ARAŞTIRMA / RESEARCH

Predictive value of traditional risk factors in the assessment of premature coronary artery disease

Erken gelişen koroner arter hastalığının değerlendirilmesinde geleneksel risk faktörlerinin prediktif değeri

Fatih Aksoy[1] (iD)

[1]Suleyman Demirel University, Medical School, Department of Cardiology, Isparta, Turkey

Abstract

Purpose: The purpose of this study was to assess frequency, risk factors of young patients with coronary artery disease (CAD).

Materials and Methods: Medical recordings of 21514 patients who underwent coronary angiography were screened for this study between January 2000 and March 2016. Patients older than 45 years old and severe valvular disease were excluded study. A total 862 patients ıncluded study. Major risk factors for CAD were identified.

Results: Out of total 862 patients studied, 595 had CAD and 267 had normal coronary arteries (NCA). The young CAD group had a significantly higher proportion of males (94.1 vs. 58.8%) and smokers (78 vs. 45%) than age-matched control patients with NCA. In patients with CAD, the rate of obesity was higher in female group than males (41 vs. 14 %) while the smoking rate was higher than female group (80 vs. 44 %). According to multivariate analysis male sex [Odds ratio (OR) = 7.3, 95% Confidence interval (CI) 4.6- 11.4] and smoking (OR= 2.3, 95% CI 1.6-3.2) were found to be independent predictors of CAD.

Conclusion: We have shown that smoking was the most important risk factor in young adults.

Keywords:. Cardiovascular Diseases, young adult, risk factors

Öz

Amaç: Bu çalışmanın amacı genç hastalarda koroner arter hastalığının (KAH) sıklığını ve risk faktörlerini değerlendirmektir.

Gereç ve Yöntem: Ocak 2000 - Mart 2016 tarihleri arasında koroner anjiyografi yapılan 21514 hastanın tıbbi kayıtları tarandı. 45 yaşından büyük ve ağır kapak hastalığı olan hastalar çalışma dışı bırakıldı. Çalışmaya toplam 862 hasta dahil edildi. KAH için başlıca risk faktörleri değerlendirilmiştir.

Bulgular: Çalışılan toplam 862 hastanın 595'inde KAH, 267'sinde normal koroner arter (NKA) vardı. genç KAH grubunda erkek yüzdesi (% 94,1 vs. % 58.8) ve sigara içme oranı (% 78 vs. % 45) yaşları açısından benzer olan NKA grubuna göre yüksekti. KAH hastalarında obezite oranı kadınlarda erkeklerden daha yüksek iken (% 41 vs. % 14), sigara içme oranı erkeklerde kadınlara göre daha yüksekti (% 80 vs. % 44). Çok değişkenli analizlere göre erkek cinsiyet [Olasılık Oranı (OO) = 7,3,% 95 Güvenlik aralığı (GA) 4,6-11,4] ve sigara (OO = 2,3,% 95 GA 1,6 – 3,2) KAH'ın bağımsız belirleyicileri olarak bulundu.

Sonuç: Genç erişkinlerde sigara içmenin en önemli risk faktörü olduğunu gösterdik

Anahtar kelimeler:. Kardiyovasküler Hastalıklar, genç erişkin, risk faktörleri

INTRODUCTION

Coronary artery disease (CAD) is a major cause of death worldwide[1]. Acute myocardial infarction (ACS), a presentation of CAD is less commonly seen in adults younger than 45 years of age than in elderly patients. However, ACS in young patients may be more devastating than older age patients due to its greater potential impact on the patient's physiology, labor lost and the socioeconomic burden[2,3]. Control of cardiovascular risk factors is of particular importance for the prevention of cardiovascular diseases. It is possible to stop progression or prevent these diseases by elimination or modification of modifiable risk factors in the light of treatment goals.

Although studies carried out in older or middle age patients, comparatively few studies have focused on the clinical presentation and risk factors of ACS in young patients[3]. The pathophysiologic changes and disease course of CAD in young patients are different from older population, and determining of these differences may contribute to prevent the disease and ameliorate the prognosis[4]. In most of these studies, young patients compared with older patients[5,6]. We researched that whether there is a difference in traditional risk factors among young patients. Additionally, in our country, there are a few published data related to this problem[6,7]. The present study examined the angiographic findings, coronary risk factors and natural history of Turkish patients' ≤45 years old with CAD.

