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Characteristics and Clinical Significance of MINOCA Syndrome in Patients with Pre-diagnosis of Acute Coronary Syndrome in the Emergency Department and Performed Coronary Angiography

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Abstract

Aim: Myocardial infarction with non-obstructive coronary arteries (MINOCA) is a condition characterized by clinical findings of acute myocardial infarction (AMI) and detection of normal/close to normal narrowing coronary arteries in coronary angiography (CAG). The aim of this study was to analyze the prevalence and demographic characteristics of MINOCA in a tertiary hospital.

Materials and Methods: This observational retrospective study included patients aged 18 years who presented to the emergency department in 2016, met the criteria for universal AMI, and had a CAG of <=50% stenosis. Patients under the age of 18 years and those likely to have a diagnosis other than AMI were excluded.

Results: In total, 4197 patients who underwent CAG with a preliminary diagnosis of AMI were evaluated, and 213 patients were included in the study. Of the MINOCA cases, 84 (60.6%) were female and 129 (39.4%) were male. The mean age was 60+/-2 years. Eight (3.8%) patients diagnosed with ST-elevation AMI. There were no ischemic electrocardiographic changes in 91 (42.7%) patients. Hypertension (HT) was the most common comorbidity (53.5%) (n=114). The relationship between advanced age and both in-hospital and 1-year mortality was statistically significant ($p<0.005$). Strong risk factors affecting the rate of CAG occlusionwere recurrence of AMI, HT, diabetes, and advanced age ($p<0.005$). Diastolic blood pressure, oxygen saturation, TIMI score, and family history were also factors associated with CAG occlusion rate ($p<0.05$).

Conclusion: There is a need for advanced scoring systems that can be used to define the diagnosis of MINOCA before CAG in emergency services.

Keywords: MINOCA, acute coronary syndrome, normal coronary angiography, emergency department

Introduction

Chest pain is one of the most common reasons for admission to emergency services and is a major cause of mortality and morbidity. Acute myocardial infarction (AMI) is one of the most important fatal diagnoses to be excluded. Clinical findings of acute myocardial ischemia accompanied by acute myocardial damage and an increase and/or decrease in cardiac troponin values accompanied by at least one of the following findings:

- Myocardial ischemia symptoms,
- New ischemic electrocardiography (ECG) changes,
- Presence of a pathological Q wave,
- Detection of regional wall motion defects that develop newly or are compatible with ischemic etiology,
- Detection of a coronary thrombus by coronary angiography (CAG) or autopsy (1).

Obstructive coronary artery disease (CAD) is defined as >50% stenosis in the coronary arteries of patients undergoing CAG for AMI. A proportion of patients with AMI undergoing CAG does not have clinically significant occlusion of the coronary arteries, which is defined as <50% stenosis. This clinical entity has been

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described as myocardial infarction with non-occluded coronary artery (MINOCA) (1,2). MINOCA was first included in the literature in the guidelines of the European Society of Cardiology (ESC) in 2017 (2). It is an important syndrome with a prevalence ranging from 2.6% to 15%, and its etiology should be investigated. It is thought that by clarifying the etiology of MINOCA, we can prevent unnecessary CAGs (3).

Among the factors that cause MINOCA, there is a wide spectrum of diseases such as myocarditis, vasospasm, thromboembolism, microvascular dysfunction, oxygen supply/demand mismatch, Takotsubo syndrome, acute pulmonary embolism, coronary thrombosis, and dissection (2-4). Therefore, the diagnostic process may require multiple diagnostic steps such as echocardiography (ECHO), left ventriculography (LVG), intracoronary imaging, computed tomography (CT), pulmonary CT angiography, and cardiac magnetic resonance (CMR) imaging. Etiology research is selected according to the suspected condition, and its treatment is tailored to the needs of the patient (5).

