuRF. Blood pressure measurements to define hypertension (ie, ≥130/80, >130/85, and >140/90 mm Hg), different parameters to define T2D including fasting blood glucose levels and HbA1c, and different lipoprotein cholesterol blood levels to define dyslipidemia (ie, total cholesterol ≥200, >200, >210, ≥212, and >240 mg/dL; LDL-C ≥130, ≥131, ≥135, >140 and >160 mg/dL, and HDL-C <40 mg/dL in men and women were adopted by different investigators.[13,14,26–29] Patients with ACS may exhibit stress-related neurohormonal activation that causes blood pressure elevation and hyperglycemia leading to over-diagnosis of hypertension and T2D.[12] Likewise, the definition of current cigarette smoking varies widely among studies. Patients were considered current smokers if they had smoked daily within the past 1 month before

hospitalization[12] or within the past 12 months,[7] or as currently smoking tobacco in any form or taking smokeless tobacco.[26,27] Smoking patterns other than cigarette smoking, such as vape and hookah (water pipe) smoking, were not included in the study. Including these latter patterns of smoking will invariably decrease the size of the SMuRF-less group.

Most of the studies of SMuRF-less patients focused on the STEMI population. However, more recent studies' main interest shifted from evaluating patients other than those with STEMI, such as those with NSTEACS, chronic coronary syndrome,[30] and patients diagnosed by CCTA rather than overt clinical syndrome.[31] This study involved a heterogeneous cohort of patients that included ACS, CSA, patients diagnosed by CCTA, those with stroke and non-coronary arterial disease. A study, similar to ours, of a heterogeneous group of 5823 patients with past history of MI and chronic stable CAD found that 3.7% were SMuRF-less, a rate similar to that in the current study.[32] This departure from enrolling only patients with clinical events ensures that those with non-obstructive ASCVD are also included in studies and registries since they would benefit from optimized secondary prevention pharmacotherapy, as recommended by recent guidelines.[33]

The clinical profiles of SMuRF-less patients are highly variable among published studies and registries from different regions in the world, in terms of age, sex, and presence of comorbid diseases. Patients with ASCVD in this region, overall, those with SMuRFs and the SMuRF-less patients are at least 10 years younger than their counterparts in the west.[15–20] Young patients (≤45 years of age) comprised 15.6% of our cohort, similar to the percentages of 11.5% and 15.0% of cohorts reported by other investigators.[11,26] Our findings of SMuRF-less patients being younger, more likely to be men than women and less likely to have comorbid disease compared with SMuRFs patients was shared by other studies.[9,12,34] On the other hand, several studies found that SMuRF-less patients were older and more likely to be women,[22,23,35] or of same age with no sex predominance compared with patients who have SMuRFs.[36] The younger age of the SMuRF-less patients in this and other studies[28,34] might explain the finding that certain comorbid diseases, such as heart failure and chronic kidney disease, obesity and metabolic syndrome, were less prevalent among this group compared with the SMuRFs patients.

It is imperative in this context to state that there are other cardiovascular risk factors, modifiable and non-modifiable, that impact the global and regional prevalence of ASCVD as well as the prognosis of affected individuals. In the Middle East, several studies have shown a high prevalence of seven traditional risk factors that included, in addition to the four SMuRFs, family history of premature ASCVD, physical inactivity and obesity.[15–20] A recent large global study showed that five modifiable risk factors were associated with incident cardiovascular disease and all-cause death (body-mass index, systolic blood pressure, non–HDL-C, current smoking, and T2D).[3,5] Furthermore, the INTERHEART study of myocardial infarction reported that 90–94% of population attributable risk could be accounted for by nine modifiable risk factors. To the four standard risk factors, INTERHEART added physical activity, dietary patterns, drinking alcohol, waist/hip ratio, and psychosocial factors.[37] The observation that only a minority of our ASCVD patients were SMuRF-less implies that the major pillar in the strategies that aim to curb the cardiovascular epidemic should focus on early diagnosis and intervention of the four SMuRFs. The small number of young women (18–50 years of age) in this study hindered drawing solid conclusions about the prevalence of novel, nontraditional cardiovascular risk factors in SMuRF-less vs SMuRFs women in this age group. A prior study confirmed findings by other investigators that certain nontraditional risk factors, such as preterm delivery, hypertensive disease of pregnancy and gestational diabetes were more prevalent in Middle Eastern young women with ASCVD compared with their age-matched healthy controls.[16]

