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Evaluation of demographic and clinical characteristics of female patients presenting with MINOCA and differences between male patients: A subgroup analysis of MINOCA-TR registry

MINOCA ile başvuran kadın hastaların demografik ve klinik özelliklerinin değerlendirilmesi ve erkek hastalarla farklılıkları: MINOCA-TR çalışmasının grup analizi

ABSTRACT

Objective: Although the prevalence and rate of myocardial infarction with non-obstructive coronary arteries (MINOCA) are higher in women than in men in previous cohorts, potential demographic and clinical differences between women who are diagnosed with MINOCA versus myocardial infarction with obstructive coronary arteries (MIOCA) have not been studied till date. In this study, we aimed to document these characteristics and to compare them between female patients with MINOCA and MIOCA.

Methods: The study was a subgroup analysis of the MINOCA-TR study. The study was a multi-center, observational cohort study that was conducted in Turkey between March 2018 and October 2018. In this study, 477 (29.3%) female patients who had been diagnosed with acute myocardial infarction were evaluated.

Results: Of these women, 49 (10.3%) were diagnosed with MINOCA (mean age 58.9±12.9 years) and 428 (89.7%) had a final diagnosis of MIOCA (mean age 67.4±11.8 years). The prevalence of hypertension, hyperlipidemia, and diabetes mellitus was significantly lower in the MINOCA group than in the MIOCA group. In addition, the MINOCA group had higher rates of recent flu history and non-ST elevation myocardial infarction (NSTEMI) presentation than the MIOCA group. There were significant clinical differences in patients with MINOCA in terms of sex. The female patients were older, had higher systolic blood pressures, and lower hemoglobin levels than male patients.

Conclusion: The study revealed that the prevalence of traditional coronary artery disease risk factors was lower in female patients with MINOCA than in those who had final diagnosis of MIOCA.

Keywords: Female, MINOCA, demographics, risk factor

ÖZET

Amaç: Daha önceki kohortlarda kadın hastalarda obstrüktif olmayan koroner arterlerle miyokart enfarktüsü (MINOCA) erkeklere göre daha yüksek oranda olmasına rağmen, MINOCA ve obstrüktif koroner arterli miyokart enfarktüsü (MIOCA) tanısı alan kadın hastalar arasındaki potansiyel demografik ve klinik farklılıklar bugüne kadar çalışılmamıştır. Bu çalışma, bu özellikleri araştırmayı ve kadın MINOCA ve MIOCA hastaları arasında karşılaştırmayı amaçladı.

Yöntemler: Çalışma, Türk popülasyonu (MINOCA-TR) kayıtlarının subgrup analizidir. Kayıt, Türkiye'de Mart 2018-Ekim 2018 tarihleri arasında yürütülen çok merkezli, gözlemsel bir kohort çalışmasıydı. Bu çalışmada 477 (%29.3) akut miyokart enfarktüsü tanısı alan kadın hasta değerlendirildi.

Bulgular: Kadınlardan 49'u (%10.3) MINOCA (ortalama yaş: 58.9±12.9 yıl) ve 428'i (%89.7) MIOCA (ortalama yaş: 67.4±11.8 yıl) tanısı almıştı. MINOCA grubunda hipertansiyon, hiperlipidemi ve diabetes mellitus prevalansları MIOCA grubuna göre anlamlı olarak daha düşüktü. Ek olarak, MINOCA grubunda MIOCA grubuna kıyasla daha yüksek oranlarda yakın zamanlı grip öyküsü ve ST yükselmesiz miyokart enfarktüsü (NSTEMI) prezentasyonu vardı. MINOCA hastalarında cinsiyet açısından önemli klinik farklılıklar vardı. Erkek vakalarla karşılaştırıldığında, kadın hastalar daha yaşlıydı, daha yüksek sistolik kan basıncına ve daha düşük hemoglobin seviyelerine sahipti.

Sonuç: Çalışma, MIOCA kesin tanısı almış kadın hastalara göre, kadın MINOCA hastalarında geleneksel koroner arter hastalığı risk faktörünün daha düşük prevalansta olduğunu ortaya koymuştur.

