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Original Article

Effect of smoking on culprit lesion plaque burden and composition in acute coronary syndrome: An intravascular ultrasound-virtual histology study

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1. Introduction

Cardiovascular diseases (CVDs) are the emerging epidemic and a prominent cause of mortality in developing countries.[1] Smoking and abnormal lipids are responsible for two-thirds of population attributable risk of acute myocardial infarction.[2] Smoking affects all phases of atherosclerosis from endothelial dysfunction to pro-thrombotic state. Impairment of vasomotor function, inflammation and oxidation of lipids are major mechanisms for initiation and progression of atherosclerosis which appear prior to the onset of structural and pathologic manifestations.[3–7] Smoking mainly leads to acute coronary events and less for the occurrence of stable angina.[8] Further, studies demonstrated a faster reversal in cardiovascular risk following smoking cessation as compared to reduction seen with cholesterol and blood pressure lowering drugs, which predominantly target atherosclerotic process.[9–11] Therefore, it is evident that thrombogenic effects of smoking predominate over gradual progressive atherosclerotic plaque formation.

Histopathological studies showed that smoking predisposes to coronary thrombosis and not associated with increase in plaque vulnerability.[12,13] However, the relationship between smoking and plaque vulnerability yielded contradictory results based on IVUS. There is an excellent correlation of virtual histology-intravascular ultrasound (VH-IVUS) with histopathology in identifying plaque components with accuracy of 87–96%.[14] The primary aim of the study was to ascertain and compare the coronary plaque features in the culprit lesions of smokers and non-smokers using VH-IVUS.

2. Materials and methods

The study was conducted at a tertiary care center in North India and was prospective observational study. Two hundred and twenty consecutive patients presenting with acute coronary syndrome (ACS) from November 2017 to October 2020 were included. Out of which 102 were current smokers (current smoking or stopped smoking within one month before enrollment) and 118 were non-smokers (never smokers). ST segment elevation myocardial infarction (STEMI) was defined as persistent chest pain atleast 30 min duration in combination with ST-segment elevation $\geq$0.1 mV in two contiguous leads on 12-lead electrocardiogram (ECG) along with a rise in cardiac enzymes. Non-ST segment elevation myocardial infarction (NSTEMI) was considered when chest pain of more than 20 min along with a rise and/or fall of cardiac biomarkers but no ST-segment elevation. Unstable angina was the presence of new onset or worsening angina with ECG changes and normal biomarkers. The culprit vessel and lesion was

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recognized based on the composite features of electrocardiogram, regional wall motion alteration on echocardiogram and angiography. The exclusion criteria were patients unwilling for revascularization, cardiogenic shock, Killip class III-IV, who had quit smoking for >1 month, tortuous coronaries, failure to pass the IVUS catheter, previous angioplasty and coronary bypass surgery. The risk factors for coronary artery disease and demographic variables were recorded. All patients provided informed and written consent in the study and ethical approval was obtained form the Institute Ethics committee. The principles outlined in the Declaration of Helsinki were adopted during the procedures.

2.1. IVUS procedure and analysis

Standard loading doses of aspirin, clopidogrel or prasugrel were administered to all patients prior to coronary intervention and imaging procedures through radial or femoral route. Intravascular imaging pull back was performed using a 20-MHz, 2.9 French, Eagle Eye® Platinum RX digital IVUS catheter (Eagle Eye, Philips Volcano, San Diego, CA, USA). Following administration of intracoronary nitroglycerine 200 mcg, motorized pull back at a speed 0.5 mm/s was initiated 15 mm distal to the lesion before any balloon predilatation, until the aorto-ostial junction. The IVUS-VH images analyzed offline by two independent investigators with no prior clinical information. All IVUS analysis was performed in accordance with standard recommendations.[15] IndecEchoplaque 4.3.12 J software (Indec Medical Systems, Inc., Santa Clara, CA, USA) was utilize for analysis. The near normal appearing cross-sectional images located within 10 mm distal and proximal to the lesion with no major intervening side branch were considered as the proximal and distal reference sites. The software detects the lumen and media-adventitia interface automatically and the results displayed. After measurement of the external elastic membrane (EEM) and lumen cross-sectional areas (CSA), EEM minus lumen CSA was the plaque and media (P&M) CSA. Plaque burden was plaque and media CSA/EEM CSA × 100. The image slice subtending largest EEM and P&M with smallest lumen CSA was the lesion site. The ratio of EEM CSA at lesion site divided by proximal and distal reference EEM CSA average value was the remodeling index. An index >1.05 (positive remodeling) and <0.95 (negative remodeling) was considered.[16] Volumetric IVUS and VH-IVUS analysis spanning a 10 mm segment centered at the minimal luminal area was measured by Simpson's rule. Virtual histology categorizes the color-coded tissue into four traits depicted as green (fibrous); yellow-green (fibro-fatty); white (dense calcium); and red (necrotic core).[17] The result of all analysis was displayed as absolute values and as plaque area or volume percentage.

