Article

Normotensive young patients with acute coronary syndrome: Etiological factors and differences in the development of critical coronary lesion

Zeynep Ece Demirbaş, Fatma Can

Abstract

Background: Acute coronary syndrome (ACS) is a leading cause of mortality worldwide, especially among young males. While the incidence of ACS decreases in older populations, it remains significant in younger individuals. This study aimed to identify clinical and biochemical differences between young ACS patients with critical atherosclerotic stenoses and those without.

Methods: The study retrospectively analyzed 55 normotensive patients aged 18-35 years diagnosed with ACS between January 2023 and January 2024. Patients were categorized as "critical" (≥70% stenosis) or "noncritical." Demographic, etiological, and biochemical parameters were compared.

Results: Critical coronary lesions were found in 32 patients (58%). Active smoking was significantly more common in the critical group ($p = 0.048$), and mean MPV was lower ($p = 0.024$). Logistic regression identified male gender ($p = 0.026$), CRP ($p = 0.010$), GGT ($p = 0.021$), and interventricular septum thickness ($p = 0.043$) as risk factors.

Conclusion: This study underscores the importance of early detection and intervention in young ACS patients, particularly in addressing modifiable risk factors like smoking, inflammation, and oxidative stress. Further studies are needed to validate these findings.

Keywords: acute coronary syndrome, young population, critical coronary lesion, atherosclerosis

Submitted 13/9/24
Cardiovasc J Afr 2025; 1–5 www.cvja.co.za

DOI: 10.5830/CVJA-2025-002

Department of Internal Medicine, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Center Training and Research Hospital, Istanbul, Turkey
Zeynep Ece Demirbaş, MD

Department of Cardiology, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Center Training and Research Hospital, Istanbul, Turkey
Fatma Can, MD, Corresponding Author, Name: Dr. Zeynep Ece Demirbaş, Address: Tıbbiye Cad. No:13 Selimiye Uskudar, 344668, İstanbul, TURKEY, Mobile no: +90 533 7192935, Email: zeynepece@gmail.com

Introduction

Acute coronary syndrome (ACS) and related complications are recognized as the leading cause of mortality worldwide.[1] Although the incidence of acute coronary syndromes tends to decrease in older populations, this is not the case for younger populations, especially males.[2] Different studies have determined different limit values for the definition of young patients. However, as the age of the studied group decreases, spontaneous coronary artery dissection, vasospastic angina, coronary embolism, methamphetamine/cocaine use and other causes other than traditional atherosclerotic risk factors are included in the etiology.[3]

Although the definition of critical coronary lesion is mostly used by clinicians, various studies have tried to determine the severity according to the degree of obstruction in percentage terms.[4] In this study, in which a coronary stenosis of 70% or more was defined as a "critical coronary lesion", we aimed to determine the clinical and biochemical differences between young patients with atherosclerotic critical stenoses and patients without atherosclerotic lesions or critical stenoses.

Methods

The records of a total of 55 patients aged 18-35 years who presented to the Emergency Department of our hospital with chest pain between January 2023 and January 2024 and were diagnosed with acute coronary syndrome were retrospectively retrieved from the hospital database. Acute coronary syndrome (ACS) was defined based on the 2023 ESC guidelines, including unstable angina or myocardial infarction diagnosed by clinical presentation, typical electrocardiographic changes, and elevated cardiac biomarkers.[5] According to the results of coronary angiography, patients with critical lesions (≥70% stenosis) in at least one coronary artery were defined as "critical" group and the remaining patients were defined as "noncritical" group. Angiographic findings were further classified according to the presence of plaque, thrombus, slow flow and dissection. Standard coronary angiography via the femoral route was performed in each patient using 6-French Judkins diagnostic catheters. The procedures were conducted with commercially available system