Anahtar Kelimeler: Kadın, MINOCA, demografik özellikler, risk faktörleri

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

Gülay Gök, M.D.[1]
Ali Çoner, M.D.[2]
Tufan Çınar, M.D.[3]
Salih Kılıç, M.D.[4]
Mustafa Yenerçağ, M.D.[5]
Ahmet Öz, M.D.[6]
Cenk Ekmekçi, M.D.[7]
Özlem Özlük, M.D.[8]
Mehdi Zoghi, M.D.[9]
Asım Oktay Ergene, M.D.[10]
Uğur Önsel Türk, M.D.[11]

[1]*Department of Cardiology, Medipol University Hospital, Istanbul, Turkey*
[2]*Department of Cardiology, Başkent University Alanya Application and Research Center, Antalya, Turkey*
[3]*Department of Cardiology, Haydarpaşa Sultan Abdulhamid Han Training and Research Hospital, Istanbul, Turkey*
[4]*Department of Cardiology, Health Sciences University Adana Training and Research hospital, Adana, Turkey*
[5]*Department of Cardiology, University of Health Sciences Samsun Training and Research Hospital, Samsun, Turkey*
[6]*Department of Cardiology, Istanbul Training and Research Hospital, Istanbul, Turkey*
[7]*Departmant of Cardiology, Tepecik Training and Research Hospital, Izmir, Turkey*
[8]*Department of Cardiology, Bursa İhtisas Training and Research Hospital, Bursa, Turkey*
[9]*Department of Cardiology, Ege University Hospital, Izmir, Turkey*
[10]*Department of Cardiology, Dokuz Eylül University Hospital, Izmir, Turkey*
[11]*Department of Cardiology, Izmir Economy University, Izmir, Turkey*

Corresponding Author:
Gülay Gök
✉ glygk84@gmail.com

Received: January 13, 2021
Accepted: August 23, 2021

Cite this article as: Gök G, Çoner A, Çınar T, Kılıç S, Yenerçağ M, Öz A, et al. Evaluation of demographic and clinical characteristics of female patients presenting with MINOCA and differences between male patients: A subgroup analysis of MINOCA-TR registry. Turk Kardiyol Dern Ars 2022;50:4-13.

DOI: 10.5543/tkda.2022.86219

A total occlusion or critical stenosis of the coronary artery because of abrupt plaque rupture/erosion is the main underlying pathophysiological mechanism in patients who present with acute myocardial infarction (AMI). However, the evidence of obstructive coronary artery disease (CAD) is not detected on coronary angiography (CAG) in about 5% of such patients, and the underlying cause of the AMI is not always apparent.[1] Therefore, patients who have less than 50% coronary artery stenosis on CAG are defined as myocardial infarction with non-obstructive coronary artery disease (MINOCA). This clinical entity usually has distinct clinical characteristics and outcomes compared with myocardial infarction with obstructive coronary artery disease (MIOCA).[2] The incidence of MIOCA is higher in men owing to the higher atherosclerotic plaque burden, and MINOCA is more commonly observed in women, and its mortality is significantly higher in women than in men.[3-5] The existence of such a sex difference is thought to be related to vascular abnormalities, such as coronary vasomotor disorder or microvascular dysfunction, which predispose women to MINOCA development.

Although the prognosis of MINOCA looks better than that of MIOCA, it may have adverse clinical outcomes, especially in women.[6] According to the Women's Ischemia Syndrome Evaluation database, 31% of all cardiovascular deaths that occurred in women were because of MINOCA.[7] More female patients with MINOCA may present with major adverse cardiac events, such as non-fatal AMI, non-fatal stroke, and heart failure (HF) hospitalization, than male patients with MINOCA.[8] To understand why major adverse cardiac event rates and deaths are higher in women, it is important to know the general characteristics of female patients with MINOCA as well as the differences in clinical and demographic characteristics and cardiovascular risk factors compared with male patients with MINOCA. Investigating these differences also has an important role in risk factor control and determination of treatment strategy.

Even though both types of AMIs are related to adverse outcomes, the treatment strategies and diagnostic tools are mainly focused on the male-dominant pattern of obstructive CAD; and these individuals are generally undertreated with no specific treatment.[9] Although there have been studies that highlight the differences in those patterns of AMI, there are still discrepancies in describing sex differences and clinical characteristics of female patients diagnosed with MINOCA in our population. To our knowledge, there is no prior study describing the clinical characteristics and demographics of female patients with MINOCA. Hence, in this study, we aimed to investigate the demographic and clinical features of female patients diagnosed with MINOCA and to compare them with male patients with MINOCA in Turkey.

