JACC
VOL. 86, NO. 2, 2025

PUBLISHED BY ELSEVIER

ORIGINAL RESEARCH

Plaque Vulnerability and Cardiovascular Risk Factor Burden in Acute Coronary Syndrome

An Optical Coherence Tomography Analysis

Marco Covani, MD,[a,b] Giampaolo Niccoli, MD, PhD,[b] Daichi Fujimoto, MD, PhD,[a] Riccardo Scalamera, MD,[a,c] Rocco Vergallo, MD, PhD,[c,d] Italo Porto, MD, PhD,[c,d] Iris McNulty, RN,[a] Hang Lee, PhD,[e] Tsunekazu Kakuta, MD, PhD,[f] Ik-Kyung Jang, MD, PhD[a,g]

ABSTRACT

BACKGROUND Cardiovascular risk factors are strongly associated with adverse clinical outcomes, including acute coronary syndrome (ACS). Although individual risk factors have been related to specific plaque phenotypes, the relationship between the cumulative number of risk factors and plaque vulnerability has not been systematically explored.

OBJECTIVES The purpose of this study was to investigate the association between the number of cardiovascular risk factors and plaque vulnerability defined by optical coherence tomography.

METHODS Patients with ACS were divided into 5 groups based on their number of traditional risk factors (diabetes, hypertension, hyperlipidemia, smoking) or into 2 groups (0-1 vs ≥2 risk factors). Features of vulnerability in both culprit and nonculprit lesions were analyzed.

RESULTS Of 2,187 plaques analyzed, 1,581 were culprit and 606 nonculprit plaques. In culprit plaques, the prevalence of lipid-rich plaques (P trend = 0.027), thin-cap fibroatheromas (P trend = 0.006), macrophages (P trend <0.001), microvessels (P trend <0.001), and cholesterol crystals (P trend = 0.032) increased as the number of risk factors increased. The presence of ≥2 risk factors was independently associated with all vulnerable features except lipid-rich plaques. Plaque rupture showed an increasing prevalence as the number of risk factors increased (P trend = 0.015), whereas plaque erosion showed a decreasing trend (P trend <0.001). In nonculprit plaques, only macrophages, cholesterol crystals, and the cumulative number of vulnerable features in each plaque exhibited a significant positive association with the number of risk factors.

CONCLUSIONS In patients with ACS, an increasing number of cardiovascular risk factors were strongly associated with greater plaque vulnerability, especially for culprit lesions. These findings may explain the relationship between traditional risk factors and adverse clinical outcomes. (JACC. 2025;86:77-89) © 2025 by the American College of Cardiology Foundation.

Listen to this manuscript's audio summary by Editor-in-Chief Dr Harlan M. Krumholz on www.jacc.org/journal/jacc.

From the [a]Cardiology Division, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA; [b]Cardiology Department, University Hospital of Parma, Parma, Italy; [c]Department of Internal Medicine and Medical Specialties (DIMI), University of Genoa, Genoa, Italy; [d]Cardiothoracic and Vascular Department (DICATOV), Istituti di Ricovero e Cura a Carattere Scientifico (IRCCS) Ospedale Policlinico San Martino, Genova, Italy; [e]Biostatistics Center, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA; [f]Department of Cardiovascular Medicine, Tsuchiura Kyodo General Hospital, Tsuchiura, Japan; and the [g]Kyung Hee University, Seoul, South Korea.

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

Manuscript received February 8, 2025; revised manuscript received April 16, 2025, accepted April 28, 2025.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2025.04.070

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

LDL = low-density lipoprotein

LRP = lipid-rich plaque

NSTE-ACS = non-ST-segment elevation acute coronary syndrome

OCT = optical coherence tomography

STEMI = ST-segment elevation myocardial infarction

TCFA = thin-cap fibroatheroma

Epidemiology studies have shown that standard modifiable cardiovascular risk factors predict a higher incidence of cardiovascular disease and poor outcomes.[1,2] Guidelines on cardiovascular disease prevention describe low-density lipoprotein (LDL) levels, high blood pressure, cigarette smoking, and diabetes mellitus as the main causal and modifiable atherosclerotic cardiovascular risk factors.[3] The atherosclerotic plaque phenotype might explain the poor outcomes in patients with risk factors. Optical coherence tomography (OCT) enables visualization of plaque structures at a microscopic level, including features of plaque vulnerability. However, previous OCT studies focused on individual risk factors rather than considering them collectively[4,5] or in specific cohorts.[6] The association between the number of risk factors and the level of plaque vulnerability has not been systematically investigated. In the present study, we sought to correlate OCT-defined plaque vulnerability with a number of risk factors, including diabetes mellitus, hypertension, hyperlipidemia, and current smoking.

SEE PAGE 90

METHODS

STUDY POPULATION. Patients with acute coronary syndrome (ACS) who underwent preintervention OCT imaging of culprit lesion were identified from 3 cohorts: the Massachusetts General Hospital OCT Registry (NCT01110538), Predictors for Coronary Plaque Erosion in Patients with Acute Coronary Syndrome Registry (NCT03479723), and the Massachusetts General Hospital and Tsuchiura Kyodo General Hospital Coronary Imaging Collaboration (NCT04523194). The Massachusetts General Hospital OCT Registry is an international, multicenter registry that enrolled patients with coronary OCT imaging from August 2010 to May 2014. The Identification of Predictors for Coronary Plaque Erosion in Patients with Acute Coronary Syndrome registry is an international, multicenter registry that enrolled ACS patients from 7 countries (Japan, China, Italy, Belgium, United States, India, and Germany) with coronary OCT imaging from October 2008 to January 2018. The Massachusetts General Hospital and Tsuchiura Kyodo General Hospital Coronary Imaging Collaboration is a single-center study that enrolled patients with coronary OCT imaging from January 2011 to July 2020.

Exclusion criteria were prior stenting at the culprit vessel, in-stent restenosis, no prepercutaneous coronary intervention OCT imaging, no identifiable culprit lesion, poor image quality, MINOCA (myocardial infarction with non-obstructive coronary arteries), SCAD (spontaneous coronary artery dissection), culprit lesion in the coronary artery bypass graft, and missing data on risk factors (Supplemental Figure 1). After screening for exclusion criteria, 1,581 patients were included in the final analysis.

The diagnosis of ACS was made according to the American Heart Association/American College of Cardiology guidelines[7,8] defined as ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation ACS (NSTE-ACS). NSTE-ACS was defined as non-ST-segment elevation myocardial infarction or unstable angina pectoris.