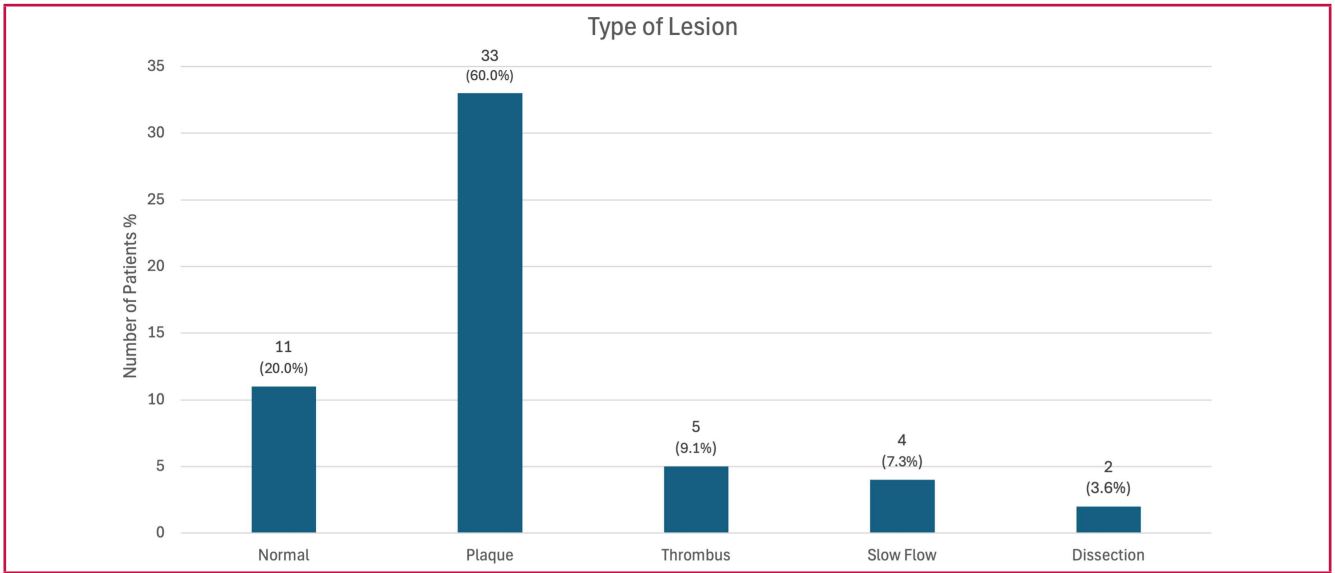

Figure 1: Types and distribution of lesions detected in coronary angiography

(Axiom Artis System, Siemens Medical Solution, Erlangen, Germany) and evaluations were performed by experienced interventional cardiologists.

Critical and noncritical groups were compared according to demographic, etiological and biochemical differences. In addition to demographic characteristics such as age and gender, smoking and presence of diabetes were questioned. Since none of the patients had a previous diagnosis of hypertension, the study was designed on normotensive patients. Since information on family history of coronary artery disease was not available retrospectively, this etiological factor could not be included. Body Mass Index (BMI) data were calculated and recorded. Hemogram parameters, creatinine (mg/dL), uric acid (mg/dL), GGT (IU/L), albumin (g/L), C- reactive protein (CRP) (mg/L), HbA1c (%), T. Cholesterol (mg/dL), LDL (mg/dL), HDL (mg/dL) and Triglyceride (mg/dL) values were noted. Interventricular septum thickness [IVS (mm)], ascending aorta diameter [AA (mm)], left ventricular end-systolic diameter [ESD (mm)] and end-diastolic diameter [EDD (mm)] measurements were recorded. It was also noted whether revascularization was achieved during coronary angiography and whether mortality was observed during hospitalization.

Statistical analysis of the data was performed using SPSS version 29.0 (SPSS Inc. IL, USA). ±During descriptive statistics, continuous parametric variables were expressed as mean standard deviation, nonparametric variables were expressed as median (minimum - maximum) and categorical variables were expressed as percentage. Normally distributed variables between the two groups were analyzed by independent t test and non-normally distributed variables were analyzed by Mann-Whitney U test. Chi square test or Fisher's Exact test was used for differences between categorical variables. Variables found to be significant in univariate regression analyses were included in multivariate logistic regression analyses. Hosmer-Lemeshow fit statistic was used to assess model fit. For statistical significance, 5% type I error level was determined. P value below 0.05 was accepted as statistically significant difference.

Results

The mean age of 55 patients with acute coronary syndrome admitted to our cardiology emergency department during the study period was 31.62 years (24-35), 17 (73.9%) were male and 74.5% were active smokers. None of them had a diagnosis of hypertension. Of the 2 patients with a diagnosis of diabetes mellitus, one had type 1 diabetes mellitus and the other had type 2 diabetes mellitus. All patients underwent coronary angiography after a diagnosis of acute coronary syndrome. At least one critical coronary lesion was detected in 32 patients (58%). The types of coronary lesions detected are summarized in Figure 1.