MATERIALS AND METHODS

From May 2000 to March 2016, the records of 21514 patients admitted to Suleyman Demirel University Hospital who had catheterization were reviewed. All patients routinely gave written informed consent for coronary angiography. Coronary angiography was performed through the femoral artery using the standard Judkins technique in the catheter laboratory of Suleyman Demirel University Medical Faculty, Dept. of Cardiology [8]. Inclusion criteria included age greater than 45 years old and presence of ACS. Exclusion criteria included age older than 45 years old, moderate to severe heart valve disease, cardiomyopathy history, and myocarditis. Diagnoses were recorded by the participating physicians based on clinical, electrocardiographic, and biochemical (elevated troponin levels) criteria. The type of myocardial infarction (ST-elevation vs. non-ST-elevation) and unstable angina were homogeneously defined and based on contemporary guidelines[9].

Out of 21514 consecutive patients performing coronary angiography, 20002 patients older than 45 years were excluded the analysis. After 203 patients with severe valve disease, 27 patients with pericarditis, 20 patients with congenital heart disease were excluded in among patients less than 45 years (Figure 1). Patients divided into two groups as normal coronary arteries (NCA) and CAD. The institutional ethics committee approved the study (13.12.2018/ number: 244) and all participants provided written informed consent. The procedures were in accordance with the ethical standards of the responsible institutional committee on human

experimentation and with the Helsinki Declaration of 1975, which was revised in 1983.

Each patient was questioned about major cardiovascular risk factors including family history of coronary artery disease, current smoking status, hyperlipidemia, hypertension, diabetes mellitus and obesity. Family history of coronary artery disease was defined as manifestation of the disease in first-grade male relatives younger than 55 years or in first-grade female relatives younger than 65 years of age. Hyperlipidemia was defined as fasting total cholesterol level >200 mg/dL or pharmacotherapy with lipid-lowering agents. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg measured before hospitalization or pharmacotherapy with antihypertensive drugs. Diabetes mellitus was defined fasting plasma glucose ≥126 mg/dL or pharmacotherapy with insulin or oral antidiabetic agents. Obesity was defined as body mass index >30 kg/m². Patients who were smoking prior to hospitalization were accepted as smokers. Significant CAD was defined as ≥ 50 % lumen diameter reduction of more than one major epicardial coronary artery at visual estimation. Coronary angiograms were reviewed by an experienced interventional cardiologist as it is done in daily clinical practice. Patients were classified as having single vessel , two vessel or multivessel disease, as having non-significant CAD (defined as lumen irregularities < 50 % lumen diameter reduction) or non-CAD (no lumen irregularities).

Statistical analysis

SPSS version 16.0 software package was used for statistical analyses in this study. Categorical variables were expressed as frequency (%) and compared with the χ2 test. Kolmogorov-Smirnov test was used to test the distribution of numeric variables; those with normal distribution were expressed as mean ± standard deviation and were compared with Student's t-test. Data without normal distribution were expressed as median (Inter-quartile range (IQR) of 25%-75% percentiles) and were compared with the Mann-Whitney U test. In all statistical analyses, p value <0.05 was considered as statistically significant. Univariate analysis of binary logistic regression was carried out to identify which factors were associated with incident CAD. After including each of these potential confounding factors, backward conditional binary logistic regression analysis was performed to

