Journal of Thrombosis and Thrombolysis (2020) 49:352–359
https://doi.org/10.1007/s11239-019-01969-9

Relative risk of plaque erosion among different age and sex groups in patients with acute coronary syndrome

Hyung Oh Kim[1] · Chong Jin Kim[2] · Weon Kim[2] · Jin-Man Cho[2] · Tsunenari Soeda[3] · Masamichi Takano[4] · Bryan P. Yan[5] · Filippo Crea[6] · Giampaolo Niccoli[6] · Rocco Vergallo[6] · Yoshiyasu Minami[7] · Takumi Higuma[8] · Shigeki Kimura[9] · Niklas Frederik Boeder[10] · Holger Nef[10] · Tom Adriaenssens[11] · Osamu Kurihara[1] · Vikas Thondapu[1] · Michele Russo[1] · Erika Yamamoto[1] · Tomoyo Sugiyama[1] · Hang Lee[12] · Tsunekazu Kakuta[13] · Taishi Yonetsu[14] · Ik-Kyung Jang[1,2]

Published online: 9 October 2019

Abstract

Postmortem studies reported plaque erosion is frequent in young women. Recent in vivo studies failed to show age and sex differences in the plaque erosion prevalence. The aim of this study was to investigate the prevalence of plaque erosion by age and sex among acute coronary syndromes (ACS) patients. From 1699 ACS patients, 1083 with plaque erosion or rupture were analyzed. Patients were categorized as 5 age groups (≤ 50, 51–60, 61–70, 71–80, ≥ 81 years). Overall prevalence of plaque erosion was similar between males and females ($p = 0.831$). Males age ≤ 50 had higher ($p = 0.018$) and age 71–80 had lower ($p = 0.006$) prevalence of plaque erosion. Females age 61–70 had higher ($p = 0.021$) and age 71–80 had lower ($p = 0.045$) prevalence of plaque erosion. In advanced age groups (≥ 71 years), rupture was the dominant etiology in both sexes. In multivariate analysis of males, age ≤ 50 demonstrated a trend to increase (OR 1.418, 95% CI 0.961–2.093, $p = 0.078$) the erosion risk. Females age ≤ 70 independently increased (OR 2.138, 95% CI 1.249–3.661, $p = 0.006$) the risk for erosion. The prevalence of plaque erosion was similar between males and females. Plaque erosion risk was increased in the males age ≤ 50 and in the females age ≤ 70 among ACS patients.

Keywords Acute coronary syndrome · Sex · Aging · Plaque erosion

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11239-019-01969-9) contains supplementary material, which is available to authorized users.

✉ Taishi Yonetsu
t-yonetsu.cvm@tmd.ac.jp

✉ Ik-Kyung Jang
ijang@mgh.harvard.edu

1 Cardiology Division, Massachusetts General Hospital, Harvard Medical School, GRB 800, 55 Fruit Street, Boston, MA 02114, USA

2 Department of Cardiovascular Medicine, Kyung Hee University, Seoul, South Korea

3 Department of Cardiovascular Medicine, Nara Medical University, Kashihara, Nara, Japan

4 Cardiovascular Center, Nippon Medical School Chiba Hokusoh Hospital, Inzai, Chiba, Japan

5 Division of Cardiology, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Sha Tin, Hong Kong

6 Department of Cardiovascular and Thoracic Science, Catholic University of the Sacred Heart, Rome, Italy

7 Department of Cardiovascular Medicine, Kitasato University School of Medicine, Sagamihara, Kanagawa, Japan

8 Division of Cardiology, St. Marianna University School of Medicine, Kawasaki, Kanagawa, Japan

9 Division of Cardiology, Kameda Medical Center, Kamogawa, Chiba, Japan

10 Department of Cardiology, University of Giessen, Giessen, Germany

11 Department of Cardiovascular Medicine, University Hospitals Leuven, Louvain, Belgium

12 Division of Biostatistics, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

13 Department of Cardiovascular Medicine, Tsuchiura Kyodo General Hospital, Tsuchiura, Ibaraki, Japan

14 Department of Interventional Cardiology, Tokyo Medical and Dental University, 1-5-45, Yushima, Bunkyo Ward, Tokyo 113-8519, Japan

Highlights

- The prevalence of plaque erosion relative to plaque rupture was compared among each age and sex group in acute coronary syndrome (ACS) patients.
- Plaque erosion was the predominant pathology of ACS in the males age ≤ 50 and in the females age 61–70.
- Plaque rupture became predominant in both sex groups when they reached age 71–80.
- Sex and age factor may be used to predict the likelihood of plaque erosion, but future validation study will be required for clinical application.