Revascularization was performed in 70.9% of the patients in total. 2 patients were also referred to cardiovascular surgery for coronary bypass surgery. Mortality was observed in 2 patients during intensive care unit follow-up. The clinical and biochemical values of the patients with and without critical lesions are summarized in Table 1. Active smoking was found to be statistically significant in patients with critical lesions compared to those without critical lesions ($p = 0.048$) and mean platelet volume (MPV) mean of the group with critical coronary lesions was significantly lower than that of the group without critical lesions ($p = 0.024$). When echocardiographic findings were analyzed, it was observed that the DSC value was higher in the group with critical lesions ($p = 0.053$).

When logistic regression analysis was performed with known risk factors that were found to be significant in one-way analyses of variance, gender, CRP, GGT and IVS were found to be independent risk factors for the development of critical coronary lesions in patients with young acute coronary syndrome. It was observed that male gender had a 24.4-fold increased relative risk compared to female gender ($p = 0.026$), while GGT and IVS had 0.927 and 0.571-fold increased risk for each unit of elevation, respectively ($p = 0.021$, $p = 0.043$) (Table 2).

Table 1: Comparison of clinical and biochemical values between groups with and without critical stenosis

	NON-CRITICAL	*CRITICAL*	*TOTAL*	*P*
n	23 (42%)	32 (58%)	55 (100%)	
Age (years)	32 (24-35)	33 (25-35)	31.62 (24-35)	0.413
Gender (male)	17 (73.9%)	28 (87.5%)	45 (81.8%)	0.290
Cigarette	14 (60.9%)	27 (84.4%)	41 (74.5%)	**0.048**
Revascularization	7 (30.4%)	32 (100%)	39 (70.9%)	**<0.05**
Mortality	0 (%0)	2 (6.3%)	2 (3.6%)	0.504
DM	0 (%0)	2 (6.3%)	2 (3.6%)	0.504
BMI (kg/m^2)	27.3 (16.0-38.7)	25.1 (21.9-34.1)	27.03 (16-38.7)	0.172
Hgb (g/dL)	14.8 ± 1.8	14.4 ± 1.0	14.5 ± 1.4	0.368
Hct (%)	43.5 ± 5.3	42.3 ± 3.0	42.8 ± 4.1	0.358
WBC (10 / L)	11.3 (10.1-17.7)	12.2 (5.4-34.6)	12.0 (10.1-34.6)	0.253
Neutrophil 10 / L)	7.25 (4.57-14.9)	9.16 (2.8-30.7)	7.85 (2.85-30.76)	0.246
Lymphocyte (10 / L)	2.54 (0.63-4.10)	2.35 (0.85-6.2)	2.5 (0.63-6.25)	0.310
PLT (10 / L)	252 (123-562)	255 (198-372)	252 (123-562)	0.314
MPV (fL)	9.1 ± 1.5	8.2 ± 1.2	8.6 ± 1.4	**0.024**
Creatinine (mg/dL)	0.82 (0.58-1.24)	0.81 (0.61-1.15)	0.82 (0.58-1.24)	0.590
Uric acid (mg/dL)	5.8 ± 1.6	6.0 ± 1.5	5.9 ± 1.6	0.697
GGT (IU/L)	31 (11-83)	24.5 (10-56)	29 (10-83)	0.233
Albumin (g/L)	4.03 ± 0.35	4.1 ± 0.23	4.07 ± 0.29	0.403
CRP (mg/L)	0.5 (2-5.2)	0.2 (0.2-2.8)	0.250 (0.2-5.2)	0.060
HbA1c (%)	5.5 (4.8-6.2)	5. 5 (4.7-10.6)	5. 5 (4.7-10.6)	0.644
Cholesterol (mg/dL)	176 (116-345)	180 (107-287)	180 (107-345)	0.463
LDL (mg/dL)	107 ± 30.4	114.5 ± 31.3	111.4 ± 30.9	0.380
HDL (mg/dL)	38.1 ± 11.3	35.1 ± 6.8	36.4 ± 9.0	0.276
TG (mg/dL)	144 (48-715)	149.5 (54-660)	148 (48-715)	0.720
IVS (mm)	10 (8-20)	10 (8-13)	10 (8-20)	0.537
AA (mm)	29 (26-39)	31 (22-37)	30.5 (22-39)	0.150
EDD (mm)	45.9 ± 4.6	48.0 ± 3.5	47.1 ± 4.1	**0.033**
ESD (mm)	28.6 ± 6.2	31.0 ± 5.3	29.9 ± 5.8	0.152