estimate the odds ratio (OR) and 95% confidence interval (95% CI) for incident CAD.
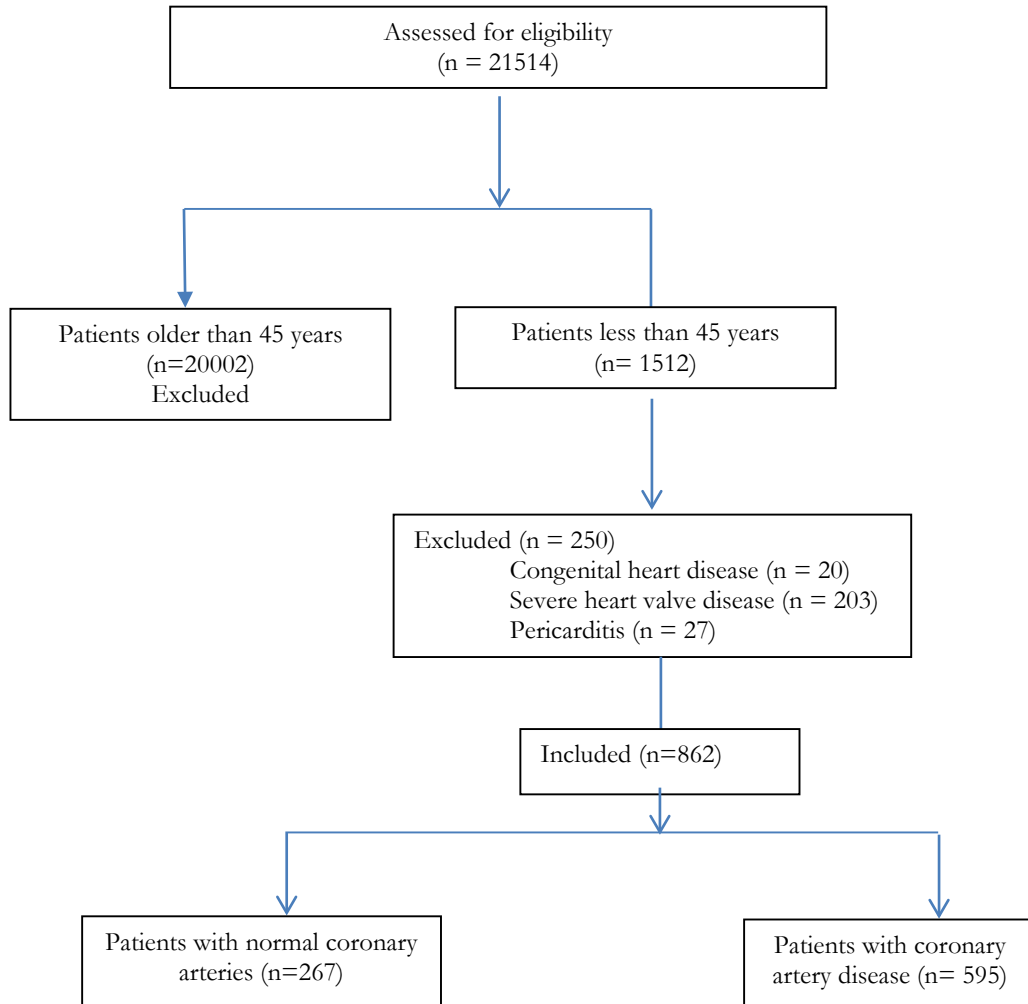

Figure 1 Flow diagram.

RESULTS

21514 patients who were performed coronary catheterization were analyzed. A total of 862 patients included study. Out of total 862 patients studied, 595 had coronary artery disease (CAD) (306 had ST segment elevation myocardial infarction, 182 had non-ST segment elevation ACS, 107 had stable angina pectoris) and 267 had normal coronary arteries. Single vessel disease was seen in 299 (53 %)

patients, two-vessel disease in 170 (30 %) patients, and three-vessel disease in 78 (13%) patients. The young CAD group had a significantly higher proportion of males (94.1 % vs. 58.8%; P < 0.001), and smokers (78 % vs. 45%; P < 0.001) than age-matched control patients with normal coronary arteries (Table1).

Left ventricle ejection fraction was significantly lower (p< 0.001) in patients with CAD than patients with NCA. The groups were similar respect to age.