ABBREVIATIONS

AMI	Acute myocardial infarction
CAD	Coronary artery disease
CAG	Coronary angiography
CRO	Contracted research organization
ECG	Electrocardiography
EUROASPIRE	European Action on Secondary and Primary Prevention by Intervention to Reduce Events
HF	Heart failure
LVEF	Left ventricular ejection fraction
MINOCA	Myocardial infarction with non-obstructive coronary arteries
MINOCA-TR	MINOCA in Turkish population
MIOCA	Myocardial infarction with obstructive coronary arteries
NSTEMI	Non-ST elevation myocardial infarction
PCI	Percutaneous coronary intervention
VIRGO	Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients

METHODS

Study cohort

The MINOCA in Turkish population (MINOCA-TR) was a multi-center, observational cohort study that was conducted in Turkey between March and October 2018. A total of 1,793 patients diagnosed with AMI on the basis of the Third Universal Definition of Myocardial Infarction and who had undergone a diagnostic CAG were screened. Of them, 1,626 patients (male 70.7%, mean age 61.5±12.5 years) with a diagnosis of acute MI from 18 universities and four private hospitals across 10 cities were enrolled in the study (Figure 1).[10,11] Consecutive patients older than 18 years of age who had been diagnosed with AMI on the basis of the Third Universal Definition of Myocardial Infarction and who had undergone a diagnostic CAG were included.[2] The diagnosis of AMI criteria included a positive cardiac biomarker and corroborative clinical evidence of an AMI, such as ischemic symptoms, new ischemic electrocardiography (ECG) changes, development of pathological Q waves, and imaging evidence of a new loss of viable myocardium, or a new regional wall-motion abnormality. Each patient enrolled in the study was managed according to the European Society of Cardiology consensus paper and guidelines.[12-14] Each participating physician solely arranged the management of treatment on their own. Potential study patients were informed about the study, and they signed informed consent after CAG (or percutaneous coronary intervention [PCI] if needed).

Exclusion criteria included patients with stable CAD, those with unstable angina pectoris, those with coronary revascularization history (PCI or coronary artery bypass grafting), patients with type 4 or type 5 AMI, patients younger than 18 years of age, patients who did not sign the informed consent, and the presence of non-cardiac cause for acute presentation.

Data collection

The design and primary results of the MINOCA-TR study were previously described.[10,11] In this study, 477 female patients (29.3%) were evaluated. Our study was a subgroup analysis of the MINOCA-TR and mainly examined the clinical features of female patients who presented with MINOCA. Baseline demographics, risk factors, and comorbidities of patients, such as history of hypertension, diabetes mellitus, flu history in the last three weeks, and smoking, were questioned and recorded. In addition, patients' vital signs, baseline electrocardiographic findings on admission, relevant echocardiographic data, laboratory parameters, and coronary angiographic results were recorded. The design of the study was reviewed

