NEÜ YAYINLARI

SELÇUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL

Araştırma Makalesi
Research Article

Selcuk Med J 2020;36(2): 116-122

DOI: 10.30733/std.2020.01381

Myocardial Injury Non-Related Atherosclerotic Plaque Disruption in Patients Younger than 40 Years Old

Kırk Yaşından Genç Hastalarda Aterosklerotik Plak Bozulması ile İlişkili Olmayan Miyokardiyal Hasar

Ahmet Seyfeddin Gurbuz[1],
Semi Ozturk[2],
Sefa Tatar[1],
Mehmet Akif Duzenli[1],
Cevat Kirma[3]

[1]Necmettin Erbakan University, Meram Faculty of Medicine, Department of Cardiology, Konya, Turkey
[2]Haseki Training and Research Hospital, Department of Cardiology, Istanbul, Turkey
[3]Kosuyolu Training and Research Hospital, Department of Cardiology, Istanbul, Turkey

Geliş Tarihi/Received: *19 July 2019*
Kabul Tarihi/Accepted: *24 September 2019*

Address correspondence to: Ahmed Seyfeddin Gurbuz, Necmettin Erbakan University, Meram Faculty of Medicine, Department of Cardiology, Konya, Turkey
e-mail: ahmetseyfeddingurbuz@hotmail.com

ORCID
Ahmet Seyfeddin Gurbuz
https://orcid.org/0000-0002-9225-925X
Semi Ozturk
https://orcid.org/0000-0001-5696-6849
Sefa Tatar
https://orcid.org/0000-0001-8703-5078
Mehmet Akif Duzenli
https://orcid.org/0000-0002-0509-1322
Cevat Kirma
https://orcid.org/0000-0001-9986-050X

Öz

Amaç: Koroner arter hastalığı nedenli miyokard infarktüsü (MICAD), miyokardiyal hasarın önde gelen nedenidir. Aterosklerotik plak bozulmasına bağlı olmayan miyokardiyal hasar (MICAD olmayan) nadir ve heterojen bir tanıdır. Genç hasta popülasyonunda MICAD iyi bilinmesine rağmen, MICAD olmayan miyokardiyal hasar tam olarak tanımlanmamıştır. Çalışmamızda 40 yaşından genç hastalarda MICAD olmayan miyokardiyal hasarın prevalansı, etiyolojisi ve beş yıllık mortalitesini araştırmayı amaçladık.
Hastalar ve Yöntem: Ocak 2010 ile Aralık 2014 arasında 40 yaşından genç akut miyokardiyal hasarı olan 292 hastayı retrospektif olarak çalışmamıza dahil ettik. Klinik, demografik, laboratuvar, anjiyografik özellikler ve beş yıllık tüm nedenlere bağlı mortalite, MICAD olmayan miyokardiyal hasar (n= 78) ve MICAD (n = 214) hastaları arasında karşılaştırıldı.
Bulgular: Hasta yaşlarının medyan değeri 36 idi. MICAD olmayan grup, MICAD grubundan daha gençti [32 (28-37) vs 37 (34-39)]. MICAD olmayan grupta kadın hastaların oranı, MICAD grubuna göre daha yüksekti (% 24.4'e karşılık % 10.3). MICAD olan hastaların çoğu ST elevasyonlu MI (% 77.1) ile başvururken, MICAD olmayan hastaların çoğu ST elevasyonu olmayan MI ile (% 89.7) başvurdu. MICAD olmayan miyokardiyal hasarın en sık görülen etiyolojileri miyokardit (% 32) ve vazospazm (% 9) idi. Yaş, kadın cinsiyet, sigara içmemek ve dislipidemi yokluğu, MİCAD olmayan miyokardiyal hasar için bağımsız öngördürücülerdi. MICAD olmayan grupta beş yıllık tüm nedenlere bağlı mortalite, MICAD grubundan anlamlı derecede daha düşüktü (% 2.6'ya karşılık% 10.3) (log-rank testi p = 0.04).
Sonuç: MICAD olmayan miyokardiyal hasar, farklı yaşlarda farklı etiyolojilere sahip heterojen bir grup hastayı temsil etmektedir. MICAD olmayan grubun düşük mortalite oranına rağmen, MICAD olmayan miyokardiyal hasarın yönetiminde farklı tanı ve tedavi stratejileri gerekmektedir.