Turkey's population is approximately 84.3 million, and approximately 300,000 cases of AMI are seen in the population every year (6). Therefore, it is important to identify the demographic and clinical characteristics of patients with MINOCA to help create a new strategic plan and approach for these patients in our population. The aim of this study was to investigate the incidence of MINOCA and the demographic and clinical characteristics of these patients in our region.

Materials and Methods

Study Population and Definition

Our study was retrospectively planned in the Emergency Department of Antalya Training and Research Hospital, a tertiary university hospital in Turkey, after the approval of the ethics committee of the Antalya Training and Research Hospital, numbered 1/3 and dated 11.01.2018. All patients aged 18 years who were diagnosed according to the third universal definition of AMI and underwent CAG in the emergency department between January 1 and December 31, 2016 were included in the study. Accordingly, AMI is defined as clinical evidence of AMI, such as ischemic symptoms along with cardiac biomarker positivity, new ischemic ECG change, pathological Q wave on ECG, and evidence of new viable myocardial tissue loss by imaging (7).

MINOCA definition, as stated in the ESC guide (7); "3. According to the "Universal definitions of AMI", it was accepted as the presence of AMI criteria and the absence of >50% lesions in major epicardial vessels in CAG and the absence of a more probable diagnosis that could be the cause of the acute presentation.

The definition of an unoccluded coronary artery is expressed as less than 50% occlusion in the American Heart Association (AHA) and ESC guidelines. The literature also classifies non-occluded vessels into 3; no stenosis is defined as "normal," "plaque" for <30% stenosis, and "mild" occlusion for ≥30% but <50% stenosis.

Study data were provided on the basis of cases meeting these definitions.

Data Collection

Patient data were obtained from the hospital's archive. Patients over the age of 18 who met the universal AMI criteria and had ≤50% stenosis at CAG were included in the study. Patients with CAGs from other health centers and/or blood tests performed or diagnosed with a high probability of non-AMI were excluded from the study. In addition, pregnancy was excluded.

Parameters included in the study:

1. Sociodemographic characteristics (age, gender),
2. Vital signs (temperature, pulse, respiratory rate, systolic and diastolic blood pressure, oxygen saturation) in the emergency room,
3. ECG findings in the emergency room,
4. Troponin and creatinine levels in the emergency department,
5. Type of chest pain,
6. Comorbid diseases,
7. History of AMI (first/recurrent),
8. History of drug/alcohol use and intoxication,
9. TIMI score,
10. Diagnosis in the emergency room [ST-elevation AMI (STEMI), non ST-elevation MI (NSTEMI)],
11. ECO findings [left ventricular wall motion defect, ejection fraction (EF) value],
12. CAG and LVG findings,
13. Main diagnosis,
14. In-hospital and 12-month mortality rates.

A standardized "Study Form" was created for the study, and the information was transferred to the computer environment after recording in this form.

CAG was performed according to the protocols of the catheter laboratory. Patients with <50% occlusion were divided into 3 main groups as normal (0% occlusion), plaque (<30% stenosis),

and mild (≥30%+<50%). Digital copies of CAGs were relieved by 2 different cardiologists who were not familiar with the clinic and the patients, and the diagnosis of MINOCA was confirmed. The mortality status of the patients was obtained from the hospital information management system for in-hospital deaths, and the 1-year mortality was obtained from the Death Information System.

Statistical Analysis

Statistical analysis of the data was performed with Statistical Package for the Social Sciences for Windows 20 package program. Whether the distribution of continuous and discrete numerical variables was close to normal was investigated using the Kolmogorov-Smirnov test. Descriptive statistics are presented as mean±standard deviation for continuous and discrete numerical variables and as number of cases and (%) for categorical variables. Categorical variables were analyzed using the chi-square test; analysis of parametric data was performed using the Student's t test; Pearson's correlation test was used to compare numerical variables. For $p<0.05$, the results were considered statistically significant.