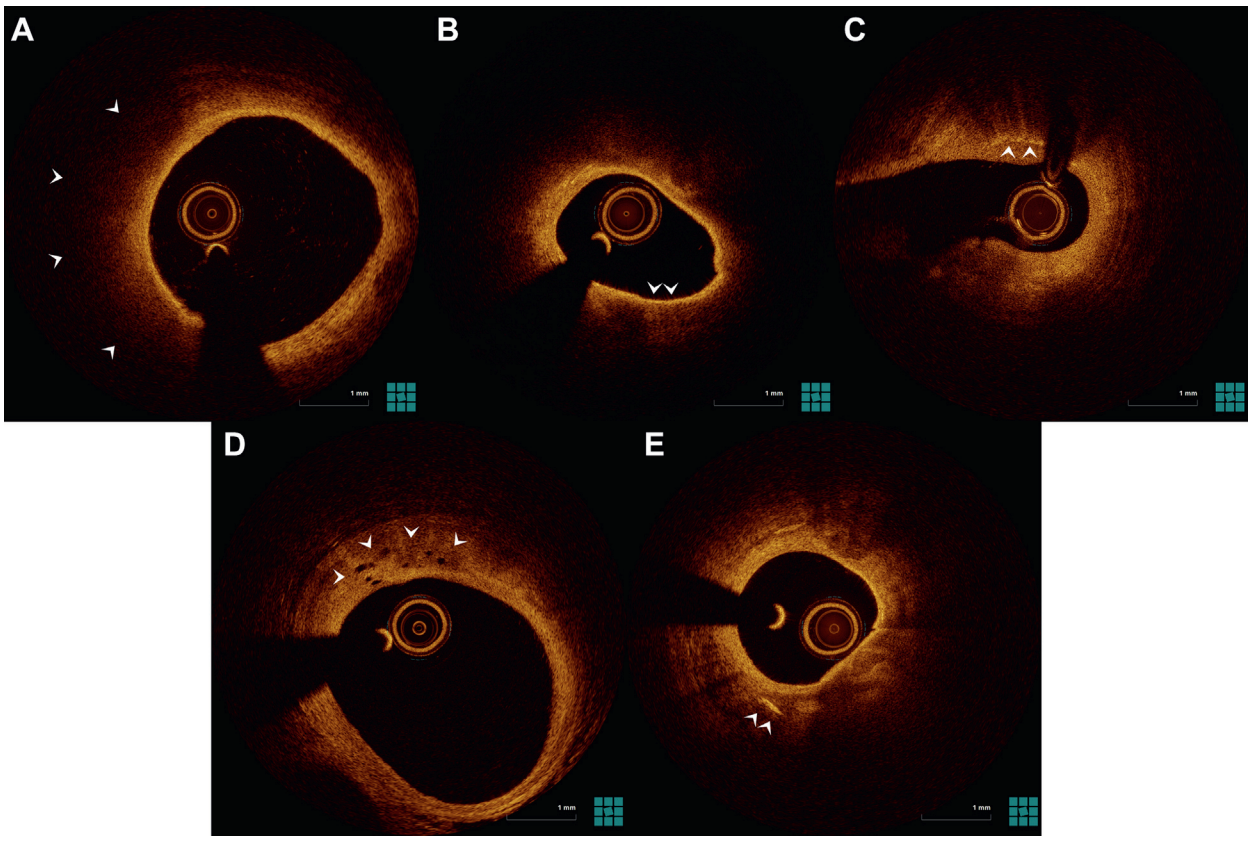
Demographic, angiographic, and OCT findings of culprit and nonculprit lesions and laboratory parameters were analyzed. In multivessel disease, the culprit lesion was identified as the lesion with the most severe stenosis or evidence of recent plaque disruption. Nonculprit lesions were defined as any stenosis >30% diameter stenosis and located at least 5 mm away from other plaques in the culprit vessel.

A detailed description of the risk factors assessment is provided in the Supplemental Methods. Two types of analyses were performed: the cohort was divided into 5 groups according to the distinct number of risk factors or into 2 groups with 0 to 1 or ≥2 risk factors, respectively. All registries were approved or deemed "Not Human Subject Research" by the Institutional Review Board at each site and conducted according to the Declaration of Helsinki.

OCT ANALYSIS. OCT imaging was performed using a frequency domain (C7/C8, OCT Intravascular Imaging System, St Jude Medical) or a time-domain (M2/M3, Cardiology Imaging Systems, LightLab Imaging) OCT system. Thrombus aspiration was allowed before OCT to facilitate the visualization of the underlying plaque, if needed. All OCT images were deidentified and submitted to the core laboratory at Massachusetts General Hospital. The images were analyzed by 2 independent investigators blinded to patient data, using an offline review workstation (St Jude Medical) and according to previously established criteria and definitions.[9] Definitions of OCT findings are detailed in the Supplemental Material. Representations of the OCT-defined vulnerable features, including lipid-rich plaque (LRP), thin-cap fibroatheroma (TCFA), macrophages, and microvessels, are shown in **Figure 1**.

STATISTICAL ANALYSIS. The Kolmogorov-Smirnov test was performed to assess whether the continuous variables followed a normal distribution. After the

FIGURE 1 **Vulnerable Features Defined by Optical Coherence Tomography**



Five main vulnerable features defined by optical coherence tomography are shown. (A) Lipid-rich plaque with arrowheads indicating signal-poor region with diffuse borders and a lipid arc ≥90°. (B) Thin-cap fibroatheroma, lipid-rich plaque with fibrous cap thickness ≤65 μm (arrowheads). (C) Macrophages, bright granular structures generating heterogeneous backward shadows (arrowheads). (D) Microvessels, small circular signal-poor regions sharply delineated (arrowheads). (E) Cholesterol crystals, thin and linear regions of high intensity signal (arrowheads).

assessment of distribution normality, no continuous variables were found to show a normal distribution. Therefore, continuous data are presented as median with lower and upper quartiles. Categorical data are summarized as absolute frequencies and percentages.

Two types of statistical analyses were performed, based on dividing the population into either 5 or 2 groups. Both analyses were conducted separately for culprit and nonculprit plaques, requiring distinct statistical approaches. Regarding the analysis of culprit plaques, in the 5-group analysis, continuous variables were compared using the Kruskal-Wallis test and categorical variables using the chi-square test. Bonferroni correction was applied whenever an overall significance was detected in a comparison involving >2 groups, requiring post hoc pairwise comparisons between categories. When post hoc pairwise comparison was required, all 10 possible pairwise subgroup comparisons were performed for each variable of interest. The significance threshold was adjusted by dividing the standard level (0.050) by the number of pairwise comparisons performed. For the pairwise post hoc comparison, the chi-square test, Fisher exact test, and Mann-Whitney U test were applied as appropriate. Significant differences in pairwise post hoc comparisons are indicated in bold in the tables. The presence of bold within the same row denotes a statistically significant difference after Bonferroni-adjusted pairwise post hoc comparison between the corresponding groups. The Cochran-Armitage trend test was used to assess trends in categorical variables across the 5 groups, whereas the Jonckheere-Terpstra test was applied for continuous variables. A 5-group subanalysis according to the clinical presentation was further conducted to evaluate the association between vulnerability and the number of risk factors in STEMI and NSTE-ACS patients.

In the 2-group analysis, continuous variables were compared using the Mann-Whitney U test, whereas categorical variables were analyzed using the chi-square test. Logistic regression models were used to estimate the association between a high number of risk factors (≥2) and the likelihood of vulnerable features in culprit plaques, taking into account potential confounding factors. Finally, to assess the association between individual risk factors and plaque vulnerability, 4 independent subanalyses were conducted, stratifying the population based on the presence of each risk factor. The nonculprit plaque analysis was performed at a plaque level, and the OCT features were assessed for each nonculprit plaque included in the study. Given that multiple nonculprit plaques could be present within the same patient, the assumption of independent observations was not met. To address this issue, generalized linear models with logit link for binary outcome using the generalized estimating equation method was applied to account for the potential intraclass correlation among the outcomes of multiple plaques within the same patient. In the 5-group analysis, 2 models were built and tested: using the number of risk factors as a categorical variable to test for any differences among the 5 groups, and using the number of risk factors as a continuous variable to test for linear trend.

Statistical significance was defined as $P < 0.050$, or Bonferroni-corrected alpha of $P < 0.050$ for the post hoc multiple comparisons. Statistical analysis was performed using SPSS software version 29.0.1 (IBM) and R software version 4.4.2 (R Foundation for Statistical Computing).

RESULTS

BASELINE PATIENT CHARACTERISTICS. A total of 2,187 plaques (1,581 culprit plaques and 606 nonculprit plaques) from 1,581 ACS patients were included in the analysis (Supplemental Figure 1). Among 1,581 patients, 470 (29.7%) exhibited at least 1 nonculprit plaque. Supplemental Table 1 details the distribution of nonculprit plaques within the study population. Within the total population, 75 patients had no risk factors, 376 had 1, 633 had 2, 415 had 3, and 82 had all 4 risk factors.

Baseline patient characteristics are shown in Table 1. The prevalence of hypertension, hyperlipidemia, diabetes mellitus, and current smoking in the entire cohort was 64.4%, 68.9%, 32.5%, and 37.6%, respectively. The group with 1 risk factor was the oldest, and the group with 4 risk factors was the youngest (across groups $P < 0.001$). The proportion of male patients increased as the number of risk factors increased, and the prevalence of obesity exhibited a similar trend. STEMI was more common in patients with ≥2 risk factors compared with those with no risk factor ($P = 0.001$), whereas NSTE-ACS showed the opposite pattern. A history of prior percutaneous coronary intervention or myocardial infarction was more frequent in patients with multiple risk factors ($P = 0.002$ and $P = 0.018$, respectively). White blood cell count was higher in patients with multiple risk factors and showed an increasing trend across the groups ($P < 0.001$, P trend <0.001).