Diabetes mellitus, hypertension, obesity, hyperlipidemia and family history of CAD rates were similar between patients with and without CAD (for both parameters p> 0 .05). In patients with CAD, the rate of obesity and hypertension was higher in female group than males (41 % vs. 14 %; P < 0.01 and 17 % vs. 33 %; P =0.02) while the smoking rate was higher in males than females (80 vs. 44 %; P < 0.01) (Table 2). Diabetes mellitus, hypertension, hyperlipidemia and family history of CAD rates were similar between male and female gender (for both parameters p> 0.05). Univariate analysis showed that smoking, male gender and obesity were significantly associated with a higher risk of CAD (Table 3).

Table 1. Baseline demographic parameters of young coronary artery disease

	NCA (n=297)	CAD (n=564)	P value
LV ejection fraction (%)	58.9±10.5	49.8±11.5	>0.001
Age (years)	39.4±6.4	39.1±8.3	0.619
Diabetes Mellitus n, (%)	37 (12.5)	85 (15)	0.181
Hypertension n, (%)	62 (20)	103 (18)	0.192
Hyperlipidemia n,(%)	63 (21)	124 (21)	0.447
Smoking n,(%)	136 (45)	443 (78)	>0.001
Obesity n,(%)	66 (22)	90 (15)	0.14
Family history n,(%)	100 (33)	174 (30)	0.207
Male gender n,(%)	175 (58)	531 (94)	>0.001

NCA: Normal coronary arteries, CAD: Coronary artery disease

Table 2. Baseline demographic parameters of patients with coronary artery disease.

	CAD (+)		
	Male (n= 539)	Female (n=33)	P value
Age (years)	39 ±8.1	37±11.1	0.276
Diabetes Mellitus n, (%)	77 (14.5)	8 (24.2)	0.106
Hypertension n, (%)	92 (17)	11 (33)	0.02
Hyperlipidemia n, (%)	114 (21)	10 (30)	0.165
Smoking n, (%)	428 (80)	14 (42)	>0.001
Obesity n, (%)	77 (14)	13 (39)	>0.001
Family history n, (%)	164 (30)	9 (27)	0.413
LV ejection fraction (%)	52.11±11	49.7± 11.5	0.465

Table 3. Predictors of coronary artery disease in Univariate and Multivariate Logistic Regression Analysis.

	Univariate		Multivariate	
	OR (95 % CI)	P value	OR (95 % CI)	P value
Smoking	4.373 (3.2-5.9)	>0.01	2.30 (1.6-3.2)	>0.01
Male gender	11 (7.3-16.8)	>0.01	7.3 (4.6-11.4)	>0.01
Obesity	1.484 (1.04-2.11)	>0.01		

A multivariate binary logistic regression analysis was carried out by including all characteristics that were associated with CAD in the univariate analysis. This analysis showed that smoking (OR: 2.30; 95 % CI: 1.6-3.2, p<0.001) and male gender (OR: 7.3; 95 % CI: 4.6-11.4, p<0.001) remained as independent factors for CAD (Table 3). Among male CAD group had a higher rate of smoking and diabetes mellitus than patients with normal coronary arteries (80 % vs. 68%; P < 0.001 and 14 % vs. 9%; P = 0.04). Hypertension, obesity, hyperlipidemia and family history of CAD rates were similar between man with and without CAD (for both parameters p> 0 .05). Left ventricle ejection fraction was significantly lower (p<0.001) in man with CAD than man with NCA (Table 3). Among female CAD group had a higher rate of

smoking than patients with normal coronary arteries (42 % vs. 14 %; P < 0.001). Diabetes Mellitus, hypertension, obesity, hyperlipidemia and family history of CAD rates were similar between man with and without CAD (for both parameters p> .05). Left ventricle ejection fraction was significantly lower (p<0.001) in female with CAD than female with NCA (Table 4).