Results

Files of 4197 patients who underwent CAG during the study period were reviewed. Two hundred-thirteen cases (5.04%) were identified as MINOCA. The mean age of the MINOCA population was 60±2 years, and 129 patients (60.6%) were female. Table 1 shows the demographic and clinical characteristics of the patients. Only 8 (3.7%) patients with MINOCA were prediagnosed with STEMI in the emergency room. ECG findings were completely normal in 91 (42.7%) patients, non-specific ST-T changes in 64 (30%) patients,

Table 1. Baseline characteristics and the factors related to occlusion rate on coronary angiography of the MINOCA population

		n	%	p value	Total
Gender	Female	84	39.4	0.16	213
	Male	129	60.6		
Drug/alcohol use or intoxication	No	211	99.1	0.02	213
	Yes	2	0.9		
Emergency room's diagnose	STEMI	8	3.8	0.86	213
	NSTEMI	205	96.2		
Hyperlipidemia	No	195	91.5	0.71	213
	Yes	18	8.5		
Hypertension	No	99	46.5	<0.005	213
	Yes	114	53.5		
Diabetes mellitus	No	148	69.5	<0.005	213
	Yes	65	30.5		
Smoking	No	169	79.3	0.75	213
	Yes	44	20.7		
Family history	No	204	95.8	<0.05	213
	Yes	9	4.2		
Malignancy	No	204	95.7	0.08	213
	Yes	9	4.3		
ACS history	First	136	63.8	<0.005	213
	Recurrent	77	36.2		
Left ventricle wall motion defect	No	136	63.8	0.34	213
	Yes	77	36.2		
Mortality	In hospital	3	1.4	<0.005	15
	In 1 year	12	5.6		
Type of chest pain	Atypical	94	44.1	0.77	213
	Typical	119	55.9		

MINOCA: Myocard infarctus with non-obstructive coronary arteries, N: number, STEMI: ST elevation myocard infarctus, NSTEMI: Non-ST elevation myocard infarctus, ACS: Acute coronary syndrome

arrhythmias in 35 (16.4%) patients (ventricular tachycardia, ventricular fibrillation, supraventricular tachycardia, atrial fibrillation), and conduction defects (left bundle branch block, right bundle branch block, and atrioventricular blocks) were found in 23 (10.8%) patients.

When cardiovascular risk factors were examined, 44 (20.7%) patients were smokers, 114 (53.5%) had hypertension (HT), 65 (30.5%) had diabetes mellitus, and 18 (8.5%) had hyperlipidemia (HPL). The mean TIMI score of patients with NSTEMI at admission was 2.37. Left ventricular EF was >50% in 159 (74.6%) patients. While 77 (36.2%) patients had previous CAG with the diagnosis of AMI, 16 (7.5%) had a previous history of coronary artery bypass grafting.

It was determined that the most common chest pain characteristic was the pressure/compression style (55.9%) and was often described as typical chest pain (Table 1).

In our study, the final diagnosis of 99 (46.5%) patients could be determined or the underlying cause could be partially explained, since the etiology research could not be performed in all aspects in our hospital. The final diagnoses are shown in Table 2.

When the TIMI scores of the cases were examined, it was found that those with a TIMI score of 3 were the most (26.3%), those with a TIMI score of 6 were the least (1.4%), and the mean TIMI score was 2.37.

When we analyzed the ECG results in the emergency department, the most common ECG finding of the cases was normal sinus rhythm (n=91) (42.7%), while the patients with blocks (n=23) (10.8%) were the least common (Table 3). In addition, most MINOCA patients diagnosed with NSTEMI (n=205, 96.2%) (Table 1).

Considering the EF values of the patients, the number of patients EF <40 is 31 (14.6%), the number of patients between 40 and 50 is 23 (10.8%), and the number of patients EF >50 is 159 (74.6%).

Considering the mortality in MINOCA cases, while there were 3 (1.4%) patients who died in the hospital, 12 (5.6%) people died from all causes within 1 year.