Anahtar Kelimeler: Akut koroner sendrom, etyoloji, miyokard enfarktüsü, miyokard hasarı, prognoz

Abstract

Aim: Myocardial infarction with coronary artery disease (MICAD) is the leading cause of myocardial injury. Myocardial injury non-related to atherosclerotic plaque disruption (non-MICAD) is a rare and heterogeneous diagnosis. Although MICAD is well studied, non-MICAD was not thoroughly identified in young patient population. We aimed to investigate the frequency, main etiologies, and five-year mortality of patients with non-MICAD younger than 40 years.
Patients and Methods: We retrospectively enrolled 292 patients with acute myocardial injury younger than 40 years between January 2010 and December 2014. Clinical, demographic, laboratory, angiographic features, and five-year all-cause mortality were compared between patients with non-MICAD (n=78) and MICAD (n=214).
Results: Median age of patients was 36. Non-MICAD group was younger than MICAD group [32 (28-37) vs 37 (34-39)]. The frequency of female patients with non-MICAD was higher than those with MICAD (24.4% vs 10.3%). Most of the patients with MICAD presented with STEMI (77.1%), while most of the patients with non-MICAD presented with non-STEMI (89.7%). Most common etiologies of non-MICAD in were myocarditis (32%) and vasospasm (9%). Age, female sex, no smoking and, absence of dyslipidemia were independent predictors for non-MICAD. Five-year all-cause mortality in non-MICAD group was significantly lower than MICAD group (2.6% vs 10.3%) (log-rank test p=0.04).
Conclusion: Non-MICAD represents a heterogeneous group of patients who had varying etiologies at different ages. Despite the lower mortality rate of non-MICAD group, different diagnostic and treatment strategies are required for management of patients with non-MICAD.

Key words: Acute coronary syndrome, etiology, myocardial infarction, myocardial injury, prognosis

INTRODUCTION

Until recently, treatment of acute myocardial infarction (MI) has focused on alleviating atherothrombotic processes that obstruct coronary blood flow. However, non-obstructive coronary artery disease has been reported in 2-25% of patients with

Cite this article as: Gurbuz AS, Ozturk S, Tatar S, Duzenli MA, Kirma C. Myocardial Injury Non-Related Atherosclerotic Plaque Disruption in Patients Younger than 40 Years Old. Selcuk Med J 2020;36(2): 116-122

Disclosure: *None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this article. The research was not sponsored by an outside organization. All authors have agreed to allow full access to the primary data and to allow the journal to review the data if requested.*

myocardial infarction (MI) (1-5). Furthermore, major adverse cardiac event (MACE) has been reported in 24% of these patients during 5 years of follow-up (6). Given the significance of this type of acute coronary syndrome, European Society of Cardiology (ESC) working group described this clinical entity as myocardial infarction with non-obstructive coronary arteries (MINOCA) in recent guideline. MINOCA was defined as the absence of obstructive (≥50%) coronary artery stenosis on angiography in any potential infarct-related artery (IRA) and absence of clinically apparent specific cause for acute presentation in patients with universal MI criteria (7). The scope of MINOCA and myocardial injury was redefined in the recent guideline. The myocardial injury defined as there is evidence of elevated cardiac troponin values (cTn) with at least one value above the 99th percentile upper reference limit (URL). The acute myocardial injury described as a rise and/or fall of cTn values. The diagnosis of MINOCA depends on myocyte injury with an underlying ischaemic mechanism. Therefore, the recent definition of MINOCA does not include non-ischemic causes such as myocarditis. Additionally, ischemic causes such as spontaneous coronary dissection and vasospasm were excluded from the redefinition of MINOCA in the recent guideline (8). Myocardial injury related to acute myocardial ischaemia due to atherosclerotic plaque disruption with thrombosis identified MICAD (8). Although the definition of MINOCA comprises a heterogeneous group of patients, two distinct pathophysiologic patterns exist; microvascular and epicardial. Regional wall motion abnormalities restricted to a single epicardial coronary artery territory on left ventricle angiography was described as 'epicardial pattern', whereas regional wall motion abnormalities extended beyond a single epicardial coronary artery territory was described as 'microvascular pattern'(9).