OCT FINDINGS AMONG THE 5 GROUPS ACCORDING TO THE NUMBER OF RISK FACTORS. In culprit plaques, OCT-defined vulnerable features, including LRP, TCFA, macrophages, and microvessels, showed significant differences among the groups (Table 2). Trend analysis across the 5 groups demonstrated a statistically significant positive association between the prevalence of all 5 OCT-defined features of plaque vulnerability and the number of risk factors (P trend for LRP = 0.027, TCFA = 0.006, macrophages <0.001, microvessels <0.001, and cholesterol crystal = 0.032) (Central Illustration, Figure 2). Furthermore, the overall number of vulnerable features also showed an increasing trend with the number of risk factors (P trend <0.001).

Quantitative OCT analysis revealed a smaller mean minimum lumen area and thinner fibrous cap thickness in groups with more risk factors. Trend analysis showed a statistically significant association between minimum lumen area, area stenosis, and fibrous cap thickness and the number of risk factors (P trend = 0.001, P trend = 0.046 and P trend= 0.012, respectively) (Supplemental Table 2).

Regarding plaque etiology, plaque rupture, plaque erosion, and calcified plaques were observed in 49.8%, 39.5%, and 10.7% of cases, respectively. Plaque rupture was more prevalent in patients with 4 risk factors than those with no or 1 risk factor (64.6% vs 40.0% and 46.3%, $P = 0.015$). Trend analysis showed a significant positive association between the prevalence of plaque rupture and the number of risk factors (P trend = 0.015). Conversely, plaque erosion showed a decreasing prevalence as the number of risk factors increased (P trend <0.001) (Central Illustration, Table 3, Figure 3).

The results of the subanalysis according to clinical presentation are presented in Table 4. The prevalence of plaque rupture was higher in STEMI patients compared with NSTE-ACS patients (58.5% vs 43.7%, respectively; $P < 0.001$), whereas plaque erosion was more prevalent in NSTE-ACS patients (31.4% vs 45.2%, $P < 0.001$). In STEMI patients, the increasing

TABLE 1 Baseline Characteristics

	Total (N = 1,581)	0 RFs (n = 75)	1 RF (n = 376)	2 RFs (n = 633)	3 RFs (n = 415)	4 RFs (n = 82)	*P* Value
Age, y	66 (57-74)	67 (56-77)	**69 (58-76)**	**67 (57-74)**	**65 (56-73)**	**61 (53-69)**	<0.001
Male	1,260 (79.7)	**52 (69.3)**	291 (77.4)	506 (79.9)	339 (81.7)	**72 (87.8)**	0.032
Clinical presentation							
Non-ST-segment elevation acute coronary syndrome	925 (58.5)	**58 (77.3)**	237 (63.0)	**347 (54.8)**	**238 (57.3)**	**45 (54.9)**	0.001
ST-segment elevation myocardial infarction	656 (41.5)	**17 (22.7)**	139 (37.0)	**286 (45.2)**	**177 (42.7)**	**37 (45.1)**	
RFs and medical history							
Hypertension	1,018 (64.4)	0 (0)	142 (37.8)	424 (67.0)	370 (89.2)	82 (100)	<0.001
Hyperlipidemia	1,189 (68.9)	0 (0)	134 (35.6)	484 (76.5)	389 (93.7)	82 (100)	<0.001
Diabetes mellitus	514 (32.5)	0 (0)	26 (6.9)	145 (22.9)	261 (62.9)	82 (100)	<0.001
Current smoking	594 (37.6)	0 (0)	74 (19.7)	213 (33.6)	225 (54.2)	82 (100)	<0.001
Obesity	95 (8.3)	**1 (2.0)**	**14 (5.8)**	**32 (6.7)**	35 (10.9)	**13 (21.7)**	<0.001
Body mass index	24.6 (22.8-27.0)	23.0 (21.0-25.3)	23.1 (22.0-26.0)	24.63 (22.9-26.7)	25.37 (23.2-27.7)	27.08 (24.6-29.3)	<0.001
Chronic kidney disease	275 (17.7)	12 (16.4)	65 (17.7)	99 (15.8)	85 (20.7)	14 (17.7)	0.390
Prior myocardial infarction	146 (9.3)	**0 (0)**	29 (7.8)	60 (9.6)	**48 (11.7)**	**9 (11.1)**	0.018
Prior percutaneous coronary intervention	194 (12.3)	**2 (2.7)**	32 (8.5)	83 (13.1)	**66 (15.9)**	11 (13.4)	0.002
Medication and laboratory findings							
Acetylsalicylic acid	329 (23.9)	9 (13.4)	64 (20.4)	142 (25.4)	102 (28.1)	12 (17.1)	0.123
P2Y12i	141 (10.5)	5 (7.9)	**20 (6.5)**	62 (11.3)	**48 (13.5)**	6 (8.6)	0.049
Beta-blocker	323 (23.5)	17 (25.4)	65 (20.6)	123 (22.0)	99 (27.1)	19 (27.1)	0.238
Angiotensin-converting enzyme inhibitor	423 (30.7)	**15 (22.4)**	**68 (21.5)**	160 (28.6)	**147 (40.2)**	**33 (47.1)**	<0.001
Statin	364 (26.4)	3 (4.5)	50 (15.9)	164 (29.3)	124 (33.9)	23 (32.9)	<0.001
White blood cell count, $\times 10^9$/L	8.50 (6.70-10.80)	**8.10 (6.30-9.41)**	**8.00 (6.21-9.91)**	8.42 (6.65-10.90)	**9.00 (6.98-11.40)**	**9.61 (7.71-11.11)**	<0.001
Low-density-lipoprotein cholesterol, mg/dL	118.8 (96.0-147.0)	103.6 (90.7-124.5)	117.0 (95.0-131.0)	118.0 (95.0-147.0)	128.0 (98.0-158.5)	132.0 (108.7-164.0)	<0.001
High-density-lipoprotein cholesterol, mg/dL	45.0 (39.0-54.0)	52.5 (41.7-66.2)	47.0 (39.0-57.8)	44.0 (39.0-53.0)	43.6 (38.0-52.0)	42.0 (37.9-47.7)	<0.001
Triglyceride, mg/dL	100.0 (61.0-154.0)	76.0 (46.0-113.0)	81.1 (49.7-127.0)	100.0 (61.0-153.0)	112.0 (65.5-168.5)	121.0 (94.0-192.0)	<0.001
HbA1c, mmol/L	5.90 (5.50-6.60)	5.57 (5.30-5.90)	5.60 (5.32-6.00)	5.80 (5.50-6.30)	6.40 (5.80-7.30)	7.20 (6.42-7.77)	<0.001
Ejection fraction, %	60 (50-65)	60 (50-66)	60 (49-66)	60 (50-66)	60 (48-65)	55 (47-64)	0.250

Values are median (Q1-Q3) or n (%). *P* values are from chi-square test for categorical variables and Kruskal-Wallis test for continuous variables. Differences in the pairwise post hoc comparison are displayed for age, male sex, clinical presentation, obesity, prior myocardial infarction, prior percutaneous coronary intervention, P2Y12i, angiotensin-converting enzyme inhibitor, and white blood cell counts. **Bold** within the same row denotes a statistically significant difference after Bonferroni-adjusted pairwise post hoc comparison between the corresponding groups.

RF = risk factor.

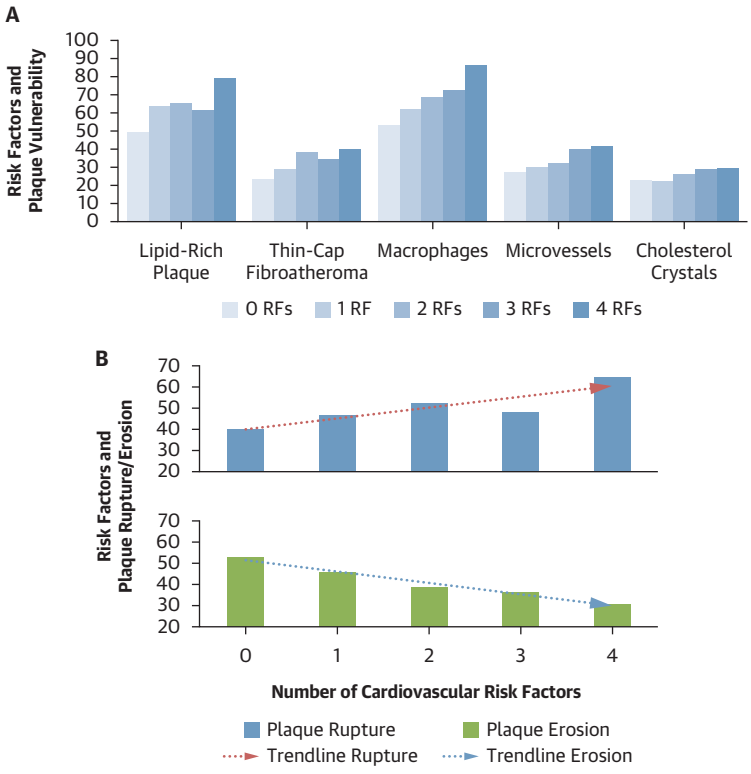
TABLE 2 Optical Coherence Tomography Findings Among 5 Groups in Culprit Plaques