Introduction

Major underlying mechanisms for acute coronary syndromes (ACS) include plaque rupture and plaque erosion [1]. Plaque rupture involves disruption of a thin fibrous cap with exposure of thrombogenic substrates to circulating blood, resulting in local thrombosis. Unlike plaque rupture in which inflammation plays a key role, the underlying mechanism for plaque erosion is less well understood. It is thought to be related to activation of Toll-like receptor-2 (TLR2), which leads to endothelial damage and denudation and subsequent formation of neutrophil extracellular traps (NETs) [2]. Several previous autopsy studies showed younger age in erosion cases compared to rupture cases [3, 4]. Most autopsy studies demonstrated a higher female proportion in erosion cases compared to ruptures [3–5]. However, several in vivo studies reported similar average age and sex distribution between plaque erosion and rupture patients [6, 7]. Plaque erosion, compared to plaque rupture, is more common in non-ST segment elevation ACS than in ST segment elevation myocardial infarction [8].

Although direct comparison of prognosis between plaque rupture and plaque erosion has not been conducted, plaque erosion was shown to be feasible for non-stent treatment, unlike plaque rupture [9]. At present, studies for relative risk of plaque erosion in ACS patients of different age group were limited. Thus, information to estimate the relative risk of plaque erosion in ACS patients of certain age group may be useful for clinicians. Patients were divided into five groups based on the age at the time of the procedure (≤ 50, 51–60, 61–70, 71–80, ≥ 81 years). The aim of the current study was to study the relative risk of plaque erosion among different age and sex groups in patients presented with ACS.

Methods

The data used in this study is from the "Identification of Predictors for Coronary Plaque Erosion in Patients with Acute Coronary Syndrome study" database [NCT03479723] which consists optical coherence tomography (OCT) images of 1518 ACS cases. Exclusion criteria for the current study were (1) poor OCT image quality, (2) calcified nodules at the culprit lesion, and (3) insufficient clinical data. The study was approved by the Institutional Review Board at each participating site. The participants gave written informed consent.

Angiographic characteristics were analyzed by Cardiovascular Angiography Analysis System (Pie Medical Imaging B.V., Maastricht, the Netherlands). Single culprit lesion identified with OCT imaging in each case was included in the current study. Underlying pathobiology of ACS was identified by using either frequency-domain OCT systems (C7/C8 ILUMIEN OCT Intravascular Imaging Systems, St. Jude Medical, St. Paul, Minnesota) or time-domain OCT systems (M2/M3 Cardiology Imaging System, St. Jude Medical, Westford, Massachusetts) during the time of coronary angiography. Preprocedural thrombectomy was performed based on the operator's discretion before the OCT procedure. All angiographic and OCT images were submitted to the Cardiology Laboratory for Integrative Physiology and Imaging (CLIPI) at Massachusetts General Hospital and were analyzed by investigators blinded to patients' data. Plaque erosion was defined according to the absence of fibrous cap disruption with attached thrombus overlying a plaque [10]. Plaque rupture was defined when there was a presence of fibrous cap discontinuity with a clear cavity formed inside [10]. Each case was assigned to either plaque erosion or plaque rupture by OCT imaging interpretation. The representative plaque erosion and plaque rupture OCT images are illustrated in Supplementary Fig. 1. Quantitative and qualitative OCT profiles were analyzed by current consensus [11].

Patients were divided into five groups based on the age at the time of the procedure (≤ 50, 51–60, 61–70, 71–80, ≥ 81 years). The prevalence of plaque erosion relative to plaque rupture was compared among each age group and between the sexes. Regression analysis was performed for each sex population to assess plaque erosion risk of the specific age group compared to the rest of the population. Multivariate analysis to determine independent risk factors was performed after the univariate analysis to see if a specific age threshold for each sex group is effective to predict plaque erosion, along with traditional cardiovascular risk factors. The age thresholds for each sex group were set according to the erosion predominant age for each group.

Categorical variables were presented as numbers and proportions and were compared using chi square test or Fisher's exact test as appropriate. Continuous variables were presented as means and standard deviations when normally distributed, and medians and interquartile ranges when nonnormally distributed, with comparing using a standardized *T* test or one-way analysis of variance. Factors with $p < 0.05$ in univariate regression analysis were

included in the multivariate regression model. A two-tailed $p < 0.05$ was considered significant. All statistical analyses were performed using SPSS 23.0 (SPSS, Inc, Chicago, IL).

Results

Among 1699 ACS patients, 458 patients were excluded due to poor OCT image quality, 157 due to calcified nodule at the culprit lesion, and one due to no age data. Therefore, 1083 cases (855 male, 228 female) were included in the analysis (Fig. 1). The time domain OCT system was used in 22.2% of male patients and 18.9% of female patients ($p = 0.272$).

Baseline characteristics, laboratory findings, and medication history according to different sex groups are summarized in Table 1. Male patients were younger, more frequently current smokers, and had less hypertension. Laboratory findings of male patients showed higher levels of hemoglobin and triglyceride, and lower levels of total cholesterol and high-density lipoprotein (HDL) cholesterol, compared to those of females. Baseline characteristics, laboratory findings, and medication history according to different age groups are summarized in Supplementary Table 1. Dyslipidemia and current smoking were most frequent in the age ≤ 50 group. Hypertension and chronic kidney disease were most frequent in the age ≥ 81 group. Angiographic and OCT characteristics according to different sex groups are summarized in Supplementary Table 2. The female group showed more frequent calcium on OCT, compared to the male group.