2.2. Statistics

Descriptive statistics was undertaken for the studied variables. Mean ± standard deviation (SD) represented for the continuous variables and numbers or percentages for categorical variables. Shapiro–Wilk test for normality for continuous variables was performed. Categorical data were analyzed by Pearson's chi-square test and student's unpaired t-test for quantitative variables. Multiple linear regression analysis was performed to control the role of known confounding variables in relation between smoking and plaque characteristics. p value < 0.05 was considered significant for all analysis. SPSS version 21.0 (Chicago, IL, USA) was availed for the data analysis.

3. Results

3.1. Patient demographics and clinical features

Of the 220 ACS patients, 102 (46.3%) were smokers. The baseline clinical characteristics are listed in Table 1. Smokers were younger than non-smokers (47.9 ± 11.8 vs.54.2 ± 11.8 years, $p < 0.001$). Females were predominantly non-smokers. High prevalence of coexisting cardiovascular risk factors like DM (27.9% vs13.7%, $p = 0.01$) and hypertension (42.4% vs 17.6%, $p = 0.03$) was noted in non-smokers. STEMI was most frequent (80%) (Table 1).

3.2. Atherosclerotic burden and plaque composition

Triple vessel disease was common in non-smokers group ($p = 0.03$). Degree of atheroma as measured by plaque burden and volume was not different between the groups Smokers displayed a better positive vessel remodeling ($p = 0.04$) (Table 2).

The absolute area and percentage values of fibrous tissue at minimal luminal site (MLS) did not reveal any difference among the groups. Smokers had higher fibro-fatty relative percentage ($p = 0.03$) but no difference in the absolute volumes. The necrotic core (NC) and dense calcium (DC) absolute areas and percentage at MLS were higher in non-smokers ($p < 0.01$) (Fig. 1, Table 3). The above findings were similarly observed with absolute volumes.

3.3. Independent associations of demographics and cardiovascular risk factors on plaque burden and composition

There was no effect of age on plaque burden and volume except that older patients had a greater DC volume ($p = 0.04$). Females showed a negative association with plaque burden and volume. Gender had no association with either NC or DC composition. Low-

Table 1
Demographic and clinical characteristics.

Variable	Smokers ($n = 102$)	Non-smokers ($n = 118$)	P
Age (years)	47.9 ± 11.8	54.2 ± 11.8	<0.001
Men/women	100/2	79/39	<0.001
Diabetes	14 (13.7%)	33 (27.9%)	0.01
Hypertension	18 (17.6%)	50 (42.4%)	0.03
F/H/O CAD	19 (18.6%)	31 (26.3%)	0.17
TC (mg/dl)	159.6 ± 46.8	151 ± 55.9	0.23
TG (mg/dl)	153.2 ± 98.1	132.3 ± 54.0	0.05
HDL (mg/dl)	37.3 ± 17.9	38.4 ± 13.4	0.63
LDL (mg/dl)	97.4 ± 43.4	93.8 ± 51.3	0.59
BMI (kg/m2)	24.7 ± 3.9	24.7 ± 6.2	0.93
LVEF (%)	46.4 ± 9.6	45.9 ± 9.3	0.76
STEMI	79 (77.5%)	97 (82.2%)	0.40
NSTEMI	11 (10.8%)	12 (10.2%)	0.90
UA	11 (10.8%)	9 (7.6%)	0.42
SVD	80 (78.4%)	79 (66.9%)	0.06
DVD	20 (19.6%)	29 (19.6%)	0.40
TVD	2 (2%)	10 (8.5%)	0.03
Drugs at admission			
Antiplatelets	1 (1%)	5 (4.2%)	0.14
ACE/ARB inhibitors	6 (5.8%)	26 (22%)	<0.001
Beta blockers	8 (7.8%)	21 (17.7%)	0.03
Statins	1 (1%)	3 (3%)	0.2
Nitrates	1 (0.01%)	3 (2.5%)	0.2
OHA	13 (13%)	31 (26%)	0.12
Insulin	1 (1%)	3 (2.5%)	0.15

F/H/O: family history, CAD: coronary artery disease, BMI: Body mass index, TC: Total Cholesterol, TG: Triglyceride, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein, LVEF: left ventricular ejection fraction, SVD: single vessel disease, DVD: double vessel disease, TVD: triple vessel disease, OHA: oral hypoglycemic agent, Data represented as mean ± standard deviation or number (%).