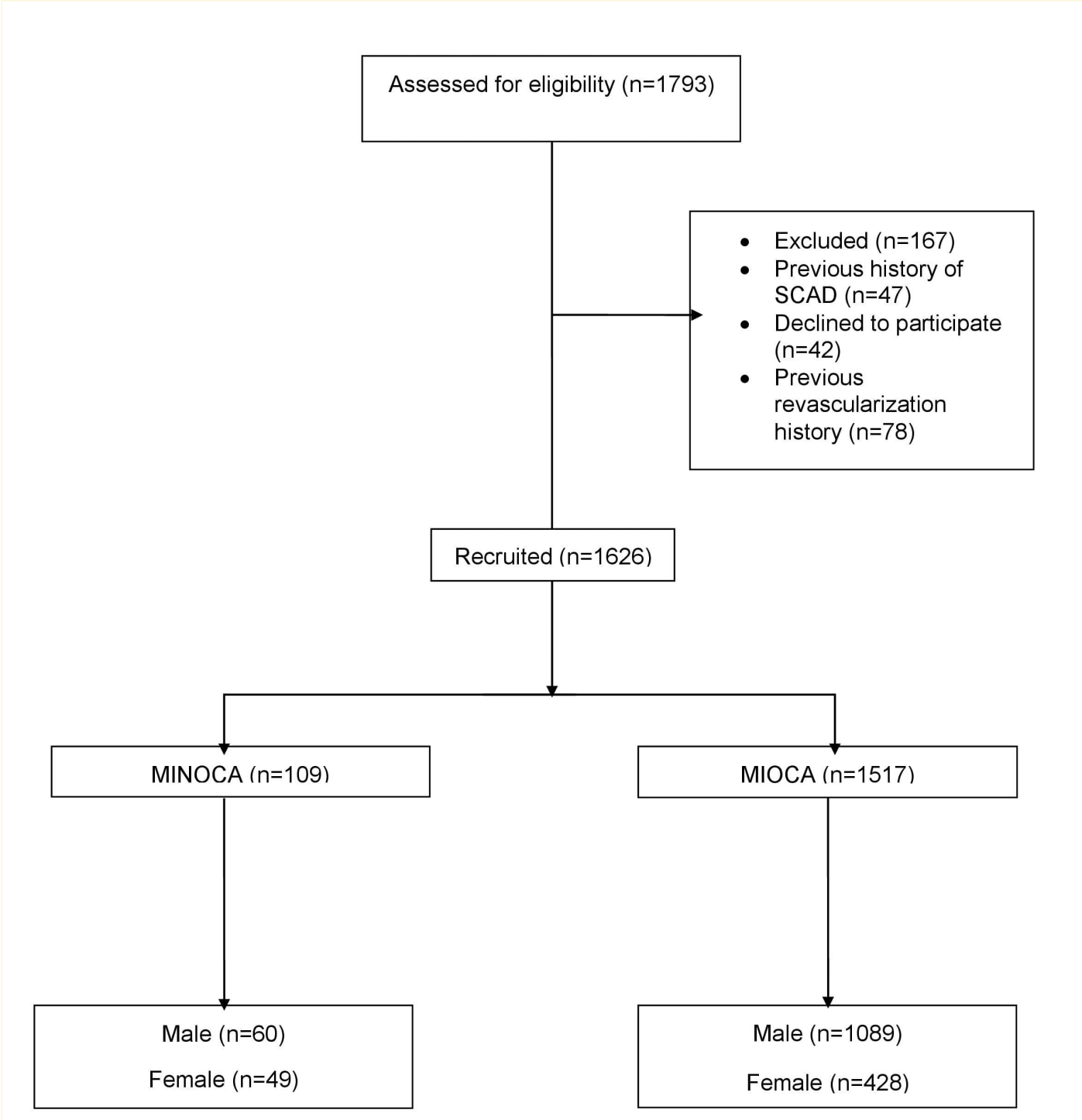

Figure 1. Flow chart of the study participants.
MINOCA: myocardial infarction with non-obstructive coronary artery disease; MIOCA: myocardial infarction with obstructive coronary artery disease.

Table 1. Comparison of clinical characteristics and electrocardiography and laboratory results of women with MINOCA versus those with MIOCA

	MINOCA (n=49)	MIOCA (n=428)	p
Demographic and clinical characteristics of patients			
Age, years, median (Q1-Q3)	55 (48-69)	68 (59-77)	<0.001
BMI, kg/m^2, median (Q1-Q3)	27.5 (25.3-32)	28.25 (25.3-31.3)	0.929
Non-smoker, n (%)	38 (77.6)	355 (82.9)	0.362
Alcohol use, n (%)	2 (4.1)	19 (4.4)	1.000
History of flu, n (%)	9 (18.4)	38 (8.9)	0.044
Family history of CAD, n (%)	14 (28.6)	99 (23.1)	0.405
Hypertension, n (%)	22 (44.9)	298 (69.6)	<0.001
Hyperlipidemia, n (%)	9 (18.4)	163 (38.1)	0.004
Diabetes mellitus, n (%)	9 (18.4)	181 (42.3)	0.001
STEMI, n (%)	1 (2.0)	183 (42.8)	<0.001
NSTEMI, n (%)	48 (98.0)	245 (57.2)	<0.001
P2Y12 antagonist received, n (%)	32 (65.3)	390 (91.1)	<0.001
Oral anti-coagulant agents, n (%)	1 (2.0)	7 (1.6)	0.583
Electrocardiography findings			
ST elevation, n (%)	1 (2.0)	186 (43.5)	<0.001
ST depression, n (%)	15 (30.6)	110 (25.7)	0.459
Echocardiography findings			
Performed echocardiography, n (%)	49 (100.0)	358 (83.6)	0.002
Mitral regurgitation +1–2, n (%)	17 (34.7)	230 (53.7)	0.011
Mitral regurgitation +3–4, n (%)	2 (4.1)	10 (2.3)	0.354
Left ventricular ejection fraction, (%)	58±7.4	48.3±10.4	<0.001
Coronary angiography results			
Access site femoral, n (%)	47 (95.9)	413 (96.5)	0.690
Radial, n (%)	2 (4.1)	15 (3.5)	0.690
PCI, n (%)	0 (0)	345 (80.6)	<0.001
CABG, n (%)	0 (0)	57 (13.3)	<0.001
Monitored with medical treatment, n (%)	49 (100)	26 (6.1)	<0.001
Laboratory data			
Index Hs-troponin-T, ng/mL, median (Q1-Q3)	7.70 (0.41-128.5)	9.88 (0.91-121)	0.591
Hemoglobin, g/dL	12.45±1.99	12.38±1.74	0.792
Random blood glucose, mg/dL, median (Q1-Q3)	116 (98-150)	139 (110-203)	<0.001
eGFR, ml/min/1.73 m^2 median (Q1-Q3)	92.3 (70.2-102.5)	83.4 (65.2-109)	0.768

BMI: body mass index; CABG: coronary artery bypass grafting; CAD: coronary artery disease; eGFR: estimated glomerular filtration rate; MINOCA: myocardial infarction with non-obstructive coronary artery disease; MIOCA: myocardial infarction with obstructive coronary artery disease; NSTEMI: non-ST elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST elevation myocardial infarction.

and approved by Dokuz Eylül University Clinical Research Ethic Committee on February 22, 2018 (423-SBKAEK). The study was also registered on www.clinicaltrials.gov (NCT03364387).