The proportion of erosion and rupture was similar in both sex groups ($p = 0.831$) (Fig. 2a). Prevalence of plaque erosion and rupture was compared in each age group. In the whole population, the age ≤ 50 group had higher ($p = 0.008$), and the age 71–80 group had lower ($p < 0.001$) prevalence of erosion (Fig. 2b). In male patients, the age ≤ 50 group had higher ($p = 0.018$) and the age 71–80 group had lower ($p = 0.006$) prevalence of erosion (Fig. 2c). In female patients, the age 61–70 group had higher ($p = 0.021$), and the age 71–80 group had lower ($p = 0.045$) prevalence of erosion (Fig. 2d).

In the whole population, the odd ratio for erosion was increased in the age ≤ 50 group (OR 1.587, 95% CI 1.127–2.236, $p = 0.008$) and decreased in the age 71–80 group (OR 0.614, 95% CI 0.462–0.815, $p < 0.001$). In males, the odd ratio for erosion was increased in the age ≤ 50 group (OR 1.540, 95% CI 1.074–2.208, $p = 0.019$) and decreased in the age 71–80 group (OR 0.629, 95% CI 0.451–0.876, $p = 0.006$). In females, the odd ratio for erosion was increased in the age 61–70 group (OR 1.970, 95% CI 1.101–3.526, $p = 0.022$) and decreased in the age 71–80 group (OR 0.566, 95% CI 0.323–0.991, $p = 0.046$) (Fig. 3).

Regression analysis to find risk factors for plaque erosion is summarized in Table 2. In univariate analysis of males, age ≤ 50 increased (OR 1.610, 95% CI 1.105–2.346, $p = 0.013$), and hypertension (OR 0.718, 95% CI 0.544–0.948, $p = 0.019$), diabetes (OR 0.674, 95% CI 0.501–0.908, $p = 0.009$), chronic kidney disease (OR 0.544, 95% CI 0.369–0.801, $p = 0.002$) decreased the risk of plaque erosion. In univariate analysis of females, age ≤ 70 increased (OR 2.216, 95% CI 1.299–3.780, $p = 0.004$) the risk of plaque erosion. In multivariate analysis of males, diabetes mellitus (OR 0.716, 95% CI 0.529–0.970, $p = 0.031$) and chronic kidney disease (OR 0.607, 95% CI 0.409–0.900, $p = 0.013$) decreased the risk for plaque erosion. Although the statistical significance was not met, age ≤ 50 in males demonstrated a trend to increase (OR 1.418, 95% CI 0.961–2.093, $p = 0.078$) the erosion risk. In multivariate

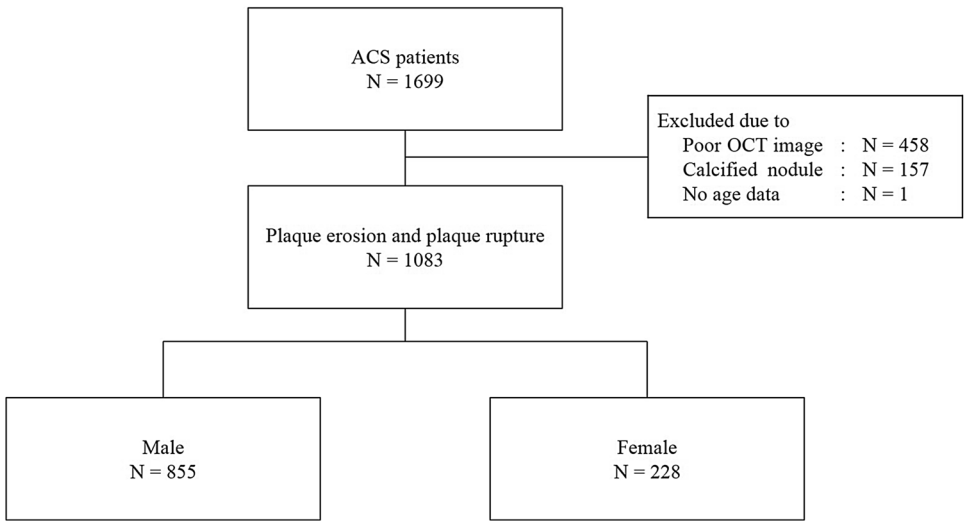


Fig. 1 Study flowchart. From 1699 ACS patients, 458 were excluded due to poor quality OCT images, 157 patients due to calcified nodule at the culprit lesion, 1 patient due to no age data. Therefore, 1083 patients (855 male, 228 female) were included in the analysis. *ACS* acute coronary syndrome, *OCT* optical coherence tomography

Table 1 Baseline characteristics and lab findings according to different sex groups