Table 2
Grey-scale IVUS parameters.

Variable	Smokers ($n = 102$)	Non-smokers ($n = 118$)	*P*
Lesion Length (mm)	27.2 ± 11.7	27.7 ± 12.05	0.75
Proximal reference			
Lumen CSA (mm^2)	9.37 ± 2.7	9.2 ± 3.2	0.77
EEM CSA (mm^2)	13.9 ± 3.7	14.5 ± 4.4	0.24
Plaque burden (%)	31.9 ± 10.4	35.6 ± 12.6	0.01
Distal reference			
Lumen CSA (mm^2)	6.4 ± 1.9	6.0 ± 1.8	0.15
EEM CSA (mm^2)	11.5 ± 2.8	11.9 ± 3.3	0.51
Plaque burden (%)	29.5 ± 11.2	32.0 ± 13.5	0.006
Average lumen CSA (mm^2)	7.9 ± 1.9	7.6 ± 2.11	0.33
Average EEM CSA (mm^2)	11.5 ± 2.8	11.9 ± 3.3	0.30
Lesion parameters			
MLD (mm)	1.6 ± 0.12	1.5 ± 0.10	0.04
Lumen CSA (mm^2)	2.7 ± 0.70	2.5 ± 0.50	0.002
EEM CSA (mm^2)	14.4 ± 3.7	14.0 ± 3.3	0.40
Plaque area (mm^2)	11.7 ± 3.4	11.5 ± 3.15	0.74
Area stenosis (%)	63.6 ± 10.7	65.5 ± 11.3	0.10
Plaque burden (%)	80.1 ± 5.5	79.5 ± 13.5	0.66
RI	1.3 ± 0.2	1.2 ± 0.2	0.04
Plaque volume (mm^3)	98.9 ± 32.1	101.1 ± 32.6	0.63

CSA: cross section area, EEM: external elastic membrane, MLD: minimal luminal diameter, RI: remodeling index.

density lipoprotein cholesterol (LDL-C) had a positive correlation with DC content ($p = 0.02$). DM and hypertension were not independently associated with atheroma or plaque composition (Table 4 and 5) (supplementary material, table 6).

3.4. Reproducibility of IVUS parameters

Intraobserver variability was analyzed by IVUS pullback twice by the same person at an interval of 3 months. Interobserver variability was assessment undertaken by two separate individuals. The intraclass correlation coefficient of plaque burden 0.94 (95% confidence interval (CI) 0.87–0.97); plaque volume was 0.92 (95% CI 0.8–0.96) and interclass coefficient of plaque burden 0.90 (95% CI 0.78–0.94); for plaque volume 0.84 (95% CI 0.72–0.91). The intraclass coefficient of necrotic core volume was 0.94 (95% CI0.9-0.97) and interclass coefficient of 0.82 (95% CI0.7–0.9). Rest of the average measurements of VH-IVUS parameters has coefficients within 95% CI suggestive of acceptable consistency.

4. Discussion

The salient findings of the present study were a) smoking did not affect the culprit lesion plaque burden and plaque vulnerability in ACS by intravascular ultrasound and virtual histology b) smoking was associated with better adaptive vascular remodeling.

4.1. Impact of smoking on plaque burden and vessel remodeling

With regard to extent of coronary artery disease, single vessel involvement constituted 78.4% and triple vessel disease in 2% of smokers. Our findings are substantiated by prior angiographic studies with documentation of less extensive coronary artery disease and fewer lesions in smokers.[18,19] Plaque burden and plaque volume representing the degree of atherosclerosis were not different between the groups. In line with our findings, Kornowski et al. demonstrated similar plaque burden and vessel lumen areas in smokers and non-smokers.[20] Moreover histopathological studies and clinical trials on thrombolytic therapy had demonstrated that smoking promotes coronary thrombosis with less residual atherosclerosis.[12,18,21–23] These findings support the hypothesis that the smoking predisposes to thrombosis against a background of less pre-existing atherosclerosis with endothelial dysfunction and prothrombotic state being the important mechanisms leading to ACS.[24,25]

Positive vessel remodeling was noted in both groups with better adaptive response in smokers. Previous IVUS studies in smokers with stable angina demonstrated negative remodeling.[26,27] However, positive remodeling in our study could be explained by the exclusive inclusion of ACS and less calcium content in smokers. Remodeling is directly correlated to inflammation and inversely to calcium.[28] The stability of the plaque is related to the higher calcium content and is observed in negatively remodeled lesions.[29] Thus, presence of inflammation and lesser calcium in the smokers would yield better adaptive remodeling.