	Total (N = 1,581)	0 RFs (n = 75)	1 RF (n = 376)	2 RFs (n = 633)	3 RFs (n = 415)	4 RFs (n = 82)	*P* Value	*P* Value for Trend
Lipid-rich plaques	1,012 (64.0)	**37 (49.3)**	239 (63.6)	**414 (65.4)**	257 (61.9)	**65 (79.3)**	0.002	0.027
Thin cap fibroatheromas	546 (34.5)	18 (24.0)	**108 (28.7)**	**241 (38.1)**	145 (34.9)	33 (40.2)	0.007	0.006
Macrophages	1,078 (68.2)	**40 (53.3)**	**232 (61.7)**	**437 (69.0)**	**298 (71.8)**	**71 (86.6)**	<0.001	<0.001
Microvessels	520 (34.0)	20 (27.8)	**110 (30.4)**	195 (31.9)	**161 (40.0)**	34 (41.5)	0.010	<0.001
Cholesterol crystals	408 (26.0)	17 (22.7)	83 (22.3)	166 (26.3)	118 (28.6)	24 (29.3)	0.272	0.032
No. of vulnerable features	2.25 ± 1.38	**1.76 ± 1.47**	**2.05 ± 1.34**	**2.30 ± 1.41**	**2.36 ± 1.38**	**2.77 ± 1.11**	<0.001	<0.001

Values are n (%) or mean ± SD. *P* values are from the chi-square test or Kruskal-Wallis test. *P* value for trend from Cochran Armitage test or Jonckheere-Terpstra test. **Bold** within the same row denotes a statistically significant difference after Bonferroni-adjusted pairwise post hoc comparison between the corresponding groups.

Abbreviation as in Table 1.

CENTRAL ILLUSTRATION **Association Between the Number of RFs, Plaque Vulnerability, and the Underlying Pathology of Acute Coronary Syndrome**



Covani M, et al. JACC. 2025;86(2):77–89.

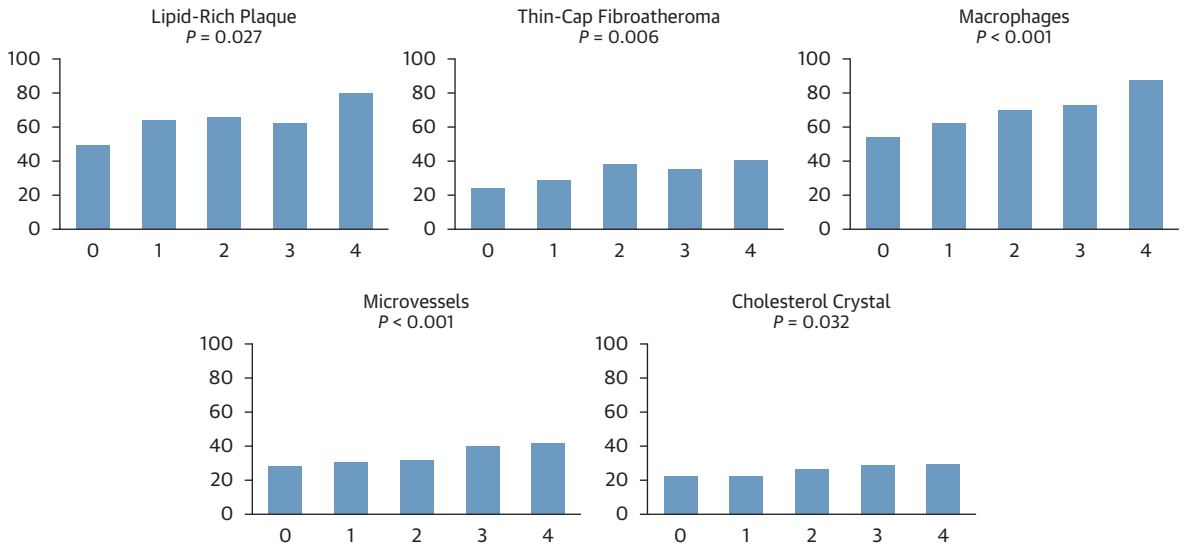
(A) Relationship between the number of risk factors (RFs) (diabetes, hypertension, hyperlipidemia, smoking) and the prevalence of OCT-defined vulnerable features in the culprit plaques. A significant positive trend was observed for each vulnerable feature. (B) Relationship between the number of RFs and the prevalence of plaque rupture or erosion in the culprit plaques. As the number of RFs increased, the prevalence of rupture increased (upper part of the chart), whereas the prevalence of erosion decreased (lower part of the chart). The dotted arrows represent the overall directional trend in plaque rupture and erosion across groups, providing a graphical illustration of the observed distribution pattern. OCT = optical coherence tomography.

trend between vulnerability and the number of risk factors remained consistent for each vulnerable feature and for plaque rupture, whereas a decreasing trend was observed for plaque erosion. In NSTE-ACS patients, the trend association was weaker, with statistical significance retained only for macrophages and microvessels (P trend $<$ 0.001 and P trend = 0.003, respectively).

For nonculprit plaques, the prevalence of vulnerable features was not significantly different among groups except for cholesterol crystals (P = 0.044). Trend analysis revealed a positive association between the number of risk factors and macrophages (P trend = 0.030) and cholesterol crystals (P trend = 0.003). The cumulative number of vulnerable features in nonculprit plaques also showed an increasing trend with the number of risk factors (P trend = 0.004) and significant difference among the groups (P = 0.049) (Supplemental Table 3, Supplemental Figures 2 and 3).

COMPARISON BETWEEN PATIENTS WITH ≤1 AND THOSE WITH ≥2 RISK FACTORS. The prevalence of TCFA (P < 0.001), macrophages (P < 0.001), microvessels (P = 0.036), and cholesterol crystals (P = 0.038) in culprit plaques was significantly higher in patients with multiple risk factors (≥2) compared with those with 0 or 1 risk factor. The prevalence of LRP tended to be higher in the group with multiple risk factors; however, the difference was not statistically significant (P = 0.141) (**Figure 4**, Supplemental Table 4). The quantitative analysis showed a smaller minimum lumen area and thinner fibrous cap

FIGURE 2 **Prevalence of Vulnerable Features in Culprit Plaques**



The prevalence of lipid-rich plaques, thin-cap fibroatheromas, macrophage, microvessels, and cholesterol crystals showed a significant positive trend with the number of risk factors. x-axis, the number of risk factors in each group; y-axis, percentage of the prevalence of each vulnerable feature. *P* value for trend from the Cochran-Armitage test is shown.

thickness in the group with multiple risk factors ($P = 0.009$ and $P = 0.002$, respectively) (Supplemental Table 5).

The results of the unadjusted and adjusted regression analyses of culprit plaques are presented in **Table 5**. Covariates were tested for collinearity, and the variance inflation factor values are reported in Supplemental Table 6. In addition to risk classification (low- and high-risk groups based on the number of risk factors: 0-1 vs ≥2), model 1 included age, sex, and clinical presentation, whereas model 2 included age, sex, clinical presentation, and plaque rupture as the ACS etiology. In both models, having ≥2 risk factors was independently associated with TCFA, macrophages, microvessels, and cholesterol crystals in culprit plaques.

For nonculprit plaques, the prevalence of vulnerable features did not significantly differ between the groups with 0 to 1 and ≥2 risk factors, except for cholesterol crystals, which were more frequent in the group with ≥2 risk factors ($P = 0.039$) (Supplemental Table 7, Supplemental Figure 4).