CAG was found to be completely normal in 87 (40.8%) patients. In patients with normal CAG, 4 cases were diagnosed as (1.9%) ectasia, 8 (3.8%) as slow flow, and 3 (1.4%) as spasms in coronaries. In 66 cases (31%), 30-50% stenosis (mild) was found;in 60 cases (28.2%), only plaque was detected.

Previous AMI history, having HT and diabetes comorbid diseases, and advanced age were strong risk factors affecting the rate of CAG occlusion ($p<0.005$). Occlusion rate was higher in MINOCA patients with these risk factors. The factors associated with the rate of obstruction in CAG are shown in Table 1. In addition, diastolic blood pressure, oxygen saturation, TIMI score in patients with NSTEMI, and family history were also factors associated with CAG occlusion rate ($p<0.05$).

Table 2. Distribution of final diagnosis of MINOCA population

Diagnosis	Frequency (n)	Percent (%)
No specific diagnosis	114	53.5
Heart valv pathologies	22	10.3
Blocs and arrhythmias	22	10.3
Heart failure	9	4.2
Coronary slow flow phenomenon	8	3.7
Ischemic cardiomyopathy	6	2.8
Takotsubo cardiomyopathy	5	2.3
Hypertrophic cardiomyopathy	4	1.8
Dilated cardiomyopathy	3	1.4
Endomyocarditis	3	1.4
Drug incompatibility	2	0.9
Vasospathic angina	2	0.9
Pericardial effusion	2	0.9
Coronary ectasia	2	0.9
Anemia	1	0.4
Methemoglobinemia	1	0.4
Peptic ulcer	1	0.4
Pneumonia	1	0.4
Postpartum cardiomyopathy	1	0.4
Right coronary artery outflow anomaly	1	0.4
String left main coronary artery	1	0.4
Suicidal drug intake (intoxication)	1	0.4
Total	213	100.0

MINOCA: Myocard infarctus with non-obstructive coronary arteries

Table 3. Distribution of ECG findings of MINOCA population in emergency room

ECG findings	Frequency (n)	Percent (%)
Normal sinus rhythm	91	42.7
Non-specific ST-T changings	64	30.0
Arrhythmias	35	16.4
Blocks	23	10.8
Total	213	100.0

ECG: Electrocardiyography, MINOCA: Myocard infarctus with non-obstructive coronary arteries

Discussion

MINOCA is a syndrome with limited researchand occurs in a small proportion of AMI cases. These patients are often treated conventionally to ensure a good prognosis. The commonly used method for MINOCA risk stratification is angiographic features. Although information on this issue was not provided in previous guidelines, attention was drawn to MINOCA for the first time in the 2017 ESC guideline for the management of AMI in STEMI patients.

Considering the prevalence of MINOCA in the literature, it varies between 2.6% and 15% (7,8). In the multicenter MINOCA-TR study by Kilic et al. (8) in Turkey, the prevalence of MINOCA was found to be 6.7%. In our study, the prevalence of MINOCA was found to be 5.04% in patients with AMI diagnosed in the emergency department, which is consistent with the literature.

When we look at the demographic characteristics, the data on the gender distribution of the MINOCA risk factors are heterogeneous, but it is more common in the female gender (9,10). In contrast, the ESC status report stated that patients with MINOCA were mostly male (2). In a large review conducted in 2018, 60% of patients with MINOCA were male and 40% were female (10). In the MINOCA-TR study female gender was found to be more dominant. As mentioned above, it can be seen that the gender distribution is heterogeneous. In our study, however, we see that the female gender is in the majority and it is compatible with the data of our country.

When we look at the literature for the affected age group, the mean age ranges between 46 and 55 years (11-15). In a 2015 review, the strongest risk factors for MINOCA were female gender and young age. In a study by Agewall et al. (2) in 2016, it was reported that MINOCA patients were younger than those with MINOCA. The mean age of the patients included in our study was 60.04 years. In this context, it is compatible with the literature.