CAG was performed according to the standard protocols of each participating laboratory. All the patients were evaluated according to the stenosis level on CAG by each participating physician. A digital copy of the CAG of these patients was collected and shipped to a contracted research organization (CRO) office for evaluation by the MINOCA adjudication committee, consisting of three invasive cardiologists. Digital copies were evaluated and reviewed for a possible overlook of Takatsubo syndrome or type I AMI. The Modified Mayo Clinic criteria for the diagnosis of Takatsubo syndrome were used. The presence of all four criteria was accepted as Takatsubo syn-

Table 2. Comparison clinical characteristics and electrocardiography and laboratory results of women with MINOCA versus men with MINOCA

	Women (n=49)	Men (n=60)	p
Demographic and clinical characteristics			
Age, mean, years	58.9±12.9	51.5±15.9	0.010
BMI, kg/m^2	28.9±5.3	26.4±3.8	0.005
Active smoker, n (%)	8 (16.3)	28 (46.7)	0.001
Alcohol use, n (%)	2 (4.1)	7 (11.7)	0.182
History of flu, n (%)	9 (18.4)	16 (26.7)	0.302
Family history of CAD, n (%)	14 (28.6)	9 (15.0)	0.084
Hypertension, n (%)	22 (44.9)	11 (18.3)	0.003
Hyperlipidemia, n (%)	9 (18.4)	11 (18.3)	0.996
Diabetes mellitus, n (%)	9 (18.4)	9 (15.0)	0.638
Systolic blood pressure, mm Hg	133.1±25.4	124.1±16.5	0.028
Diastolic blood pressure, mm Hg	78.9±14.2	76.9±9.5	0.386
P2Y12 antagonist received, n (%)	32 (65.3)	41 (68.3)	0.738
Electrocardiography findings			
Atrial fibrillation, n(%)	2 (4.1)	2 (3.3)	1.000
ST elevation, n (%)	1 (2.0)	5 (8.3)	0.220
ST depression, n (%)	15 (30.6)	19 (31.7)	0.906
STEMI, n (%)	1 (2.0)	5 (8.3)	0.220
NSTEMI, n (%)	48 (98.0)	55 (91.7)	0.220
Echocardiography findings			
Performed echocardiography, n (%)	49 (100)	60 (100)	<0.999
Left ventricular ejection fraction, n (%)	58.1±7.4	58.6±7.6	0.756
Mitral regurgitation +1 and +2, n (%)	17 (34.7)	20 (33.3)	0.881
Coronary angiography results			
Access site femoral, n (%)	47 (95.9)	52 (86.7)	0.180
Radial, n (%)	2 (4.1)	8 (13.3)	0.180
Laboratory data			
Index-high-sensitive troponin T, ng/mL, median (Q1-Q3)	7.70 (0.41-128)	4.09 (0.48-103)	0.333
Hemoglobin, g/dL	12.4±2.0	14.1±2.0	<0.001
Random blood glucose, mg/dL, median (Q1-Q3)	116 (98-150)	110 (91.7-152)	0.876
eGFR, mL/min/1.73 m^2	92.3 (70-102.4)	111 (95-137.4)	<0.001

BMI: body mass index; CAD: coronary artery disease; eGFR: estimated glomerular filtration rate; MINOCA: myocardial infarction with non-obstructive coronary artery disease; MIOCA: myocardial infarction with obstructive coronary artery disease; NSTEMI: non-ST elevation myocardial infarction; STEMI: ST elevation myocardial infarction.

drome; 1) transient hypokinesia, dyskinesia, or akinesia of the LV mid-segments with or without apical involvement; regional wall-motion abnormalities extending beyond a single epicardial vascular distribution, and a stressful trigger is often, but not always, present; 2) absence of obstructive CAD or angiographic evidence of acute plaque rupture; 3) new ECG abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in the cardiac troponin level; and 4) absence of pheochromocytoma or myocarditis.[15]

Definitions

AMI was defined as the increase of cardiac biomarkers at least >99th percentile of the upper reference along with clinical evidence of acute myocardial ischemia, including symptoms, ECG changes, development of pathological Q waves, and imaging evidence of a new loss of viable myocardium or a new regional wall-motion abnormality.