4.2. Impact of smoking on plaque vulnerability

The pathophysiological mechanisms underlying ACS is are mainly plaque rupture or erosion. The larger necrotic core with a thin fibrous cap is an important feature of unstable or rupture prone plaques leading to thrombosis when necrotic tissue exposed to blood stream after rupture.[30] In the present study, there was no association with smoking and necrotic core area or volumes. With regard to plaque composition, previous studies yielded contradictory results in smokers. Bolorunduro et al, in a retrospective study in patients with ACS and stable angina revealed increased NC in smokers ($p = 0.01$).[31] In contrary, Buljubasic et al. demonstrated no association of smoking with NC or thin cap fibroatheroma lesions in non-culprit coronary artery lesions.[32] Similarly our study revealed no relation of smoking with plaque burden and plaque vulnerability in culprit lesions in ACS. Further the international virtual histology registry too demonstrated that in stable angina, smoking was not associated with a specific plaque composition in the studied population.[33] Histopathological studies on sudden cardiac death patients had higher propensity of plaque erosions in smokers and found no association of smoking with number of vulnerable plaques.[12,13,34] Optical coherence tomography (OCT) imaging studies too demonstrated plaque erosions more frequent in smokers.[35,36] PROSPECT study showed that high-risk lesions were characterized by combination of higher necrotic core, large plaque burden (>70%) and small luminal area (<4.5 mm^2).[37] The paradoxical effect of smoking on extent of atherosclerosis and plaque vulnerability; support the possibility that endothelial dysfunction,