	Male (N = 855)	Female (N = 228)	p value
Baseline characteristics			
Age, years	63 (54–72)	71 (63–77)	< 0.001
Pathology			0.831
Plaque erosion	378 (44.2)	99 (43.4)	
Plaque rupture	477 (55.8)	129 (56.6)	
Type of ACS			0.078
Myocardial infarction	734 (85.8)	185 (81.1)	
Unstable angina pectoris	121 (14.2)	43 (18.9)	
Hypertension	526 (61.5)	157 (68.9)	0.041
DM	261 (30.5)	69 (30.3)	0.939
Dyslipidemia	604 (70.6)	167 (73.2)	0.441
CKD	137 (16.0)	28 (12.3)	0.162
Current smoking	395 (46.2)	54 (23.7)	< 0.001
Previous MI	65 (7.6)	10 (4.4)	0.089
Previous PCI	81 (9.5)	15 (6.6)	0.172
Preprocedural thrombectomy	364 (42.6)	95 (41.7)	0.134
Number of diseased vessel			0.121
1 vessel	520 (62.7)	150 (67.9)	
2 vessels	221 (26.6)	57 (25.8)	
3 vessels	89 (10.7)	14 (6.3)	
Lab findings			
Hemoglobin, g/dL	14.4 (± 1.6)	12.9 (± 1.5)	< 0.001
Total cholesterol, mg/dL	177 (± 62)	190 (± 62)	0.008
LDL cholesterol, mg/dL	117 (± 50)	121 (± 53)	0.238
HDL cholesterol, mg/dL	42 (± 17)	49 (± 17)	< 0.001
Triglyceride, mg/dL	119 (± 107)	100 (± 70)	0.014
Creatinine, mg/dL	0.74 (± 0.40)	0.63 (± 0.35)	0.054
Hemoglobin A1C, %	6.8 (± 2.4)	6.6 (± 2.1)	0.384
Troponin I, ng/mL	4.5 (± 14.3)	7.1 (± 19.0)	0.222

Values are expressed as median (IQR), mean (SD) and number (%)

CKD chronic kidney disease, *DM* diabetes mellitus, *HDL* high-density lipoprotein, *IQR* interquartile range, *LDL* low-density lipoprotein, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *SD* standard deviation

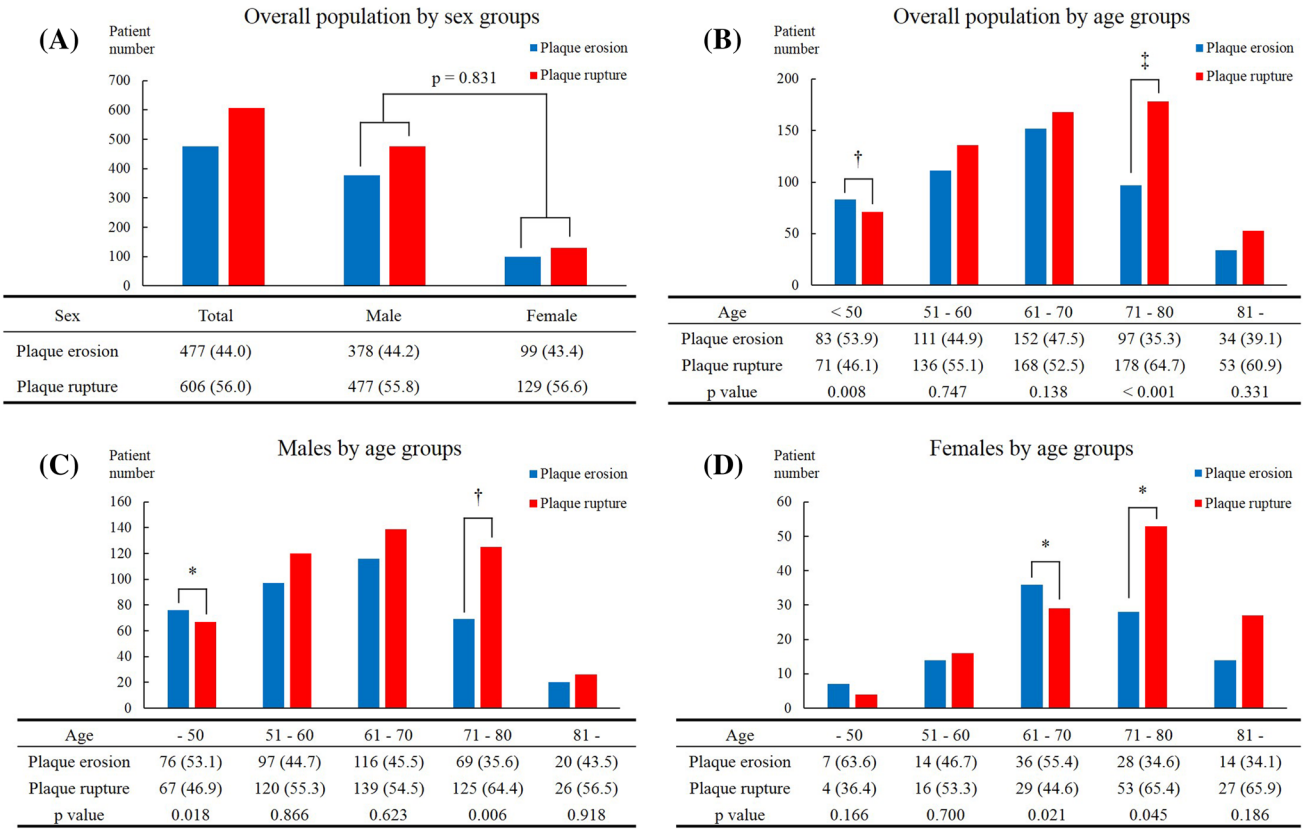
analysis of females, age ≤ 70 increased (OR 2.138, 95% CI 1.249–3.661, p = 0.006) the erosion risk.