In a study involving only STEMI patients, 58.1% of MINOCA cases presented with typical symptoms (15). This rate is 87.6% in patients with occluded coronary arteries (15). In a large review conducted in 2015, it was found that chest pain was less common in female patients with MINOCA (16). In a gender-focused review conducted in 2016, the most common symptom was typical chest pain (17). Moreover, female patients described chest pain as often crushing, compressive, and constricting and stated that it was accompanied by decreased functional capacity, back pain, and jaw and neck pain (18). In a review of a comprehensive study conducted in 2018, they reported that cases with MINOCA often present with atypical symptoms compared with cases with occluded coronary arteries (12). When we look at the type of chest pain in our study, it is seen that the most common type of pressure/squeeze (26.3%) is the feeling of distress (24.4%) and shortness of breath (18.8%) in the other types. Considering the differences in the literature, it is concluded that MINOCA cases can present with both typical and atypical symptoms. In our study, the patient admitted to the emergency room mainly had typical chest pain, which is compatible with the literature.

When we examine the traditional risk factors of MINOCA, different trends are observed. In a large systematic review conducted in 2015, although the incidence of HPL in MINOCA cases was low, other risk factors were similar (14). According to this study, the rate of HPL was 32% in patients with occluded coronary arteries, whereas this rate was 21% in MINOCA cases, and the difference was found to be significant (14). In a meta-analysis published in 2016, it was reported that diabetes (RR: 0.57), HT (RR: 0.87) and HPL (RR: 0.75), which are classical risk factors, are less common in MINOCA cases (13). In the review published in 2018, the incidence of traditional risk factors was 8.7% in patients with occluded coronary arteries, whereas this rate was 1.3% in MINOCA cases, and the difference was found to be significant (12). Again, in a review published in 2018, HT and diabetes were reported less frequently in MINOCA cases, whereas smoking was more common (odds ratio: 1.9) (10). Among the comorbid diseases in our study, HT (53.5%) was the most common, followed by CAD (36.2%) and diabetes (30.5%). When our study is evaluated in terms of risk factors, it is not compatible with the literature. The fact that the patients included in our study only applied from the emergency department and excluded elective cases may be the reason for this incompatibility. In addition, local comorbidities may differ between regions. Considering that other studies were conducted in European and American societies, we believe that the distribution of comorbidities in the Turkish population may be different.

When we look at the literature, there seems to be only one study evaluating MINOCA patients using risk scoring systems. In a study conducted by Pepine et al. (16) in 2015, the GRACE score was used, and it was found that patients with MINOCA who had a fatal course in the 30-day period had a higher GRACE score at admission than those with MINOCA who were not fatal (14). We used TIMI risk scoring in this study. In our study, the TIMI score was predominantly 3 (26.3%) and generally 1 (19.2%), 2 (21.6%), and 3 (26.3%). The mean TIMI score was 2.37. We found that our patients had a moderate TIMI risk score, but evaluation could not be performed because there is no similar comparison in the literature.

In an evaluation made according to ECG findings, T-segment elevation was found to be 14.8% and non-specific T wave changes were found to be around 60% (19). In the review of the CRUSADE

study in 2009, ECGs of cases with no coronary artery occlusion were examined, and it was found that 71% of MINOCA cases had no ST changes, 21% had ST depression, and 7% had ST elevation (20). In another review published in 2011, ST elevation was found in 36.3% of the cases, ST depression in 15.4%, pathological Q waves in 13.42%, T wave changes in 27.5%, and left bundle branch block in 2.3% (21). In our study, the most common ECG finding was normal sinus rhythm ECG (42.7%), and non-specific ST-T changes (30%) were observed, and the results are consistent with the literature.