Table 4 Atherosclerotic risk factors among genders

	Male gender			Female gender		
	NCA (n=175)	CAD (n=531)	P value	NCA (n=121)	CAD (n=33)	P value
Diabetes Mellitus n,(%)	16 (9)	77 (14)	0.04	21 (17)	8 (24)	0.254
Hypertension n,(%)	22 (12)	92 (17)	0.08	40 (33)	11 (33)	0.566
Hyperlipidemia n,(%)	34 (19)	114 (21)	0.323	29 (24)	10 (30)	0.298
Smoking n,(%)	119 (68)	428 (80)	>0.001	17 (14)	14 (42)	>0.001
Obesity n,(%)	28 (16)	77 (14)	0.354	38 (31)	13 (39)	0.254
Family history n,(%)	46 (26)	164 (30)	0.145	24 (44)	9 (27)	0.05
LV ejection fraction (%)	56.9± 11	49.7±11.5	>0.001	61.0±8.7	52.1±11.0	0.003
Age (years)	38.5±6.9	39.2±8.1	0.331	40.6±5.2	30.5±11.1	0.025

Table5. Univariate regression analysis of smoking among genders

	Univariate analysis			
	Male gender		Female gender	
	OR (95 % CI)	P value	OR (95 % CI)	P value
Smoking	1.955 (1.3-2.8)	>0.01	4.5 (1.9-10.6)	>0.01

Univariate analysis showed that smoking was significantly associated with a higher risk of CAD in men and women separately (for men OR: 1.99; 95 % CI: 1.3-2.8, p<0.001 and for women OR: 4.5; 95 % CI: 1.9-10.6, p<0.001 (Table 5).

DISCUSSION

The current study showed that smoking was independently associated with the CAD in patients under the age of 45 whom presenting with acute coronary syndrome. Most of the risk factors for CAD were similar for men and women. Additionally, smoking had more detrimental effects on women than men for CAD risk. Surprisingly, traditional cardiovascular risk factors except of smoking and male gender were not associated with CAD in the total group. However, since it is suspected that there are strong gender differences in prognostic markers we performed a sex-specific analysis. In this analysis hypertension and obesity were higher in women. Then, we carried out an analysis for only men and women. In this analysis, smoking and diabetes mellitus rates were higher in men with CAD than in men with NCA. Interestingly, although smoking rate was higher in men than women, this risk factor was more strongly associated with CAD in women.

Cigarette smoking is the most common and most modifiable risk factor in young patients[10]. Smoking was both a risk factor for CAD, and a strong predictor of CAD mortality, although the risk decreased with smoking cessation [11]. Additionally, previous studies have showed that smoking is the most common risk factor associated with the complexity and severity of coronary artery disease and is significantly associated with increased risk of coronary plaque rupture, myocardial infarction, and increased cardiovascular morbidity and mortality [12-14]. Kannel et al.[15] found in patients included in the Framingham Heart Study that smoking was associated with a three-fold increase in the relative risk for CAD in smokers age 35 to 44, compared to nonsmokers. Smoking caused dysfunction and injury of the vascular intima by releasing catecholamine and increased oxidative stress[16,17]. In recent studies, smoking was determined the most strongly associated risk factor for CHD in young adults. Oliveira et al showed that adults <45 years of age

found an eightfold increase of AMI for those who smoked >25 cigarettes/day compared with those who had never smoked[18]. In the present study, we found that smoking was the most important risk factor among young adults and smoking was associated with a 4.5-fold increase in the relative risk for CAD among females, 1.9-fold increase among males. In Coronary Artery Surgery Study, Zimmerman et al. [19] found that current smoking was more frequent in young patients. In Michigan Medical Center, Doughty et al. [20] determined of patients ≤45 years old, 76.5% were smokers (P =.003) with a decreasing trend as age increased. Recent studies supported our results. Another study found that 75 % of young adults (< 35 years) with ACS were current smokers [21]. In our study, although smoking rate was higher in men than women, this risk factor was more strongly associated with CAD in women. In carried out univariate analysis among genders, compared with non-smokers, female current smokers had a relative risk of CAD of 4.5 (range 1.9-10.6) and male smokers 1.95 (1.3-2.8). Although CAD has seen lower among women than men, cigarette smoking has been associated with a higher relative risk of myocardial infarction and higher CAD mortality among women than men. Prescott and colleagues [22] carried out a longitudinal population study by followed 11 472 women and 13 191 men for a mean of 12.3 years. They found compared with non-smokers, female current smokers had a relative risk of myocardial infarction of 2.24 (range 1.85-2.71) and male smokers 1.43 (1.26-1.62); ratio 1.57 (1.25-1.97). The risks associated with smoking, measured by both current and accumulated tobacco exposure, were consistently higher in women than in men and did not depend on age. Women might be more sensitive to the damaging effects of smoking [22,23]. This more harmfully effects of smoking in women may associate with hormonal factors. Cigarette smoking includes reproductive toxicants and smoking has been associated with infertility, younger age at menopause and menstrual disorders[24]. The mechanism of these and other reported effects is not known but may alter the metabolism of estradiol by components of tobacco smoke, leading to enhanced formation of the inactive catechol estrogens, with smoking suggested as having anti-estrogenic effects[25]. The finding of the present study is that smoking was the only modifiable risk factor in ≤45-year old patients, suggesting that most of the acute myocardial infarction cases in this age group could be prevented only by smoking cessation.