Myocardial ischaemia due to oxygen supply/demand imbalance and other causes of myocardial injury such as heart failure, takotsubo syndrome, cardiomyopathy, myocarditis, sepsis, chronic kidney disease, subarachnoid haemorrhage, infectious disease, pulmonary hypertension, stroke, and MINOCA were included in non-MICAD group in our study. Considering the MINOCA definition in the previous guideline, the definition of MINOCA in previous studies is equivalent to the non-MICAD group in our study. Previous studies demonstrated that MINOCA were more frequent in young and female patients compared those with MI with coronary artery disease (MICAD) (10,11). In our study, we aimed to determine the frequency of non-MICAD group and MICAD group in patients with myocardial injury underwent coronary angiography, association between traditional cardiovascular (CV) risk factors in young patients. Additionally, we compared long- term mortality rates of patients with non-MICAD group and MICAD group.

PATIENTS AND METHODS

Study population and Data Collection

536 of 35782 patients, who underwent coronary angiography between January 2010 and December 2014 in multicenter - aged between 18 and 40- were retrospectively screened in 2018. Screening was determined as patients who underwent selective coronary angiography with or without ventriculography under 40 years of age using hospital database (Figure 1). 38 patients with the previous history of coronary artery disease were excluded from the study. 292 of 498 patients, who were diagnosed as acute myocardial injury according to the ESC guideline