Discussion

So far, no study specifically focused on the prevalence of erosion in relation to different age groups. Plaque erosion was the predominant pathology in the males age of ≤ 50 and in the females age of 61–70. Plaque rupture became predominant in both sex groups when they reach age of 71–80.

In this study, the proportion of plaque erosion in relation to plaque rupture is higher in the younger age groups. Libby et al. proposed "two hit hypothesis" for the development of plaque erosion, which is independent from chronic vascular inflammation [2]. (1) The 'first hit' consists of initial endothelial injury mediated by TLR2 expression from local blood flow perturbation. (2) The 'second hit' involves locally recruited granulocytes near injured intimal surface by chemokines, undergoing a specialized cell death forming NETs which promote thrombosis. The chronic inflammation independent mechanism of plaque erosion represents the earlier stages of atherosclerosis. On the other hand, plaque rupture develops at the advanced stage of atherosclerosis [12].

The prevalence of plaque rupture was significantly higher in the age groups 71–80 and ≥ 81 years. Current understanding is that atherosclerosis is an inflammatory process [13]. It has been reported that bone marrow-derived progenitor cells suppress inflammatory insult to the endothelium so that arterial homeostasis is maintained. However, aging could



Sex	Total	Male	Female
Plaque erosion	477 (44.0)	378 (44.2)	99 (43.4)
Plaque rupture	606 (56.0)	477 (55.8)	129 (56.6)

Age	< 50	51 - 60	61 - 70	71 - 80	81 -
Plaque erosion	83 (53.9)	111 (44.9)	152 (47.5)	97 (35.3)	34 (39.1)
Plaque rupture	71 (46.1)	136 (55.1)	168 (52.5)	178 (64.7)	53 (60.9)
p value	0.008	0.747	0.138	< 0.001	0.331

Age	- 50	51 - 60	61 - 70	71 - 80	81 -
Plaque erosion	76 (53.1)	97 (44.7)	116 (45.5)	69 (35.6)	20 (43.5)
Plaque rupture	67 (46.9)	120 (55.3)	139 (54.5)	125 (64.4)	26 (56.5)
p value	0.018	0.866	0.623	0.006	0.918

Age	- 50	51 - 60	61 - 70	71 - 80	81 -
Plaque erosion	7 (63.6)	14 (46.7)	36 (55.4)	28 (34.6)	14 (34.1)
Plaque rupture	4 (36.4)	16 (53.3)	29 (44.6)	53 (65.4)	27 (65.9)
p value	0.166	0.700	0.021	0.045	0.186

Fig. 2 Prevalence of plaque erosion and plaque rupture. Prevalence of plaque erosion (blue) and plaque rupture (red) was compared. **a** Males and females had similar proportions of plaque erosion. **b** In the overall population, patients of age ≤ 50 had higher and patients of age 71–80 had a lower prevalence of plaque erosion. **c** In males, patients of age ≤ 50 had higher and patients of age 71–80 had a lower prevalence of plaque erosion. **d** In females, patients of age 61–70 had higher and patients of age 71–80 had a lower prevalence of plaque erosion. Values are expressed as number (%). Percentages are calculated based on sex (**a**) and age (**b–d**) groups.*p < 0.05, †p < 0.01, ‡p < 0.001

impair the function of these cells, resulting in the progression of atherosclerosis [14]. Another possible hypothesis is the shortening of telomere length with aging. As telomeres shorten, telomere-dependent senescence and apoptosis occur, therefore secretion of proinflammatory cytokines promote atherosclerosis [15].

In females, the predominant mechanism of ACS abruptly changes from erosion to rupture between 60 and 70′s. Estrogen is atheroprotective, because of its vasodilatory, anti-inflammatory and sympathetic tone decreasing effects [16]. Testosterone increases monocyte adhesion to endothelial cells with vascular cell adhesion molecule-1 [17] and associated with increased accumulation of body fat by down-regulation of hormone-sensitive lipase or upregulation of phosphodiesterase-3B [18]. An animal study reported the permissive role of testosterone in vascular dysfunction and hypertension through the renin-angiotensin system [19]. Therefore, testosterone promotes atherosclerosis. Sex hormone binding globulin (SHBG) is known to antagonize testosterone with decreasing the bioavailable form of testosterone [20]. After physiologic menopause, the level of estrogen and SHBG is decreased, and testosterone is relatively maintained in females [21]. In this endocrinologic environment, the protective effects of estrogen and SHBG for advanced atherosclerosis complication may be depleted, and atherosclerosis promoting effect of testosterone might be relatively robust. Therefore, plaque rupture by advanced atherosclerosis may become dominant with post-menopausal age.