OCT FINDINGS ACCORDING TO THE PRESENCE OF INDIVIDUAL RISK FACTORS. The results of the subanalyses based on individual risk factors are presented in Supplemental Table 8. Only current smoking was found to be positively associated with a higher prevalence of LRP and plaque rupture ($P = 0.003$ and $P = 0.017$, respectively). Hypertension and diabetes were negatively associated with plaque erosion ($P = 0.002$ and $P = 0.004$, respectively). Additionally, the prevalence of macrophages was

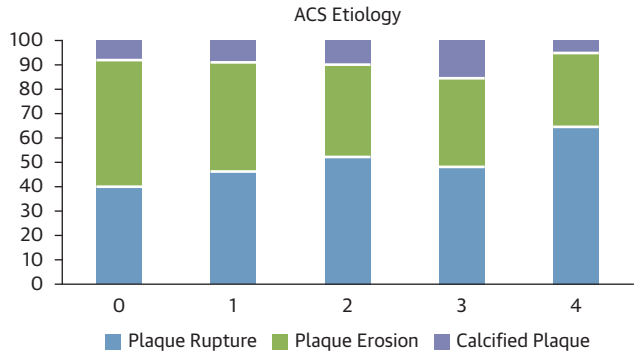
TABLE 3 **Optical Coherence Tomography–Defined Etiology of the Acute Coronary Syndrome**

	Total (N = 1,581)	0 RFs (n = 75)	1 RF (n = 376)	2 RFs (n = 633)	3 RFs (n = 415)	4 RFs (n = 82)	*P* Value	*P* Value for Trend
Plaque rupture	788 (49.8)	**30 (40.0)**	**174 (46.3)**	331 (52.3)	200 (48.2)	**53 (64.6)**	0.007	0.015
Plaque erosion	624 (39.5)	39 (52.0)	169 (44.9)	240 (37.9)	151 (36.4)	25 (30.5)	0.005	<0.001
Calcified plaque	169 (10.7)	6 (8.0)	**33 (8.8)**	62 (9.8)	**64 (15.4)**	4 (4.9)	0.004	0.066

Values are n (%). *P* values are from chi-square test for plaque rupture and plaque erosion and from Fisher exact test for calcified plaque. *P* value for trend from Cochran Armitage test. **Bold** within the same row denotes a statistically significant difference after Bonferroni-adjusted pairwise post hoc comparison between the corresponding groups.

Abbreviation as in **Table 1**.

FIGURE 3 Optical Coherence Tomography-Defined Etiology of the ACS Among the 5 Groups



Optical coherence tomography-defined etiology mechanism among the groups is shown. As the number of risk factors increased, the prevalence of plaque rupture increased, whereas the prevalence of erosion decreased. x-axis, the number of risk factors in each group. y-axis percentage of prevalence of each ACS etiology. ACS = acute coronary syndrome.

higher in the presence of diabetes, hypertension, and smoking.

DISCUSSION

The main findings of our study are as follows. First, the prevalence of vulnerable features for the culprit lesion increases proportionally with the number of risk factors, especially in STEMI patients. Second, having ≥2 risk factors is independently associated with OCT-defined vulnerable features in culprit plaques, regardless of clinical characteristics or ACS etiology. Third, nonculprit plaques show a weaker association between the number of risk factors and vulnerability. Finally, plaque rupture becomes more frequent as the number of risk factors increases, whereas plaque erosion shows the opposite trend.

NUMBER OF RISK FACTORS AND PLAQUE VULNERABILITY. Previous studies have explored the association between cardiovascular risk factors and OCT-defined vulnerable features.[4-6] A study from our laboratory demonstrated that the prevalence of LRPs in women with hyperlipidemia, hypertension, or current smoking increases with age.[6] Similarly, Suzuki et al[4] provided a detailed analysis of vulnerable plaque features in diabetic patients, showing a higher prevalence compared with nondiabetic individuals. In line with these findings, Ueyama et al[5] observed an increasing prevalence of TCFA in patients with elevated HbA1c levels. Moreover, multiple studies showed a shift toward a less vulnerable plaque phenotype after high-intensity lipid-lowering therapy.[10,11]

To the best of our knowledge, this study includes the largest population in which the prevalence of risk factors has been comprehensively analyzed in relation to OCT-defined vulnerable plaque features.

TABLE 4 Optical Coherence Tomography Findings Among 5 Groups in Culprit Plaques in ST-Segment Elevation Myocardial Infarction and Non-ST-Segment Elevation Acute Coronary Syndrome

ST-Segment Elevation Myocardial Infarction Population	Total (N = 656)	0 RFs (n = 17)	1 RF (n = 139)	2 RFs (n = 286)	3 RFs (n = 177)	4 RFs (n = 37)	*P* Value	*P* Value for Trend
Lipid-rich plaques	440 (67.1)	**7 (41.2)**	87 (62.6)	188 (65.7)	128 (72.3)	**30 (81.1)**	0.016	0.001
Thin cap fibroatheromas	255 (38.9)	3 (17.6)	43 (30.9)	116 (40.6)	77 (43.5)	16 (43.2)	0.058	0.008
Macrophages	459 (70.0)	12 (70.6)	**84 (60.4)**	**200 (69.9)**	129 (72.9)	**34 (91.9)**	0.004	0.001
Microvessels	172 (27.0)	4 (23.5)	32 (24.4)	67 (23.9)	53 (30.8)	16 (43.2)	0.088	0.021
Cholesterol crystals	155 (23.7)	3 (17.6)	26 (18.7)	65 (22.9)	49 (27.8)	12 (32.4)	0.232	0.019
Plaque rupture	384 (58.5)	7 (41.2)	71 (51.1)	167 (58.4)	111 (62.7)	28 (75.7)	0.026	0.001
Plaque erosion	206 (31.4)	**9 (52.9)**	**52 (37.4)**	**98 (34.3)**	**38 (21.5)**	9 (24.3)	0.003	< 0.001
Non-ST-Segment Elevation Acute Coronary Syndrome Population	**Total (N = 925)**	**0 RFs (n = 58)**	**1 RF (n = 237)**	**2 RFs (n = 347)**	**3 RFs (n = 238)**	**4 RFs (n = 45)**	***P* Value**	***P* Value for Trend**
Lipid-rich plaques	572 (61.8)	30 (51.7)	152 (64.1)	226 (65.1)	**129 (54.2)**	**35 (77.8)**	0.004	0.865
Thin cap fibroatheromas	290 (31.4)	15 (25.9)	65 (27.4)	125 (36.1)	68 (28.6)	17 (37.8)	0.096	0.282
Macrophages	619 (66.9)	**28 (48.3)**	148 (62.4)	**237 (68.3)**	**169 (71.0)**	**37 (82.2)**	0.001	< 0.001
Microvessels	348 (39.0)	16 (29.1)	**78 (33.8)**	128 (38.6)	**108 (47.0)**	18 (40.0)	0.025	0.003
Cholesterol crystals	253 (27.5)	14 (24.1)	57 (24.4)	101 (29.2)	69 (29.2)	12 (26.7)	0.671	0.271
Plaque rupture	404 (43.7)	23 (39.7)	103 (43.5)	164 (47.3)	89 (37.4)	25 (55.6)	0.072	0.950
Plaque erosion	418 (45.2)	30 (51.7)	117 (49.4)	142 (40.9)	113 (47.5)	16 (35.6)	0.116	0.162

Values ate n (%). *P* values are from the chi-square test. *P* values for trend are from the Cochran Armitage test. **Bold** within the same row denotes a statistically significant difference after Bonferroni-adjusted pairwise post hoc comparison between the corresponding groups.

Abbreviation as in Table 1.

Our approach assessed risk factors collectively as an indicator of overall cardiovascular risk rather than as isolated variables. A similar approach was used by several groups for prognostic stratification[12-16] and was recently adopted in the latest chronic coronary syndromes guidelines from the European Society of Cardiology for estimating the probability of obstructive coronary artery disease.[17] However, there is no unified consensus on which risk factors should be considered "standard modifiable risk factors." For our analysis, we selected those with consistent agreement across prior studies[12-16] and according to the indications from the European Society of Cardiology guidelines on cardiovascular disease prevention.[3] Although the association between obesity and cardiovascular risk is well established, several observations highlight its potential role as a causal factor in the development of other risk factors, particularly hypertension, dyslipidemia, and diabetes.[18] Furthermore, adding adiposity parameters to traditional risk factors did not improve risk discrimination in a large cohort of patients,[19] suggesting that the increased risk associated with obesity may be driven by altered intermediate risk factors. For this reason, and considering the need to minimize further population fragmentation, obesity was not included on the same level as other risk factors in our group stratification strategy. In line with these considerations and consistent with previous reports,[18] our study shows that obesity appears to be strongly associated with a greater number of risk factors, further reinforcing its potential causal relationship with them.