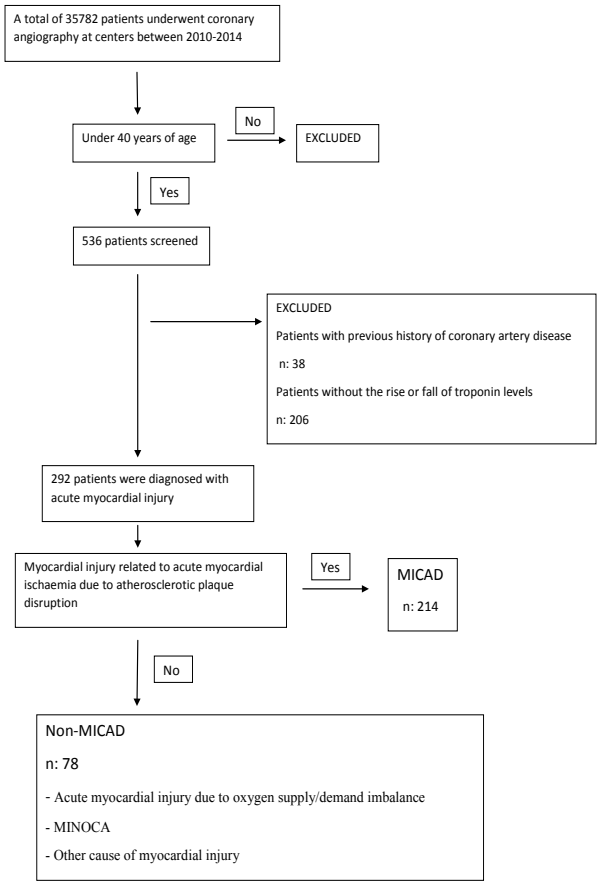

Figure 1. Patient flowchart

mentioned above, were included in the study (8). MI subgroup (STEMI or non-STEMI) on admission was defined by an expert cardiologist depending on electrocardiography and Troponin I levels. Angiograms were reviewed by an expert cardiologist to identify coronary anatomy, severity of coronary stenosis and pathologies such as spontaneous coronary artery dissection (SCAD), myocardial bridging, vasospasm, presence of thrombus formation, coronary slow flow phenomenon (CSFP), coronary artery ectasia (CAE). SCAD is defined as spontaneous tearing of the coronary artery wall, which is not related to atherosclerotic and iatrogenic causes. Myocardial bridging is the compression of the myocardium, usually during systole, on the coronary artery in the myocardium instead of normal epicardial course. Coronary artery vasospasm is a temporary and reversible vasoconstriction of the major epicardial coronary artery causing myocardial ischemia. CAE is defined as a localized or diffuse dilation of the coronary artery with a diameter of at least 1.5 times the adjacent normal coronary artery. Coronary slow flow is a slow antegrade transition of blood through one or more vessels of the coronary tree. Patients were then divided into two groups according to the presence of any epicardial coronary artery stenosis of at least 50%. Left ventricle angiogram or echocardiography was reviewed to detect presence or absence of regional wall abnormalities and cardiomyopathy. Clinical, demographic and laboratory data were collected by using the hospital database. Eventual diagnosis of MINOCA was established according to the ESC Guideline mentioned above (8). Acute myocardial ischaemia due to oxygen supply/demand imbalance, other cause of myocardial injury and MINOCA included non-MICAD group. Mean follow-up was 57.3±0.8 months and five-year all-cause mortality was the primary endpoint. Follow-up was completed for all patients by scanning the records in the National Death Notification System (https://obs.gov.tr/). Hypertension was diagnosed based on the following criteria: Office systolic blood pressure ≥140 mmHg and / or diastolic blood pressure ≥90 mmHg or any antihypertensive treatment during the admission. Diabetes mellitus (DM) was diagnosed according to these criteria: Fasting plasma glucose level ≥126 mg / d L or hypoglycemic drug history taken during admission. LDL-cholesterol level ≥130 mg/dL, serum triglyceride level >150 mg/dL, HDL-cholesterol in women ≤ 50 mg/dL, in men ≤ 40 mg/dL or lipid-lowering drug use was defined as dyslipidemia. The study protocol was approved by ethics committee of Necmettin Erbakan University Meram Medicine Faculty (2019/1754) in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 19.0 (IBM Corp. Armonk, NY). Descriptive statistics are reported as mean ± standard deviation for continuous variables with normal distribution or median (25th-75th percentiles) values for continuous variables without normal distribution and as frequency with percentages for the categorical variables. The Kolmogorov-Smirnovtest was used to analyze the normality of the data. Categorical variables were compared using the chi-square test. A binary logistic regression analysis was applied in order to identify independent predictors of non-MICAD group. Kaplan–Meier analysis with the log-rank test for survival analysis was applied. The significance level was accepted as $p<0.05$ in all statistical analyses.

RESULTS

Of 292 patients with MI, 78 patients (26.7%) were included non-MICAD group and 214 patients (73.3%) were included MICAD group. The median age of the patient population was 36 and non-MICAD group was younger than MICAD group [32 (28-37) vs 37 (34-39) $p<0.001$]. Non-MICAD group and MICAD group were more frequent in male, however, female patients were more frequent in non-MICAD group compared with MICAD group (24.4% vs 10.3% $p=0.002$). Demographic, clinical and laboratory characteristics of patients were presented in Table 1. Diabetes, dyslipidemia, and smoking were more frequent in patients with MICAD compared those with non-MICAD. Most of the patients with MICAD presented with STEMI (77.1%) while most of the non-MICAD group presented with non-STEMI (89.7%). More patients with MICAD presented with cardiogenic shock than non-MICAD group. At the time of admission, leukocyte levels of patients with MICAD were higher than those with non-MICAD group. Hospital stay of patients with MICAD was significantly longer than non-MICAD group [4 (3-6) vs 3 (2-4.75), $p=0.003$]. Subgroup diagnoses of 78 patients of non-MICAD group were presented in Table 2. Most frequent diagnoses were myocarditis (32.1%) and vasospasm (9%). 8.9% of patients with MICAD had multivessel disease, 0.9% had left main disease whereas 1.4% had chronic total occlusion. Among CV risk factors age, female gender,

Table 1. Demographic, clinical, laboratory characteristics and follow-up information of non-MICAD and MICAD groups.