Previous studies determined that CAD is predominantly seen in male[26,27]. Overall, 94 % of our patients were male, confirming previous studies. Diabetes Mellitus and hypertension appear to be less common in young patients with CAD than in older patients[19,28]. Similarly, in our study diabetes mellitus and hypertension rates were found similar in patients with CAD and in patients with NCA. However, hypertension rates were higher in female CAD patients than male CAD patients and diabetes mellitus rates were higher in males with CAD than males with NCA.

Cardiovascular disease (CVD) remains the most frequent cause of death in both men and women. In our study smoking was the most important modifiable risk factor in young patients. Smoking cessation should be recommended to all patients. The present study, which is the first epidemiologic study investigating risk factors for CAD in Turkish population, showed that the potentially modifiable risk factors, especially smoking, had high prevalence in patients with CAD living in region of lakes, in Turkey. This finding pointed out the importance of struggle against modifiable risk factors. Public health policies should be established for smoking cessation. In conclusion, individuals with risk factors should receive more attention to reduce unfavorable cardiovascular risk factors, and the development of future cardiovascular events. More aggressive management to prevent risk factors will probably play a strong protective role against most CAD cases especially among young individuals.

There are several limitations in our study. First, this study is retrospective and single-center study. Therefore, further studies are needed to draw definite conclusions. Finally, our analysis involved a simple baseline determination at a single time point that may not reflect the patient status over long periods.

REFERENCES

1. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ et al. Heart disease and stroke statistics—2014 update: a report from the American Heart Association. Circulation. 2013:129:e28-292.

2. Rubin JB, Borden WB. Coronary heart disease in young adults. Curr Atheroscler Rep. 2012;14:140-9.

3. Arzamendi D, Benito B, Tizon-Marcos H, Flores J, Tanguay JF et al. Increase in sudden death from coronary artery disease in young adults. Am Heart J. 2011;161:574-80.

4. Egred M, Viswanathan G, Davis G. Myocardial infarction in young adults. Postgrad Med J. 2005;81:741-5.

5. Chouhan L, Hajar HA, Pomposiello JC. Comparison of thrombolytic therapy for acute myocardial infarction in patients aged< 35 and> 55 years. Am J Cardiol. 1993;71:157-9.

6. Aygül N, Özdemir K, Abacı A, Aygül MÜ, Düzenli MA, Vatankulu MA et al. Prevalence of risk factors of ST segment elevation myocardial infarction in Turkish patients living in Central Anatolia. Anadolu Kardiyol Derg. 2009;9:3-8.

7. Köz C, Çelebi H, Yokuşoğlu M, Baysan O, Haşimi A, Serdaroğlu M, et al. The relation between coronary lesion distribution and risk factors in young adults. Anadolu Kardiyol Derg. 2009;9:91-5.

8. Judkins MP. Selective coronary arteriography. I. A percutaneous transfemoral technic. Radiology. 1967;89:815-24.

9. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Third universal definition of myocardial infarction. Circulation. 2012;126:2020-35.

10. Rathod KS, Jones DA, Gallagher S, Rathod VS, Weerackody R, Jain AK et al. Atypical risk factor profile and excellent long-term outcomes of young patients treated with primary percutaneous coronary intervention for ST-elevation myocardial infarction. Eur Heart J Acute Cardiovasc Care. 2016;5:23-32.