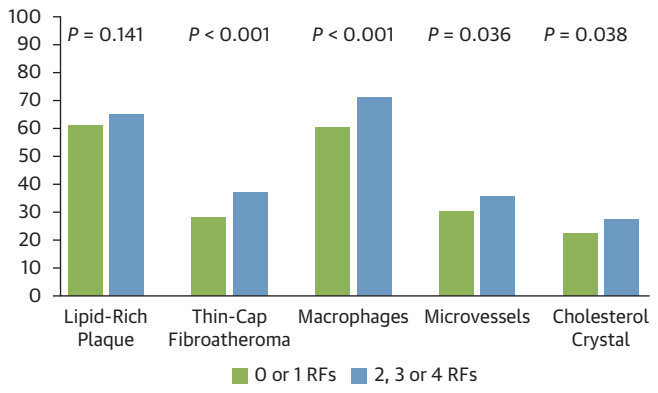
Previous studies examined the association between the overall cardiovascular risk and plaque vulnerability in the entire coronary tree and did not demonstrate a significant correlation with key OCT-defined vulnerable features.[20] However, leveraging the large size of our study population, we identified a significant association between the number of risk factors and vulnerability in culprit plaques, with an increasing trend observed for each vulnerable feature independently. When we evaluated vulnerability by the number of vulnerable features within the plaque, a strong association with the number of risk factors was also demonstrated. By contrast, we did not observe a strong association in nonculprit plaques, consistent with prior reports.[20]

Additionally, we sought to determine whether individual risk factors were associated with a specific plaque phenotype or vulnerable pattern. To do so, the population was stratified based on the presence of each individual risk factor, and differences in the prevalence of vulnerable features between groups were analyzed. Although there was a general trend toward greater vulnerability in groups with the respective risk factor, only current smoking was found to be significantly associated with a higher prevalence of LRP and, consequently, with plaque rupture. These findings suggest that risk factors may not induce vulnerability through distinct and independent mechanisms. Instead, they appear to converge on a common final pathway, which may ultimately serve as the principal driver of plaque vulnerability. If this finding were to be confirmed, it would further support the idea that cardiovascular risk is the result of a complex interplay of multiple factors and cannot be fully represented by the presence of isolated factors.

Several studies have highlighted the role of cardiovascular risk factors in promoting vascular inflammation and endothelial damage. For instance, diabetes induces the activation of inflammatory pathways through the interaction between advanced glycation end products (AGEs), formed as a result of uncontrolled hyperglycemia, and their receptor RAGE (receptor for advanced glycation end products).[21] Similarly, oxidized LDL cholesterol is well established as a driver of plaque inflammation,[22] whereas smoking has shown systemic proinflammatory effects.[23] Hypertension contributes by causing endothelial damage, ultimately leading to vascular inflammation.[24]

Vascular inflammation plays a pivotal role in atherosclerosis progression.[25] In this context, pericoronary adipose tissue attenuation has emerged as a

FIGURE 4 Prevalence of Vulnerable Features Between 2 Groups in Culprit Plaques



Thin-cap fibroatheromas, macrophages, microvessels, and cholesterol crystals showed a significantly higher prevalence in the group with ≥2 risk factors (RFs). x-axis, vulnerable features in patients with 0 to 1 RFs and in those with ≥2 RFs; y-axis, the percentage of the prevalence of the vulnerable features. *P* value from the chi-square test is shown.

TABLE 5 Unadjusted and Adjusted Regression Analysis of High-Risk Patients for Vulnerable Features in Culprit Plaques

	Unadjusted Analysis		Adjusted Analysis by Model 1		Adjusted Analysis by Model 2	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Thin-cap fibroatheroma RFs ≥2	1.52 (1.20-1.93)	<0.001	1.44 (1.12-1.87)	0.005	1.41 (1.03-1.92)	0.030
Macrophages RFs ≥2	1.64 (1.31-2.06)	<0.001	1.58 (1.23-2.03)	<0.001	1.54 (1.18-2.00)	0.001
Microvessels RFs ≥2	1.29 (1.02-1.64)	0.036	1.39 (1.06-1.82)	0.018	1.38 (1.05-1.81)	0.020
Cholesterol crystals RFs ≥2	1.31 (1.01-1.70)	0.038	1.38 (1.03-1.87)	0.033	1.35 (1.01-1.83)	0.049

Model 1 includes risk factors, age, sex, and ST-segment elevation myocardial infarction as clinical presentation. Model 2 includes risk factors, age, sex, ST-segment elevation myocardial infarction as clinical presentation, and plaque rupture as the acute coronary syndrome etiology.

Abbreviation as in Table 1.

novel marker for coronary vascular inflammation.[26] Studies have shown higher pericoronary adipose tissue attenuation at culprit plaques in ACS compared with SAP (stable angina pectoris)[27] and in culprit plaques compared with nonculprit plaques.[28] Furthermore, pericoronary adipose tissue attenuation has been associated with several OCT-defined vulnerable features,[29] supporting the link between plaque vulnerability and plaque inflammation.

In our results, the white blood cell count showed an increasing trend as the number of risk factors increased, suggesting that patients with multiple risk factors are likely to have higher systemic inflammation and greater coronary vulnerability. These findings reinforce the connection between traditional risk factors and vascular inflammation, emphasizing that risk factors may promote plaque vulnerability by amplifying both local and systemic inflammatory processes, ultimately contributing to a more vulnerable phenotype.

CLINICAL OUTCOMES AND RISK FACTORS. Modifiable cardiovascular risk factors are widely used to predict cardiovascular events in the general population. Myocardial infarction is attributed to 9 modifiable risk factors in 90% of cases,[1] and 71% of all cardiovascular diseases are linked to 14 modifiable factors, including smoking, high ApoB/ApoA1 ratio, hypertension, diabetes, abdominal obesity, psychological factors, dietary habits, physical activity, education, and pollution.[2] In populations without a history of cardiovascular disease, >50% of cardiovascular events and 20% of all-cause mortality are attributable to 5 key risk factors: diabetes, hypertension, hyperlipidemia, smoking, and obesity.[30] A recent international, multicenter registry demonstrated that a higher number of risk factors was linked to an increased risk of target lesion failure and myocardial infarction at the 1-year follow-up in ACS patients.[12] Furthermore, another study validated the risk factor count system, demonstrating a lower probability of obstructive coronary artery disease in patients with 0 or 1 risk factors, including diabetes, dyslipidemia, hypertension, smoking, and family history of coronary artery disease, compared with those with ≥2 risk factors.[31]

OCT-defined vulnerable features have previously been reported to be associated with worse clinical outcomes and cardiovascular events.[32,33] Our study showed a strong association between the number of risk factors and OCT-defined vulnerable features in culprit plaques. Categorizing patients into low- or high-risk groups (0-1 vs ≥2 risk factors) has demonstrated that high-risk patients exhibited significantly greater plaque vulnerability. Adjusted regression analysis confirmed that ≥2 risk factors was independently associated with TCFA, macrophages, microvessels, and cholesterol crystals, irrespective of clinical and OCT findings. Although the association between risk factors and poor outcomes is well established, the mechanisms through which risk factors contribute to increased event rates remain incompletely understood. This gap in evidence presents methodological challenges, because it requires integrating plaque biology with clinical data from a large population. Our study bridges this gap in knowledge by linking the number of risk factors to plaque phenotype as visualized by OCT, demonstrating greater plaque vulnerability in high-risk patients.

More than one-half of recurrent events in post-ACS patients are not caused by target lesion failure but arise from nonculprit plaques.[34,35] We extended our analysis to nonculprit plaques to investigate whether a higher cardiovascular risk profile correlates with

increased vulnerability in these plaques. Our study showed that nonculprit plaques exhibited a similar trend: a higher prevalence of vulnerable features in the patients with more risk factors, albeit the difference was less robust. A possible explanation could be related to the distinct pathophysiological characteristics of culprit plaques compared with nonculprit plaques, including a higher degree of vascular inflammation and greater stenosis.[28,36] These factors may influence the relationship between vulnerability and risk factors, making culprit plaques more susceptible to their detrimental effect. For instance, a higher degree of stenosis may be more affected by hypertension, altering shear stress dynamics,[37] whereas increased inflammation could enhance LDL transcytosis,[38] making it more sensitive to plasma LDL levels. The weaker association between risk factors and OCT-defined vulnerable features in nonculprit plaques supports the notion that atherosclerosis is a panvascular process with geographic and temporal variations in inflammatory or metabolic activities. A single time-point assessment, capturing a specific point in the natural history of the disease, may not accurately reflect the patient's overall risk and might not fully capture the connection between the risk profile and coronary artery vulnerability. Nevertheless, our study exclusively included information from the target vessel. Expanding the analysis to the entire coronary tree in a larger population could provide further insights into the association between coronary vulnerability and risk profile, potentially confirming the statistical significance of the trend we observed. This would further underscore the importance of an aggressive approach against risk factors, both in primary and secondary prevention.