	Non-MICAD n:78	MICAD n:214	p value
Age (years)	32 (28-37)	37 (34-39)	<0.001
Sex (female), n(%)	19 (24.4)	22 (10.3)	0.002
BMI (kg/m^2)	28.0±3.4	27.8±2.8	0.7
Risk Factors			
Dyslipidemia, n(%)	24 (30.8)	97 (45.3)	0.03
Diabetes, n(%)	12 (7.7)	39 (18.2)	0.03
Hypertension, n(%)	25 (32.1)	76 (35.5)	0.6
Smoking, n(%)	19 (24.4)	89 (41.6)	0.007
ECG presentation			
STEMI	8 (10.3)	165 (77.1)	<0.001
Non-STEMI	70 (89.7)	49 (22.9)	<0.001
Laboratory			
Urea (mg/dl)	27.2±8.9	27.8±8.5	0.7
Creatinine (mg/dl)	0.85±0.21	0.80±0.21	0.3
Hb (g/dl)	14.4±1.6	14.4±1.6	0.97
Platelet (103/mm^3)	252.6±87.6	284.0±78.3	0.07
Leukocyte(103/mm^3)	11.4±2.5	14.3±5.4	<0.001
Clinical Manifestations			
Ventricular arrhythmia	1 (1.3)	13 (6.1)	0.09
Complete AV block	0 (0)	2 (0.9)	0.4
Cardiac Arrest	0 (0)	8 (3.7)	0.08
Cardiogenic Shock	0 (0)	10 (4.8)	0.05
Follow-up			
Duration of hospitalization (day)	3 (2-4.75)	4 (3-6)	0.003
In-Hospital Mortality	0 (0)	6 (2.8)	0.1
One-Year Mortality	1 (1.3)	12 (5.6)	0.1
Five-Year Mortality	2 (2.6)	22 (10.3)	0.04

MICAD, Myocardial infarction with obstructive coronary artery disease; BMI, Body Mass Index; STEMI, ST-Elevation Myocardial Infarction; Hb, Hemoglobin

no smoking and absence of dyslipidemia were determined as independent predictors of non-MICAD group in multivariate analysis (Table 3). In-hospital mortality and one-year all cause mortality rates were lower in non-MICAD group albeit statistical non-significance (Table 1). Five-year all-cause mortality rate in non-MICAD group was significantly lower than MICAD group [2.6% (n=2) vs 10.3% (n=22) (log-rank test p=0.04)](Figure 2).

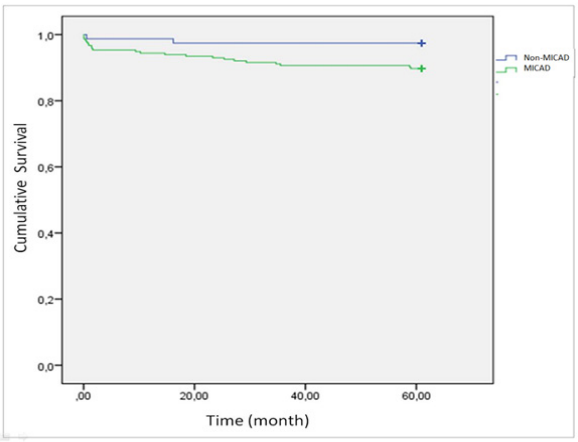

Figure 2. Kaplan–Meier analysis for five -year all-cause mortality in non-MICAD and MICAD groups.

Table 2. Subgroup diagnosis of non-MICAD group

Final Diagnosis	Prevalance N (%)
Myocarditis	25 (32.1)
Vasospasm	7 (9)
Muscular Bridge	3 (3.8)
Cardiomyopathy	4 (5.1)
Tachyarrhythmia-induced infarct	4 (5.1)
Coronary slow flow phenomenon	4 (5.1)
Coronary artery ectasia	2 (2.6)
Coronary artery anomaly	3 (3.8)
Spontaneous coronary dissection	4 (5.1)
Coronary embolism	2 (2.6)
Sepsis	2 (2.6)
Pulmonary embolism	1 (1.3)
Takotsubo Cardiomyopathy	1 (1.3)
Severe Anemia	1 (1.3)
Diagnosis (Unknown)	15 (19.2)

Table 3. Multivariate analysis of cardiovascular risk factors for non-MICAD group

	p value	OR	95% CI
Age	<0.001	1.21	1.13-1.30
Sex (Female)	0.001	3.48	1.62-7.49
Smoking (None)	0.03	2.05	1.07-3.91
Diabetes (None)	0.4	1.5	0.58-3.91
Hypertension (None)	0.9	1.02	0.46-2.28
Dyslipidemia (None)	0.02	2.48	1.13-5.43