11. Keto J, Ventola H, Jokelainen J, Linden K, Keinänen-Kiukaanniemi S, Timonen M et al. Cardiovascular disease risk factors in relation to smoking behaviour and history: a population-based cohort study. Open Heart. 2016;3:e000358.

12. Buljubasic N, Akkerhuis KM, de Boer SP, Cheng JM, Garcia-Garcia HM, Lenzen MJ et al. Smoking in relation to coronary atherosclerotic plaque burden, volume and composition on intravascular ultrasound. PloS One. 2015;10:e0141093.

13. Yano M, Miura S-i, Shiga Y, Miyase Y, Suematsu Y, Norimatsu K et al. Association between smoking habits and severity of coronary stenosis as assessed by coronary computed tomography angiography. Heart Vessels. 2016;31:1061- 8.

14. Qu Y, Zhang F, Yang J, Dai Y, Li C, Yang H et al. Clinical characteristics and outcomes in Asian patients with premature coronary artery disease: insight from the FOCUS registry. Angiology. 2019:70:554-60.

15. Kannel WB, Mcgee DL, Castelli WP. Latest perspectives on cigarette smoking and cardiovascular disease: the Framingham Study. Journal of Cardiac Rehabilitation. 1984;4:267-77.

16. Jackson E. Cardiovascular risk of smoking and benefits of smoking cessation. UpToDate (Eds CP Cannon, BJ Downey) Available from https://www.uptodate.com/contents/cardiovascular -risk-of-smoking-and-benefits-of-smoking-cessation. Accessed 20.07.2018.

17. Altuntaş I, Dane Ş, Gümüştekin K. Effects of cigarette smoking on lipid peroxidation. J Basic Clin Physiol Pharmacol. 2002;13:69-72.

18. Oliveira A, Barros H, Maciel MJ, Lopes C. Tobacco smoking and acute myocardial infarction in young adults: a population-based case-control study. Prev Med. 2007;44:311-6.

19. Zimmerman FH, Cameron A, Fisher LD, Grace N. Myocardial infarction in young adults: angiographic characterization, risk factors and prognosis (Coronary Artery Surgery Study Registry). J Am Coll Cardiol. 1995;26:654- 61.

20. Doughty M, Mehta R, Bruckman D, Das S, Karavite D, Tsai T et al. Acute myocardial infarction in the young—The University of Michigan experience. Am Heart J. 2002;143:56- 62.

21. Schoenenberger AW, Radovanovic D, Stauffer J-C, Windecker S, Urban P, Niedermaier G et al. Acute coronary syndromes in young patients: presentation, treatment and outcome. Int J Cardiol. 2011;148:300-4.

22. Prescott E, Hippe M, Schnohr P, Hein HO, Vestbo J. Smoking and risk of myocardial infarction in women and men: longitudinal population study. BMJ. 1998;316:1043.

23. Prescott E, Osler M, Anderson PK, Hein HO, Borch-Johnsen K, Lange P et al. Mortality in women and men in relation to smoking. Int J Epidemiol. 1998;27:27-32.

24. General US. Youth Violence: A Report of the Surgeon General. Washington DC, US Department of Health and Human Services, 2001.

25. Baron JA, La Vecchia C, Levi F. The antiestrogenic effect of cigarette smoking in women. Am J Obstet Gynecol. 1990;162:502-14.

26. Pineda J, Marín F, Roldán V, Valencia J, Marco P, Sogorb F. Premature myocardial infarction: clinical profile and angiographic findings. Int J Cardiol. 2008;126:127-9.

27. Sozzi FB, Danzi GB, Foco L, Ferlini M, Tubaro M, Galli M et al. Myocardial infarction in the young: a sex-based comparison. Coron Artery Dis. 2007;18:429-31.

28. Cole JH, Miller JI, Sperling LS, Weintraub WS. Long-term follow-up of coronary artery disease presenting in young adults. J Am Coll Cardiol. 2003;41:521-8.