NUMBER OF RISK FACTORS AND PATHOLOGY OF ACS. Plaque erosion is responsible for 25% to 40% of ACSs.[39-41] Several studies have characterized the clinical and laboratory profiles of patients with ACS and erosion at the culprit plaque, demonstrating a younger age, lower prevalence of cardiovascular risk factors,[42] and more frequent presentation as non-STEMI.[43] Furthermore, erosion occurs more commonly in plaques with a less vulnerable phenotype[40,44] and a lower grade of inflammation.[45] Taken together, these findings suggest a distinct pathophysiological mechanism underlying erosion compared with plaque rupture, which is based on endothelial denudation and subsequent thrombus expansion.[43]

Our findings showed that the prevalence of erosion decreased as the number of risk factors increased, indicating that vascular inflammation might not play a key role in the pathogenesis of erosion. Instead, complex interactions among endothelial dysfunction, local hemodynamics, coagulability, and other factors such as spasm may lead to endothelial denudation and erosion.[46] The observed trend in white blood cell concentration further supports these findings as, consistent with previous studies,[45] patients with higher systemic inflammation are more likely to experience ACS due to plaque rupture.

Furthermore, when the relationship between risk factors and vulnerability is analyzed based on clinical presentation, a strong association is evident in STEMI patients, whereas a less pronounced association is observed in NSTE-ACS patients. These findings may be attributed to the higher tendency of plaque erosion to manifest as NSTE-ACS. This observation is supported by our results, as the NSTE-ACS cohort exhibited a more evenly distributed etiology between erosion and rupture, whereas STEMI patients predominantly presented with plaque rupture. These findings further emphasize that traditional risk factors may contribute to increased coronary vulnerability, which primarily promote plaque rupture, and ultimately likely leads to STEMI. However, the association between traditional risk factors and vulnerability does not fully explain the relationship between risk profile and the occurrence of NSTE-ACS. Because this clinical phenotype is more frequently associated with plaque erosion, it may be influenced by alternative risk factors acting at the coronary level through mechanisms independent of increased vulnerability. Specifically, it is possible that factors such as environmental pollution, food contaminants, or other yet unexplored elements primarily affect endothelial function, thereby increasing the risk of plaque erosion without influencing the overall grade of vulnerability.

Over the past decades, advancements in the awareness and optimized management of traditional risk factors have led to a marked reduction in the overall incidence of ACS.[47,48] However, this progress may have contributed to a proportional increase in ACS cases attributed to plaque erosion.[49] Epidemiological data indicate that between 11% and 27% of patients with ACS do not exhibit traditional risk factors,[13-16] with some studies reporting an increasing prevalence of such cases over time.[15] In our study, consistent with previous reports, most patients without traditional risk factors who experienced ACS were found to have plaque erosion. These findings suggest that the portion of ACS cases that occurs in patients without traditional risk may predominantly be explained by plaque erosion, further highlighting the potential contribution of other, yet unidentified or unexplored, risk factors in its pathogenesis.

Nevertheless, it is important to note that in previous reports, ACS patients without risk factors predominantly experienced STEMI,[13] which is less commonly associated with plaque erosion.[43] This discrepancy may be explained by the nature of our data, which exclusively includes patients undergoing OCT-guided percutaneous coronary intervention, potentially favoring the selection of non-STEMI cases. This evolving scenario highlights the need for further research to elucidate the mechanisms driving plaque erosion and to identify nontraditional risk factors to refine diagnostic and therapeutic strategies.

STUDY LIMITATIONS. First, this study included a retrospective analysis of multicenter databases. Thus, selection bias cannot be excluded. Second, the number of nonculprit plaques was small, and the analysis was limited to the target vessel. Third, the absence of outcome data does not allow us to directly link the risk factors with plaque vulnerability and prognosis; moreover, the cross-sectional study design prevents the identification of a causal relationship between risk factors and plaque vulnerability. Fourth, the assessment of risk factors across the 3 registries was conducted using different methods, and some heterogeneity cannot be excluded. Finally, our study lacks external validation. To address this issue, further longitudinal studies need to be conducted to confirm the robustness of the results.

CONCLUSIONS

Our study provides a comprehensive assessment of plaque vulnerable characteristics associated with cardiovascular risk factors, both individually and in combination, in a large cohort of ACS patients. In culprit plaques, as the number of risk factors increases, plaque vulnerability also increases, and those with ≥2 risk factors are independently associated with a higher prevalence of vulnerable features. Moreover, this association is particularly strong in STEMI patients, where plaque rupture is the predominant etiological mechanism. In nonculprit plaques, the association between risk profile and vulnerability is less evident. These results may explain the poor outcomes in patients with multiple risk factors and provide insight into the role of risk factors in developing plaques with vulnerable phenotypes while underlying the need to explore new risk determinants associated with the onset of plaque erosion.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Scalamera has received a grant from the "Enrico ed Enrica Sovena" Foundation, Rome, Italy. Dr Vergallo is a consultant or speaker for Abbott Vascular, ABIOMED, Amgen, Daiichi-Sankyo, Edwards Lifesciences, Medtronic, Novartis, and Philips. Dr Porto is a consultant or speaker for Medtronic, Siemens, GE, ABIOMED, Philips, Sanofi, Amgen, Daiichi-Sankyo, AstraZeneca, Bayer, and PIAM. Dr Jang has received educational grants from Abbott Vascular; and has been supported by Mrs Gillian Gray through the Allan Gray Fellowship Fund in Cardiology and Mukesh and Priti Chatter through the Chatter Foundation. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Ik-Kyung Jang, Allan and Gill Gray Professor of Medicine, Harvard Medical School, Cardiology Division, Massachusetts General Hospital, 55 Fruit Street, GRB 800, Boston, Massachusetts 02114, USA. E-mail: ijang@mgh.harvard.edu.

REFERENCES

1. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937–952.

2. Yusuf S, Joseph P, Rangarajan S, et al. Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. *Lancet*. 2020;395:795–808.

3. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2021;42:3227–3337.

4. Suzuki K, Niida T, Yuki H, et al. Coronary plaque characteristics and underlying mechanism of acute coronary syndromes in different age groups of patients with diabetes. *J Am Heart Assoc*. 2023;12:e031474.

5. Ueyama H, Yasumura K, Okamoto N, et al. Relationship between hemoglobin A1C and characteristics of plaque vulnerability in stable coronary disease: an optical coherence tomography study. *Int J Cardiovasc Imaging*. 2022;38:473–482.

6. Seegers LM, Yeh DD, Wood MJ, et al. Cardiovascular risk factors and culprit plaque characteristics in women with acute coronary syndromes. *Am J Cardiol*. 2023;207:13–20.

7. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;61(4):e78–e140.

8. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;64(24):e139–e228.

9. Araki M, Park S-J, Dauerman HL, et al. Optical coherence tomography in coronary atherosclerosis assessment and intervention. *Nat Rev Cardiol*. 2022;19:684–703.

10. Räber L, Ueki Y, Otsuka T, et al. Effect of alirocumab added to high-intensity statin therapy on coronary atherosclerosis in patients with acute myocardial infarction: the PACMAN-AMI randomized clinical trial. *JAMA*. 2022;327:1771–1781.

11. Nicholls SJ, Kataoka Y, Nissen SE, et al. Effect of evolocumab on coronary plaque phenotype and

burden in statin-treated patients following myocardial infarction. *JACC Cardiovasc Imaging*. 2022;15:1308–1321.

12. Kobo O, Levi Y, Abu-Fanne R, et al. Impact of the number of modifiable risk factors on clinical outcomes after percutaneous coronary intervention: an analysis from the e-Ultimaster registry. *Int J Cardiol Heart Vasc*. 2024;51:101370.