DISCUSSION

The present study reports prevalence, predictors and mortality rate of myocardial injury non-related to atherosclerotic plaque disruption (non-MICAD) in a very young population. The frequency of non-MICAD was relatively higher in our study compared with studies involving older patients (11-13). Even in our very young patient population, non-MICAD group was younger than patients with MICAD. Non-MICAD group was more likely to be female, non-smoker and normolipidemic compared with patients with MICAD in our study. Compatible with previous studies, five-year all-cause mortality rate was lower in non-MICAD group than patients with MICAD (11-14). Since MINOCA is relatively a new clinical definition, underlying causes, association with CV risk factors and prognosis were not thoroughly investigated. In a systematic review of patients with MI, the prevalence of MINOCA was 6%, median age was 55 and 40% of patients were women (11). In a recent study involving patients with premature MI younger than 55 years of age, the prevalence of MINOCA was reported as 8% whereas women comprise 41% of patients with MINOCA (12). In our study, the prevalence of non-MICAD group was 26% and the frequency of women in non-MICAD was higher than in MICAD (24% vs 10%). The ACTION registry demonstrated in male patients that prevalence of MINOCA increased in younger patients (13). Most of our patient population is composed of young males, this may result in a higher prevalence of non-MICAD and, relatively lower proportion of women with non-MICAD in our study compared with studies involving older patients. In the aforementioned systemic review, hyperlipidemia was less common in patients with MINOCA than in patients with MICAD, however, diabetes, hypertension and smoking were not different between two groups (11). In the ACTION registry, patients with MINOCA had fewer traditional CV risk factors including dyslipidemia, diabetes mellitus, and tobacco use compared with patients with MICAD (13). Consistent with the ACTION registry, we demonstrated that dyslipidemia, smoking, and diabetes were less frequent in non-MICAD group compared to patients with MICAD in a young population. Age, female sex, no tobacco use, absense of previous MI, non-STEMI, atrial fibrillation (AF) were independent predictors of MINOCA (6). Among CV risk factors age, female sex, no smoking, and absence of dyslipidemia were independent predictors for non-MICAD group in our study.

Patients presenting with new ST-segment elevation with a significant increase in troponin levels and non-obstructive CAD on angiography should be diagnosed as MINOCA. Diagnosing these patients as "false-positive STEMI" will result in an inadequate evaluation and inappropriate treatment (15,16). Previous studies demonstrated that most of the patients with MINOCA were diagnosed as non-STEMI, furthermore proportion of non-STEMI in MINOCA was more than in MICAD. The frequency of patients with STEMI in non-MICAD group is 7-38% in previous studies, which is 10% in our study (6,10-13). The proportion of patients with increased CRP was found to be higher in patients with MICAD compared with patients with MINOCA (12). Compatible with this data, we found that leukocyte counts in patients with MICAD were higher than those with non-MICAD group. In the ACTION registry, in-hospital mortality rate was lower in patients with MINOCA than MICAD. Among patients with MICAD, women had higher mortality rate than men. No sex difference in mortality rate was observed in patients with MINOCA. Furthermore, in-hospital mortality rate was 0.5% in patients with MINOCA younger than 50 years (13). Pooled analysis of 8 studies demonstrated that in-hospital and 12 months all-cause mortality rate were 0.9% and 4.7% in patients with MINOCA. In addition, these mortality rates were lower than those with MICAD (11). In KOREAN MI registry, one-year mortality of patients with MINOCA and patients with MI with one or two vessel CAD were similar, while patients with three-vessel or left main diseases had higher mortality (17). In a study involving patients with MI younger than 55 years, cardiac and non-cardiac one-year mortality rates were similar in patients with MINOCA and MICAD, whereas MACE and adverse events were higher in patients with MICAD (12). In our study, in-hospital and one-year all-cause mortality rates were lower in non-MICAD group albeit statistical non-significance. In COAPT study which followed patients with MI for five years, the mortality rate of patients with MINOCA was lower than MICAD (10.9%

vs 16%) (14). In a single-center retrospective study with a mean age of 66, five-year mortality rate of patients with MINOCA was 8.7% and lower than those with MICAD (10). In our retrospective study, which included very young patients with acute myocardial injury, five-year all-cause mortality rate of non-MICAD group was 2.6%. In a recent study, old age, diabetes, current smoking, previous stroke, COPD, previous or current cancer, decreased LVEF, higher levels of creatinine and CRP were independent predictors of long-term all-cause mortality in patients with MINOCA (6).