Age and sex of a patient are readily available. The age ≤ 50 males and the age ≤ 70 females increased the likelihood of plaque erosion in ACS patients. Recent studies suggested that in a selected group of ACS patients caused by plaque erosion, conservative management with antithrombotic therapy without coronary stenting might be an option [9, 22]. If patients with ACS caused by plaque erosion can be identified at the emergency department, those patients can be triaged to a conservative management

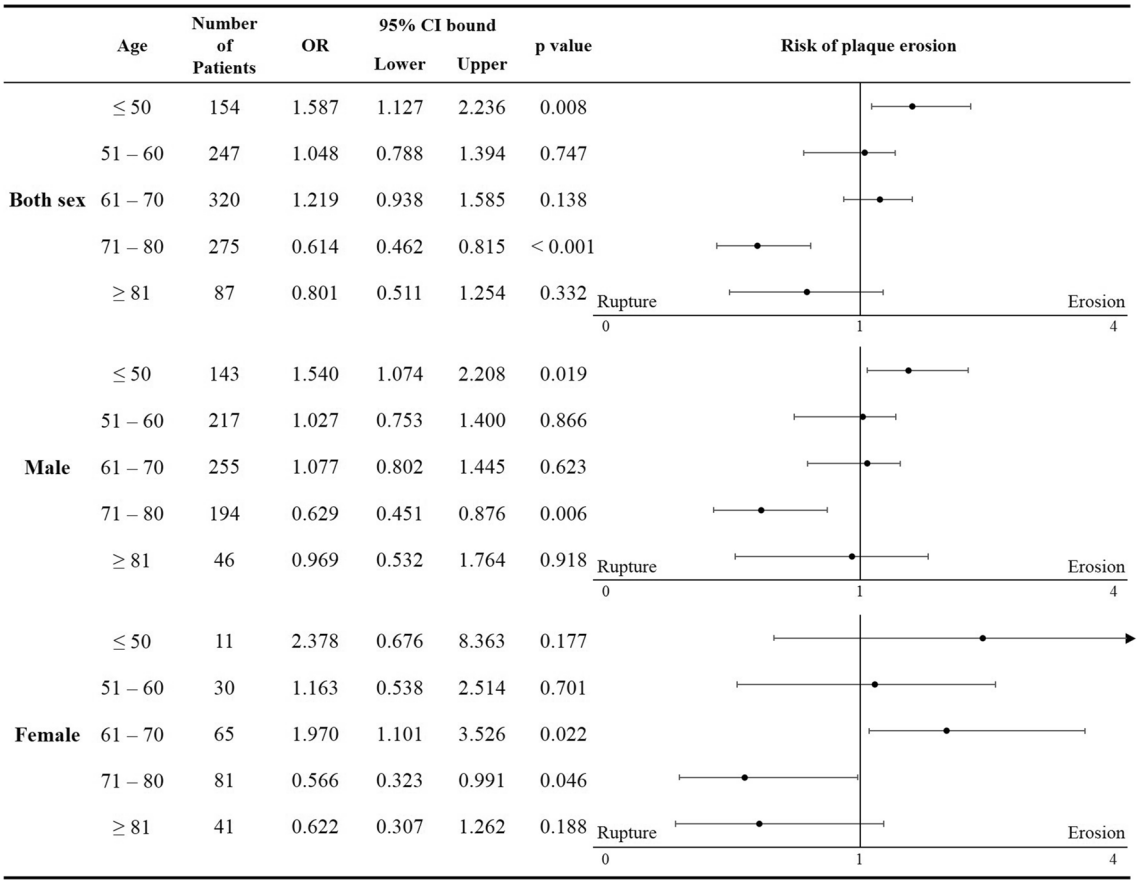


Fig. 3 Risk of plaque erosion in different age and sex groups. Logistic regression was done for the plaque erosion probability assessment in different age and sex groups. In the overall population, the probability of plaque erosion was increased in the age ≤ 50 group and decreased in the age 71–80 group. The probability of plaque erosion of male patients was increased in the age ≤ 50 group and decreased in the age 71–80 group. The probability of female patients was increased in the age 61–70 group and decreased in the age 71–80 group. Higher plaque erosion risk was noted as blue, while higher plaque rupture risk was noted as red. *CI* confidence interval, *OR* odds ratio

pathway without invasive procedures. To be able to achieve this ultimate goal, we need more information to narrow down the whole cohort to a subgroup of patients with high likelihood of plaque erosion. The information that plaque erosion is more frequent in men age ≤ 50 and women age ≤ 70 will be helpful to identify those patients with a higher chance of plaque erosion.