Scientific evidence on the pathogenesis and etiology of SMuRF-less MI is limited.[38] Several potential factors could contribute to the occurrence of ASCVD in SMuRF-less patients including chronic systemic inflammatory process leading to high levels of intra-coronary pro-inflammatory cytokines that trigger, initiate and sustain atherothrombosis.[8,9,12,21,39] Coronary dissection, embolism and prolonged spasm, and the use of cocaine have also been implicated in the pathogenesis of ASCVD in SMuRF-less patients.[40]

The utilization of key evidence-based secondary cardiovascular prevention medications (oral antiplatelet medications, statins, renin angiotensin system blockers and beta blockers) was significantly lower among the SMuRF-less patients than patients with SMuRFs. This finding is consistent with findings by other investigators.[2,8–10,12,18,28,40,41] The younger age, absence of hypertension, T2D and dyslipidemia, and the lower prevalence of heart failure in the SMuRF-less group may explain the lower utilization of these guideline-recommended medications.

In the subgroup of patients who sustained an acute cardiovascular event at least one year prior to enrollment in this study (56%), there was a higher one-year mortality rate among the SMuRF-less patients than the SMuRF patients. Data on short- and long-term survival in SMuRF-less patients are inconsistent due the inhomogeneous population studied, variable endpoints defined by the studies, and different follow up durations. Some investigators reported an increased in-hospital mortality in SMuRF-less patients.[28,29] Another study did not find in-hospital mortality difference between the SMuRF-less and ≥ SMuRFs groups despite excess cardiac arrest, STEMI and cardiogenic shock in the former group.[26] Likewise, long-term outcomes also yielded mixed results. A study concluded that the 5-year mortality was not different between the SMuRFless and ≥1 SMuRF group,[26] but more favorable long-term outcomes among the SMuRF-less patients was observed by other investigators.[9,34,40]

Study Limitations

There are a number of limitations in our study that warrant discussion. Despite a rigorous adjustment for various factors, our findings may still be susceptible to unmeasured confounding. Part of data was collected retrospectively from previous studies with potential risk of selection bias. Although standard and rigorous methodology was used to collect data, there is a possibility that SMuRF-less patients may have been misclassified due to missing data on risk factors present at baseline. Additionally, misclassification in the presence or absence of risk factors may be inevitable due to being self-reported in some cases, thus leading to over- or under-estimation of the four SMuRFs. The study recruited patients from tertiary care centers; hence the generalizability of our findings to the general populations in the country and region may not be applicable. Another limitation of the study is the fact that the sample of the recruited patients was a convenience sample rather than random sampling. This is associated with a considerable degree of bias and underestimation of the risk of ASCVD in SMuRF-less individuals. Despite this fact, almost all of the published studies on SMuRF-less patients have recruited their participants using convenience sampling from patients evaluated at in- and out-patient cardiology services.

Despite these limitations, the study provides, for the first time in the region, a contemporary evaluation of the prevalence of a rather large list of risk factors of cardiovascular disease, and adds new data to the expanding global literature on SMuRF-less cohorts reported on patient cohorts from South East Asia, Asia Pacific, and western hemisphere.

In conclusion, the major finding by this study from the Middle East was that only a minority of ASCVD patients were SMuRF-less. In communities where SMuRF-less patients comprise very low percentages (<5%) of the ASCVD populations, the focus of cardiovascular prevention efforts relies mainly on targeted population-based strategies for early diagnosis and treatment of the highly prevalent four SMuRFs. In any case, it is important to improve the visibility of the SMuRF-less population in future clinical trials,[40] and much remains to be elucidated in the group of SMuRF-less patients' burden, clinical profiles, pathogenesis and long-term outcomes in populations with different regional and ethnic backgrounds. An international, multidisciplinary team has been assembled recently to develop an evidence-based clinical pathway for SMuRFless CAD patients. A proposed pathway suggest the need for a confirmed diagnosis of ASCVD, a true SMuRF-less status, ensures evidence-based secondary prevention, and considers additional tests and interventions.[42]

Data Accessibility

Data, structured methodology, and results are available upon request from the corresponding author (a.hammoudeh@istisharihospital.com).

Author Contributions

All authors made a significant contribution to the work presented in the study conception, study design, execution, data acquisition, data analysis and interpretation; took part in drafting, revising, critically reviewing the manuscript; gave final approval of the version to be published; have agreed on the this journal that received the manuscript for publication; and agreed to be accountable for all aspects of the work.

Disclosure

The work was presented in an abstract from at the American Heart Association congress in November 2024 and the poster's abstract was published in "Circulation" in AHA/ASA Journals: http://www.ahajournals.org/doi/10.1161/circ.150.suppl_1.4120131. The authors report no competing interests in this work.

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