(AA: Ascending Aorta; AIP: Atherogenic Plasma Index; BMI: Body Mass Index; CRP: C-Reactive Protein; DM: Diabetes Mellitus; EDD: End Diastole Diameter; ESD: End Systolic Diameter; GGT: Gamma-Glutamyl Transferase; HDL: High Density Lipoprotein IVS: Interventricular septum; LDL: Low Density Lipoprotein; MPV: Mean Platelet Volume; PLT: Platelets; TG: Triglyceride; WBC: White Blood Cell)

Discussion

In this study, we investigated the etiological and clinical factors associated with the development of critical coronary lesions in patients with acute coronary syndrome (ACS) aged 18-35 years. The results showed that a significant proportion (58%) of young ACS patients had critical coronary lesions. When coronary lesions other than atherosclerotic lesions such as thrombus, dissection and slow flow were excluded, coronary arteries were completely normal in 20% of cases. Atherosclerotic plaque rupture is still the leading etiological cause of ACS in young patients with a rate of 60-65%.[3] In a study by Fournier et al. in patients under 40 years of age with ACS, angiographically normal coronary vessels were observed in 10 (34%) of 29 patients under 35 years of age.[6] One possible explanation for this is that there has been an increasing trend of atherosclerotic coronary lesions among the younger population since the 1996 study. However, Gupta et al. did not observe a statistically significant difference between hospitalizations due to ACS in the subgroups aged 30-34 and 35-39 years between 2001 and 2010.[2] Looking at the trend of risk factors for atherosclerosis over the years, in a study comparing groups of adolescents aged 12-19 years from the United States of America between 2001 and 2020, Qu et al. showed that despite the increasing trend in prediabetes and obesity in the last two decades, hyperlipidemia, smoking and inactivity decreased, while the rates of hypertension, diabetes and unhealthy diet did not change.[7]

Table 2: Independent risk factors found to be significant in logistic regression analysis of risk factors for the development of critical coronary lesions

	RR (95% CI)	*P*
Gender (male)	24.496 (1.466-409.385)	**0.026**
CRP (mg/L)	0.097 (0.017-0.567)	**0.010**
GGT (IU/L)	0.927 (0.869-0.989)	**0.021**
IVS (mm)	0.571 (0.332-0.982)	**0.043**

(CRP: C-Reactive Protein; GGT: Gamma-Glutamyl Transferase; IVS: Interventricular septum; RR: Relative Risk)

Cigarette smoking has been identified as an important risk factor for the development of critical coronary lesions.[8] Again, Fournier et al. 94.5% of patients under 40 years of age with ACS were smokers. The fact that the smoking rate of 74.5% in our study was higher in the critical lesion group indicates that smoking increases the risk of coronary artery disease at a young age. However, it was thought that one of the possible reasons why it was not detected as an independent risk factor in logistic regression analysis may be the low duration of exposure.

In addition, gender differences were also evident in our study, and it was observed that males had approximately 24 times higher risk of developing critical lesions than females. This finding suggests that males are at higher risk for ACS and related serious complications at a young age. In previous studies, it is also known that female gender has an advantage over male gender for the risk of acute coronary syndrome, especially at younger ages.[8,9] It is also known that obstructive lesions are less common in women with young coronary artery disease.[10]

In our study, biochemical analyses revealed that critical lesions were associated with low MPV values. In a review of studies in the literature on coronary artery disease and MPV, it is known that coronary artery disease patients have higher MPV values than healthy control groups.[11] In thromboembolic events such as ACS, elevated MPV has been associated with more active and larger young platelets.[12] However, in our study, contrary to the general trend, the mean MPV was lower in the critical coronary lesion group than in the non-critical group. In one of the studies supporting this, Mathur et al. found higher MPV values in patients with unstable angina and myocardial infarction compared to healthy controls, but showed that the mean MPV in the myocardial infarction group was lower than in the unstable angina group.[13] In another study, Wada et al. found an increased risk of major cardiac events and all-cause mortality in stable coronary artery disease patients with low MPV values.[14] To the best of our knowledge, we believe that this negative correlation, which we have found for the first time, may be explained by the lower exposure to chronic inflammatory processes in young patients in the critical lesion group. However, we believe that in vivo studies on platelet anatomy and functions especially in this age group may contribute to this view.