This study has several limitations. First, calcified nodules are not included in the analysis. This group was excluded because it comprises only 4–8% of the total ACS population [10]. Second, the number of male patients in the age ≥ 81 group and the number of female patients in each group were small. Third, demographics, laboratory findings, medication history, preprocedural thrombectomy rate, and calcium observed on OCT were not evenly distributed among the different groups. Fourth, this study used two different OCT systems (frequency-domain and time-domain OCT). However, the distribution of plaque morphology examined by each system did not differ significantly between the two groups except calcium. Fifth, potential selection bias could not be excluded with the retrospective design of the study.

Conclusion

There was no sex difference in the prevalence of plaque erosion. Erosion was the predominant mechanism of ACS in males up to 50 years old and in females up to their 60′s. In all patients, plaque rupture was the predominant mechanism of ACS from their 70′s onward. Between 60 and 70′s of females, there was an abrupt change in the predominant mechanism of ACS from erosion to rupture.

Table 2 Regression analysis for independent risk factor for plaque erosion

Sex	Variables	Univariate analysis		Multivariate analysis	
		OR (95% CI)	p value	OR (95% CI)	p value
Male	Age ≤ 50	1.610 (1.105–2.346)	0.013	1.418 (0.961–2.093)	0.078
	Hypertension	0.718 (0.544–0.948)	0.019	0.806 (0.605–1.074)	0.141
	Dyslipidemia	0.852 (0.634–1.145)	0.228		
	DM	0.674 (0.501–0.908)	0.009	0.716 (0.529–0.970)	0.031
	CKD	0.544 (0.369–0.801)	0.002	0.607 (0.409–0.900)	0.013
	Current smoking	0.982 (0.691–1.188)	0.473		
Female	Age ≤ 70	2.216 (1.299–3.780)	0.004	2.138 (1.249–3.661)	0.006
	Hypertension	0.907 (0.516–1.595)	0.735		
	Dyslipidemia	0.728 (0.404–1.311)	0.290		
	DM	1.188 (0.673–2.096)	0.553		
	CKD	0.479 (0.202–1.139)	0.096	0.532 (0.221–1.284)	0.160
	Current smoking	1.486 (0.802–2.753)	0.209		

CI confidence interval, *CKD* chronic kidney disease, *DM* diabetes mellitus, *OR* odds ratio

Acknowledgements IK Jang's research was supported by Mr. Michael and Mrs. Kathryn Park and by Mrs. Gill and Mr. Allan Gray. The authors thank Mr. Gregory Gheewalla for his edit.

Compliance with ethical standards

Disclosure Nothing to disclose.

References

1. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM (2000) Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. Arterioscler Thromb Vasc Biol 5:1262–1275
2. Libby P, Pasterkamp G, Crea F, Jang IK (2019) Reassessing the mechanisms of acute coronary syndromes. Circ Res 1:150–160. https://doi.org/10.1161/circresaha.118.311098
3. Burke AP, Farb A, Malcom GT, Liang Y, Smialek J, Virmani R (1998) Effect of risk factors on the mechanism of acute thrombosis and sudden coronary death in women. Circulation 21:2110–2116
4. Kramer MC, Rittersma SZ, de Winter RJ, Ladich ER, Fowler DR, Liang YH, Kutys R, Carter-Monroe N, Kolodgie FD, van der Wal AC, Virmani R (2010) Relationship of thrombus healing to underlying plaque morphology in sudden coronary death. J Am Coll Cardiol 2:122–132. https://doi.org/10.1016/j.jacc.2009.09.007
5. Arbustini E, Dal Bello B, Morbini P, Burke AP, Bocciarelli M, Specchia G, Virmani R (1999) Plaque erosion is a major substrate for coronary thrombosis in acute myocardial infarction. Heart 3:269–272
6. Niccoli G, Montone RA, Di Vito L, Gramegna M, Refaat H, Scalone G, Leone AM, Trani C, Burzotta F, Porto I, Aurigemma C, Prati F, Crea F (2015) Plaque rupture and intact fibrous cap assessed by optical coherence tomography portend different outcomes in patients with acute coronary syndrome. Eur Heart J 22:1377–1384. https://doi.org/10.1093/eurheartj/ehv029
7. Yonetsu T, Lee T, Murai T, Suzuki M, Matsumura A, Hashimoto Y, Kakuta T (2016) Plaque morphologies and the clinical prognosis of acute coronary syndrome caused by lesions with intact fibrous cap diagnosed by optical coherence tomography. Int J Cardiol. https://doi.org/10.1016/j.ijcard.2015.11.030
8. Partida RA, Libby P, Crea F, Jang IK (2018) Plaque erosion: a new in vivo diagnosis and a potential major shift in the management of patients with acute coronary syndromes. Eur Heart J 22:2070–2076. https://doi.org/10.1093/eurheartj/ehx786
9. Jia H, Dai J, Hou J, Xing L, Ma L, Liu H, Xu M, Yao Y, Hu S, Yamamoto E, Lee H, Zhang S, Yu B, Jang IK (2017) Effective anti-thrombotic therapy without stenting: intravascular optical coherence tomography-based management in plaque erosion (the EROSION study). Eur Heart J 11:792–800. https://doi.org/10.1093/eurheartj/ehw381
10. Jia H, Abtahian F, Aguirre AD, Lee S, Chia S, Lowe H, Kato K, Yonetsu T, Vergallo R, Hu S, Tian J, Lee H, Park SJ, Jang YS, Raffel OC, Mizuno K, Uemura S, Itoh T, Kakuta T, Choi SY, Dauerman HL, Prasad A, Toma C, McNulty I, Zhang S, Yu B, Fuster V, Narula J, Virmani R, Jang IK (2013) In vivo diagnosis of plaque erosion and calcified nodule in patients with acute coronary syndrome by intravascular optical coherence tomography.