13. Kong G, Chin YH, Chong B, et al. Higher mortality in acute coronary syndrome patients without standard modifiable risk factors: results from a global meta-analysis of 1,285,722 patients. *Int J Cardiol*. 2023;371:432–440.

14. Figtree GA, Vernon ST, Hadziosmanovic N, et al. Mortality and cardiovascular outcomes in patients presenting with non-ST elevation myocardial infarction despite no standard modifiable risk factors: results from the SWEDEHEART Registry. *J Am Heart Assoc*. 2022;11:e024818.

15. Vernon ST, Coffey S, Bhindi R, et al. Increasing proportion of ST elevation myocardial infarction patients with coronary atherosclerosis poorly explained by standard modifiable risk factors. *Eur J Prev Cardiol*. 2017;24:1824–1830.

16. Moledina SM, Rashid M, Nolan J, et al. Addressing disparities of care in non-ST-segment elevation myocardial infarction patients without standard modifiable risk factors: insights from a nationwide cohort study. *Eur J Prev Cardiol*. 2022;29:1084–1092.

17. Vrints C, Andreotti F, Koskinas KC, et al. 2024 ESC guidelines for the management of chronic coronary syndromes. *Eur Heart J*. 2024;45:3415–3537.

18. Yamada T, Kimura-Koyanagi M, Sakaguchi K, Ogawa W, Tamori Y. Obesity and risk for its comorbidities diabetes, hypertension, and dyslipidemia in Japanese individuals aged 65 years. *Sci Rep*. 2023;13:2346.

19. Emerging Risk Factors Collaboration, Wormser D, Kaptoge S, et al. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. *Lancet*. 2011;377:1085–1095.

20. Vergallo R, Xing L, Minami Y, et al. Associations between the Framingham Risk Score and coronary plaque characteristics as assessed by three-vessel optical coherence tomography. *Coron Artery Dis*. 2016;27:460–466.

21. Twarda-Clapa A, Olczak A, Białkowska AM, Koziołkiewicz M. Advanced glycation end-products (AGEs): formation, chemistry, classification, receptors, and diseases related to AGEs. *Cells*. 2022;11:1312.

22. Borén J, Chapman MJ, Krauss RM, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J*. 2020;41:2313–2330.

23. Messner B, Bernhard D. Smoking and cardiovascular disease: mechanisms of endothelial dysfunction and early atherogenesis. *Arterioscler Thromb Vasc Biol*. 2014;34:509–515.

24. Alexander RW. Theodore Cooper Memorial Lecture. Hypertension and the pathogenesis of atherosclerosis. Oxidative stress and the mediation of arterial inflammatory response: a new perspective. *Hypertens Dallas Tex 1979*. 1995;25:155–161.

25. Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med*. 1999;340:115–126.

26. Oikonomou EK, Marwan M, Desai MY, et al. Non-invasive detection of coronary inflammation using computed tomography and prediction of residual cardiovascular risk (the CRISP CT study): a post-hoc analysis of prospective outcome data. *Lancet*. 2018;392:929–939.

27. Araki M, Sugiyama T, Nakajima A, et al. Level of vascular inflammation is higher in acute coronary syndromes compared with chronic coronary disease. *Circ Cardiovasc Imaging*. 2022;15:e014191.

28. Goeller M, Achenbach S, Cadet S, et al. Pericoronary adipose tissue computed tomography attenuation and high-risk plaque characteristics in acute coronary syndrome compared with stable coronary artery disease. *JAMA Cardiol*. 2018;3:858–863.

29. Yuki H, Sugiyama T, Suzuki K, et al. Coronary inflammation and plaque vulnerability: a coronary computed tomography and optical coherence tomography study. *Circ Cardiovasc Imaging*. 2023;16:e014959.

30. Global Cardiovascular Risk Consortium, Magnussen C, Ojeda FM, et al. Global effect of modifiable risk factors on cardiovascular disease and mortality. *N Engl J Med*. 2023;389:1273–1285.

31. Winther S, Schmidt SE, Mayrhofer T, et al. Incorporating coronary calcification into pre-test assessment of the likelihood of coronary artery disease. *J Am Coll Cardiol*. 2020;76:2421–2432.

32. Kubo T, Ino Y, Mintz GS, et al. Optical coherence tomography detection of vulnerable plaques at high risk of developing acute coronary syndrome. *Eur Heart J Cardiovasc Imaging*. 2021;22:1376–1384.

33. Xing L, Higuma T, Wang Z, et al. Clinical significance of lipid-rich plaque detected by optical coherence tomography: a 4-year follow-up study. *J Am Coll Cardiol*. 2017;69:2502–2513.

34. Erlinge D, Maehara A, Ben-Yehuda O, et al. Identification of vulnerable plaques and patients by intracoronary near-infrared spectroscopy and ultrasound (PROSPECT II): a prospective natural history study. *Lancet*. 2021;397:985–995.

35. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med*. 2011;364:226–235.

36. Kuneman JH, van Rosendael SE, van der Bijl P, et al. Pericoronary adipose tissue attenuation in patients with acute coronary syndrome versus stable coronary artery disease. *Circ Cardiovasc Imaging*. 2023;16:e014672.

37. Yang JW, Cho KI, Kim JH, et al. Wall shear stress in hypertensive patients is associated with carotid vascular deformation assessed by speckle tracking strain imaging. *Clin Hypertens*. 2014;20:10.

38. Zhang Y, Yang X, Bian F, et al. TNF-α promotes early atherosclerosis by increasing transcytosis of LDL across endothelial cells: crosstalk between NF-κB and PPAR-γ. *J Mol Cell Cardiol*. 2014;72:85–94.

39. Higuma T, Soeda T, Abe N, et al. A combined optical coherence tomography and intravascular ultrasound study on plaque rupture, plaque erosion, and calcified nodule in patients with ST-segment elevation myocardial infarction: incidence, morphologic characteristics, and outcomes after percutaneous coronary intervention. *JACC Cardiovasc Interv*. 2015;8:1166–1176.

40. Jia H, Abtahian F, Aguirre AD, et al. In vivo diagnosis of plaque erosion and calcified nodule in patients with acute coronary syndrome by intravascular optical coherence tomography. *J Am Coll Cardiol*. 2013;62:1748–1758.

41. Niccoli G, Montone RA, Di Vito L, et al. Plaque rupture and intact fibrous cap assessed by optical coherence tomography portend different outcomes in patients with acute coronary syndrome. *Eur Heart J*. 2015;36:1377–1384.

42. Yamamoto E, Yonetsu T, Kakuta T, et al. Clinical and laboratory predictors for plaque erosion in patients with acute coronary syndromes. *J Am Heart Assoc*. 2019;8:e012322.

43. Fahed AC, Jang I-K. Plaque erosion and acute coronary syndromes: phenotype, molecular characteristics and future directions. *Nat Rev Cardiol*. 2021;18:724–734.

44. Farb A, Burke AP, Tang AL, et al. Coronary plaque erosion without rupture into a lipid core. A frequent cause of coronary thrombosis in sudden coronary death. *Circulation*. 1996;93:1354–1363.

45. Nakajima A, Sugiyama T, Araki M, et al. Plaque rupture, compared with plaque erosion, is associated with a higher level of pancoronary inflammation. *JACC Cardiovasc Imaging*. 2022;15:828–839.

46. Libby P, Pasterkamp G, Crea F, Jang I-K. Reassessing the mechanisms of acute coronary syndromes. *Circ Res*. 2019;124:150–160.

47. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med*. 2010;362:2155–2165.

48. Neumann JT, Goßling A, Sörensen NA, Blankenberg S, Magnussen C, Westermann D. Temporal trends in incidence and outcome of acute coronary syndrome. *Clin Res Cardiol*. 2020;109:1186–1192.

49. Pasterkamp G, den Ruijter HM, Libby P. Temporal shifts in clinical presentation and underlying mechanisms of atherosclerotic disease. *Nat Rev Cardiol*. 2017;14:21–29.

KEY WORDS acute coronary syndrome, atherosclerosis, cardiovascular risk factors, optical coherence tomography, vulnerable plaque

APPENDIX For a supplemental Methods section as well as supplemental tables and figures, please see the online version of this paper.

Go to https://www.acc.org/jacc-journals-cme to take the CME/MOC quiz for this paper.