There are literature reports that patients with MINOCA were hospitalized with the prediction of severe NSTEMI (2). In 2017, MINOCA was detected in 7% of STEMI cases and MINOCA results in 17% of NSTEMI cases (18). In another large version published in 2017, 8.9% of NSTEMI cases and 1.6% of STEMI cases were diagnosed with MINOCA (10). In a 2016 meta-analysis, MINOCA was found to be less common (RR: 0.20) in STEMI cases (13). Our aim is also compatible with the literature, and we believe that 96.2% of MINOCA patients were hospitalized with predicted NSTEMI.

According to the evaluation of left ventricular wall movements and EFs by transthoracic ECHO, it is stated in the literature that EF is 50% in MINOCA patients (12,13,17,22). According to our study, to consider the heterogeneity in the literature, the mean EF was calculated as 54.6% (+-12.5) and was generally compatible with the literature.

In the review that also formed the basis of the 2017 ESC guideline (18), myocarditis (33%), subendocardial infarct (26%), Takotsubo cardiomyopathy (CMP) (18%), and pericarditis (7%) were determined as the definitive diagnosis after cardiac MRI in the differential diagnosis of MINOCA patients (2,4). However, no diagnosis could be reached by CMR imaging in 26% of the cases. In the same review, provocative spasm testing was performed in 402 MINOCA cases, and inducible spasm was detected in 28-36% of them. The final diagnoses included in the study of 178 cases in which CAG was performed after the preliminary diagnosis of NSTEMI and diagnosed as MINOCA in 2017 (2) were variant angina (10.1%), myocarditis (8.9%), Takotsubo CMP (8.9%), tachyarrhythmia-related chest pain (6.7%), and non-cardiac pain (9.6%). In our study, there were limitations in determining the final diagnosis and etiological factors, since the etiology research could not be performed in all aspects in our hospital. In our study, there were 99 (46.5%) patients who could be diagnosed or whose underlying cause could be partially explained. In these patients, the diagnoses were tachy-bradyarrhythmia-related chest pain (22%), heart valve pathologies (22%), Takotsuba CMP (5%), and CMP (9%) and were generally consistent with the literature.

When we look at the studies analyzing the prognosis of patients with MINOCA, they are quite heterogeneous in terms of follow-up times, cardiac mortality, and recurrent AMI. In studies, 12-month mortality rates ranged from approximately 1% in-hospital to a total of 1.2-4.7% (12-14,22). In our study, the in-hospital mortality was 1.4% for MINOCA cases, whereas the 1-year mortality was 5.6%, which was consistent with the literature.

Study Limitations

The AHA and ESC guidelines differ in including certain diagnoses, such as Takotsubo syndrome, in MINOCA. In our study, we evaluated these diagnoses under the MINOCA sub-title as included in the ESC guidelines.

The cases included in our study belonged to the 1-year cross-sectional period and were retrospectively included. In the evaluation, using the Hospital Information Management System retrospectively for some patients and obtaining information by interviewing their families (on the phone) for some patients can be considered as a limitation.

In our hospital, CAG is not applied to all patients who meet the definition of NSTEMI. Only those with a high probability of obstructive CAD were selected, and patients without traditional cardiovascular risk factors but with a high probability of MINOCA, such as younger patients and female patients, may not have undergone CAG. This may affect the prevalence of MINOCA.

Etiology research is not conducted in our hospital.

Conclusion

Considering the 14% mortality and unexpected cardiac event rates reported in the literature, the etiology of MINOCA cases needs to be clarified. Risk factors for these cases should be determined, and separate risk scoring systems should be established. Thus, the treatment of cases can be organized effectively and unnecessary interventions can be prevented.

Ethics

Ethics Committee Approval: The study was approved by the Antalya Training and Research Hospital of Ethics Committee (decision no: 1/3, date: 11.01.2018).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.K., E.K., Concept: A.K., F.Y., M.K., Design: E.K., M.K., Data Collection or Processing: A.K., Analysis or Interpretation: F.Y., Literature Search: A.K., M.K., R.N.O., Writing: A.K., E.K., M.K., R.N.O.

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