Heterogeneous etiology of acute myocardial injury makes the diagnosis challenging. Therefore, careful evaluation of angiography and left ventriculography in addition to rigorous clinical evaluation are required to determine etiology of acute myocardial injury. On the other hand, further investigation such as CT angiography to diagnose pulmonary embolism, cardiac imaging to detect myocardial pathologies, provocation tests to detect microvascular and epicardial spasm, drug screening for substance abuse and thrombophilia screening for coronary thrombus or embolism may be needed. Intravascular ultrasound (IVUS) or optical coherence tomography (OCT) may be considered for the exact diagnosis of pathologies such as invisible plaque rupture and ulceration, spontaneous dissection, thrombus or emboli (8,9). Endomyocardial biopsy might be considered to verify myocarditis, particularly in fulminant cases (18). In a recent, retrospective study involving all age groups, takotsubo cardiomyopathy (20%), myocarditis (18%), coronary embolism due to AF (10%) were the most common etiologies of MINOCA (10). In our study, we found myocarditis (32%) and vasospasm (9%) were the most common etiologies in non-MICAD group younger than 40 years. Takotsubo cardiomyopathy is more common in postmenopausal women exposed to physical or emotional stress (19). Both frequencies of AF and embolic complications increase with age (20). Myocarditis is usually diagnosed in young patients and with a recent history of infection (21). Etiologies of non-MICAD group in young patients might differ from those in the general population due to the aforementioned reasons. We could not identify the etiology of non-MICAD group in a quarter of patients. This situation may be related with challenging diagnoses such as microvascular dysfunction, invisible plaque rupture or ulcer and thrombus or emboli. Need for advanced technologies such as OCT, IVUS, Fractional Flow Reserve (FFR), etc. may cause underdiagnosis of MINOCA.

The primary limitation of our study was the retrospective nature. Another important limitation was that coronary microvascular dysfunction (CMD) was not evaluated with measurement of coronary flow reserve (CFR) or noninvasive imaging such as positron emission tomography (PET) or cardiac magnetic resonance imaging (cMRI). For this reason, we could not determine the frequency of CMD. In addition, only about a quarter of myocarditis were diagnosed by cMRI and others were diagnosed by clinical and echocardiographic evaluation. IVUS or OCT were not performed to detect invisible plaque rupture or ulcer, spontaneous dissection, and thrombus or emboli. Hyperventilation and cold pressor tests were being used for detection of vasospasm due to inadequacy of ergonovine in our country at that time.

CONCLUSION

In our retrospective study, involving patients with MI underwent coronary angiography, younger than 40 years without a previous history of coronary artery disease, the frequency of non-MICAD group was 26.7%. Non-MICAD group represents a group of heterogeneous patients who had varying etiologies at different ages. Most common etiologies of the non-MICAD group in this age group were myocarditis and vasospasm. Age, female sex, no smoking and absence of dyslipidemia were independent predictors for non-MICAD group. The long-term all-cause mortality rate of non-MICAD group was 2.6% which is less than MICAD. Despite low mortality rate of non-MICAD group, the mortality rate may be further reduced by identifying etiology of non-MICAD group better. There is a need for prospective studies with a large number of patients where the diagnosis of non-MICAD and its etiology is systematically evaluated.