MINOCA was accepted based on the current opinion paper of the ESC working group that focused on the clinical

context of MINOCA.[2] In our study, MINOCA was accepted following CAG in patients who presented with features that were consistent with those of acute MI as detailed by the following criteria: AMI criteria (Third Universal Definition of Myocardial Infarction); non-obstructive coronary arteries on CAG; and the absence of a clinically overt, specific cause for acute presentation. The term non-obstructive coronary arteries on CAD referred to the absence of obstructive CAD on angiography (i.e., no coronary artery stenosis of ≥50%) in any possible infarct-related artery. The term included angiographically normal coronary arteries (no stenosis >30%) and mild coronary atherosclerosis (stenosis >30% but <50%).

Statistical analysis

Continuous variables were presented as mean (SD) or median (25^{th}-75^{th} percentile). The Kolmogorov-Smirnov test was performed to assess whether continuous variables had a normal distribution. Levene's test was performed to determine variance equality. The variables with normal distribution were compared with the Student's t-test, and those without normal distribution were compared with the Mann-Whitney U test. The categorical variables were reported as numbers and percentages (%). The nominal data were compared using the chi-squared or Fisher's exact tests. Univariate logistic regression analysis was performed to identify the association between associates and MINOCA. Variables with a p<0.25 in univariate logistic regression analysis were entered into a multivariate logistic regression using the backward LR method. The goodness of fit for the logistic regression model was assessed by the Hosmer-Lemeshow statistic. The Hosmer-Lemeshow statistic did not suggest a lack of fit (χ^2=2.565, p=0.959). p value <0.05 was determined as statistically significant. Statistical analyses were performed with the SPSS version 20.0 software (IBM Corp., Armonk, NY, USA).

RESULTS

Of the study population (1,626 patients [men 70.7% and mean age 61.5±12.5 years]), 109 patients were diagnosed with MINOCA. The female proportion of patients diagnosed with MINOCA was higher than that of the MIOCA group. Female patients with MINOCA were significantly younger than those with MIOCA (n=49 [45%], mean age 58.9±12.9 years versus n=428 [28.2%], mean age 67.4±11.8 years, p<0.001, respectively). The frequencies of hypertension, hyperlipidemia, and diabetes mellitus were significantly lower in female patients with MINOCA than in the MIOCA group (Table 1). The female patients with MINOCA also had a higher incidence of a previous history of flu and higher rates of presentation with non-ST elevation myocardial infarction (NSTEMI) compared with those of the MIOCA group (Table 1). Nearly one-third of the female patients with MINOCA had an ST depression on ECG upon admission, which was higher than the MIOCA group. The clinical presentation of all the patients was mostly Killip class I, which was not statistically different between the groups. Echocardiography was performed in almost 95.9% of patients with MINOCA. The mean left ventricular ejection fraction (LVEF) values were higher in female patients with MINOCA than in those with MIOCA. Female patients diagnosed with MINOCA were less likely to receive a loading dose of a P2Y12 inhibitor before CAG.

CAG results

After the diagnostic CAG, all female patients with MINOCA were followed up with medical treatments and did not require revascularization strategies, including PCI or CABG. However, the majority of the patients with MIOCA were revascularized via PCI (80.6%). CABG was the preferred revascularization technique in only 13.3% of patients with MIOCA. The preferred access site for diagnostic CAG was mostly femoral in both the groups (95.9% versus 96.5%).

The comparison of clinical features between female and male patients diagnosed with MINOCA is shown in Table 2. Female patients were older, obese, and more likely to have hypertension compared with male patients. However, alcohol and smoking habits were more common in male patients. Both groups were not different in terms of ECG and echocardiographic findings. Laboratory results showed that female patients with MINOCA had lower hemoglobin and estimated glomerular filtration rate than male patients with MINOCA. However, their index-high-sensitive troponin T and random blood glucose levels were similar.

Both univariate and multivariate logistic regression analyses were performed to predict independent predictors of MINOCA. In univariate analyses, age and a previous history of flu, NSTEMI, hypertension, hyperlipidemia, and diabetes were predictors of MINOCA. These variables were included into the multivariate logistic regression analyses. According to multivariate logistic regression analyses, age (Odds ratio [OR]: 0.950, 95% confidence interval [CI]: 0.925-0.975; p<0.001), hypertension (OR: 2.151, 95% CI 1.100-4.208; p=0.025), hyperlipidemia (OR: 2.660, 95% CI: 1.186-5.967; p=0.018), presentation with NSTEMI (OR: 36.963 95% CI: 4.964-275.229; p<0.001), and diabetes mellitus (OR: 2.978, 95% CI 1.331-6.663; p=0.008) were predictors of MINOCA in female patients.