J Am Coll Cardiol 19:1748–1758. https://doi.org/10.1016/j.jacc.2013.05.071
11. Tearney GJ, Regar E, Akasaka T, Adriaenssens T, Barlis P, Bezerra HG, Bouma B, Bruining N, Cho JM, Chowdhary S, Costa MA, de Silva R, Dijkstra J, Di Mario C, Dudek D, Falk E, Feldman MD, Fitzgerald P, Garcia-Garcia HM, Gonzalo N, Granada JF, Guagliumi G, Holm NR, Honda Y, Ikeno F, Kawasaki M, Kochman J, Koltowski L, Kubo T, Kume T, Kyono H, Lam CC, Lamouche G, Lee DP, Leon MB, Maehara A, Manfrini O, Mintz GS, Mizuno K, Morel MA, Nadkarni S, Okura H, Otake H, Pietrasik A, Prati F, Raber L, Radu MD, Rieber J, Riga M, Rollins A, Rosenberg M, Sirbu V, Serruys PW, Shimada K, Shinke T, Shite J, Siegel E, Sonoda S, Suter M, Takarada S, Tanaka A, Terashima M, Thim T, Uemura S, Ughi GJ, van Beusekom HM, van der Steen AF, van Es GA, van Soest G, Virmani R, Waxman S, Weissman NJ, Weisz G (2012) Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: a report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. J Am Coll Cardiol 12:1058–1072. https://doi.org/10.1016/j.jacc.2011.09.079
12. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB (2008) General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 6:743–753. https://doi.org/10.1161/circulationaha.107.699579
13. Ross R (1999) Atherosclerosis—an inflammatory disease. N Engl J Med 2:115–126. https://doi.org/10.1056/nejm199901143400207
14. Head T, Daunert S, Goldschmidt-Clermont PJ (2017) The aging risk and atherosclerosis: a fresh look at arterial homeostasis. Front Genet. https://doi.org/10.3389/fgene.2017.00216
15. Wang JC, Bennett M (2012) Aging and atherosclerosis: mechanisms, functional consequences, and potential therapeutics for cellular senescence. Circ Res 2:245–259. https://doi.org/10.1161/circresaha.111.261388
16. Miller VM, Duckles SP (2008) Vascular actions of estrogens: functional implications. Pharmacol Rev 2:210–241. https://doi.org/10.1124/pr.107.08002
17. McCrohon JA, Jessup W, Handelsman DJ, Celermajer DS (1999) Androgen exposure increases human monocyte adhesion to vascular endothelium and endothelial cell expression of vascular cell adhesion molecule-1. Circulation 17:2317–2322
18. Zang H, Ryden M, Wahlen K, Dahlman-Wright K, Arner P, Linden Hirschberg A (2007) Effects of testosterone and estrogen treatment on lipolysis signaling pathways in subcutaneous adipose tissue of postmenopausal women. Fertil Steril 1:100–106. https://doi.org/10.1016/j.fertnstert.2006.11.088
19. Mishra JS, More AS, Gopalakrishnan K, Kumar S (2018) Testosterone plays a permissive role in angiotensin II-induced hypertension and cardiac hypertrophy in male rats. Biol Reprod. https://doi.org/10.1093/biolre/ioy179
20. Haffner SM, Katz MS, Stern MP, Dunn JF (1989) Association of decreased sex hormone binding globulin and cardiovascular risk factors. Arteriosclerosis 1:136–143
21. Burger HG, Dudley EC, Cui J, Dennerstein L, Hopper JL (2000) A prospective longitudinal study of serum testosterone, dehydroepiandrosterone sulfate, and sex hormone-binding globulin levels through the menopause transition. J Clin Endocrinol Metab 8:2832–2838. https://doi.org/10.1210/jcem.85.8.6740
22. Xing L, Yamamoto E, Sugiyama T, Jia H, Ma L, Hu S, Wang C, Zhu Y, Li L, Xu M, Liu H, Bryniarski K, Hou J, Zhang S, Lee H, Yu B, Jang IK (2017) EROSION Study (effective anti-thrombotic therapy without stenting: intravascular optical coherence tomography-based management in plaque erosion): a 1-year follow-up report. Circ Cardiovasc Interv. https://doi.org/10.1161/circinterventions.117.005860