When echocardiographic findings were analyzed, the fact that end-diastolic diameter (EDD) values were higher in the critical lesion group suggests that there may be significant changes in the cardiac structure in these patients. One of the possible causes is thought to be myocardial remodeling process.[15] In our study, interventricular septum thickness (IVS) was also found to be an independent predictor of critical lesions. In a prospective study

of 5888 patients with a mean age of 73 years, it was observed that the incidence of coronary artery disease and heart failure was higher in the group with the highest IVS thickness at 6-7 years of follow-up.[16] However, since the echocardiographic imaging of our patients was performed after ACS, it may be difficult to say that this relationship plays a role as an etiological factor. Nevertheless, since the predictive value of IVS thickness in patients with coronary artery disease, including all-cause mortality, has been demonstrated.[17] The correlation with critical lesions in young patient groups emphasizes the importance of this parameter.

Logistic regression analyses revealed that gender, CRP and GGT values were independent risk factors for the development of critical coronary lesions, as were gender and IVS. CRP was found to be an important factor in the development of critical coronary lesions and correlated with lesion grade.[18] CRP is an indicator of systemic inflammation in acute coronary syndromes and high CRP levels in this study seem to be an unfavorable factor for the presence of critical lesions. Similarly, serum GGT levels were found to be a significant risk factor for the development of critical lesions. GGT is an indicator of liver function and oxidative stress.[19] Elevated GGT levels indicate increased oxidative stress, which may lead to damage to the vessel wall and plaque formation.[20] In addition, an association of increased GGT values with ACS as a result of hepatic congestion accompanying deteriorating cardiac function has been demonstrated.[21] Our study is valuable in terms of clearly demonstrating this relationship especially in young coronary artery disease patients. It is thought that monitoring of GGT levels in young patients may be useful in the evaluation of the risk of coronary artery disease.

One of the limitations of the study was the lack of family history information in terms of coronary artery disease. It is known that family history is an important and independent risk factor for coronary artery disease, especially at a young age.[22] However, Zimmerman et al. have shown that family history is a factor, especially in young men under 35 years of age.[23] Another limitation is the predominance of male participants (73.9%) may reduce the generalizability of the findings to young females. Also, the relatively small sample size (55 patients) restricts the statistical power and generalizability of the results, but it underscores the rarity of ACS in normotensive young patients and the importance of identifying this subgroup. Furthermore, the absence of advanced imaging modalities such as IVUS (Intravascular Ultrasound) or OCT (Optical Coherence Tomography) unfortunately prevents a more detailed evaluation of coronary lesions. European Association of Percutaneous Cardiovascular Interventions (EAPCI) consensus report on the clinical use of intracoronary imaging suggests that intravascular imaging can provide additional important diagnostic information when confronted with angiographically ambiguous lesions and allows assessment of plaque morphology enabling identification of vulnerability characteristics which may be valuable for young ACS patients.[24] There are also atherosclerosis-associated gene mutation studies that may lead to the development of critical coronary lesions at a young age.[25,26] In addition to other traditional risk factors, new gene studies in this field will be necessary to elucidate the formation of occlusive coronary lesions. Future studies addressing these limitations are needed to provide a more comprehensive understanding of ACS in young, normotensive patients.

Conclusion

In conclusion, this study identified smoking, CRP, GGT, and interventricular septum thickness as independent predictors of critical coronary lesions in normotensive young ACS patients. These findings may contribute to the development of early diagnosis and treatment strategies for coronary artery disease at the young age group. In particular, strategies such as reducing smoking, controlling inflammation and minimizing oxidative stress may improve the prognosis of these patients. In order to determine the propensity for atherosclerosis in young patient groups, clinical studies on higher patient populations, supported by risk factors and prevalence studies, are needed. Future prospective studies will allow the validation of these risk factors in larger patient groups and the development of new preventive measures.

Acknowledgements

The authors declare that this study has not been previously presented at any scientific meeting or conference. There are no other contributors to acknowledge. The authors declare that there is no conflict of interest.

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