DISCUSSION

In this study, we observed that female patients with MINOCA were older, obese, and hypertensive than male patients with MINOCA. In addition, age, hypertension, hyperlipidemia, diabetes, and NSTEMI were independent predictors of MINOCA in our study.

There were significant clinical differences between female patients with MINOCA and MIOCA. Similar to other stud-

ies, female patients with MINOCA were younger with fewer cardiac risk factors and more commonly presented with ST depression on ECG than those with MIOCA.[5-8] There were also significant clinical differences in patients with MINOCA in terms of sex. Female patients were older, had higher systolic blood pressures, and lower hemoglobin levels than male patients with MINOCA.

In both sexes, cardiovascular risk factors were found to increase with age. However, the increase in cardiovascular risk factors was sharper in women than in men.[16] Accordingly, in our study, female patients with MINOCA were older and had higher rates of cardiovascular risk factors compared with male patients with MINOCA. This could be owing to a greater proportion of increase in cardiovascular risk factors with aging in female patients with MINOCA than in male patients with MINOCA. Despite having less obstructive CAD, women with MINOCA had higher rates of cardiovascular disease risk factors. This finding might be related to the older age of female patients with MINOCA compared with male patients with MINOCA.[16] Age has also been found to be the most associated risk factor for CAD in the Turkish population in the TEK-HARF study.[17] In the European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) study that was conducted in patients hospitalized with acute coronary syndrome, conditions such as hypertension, hyperlipidemia, diabetes mellitus, and obesity were higher in women than in men.[18] The prevalence of cardiovascular disease risk factors was also higher in the Turkish female population.[19] Similarly, in our study, female patients with MINOCA had higher rates of hypertension and obesity than male patients with MINOCA. However, the prevalence of hyperlipidemia and diabetes mellitus was similar. This might be related to non-plaque-mediated mechanisms of MINOCA. Plaque-mediated coronary obstructions are mainly related to having cardiovascular risk factors, including hyperlipidemia and diabetes mellitus. The pathophysiologic mechanism might likely explain the differences in the clinical profile of female patients with MINOCA.[5]

Our study also found that the smoking rates in female patients with MINOCA were higher compared with the general smoking rates in women, according to the Turkish Statistical Institute data (16.3% versus 14.9%).[20] The prevalence of diabetes mellitus was higher in female patients with MINOCA than in the study conducted in the general Turkish population (18.4% versus 8.9%).[21] The mean body index of female patients with MINOCA was higher than that of the general female population in Turkey (28.9 versus 26.4).[21]

Female patients with MIOCA were also older than those with MINOCA. Accordingly, cardiovascular risk factors, including hyperlipidemia, diabetes mellitus, and hypertension, were higher in female patients with MIOCA than in female patients with MINOCA. However, in studies comparing obstructive and non-obstructive CAD in young patients, cardiovascular risk factors were high in those with obstructive CAD. In the Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) study[4] that was conducted in relatively young patients, cardiovascular risk factors were higher in patients with obstructive CAD than in those with non-obstructive CAD even though the mean age was similar in both the groups. Therefore, higher cardiovascular risk factors in obstructive CAD compared with non-obstructive CAD may not be attributable only to advanced age.

In our study, female patients with MINOCA were older than male patients. This finding was similar to that of the study conducted by Sedlak et al.[8] The association of older age in female patients with MINOCA may be attributable to the protective effect of estrogen at an early age in the pre-menopausal period.[22] During the menopause transition, blood pressure begins to rise in women. Elevated blood pressure often disrupts endothelial and microvascular functions, which have an additive role in the impaired vascular structure in female patients with MINOCA. As the specific mechanism of MINOCA is thought to be associated with the presence of impaired vascular structure and/or endothelial dysfunction, the presence of higher blood pressure in female patients with MINOCA compared with that of male patients with MINOCA may support the higher rate of vascular dysfunction in women in our study. This finding was similar to the study conducted by Murthy et al.[23] In our study, male patients with MINOCA had a higher rate of smoking than female patients with MINOCA. This finding was similar to the results of the EUROASPIRE IV study of Turkey.[18] Obesity is also one of the important cardiovascular risk factors causing microvascular dysfunction.[24] In parallel, in our study, body mass index was higher in female patients with MINOCA than in male patients with MINOCA.