Conflict of interest: *Authors declare that there is no conflict of interest between the authors of the article.*

Financial conflict of interest: *Authors declare that they did not receive any financial support in this study.*

Address correspondence to: *Ahmed Seyfeddin Gurbuz, Necmettin Erbakan University, Meram Faculty of Medicine, Department of Cardiology, Konya, Turkey*
Telephone: *+905554971845*
e-mail: *ahmetseyfeddingurbuz@hotmail.com*

REFERENCES

1. Bugiardini R, Manfrini O, De Ferrari GM. Unanswered

questions for management of acute coronary syndrome: Risk stratification of patients with minimal disease or normal findings on coronary angiography. Arch Intern Med 2006;166:1391-5.
2. Gehrie ER, Reynolds HR, Chen AY, et al. Characterization and outcomes of women and men with non-ST-segment elevation myocardial infarction and nonobstructive coronary artery disease: Results from the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) quality improvement initiative. Am Heart J 2009;158:688-94.
3. Bugiardini R, Bairey Merz CN. Angina with "normal" coronary arteries: A changing philosophy. JAMA 2005;293:477-84.
4. Crea F, Camici PG, De Caterina A, et al. Chronic ischaemic heart disease. In: Camm AJ, Lu¨scher TF, Serruys P, eds. The ESC Textbook of Cardiovascular Medicine. New York, NY: Oxford University Press 2009:657-60.
5. Larsen AI, Galbraith PD, Ghali WA, et al. Characteristics and outcomes of patients with acute myocardial infarction and angiographically normal coronary arteries. Am J Cardiol 2005;95(2):261-3.
6. Nordenskjöld AM, Baron T, Eggers KM, et al. Predictors of adverse outcome in patients with myocardial infarction with non-obstructive coronary artery (MINOCA) disease. Int J Cardiol 2018;261:18-23.
7. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2017;39:119-77.
8. Thygesen K, Alpert JS, Jaffe AS, et al. ESC Scientific Document Group. Fourth universal definition of myocardial infarction (2018). Eur Heart J 2018 Aug 25.
9. Niccoli G, Scalone G, Crea F. Acute myocardial infarction with no obstructive coronary atherosclerosis: Mechanisms and management. Eur Heart J 2015;36(8):475-81.
10. Montenegro Sá F, Ruivo C, Santos LG, et al. Myocardial infarction with nonobstructive coronary arteries: A single-center retrospective study. Coron Artery Dis 2018 Mar 31.
11. Pasupathy S, Air T, Dreyer RP, et al. Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries. Circulation 2015;131:861-70.
12. Raparelli V, Elharram M, Shimony A, et al. Myocardial infarction with no obstructive coronary artery disease: Angiographic and clinical insights in patients with premature presentation. Can J Cardiol 2018;34(4):468-76.
13. Smilowitz NR, Mahajan AM, Roe MT, et al. Mortality of myocardial infarction by sex, age, and obstructive coronary artery disease status in the ACTION registry-GWTG (acute coronary treatment and intervention outcomes network registry-get with the guidelines). Circ Cardiovasc Qual Outcomes 2017;10(12):e003443.
14. Bainey KR, Welsh RC, Alemayehu W, et al. Population-level incidence and outcomes of myocardial infarction with non-obstructive coronary arteries (MINOCA): Insights from the Alberta contemporary acute coronary syndrome patients invasive treatment strategies (COAPT) study. Int J Cardiol 2018;264:12-17.
15. McCabe JM, Armstrong EJ, Kulkarni A, et al. Prevalence and factors associated with false-positive ST-segment elevation myocardial infarction diagnoses at primary percutaneous coronary intervention-capable centers: A report from the Activate-SF registry. Arch Intern Med 2012;172:864-71.
16. Chung SL, Lei MH, Chen CC, et al. Characteristics and prognosis in patients with false-positive ST-elevation myocardial infarction in the ED. Am J Emerg Med 2013;31:825-29.
17. Kang WY, Jeong MH, Ahn YK, et al. Are patients with angiographically near-normal coronary arteries who present as acute myocardial infarction actually safe? Int J Cardiol 2011 21;146(2):207-12.
18. Arık OZ, Özkan B, Kutlu R, et al. Relationship between platelet indices and international normalized ratio in patients with non-valvular atrial fibrillation. Platelets 2014;25(5):311-6.
19. Veillet-Chowdhury M, Hassan SF, Stergiopoulos K. Takotsubo cardiomyopathy: A review. Acute Card Care 2014;16(1):15-22.
20. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37(38):2893-962.
21. Caforio AL, Pankuweit S, Arbustini E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: A position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2013;34(33):2636-48.