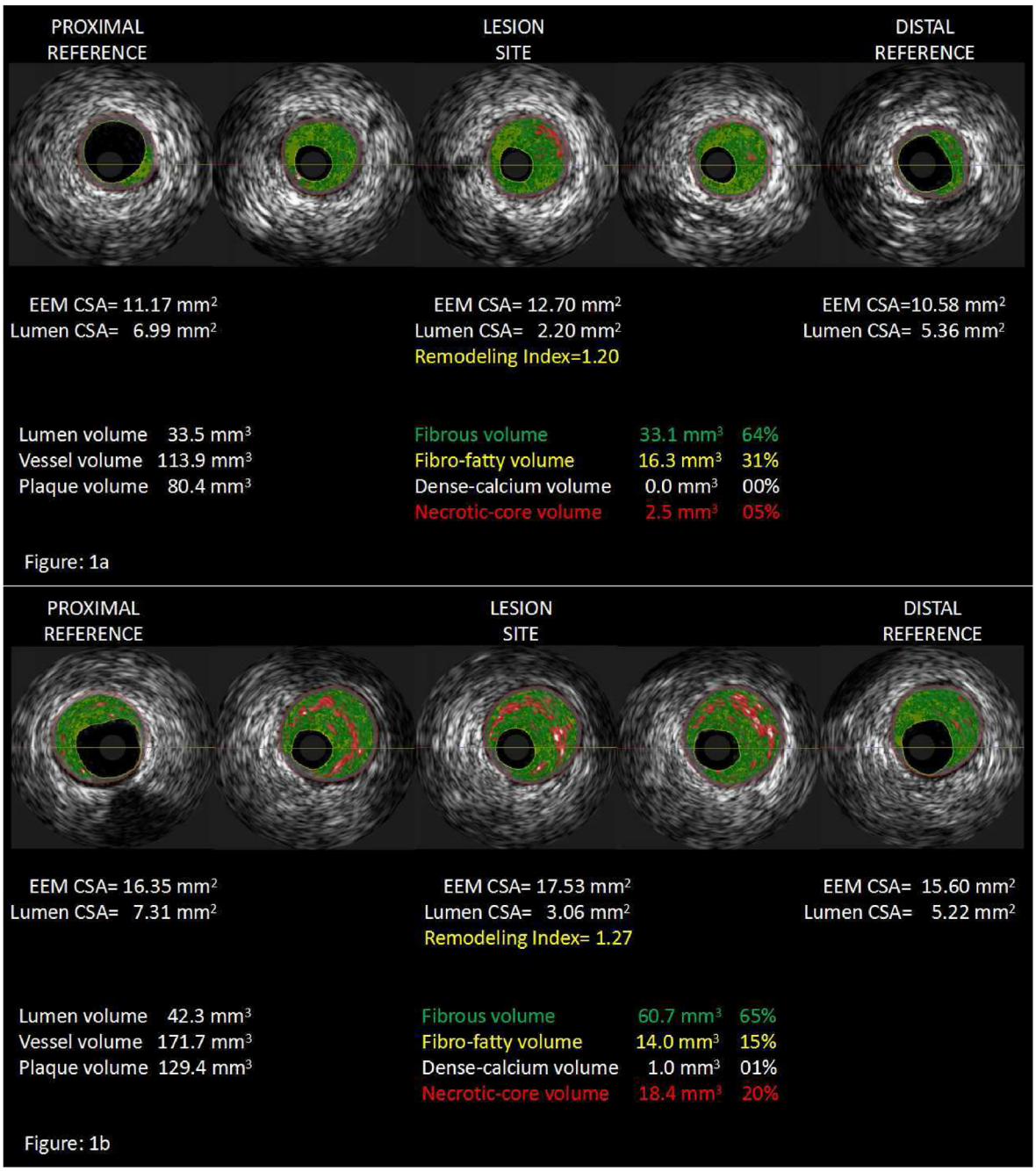

Fig. 1. Cross-sectional image on virtual histology (VH) intravascular ultrasound (IVUS) from distal to proximal in same lesion in smoker and never smoker (Fig. 1a and Fig. 1b). Images in non-smokers (Fig. 1b) shows large amount of necrotic core area. EEM: external elastic membrane, CSA: cross sectional area.

exaggerated inflammatory state and prothrombotic state may contribute to acute coronary events.

4.3. Impact of other cardiovascular risk factors on plaque burden and vulnerability

Prior studies have shown that coexisting cardiovascular risk factors are less frequent in smokers as compared to non-smokers and are in line with our findings.[38] The present study did not find any independent association between plaque burden and composition with risk factors like diabetes, hypertension and hyperlipidemia. The absence of the difference could be appertained that diabetic patients had good glycemic control and few patients on insulin therapy. The average values of total cholesterol and LDL were within normal limits with TC/HDL ratio <5. Furthermore, pathological studies on men with sudden cardiac death demonstrated that high-risk coronary lesions were not independently associated with diabetes, hypertension or age.[12] So, the above findings support the concept that the atherosclerotic plaque progression and plaque vulnerability may be influenced by complex mutual interaction of multiple factors like body mass index, dyslipidemia, metabolic syndrome, apart from hypertension and diabetes.

Table 3
Virtual Histology- IVUS parameters.

Variable	Smokers ($n = 102$)	Non-smokers($n = 118$)	*P*
Minimal luminal site			
Fibrous area (mm^2)	5.1 ± 2.1	5.1 ± 1.8	0.94
Fibro-fatty area (mm^2)	2.6 ± 1.5	2.4 ± 1.4	0.12
Necrotic core area (mm^2)	0.7 ± 0.6	0.9 ± 0.7	0.004
Dense calcium area (mm^2)	0.1 ± 0.2	0.2 ± 0.3	0.008
Fibrous tissue (%)	60.2 ± 9.8	60.3 ± 8.5	0.87
Fibro-fatty (%)	30.4 ± 12.6	26.9 ± 11.6	0.04
Necrotic core (%)	7.7 ± 6.1	10.5 ± 6.9	0.003
Dense calcium (%)	1.3 ± 2.4	2.1 ± 3.2	0.04
Maximum necrotic core site			
Fibrous area (mm^2)	4.62 ± 2.10	4.64 ± 1.54	0.95
Fibro-fatty area (mm^2)	1.87 ± 1.25	1.64 ± 1.05	0.13
Necrotic core area (mm^2)	1.1 ± 0.8	1.3 ± 0.7	0.03
Dense calcium area (mm^2)	0.2 ± 0.3	0.3 ± 0.3	0.03
Fibrous tissue (%)	59.85 ± 9.16	58.99 ± 7.91	0.45
Fibro-fatty (%)	23.63 ± 11.54	20.15 ± 9.87	0.02
Necrotic core (%)	14.3 ± 7.8	17.1 ± 7.5	0.008
Dense calcium (%)	2.3 ± 3.2	3.5 ± 3.4	0.006
Segment analysis			
Fibrous vol. (mm^3)	41.4 ± 16.8	42.6 ± 15.9	0.60
Fibro-fatty vol. (mm^3)	21.3 ± 12.1	20.2 ± 12.4	0.50
Necrotic core vol. (mm^3)	5.3 ± 4.3	7.0 ± 4.7	0.006
Dense calcium vol. (mm^3)	0.90 ± 1.3	1.6 ± 1.8	0.001
Fibrous tissue (%)	60.4 ± 7.3	60.2 ± 6.7	0.80
Fibro-fatty (%)	30.5 ± 9.5	27.7 ± 9.9	0.03
Necrotic core (%)	7.6 ± 5.1	9.9 ± 5.9	0.003
Dense calcium (%)	1.3 ± 2.1	2.4 ± 2.8	0.001
NC/DC	12.5 ± 12.6	9.6 ± 13.05	0.13