Similar to previous studies, the clinical presentation was mostly NSTEMI in our study.[25-28] The rate of ST depression on admission was significantly higher in female patients with MINOCA than in those with MIOCA. This result may be related to patchy areas of subendocardial ischemia because of either microvascular dysfunction, spasm, microthrombosis, or inflammation, which contribute to subendocardial myocardial ischemia.[5,22] Although the specific mechanism is not fully understood, the presence of impaired vascular structure and/or endothelial dysfunction appears to be more frequent in female patients, which may be responsible for the more common observation of ST depression on ECG. In addition, according to the study by Reynolds et al.,[29] the underlying mechanism of MINOCA was ischemic (because of either plaque rupture, intraplaque cavity,

or layered plaque) in approximately 75.5% of women with non-obstructive coronary arteries. Consequently, ECG findings among these patients might be owing to the presence of ischemia.

The presence of less obstructive CAD in women with MINOCA should not be viewed as having a good prognosis. It is noteworthy that women with MINOCA have an increased risk of future HF hospitalizations, which ultimately increases the burden of healthcare cost expenditure.[7] Therefore, standard echocardiography is recommended to rule out other pathologies in patients without obstructive CAD on CAG.[30] Considering these recommendations, echocardiography was performed in almost all the patients with MINOCA in our study, and preserved LV systolic functions were found in those patients.

We believe that our study will increase the awareness of differences in sex in patients with MINOCA. Our results warrant further studies to investigate the underlying pathophysiologic mechanism in women with MINOCA.

Limitations

Our study had some limitations, including mainly the relatively small number of women with MINOCA. Second, the short- and medium-term prognoses of women with MINOCA were not included. Women having specific risk factors, such as pregnancy-associated complications (gestational hypertension, diabetes mellitus, preeclampsia, and miscarriages), were not evaluated in this study. Autoimmune diseases, menstrual history, menopause, polycystic ovarian disease, and hypercoagulopathy syndromes were not studied, which was another important limitation. This study was a national registry across Turkey and may not reflect the global perspective. In addition, medication usages of the patients were not recorded; and their laboratory values including lipid, C-reactive protein, D-dimer, and NT-proBNP levels were not recorded. Another limitation was that troponin assays used in laboratories might differ between the centers. Finally, other possible mechanisms of MINOCA, including coronary dissection, thromboembolism, coronary artery spasm, and plaque rupture or erosion, were not assessed using non-invasive (coronary computed tomography angiography or cardiac magnetic resonance imaging) and invasive (intravascular ultrasonography, optical coherence tomography, ergonovine/acetylcholine test, and endomyocardial biopsy) diagnostic modalities on the basis of the suspected diagnosis during the index hospitalization because of the observational nature of the study.

CONCLUSION

In our study, there were significant differences, including age and cardiovascular risk factors such as hypertension, hyperlipidemia, and diabetes mellitus, between female patients with MINOCA and with MIOCA in the Turkish population. There were also important clinical differences in terms of age, obesity, cardiovascular risk factors, and baseline hemoglobin levels in patients with MINOCA according to sex. Our results showed that age, hypertension, hyperlipidemia, diabetes, and NSTEMI independently predicted the presence of MINOCA.

Ethics Committee Approval: Ethics committee approval was received for this study from the Dokuz Eylül University Clinical Research Ethics Committee (Approval Date: February 2, 2018; Approval Number: 423-SBKAEK).

Informed Consent: Written informed consent was obtained from all participants of this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.O.E.; Design - M.Z.; Data Collection and/or Processing - S.K., M.Y.; Analysis and/or Interpretation - Ö.Ö., A.Ç., T.Ç., A.Ö.; Literature Search - C.E.; Writing - G.G.; Critical Revision - U.Ö.T.

Collaborators: Gökhan Aydın, Yasemin Kılavuz Doğan, Yunus Çelik, Sümeyya Özer, Abdullah Özçelik, Zeynel İnan, Ahmet Soylu, Abdullah İçli, Ahmet Gürbüz, Şıho Hidayet, İsmail Ünğan, Mustafa Taşcanov, Ramazan Düz, Veli Polat, Hakan Özkan, Mehmet Özyaşar, Kamil Tülüce, Devrim Kurt, Nurullah Çetin, Murat Gül, Sinan İnci, Fatma Yılmaz Çoşkun, Hasan Arı, Aslı Vural, İnan Multu, Yiğit Yılıncıoğlu, Ahmet Karagöz, Lütfü Bekar, Ayşe Akdeniz, Oğuz Kılıç, Ali Doğan, Ebru Özpelit, Osman Karaaslan, Fikret Keleş, Samet Yılmaz

Funding: This study was sponsored by the Cardiovascular Academy Society.

Conflict of Interest: None.

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