Vol: volume, NC/DC: necrotic core/dense calcium.

Table 4
Multivariate Predictors of grey-scale IVUS parameters.

Variable	Plaque volume		Lumen CSA at MLS		Plaque burden at MLS		RI	
	B coefficient	*P*	B coefficient	*P*	B coefficient	*P*	B coefficient	*P*
Age	0.09	0.67	−0.007	0.06	0.06	0.07	0.00	0.85
Sex	−23.9	0.004	0.17	0.22	−3.14	0.01	0.11	0.05
BMI	0.12	0.82	0.001	0.94	0.06	0.45	0.009	0.02
DM	−0.72	0.91	−0.30	0.01	1.29	0.21	0.05	0.26
HTN	2.62	0.67	0.02	0.85	−0.28	0.77	−0.03	0.45
Smoking	−10.4	0.09	0.22	0.05	−2.21	0.02	0.10	0.02
LDL	−0.08	0.14	−0.001	0.56	0.01	0.24	0.00	0.67

DM: diabetes, HTN: hypertension, BMI: body mass index, LDL: Low-density lipoprotein, MLS: minimal luminal site, CSA: cross-section area, RMI: remodeling index, B-coefficient: unstandardized coefficient, Associations tested by multiple linear regression analysis.

Table 5
Multivariate Predictors of VH-IVUS parameter-necrotic core.

Variable	Necrotic core vol		Necrotic area at MLS		Necrotic area at Max. NCS	
	B coefficient	*P*	B coefficient	*P*	B coefficient	*P*
Age	0.01	0.53	0.004	0.40	0.01	0.04
Sex	−1.7	0.09	−0.11	0.48	−0.41	0.02
BMI	0.09	0.20	0.02	0.10	0.01	0.33
DM	0.02	0.98	−0.02	0.84	−0.08	0.58
HTN	1.1	0.17	0.10	0.37	0.17	0.20
smoking	−1.0	0.19	−0.16	0.17	−0.14	0.29
LDL	0.008	0.25	0.002	0.07	0.002	0.11

MLS: minimal luminal site, Max. NCS: Maximum necrotic core site, B-coefficient: unstandardized coefficient, Associations tested by multiple linear regression analysis.

4.4. Effect of smoking on cardiovascular risk and benefits of smoking cessation

A systemic review of 20 studies demonstrated a 36% relative risk reduction of mortality in patients who quit smoking in comparison to continued smoking.[39] Quitting smoking before 40 years of age decreases the cardiovascular deaths associated with smoking continuation by about 90%.[40] The results of the present study indirectly supports the concept that rather than gradual atherosclerotic progression and plaque vulnerability in smokers, other mechanisms involving vasomotor function and prothrombotic state might play a key role in acute cardiovascular events. Therefore, underscores the importance of smoking cessation leading to reversal of the early pathophysiological effects and in a complete manner after certain time period.

5. Limitations

This study was a mono-centric observational study. The dose response relationship of smoking with plaque burden and vulnerability couldn't be studied, as there was no data regarding quantity and duration of smoking. A further limitation in the study was the lack of assessment of biomarkers of inflammation like hs-CRP. The misinterpretation of thrombus as fibrous/fibro fatty traits on the VH-IVUS is an important inherent limitation.

6. Conclusion

The association of smoking with plaque burden and plaque vulnerability couldn't be demonstrable in this IVUS-VH study in patients with ACS. Smokers have better vascular remodeling.

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Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2021.09.005.

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