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ORIGINAL ARTICLE

Acute Myocardial Infarction with Non-Obstructive Coronary Arteries – Stratifying the Risk of a "new" Clinical Entity using an "Old" Tool

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Abstract

Background: Some of the patients admitted for acute myocardial infarction have non-obstructive coronary artery disease (MINOCA). Their prognosis is not always benign, making it necessary the development of tools for risk stratification of these patients.

Objectives: To describe the characteristics of a sample of patients admitted for suspected MINOCA and to evaluate the prognostic value of GRACE score in this population.

Methods: This was a retrospective, observational, single-center, cohort study involving 56 consecutive patients with MINOCA. During one-year follow-up, patients were assessed for mortality and major adverse cardiovascular events (MACE) – a composite of all-cause mortality and hospitalization due to acute myocardial infarction, heart failure, ischemic stroke, and acute limb ischemia. Statistical analysis was performed using a non-parametric approach, with the Mann-Whitney U test for quantitative variables and ROC curves for assessing the discriminatory power of the Grace score in predicting cardiovascular events. The level of significance was set at 5%.

Results: Of the 56 MINOCA patients included in the study (median age 67 years), 55.4% were female. During the one-year follow-up, mortality rate was 5.5% and 9.1% of patients had MACE. A higher GRACE score was associated with mortality (p = 0.019; AUC 0.907; 95%CI 0.812–1.000; cut off 138) and MACE (p =0.034; AUC 0.790; 95%CI 0.632–0.948; cutoff 114).

Conclusion: The definition of MINOCA includes various diagnoses and prognoses, and the GRACE score is useful for risk stratification of patients with this condition.

Keywords: Myocardial Infarction; Coronary Angiography; Coronary Artery Disease; Magnetic Resonance Spectroscopy/diagnosis; Prognosis.

Introduction

The association between acute myocardial infarction (AMI) and obstructive coronary artery disease, which is found in more than 90% of AMI patients, has been known for a long time.[1] However, nearly 10% of AMI patients do not have obstructive plaques, a finding that has been reproduced in several studies.[2-4] A clinical presentation with symptoms, electrocardiographic and laboratory changes typical of AMI, in the absence of obstructive coronary atherosclerosis, had long been considered as false positive.[5] However, more recent studies have reported that the prognosis of these patients may not be favorable, with rates of mortality and major adverse cardiovascular events (MACE) similar to those of patients with obstructive disease.[6]

For this reason, the term MINOCA (myocardial infarction with non-obstructive coronary arteries) has been introduced to describe AMI patients without significant coronary artery disease, and

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already included in the fourth Universal Definition of Myocardial Infarction.[7]

Several mechanisms have been proposed for the development of MINOCA, including the rupture of a nonobstructive plaque, coronary thromboembolism, other type 2 myocardial infarctions and vasospasm. Myocarditis and Takotsubo syndrome can cause nonischemic myocardial injury, with clinical features similar to those of acute coronary syndrome.[8]

Considering the myriad of possible diagnoses and the lack of scientific evidence,[9] the ideal therapeutic approach to these patients is still uncertain. It has been strongly recommended the investigation, identification, and treatment of the underlying disease. Likewise, the clinical course and prognosis of MINOCA patients is also heterogeneous; while most patients recover from the disease without any cardiac sequelae, a worrying minority of patients have an unfavorable course, with a one-year mortality rate of nearly 5%.[10] Therefore, improving the prognostic stratification of patients with MINOCA is highly needed. The Global Registry of Acute Coronary Events (GRACE) score has been widely used for stratification of in-hospital mortality at 1 and 3 years after acute coronary syndrome.[11-13]

Objectives

The present study aimed to describe characteristics of patients admitted for MINOCA to a single center during a four-year period (from 2014 to 2017). In addition, the study aimed to evaluate the GRACE score for prognostic stratification of patients with MINOCA during a one-year follow-up.

Methods

This was a retrospective, observational, single-center, cohort study that included consecutive patients admitted to a Cardiology unit with a diagnosis of MINOCA, from January 01, 2014 to December 01, 2017. The diagnosis of MINOCA was established by the researchers after review of patients' clinical records, according to the European Society of Cardiology (ESC) criteria:[8] to fulfill the fourth Universal Definition of Myocardial Infarction criteria for AMI;[7] absence of obstructive epicardial coronary artery disease (absence of stenosis greater than 50%); and absence of a clinically overt specific cause for the acute presentation. Patients with suspected myocarditis (pleuritic pain, increase in inflammatory markers, respiratory infection, or gastrointestinal infection in the last four weeks) or with a diagnosis of myocarditis confirmed by cardiac magnetic resonance (CMR) (according to the ESC Working Group criteria),[14] and patients with suspected Takotsubo syndrome (according to the InterTAK diagnostic criteria established in the International Expert Consensus Document on Takotsubo Syndrome)[15] were excluded. A flowchart of patients' selection process is depicted in Figure 1.

Demographic, clinical, laboratory, electrocardiographic, echocardiographic, and angiographic data, as well as information on treatment during hospitalization were collected from patients' medical records.

Dyslipidemia was defined as increased levels of low-density lipoprotein (LDL) cholesterol in patients taking lipid-lowering drug, or LDL levels at admission that would qualify patients for lifestyle changes and/or pharmacological therapy, according to the 2019 ESC guidelines for management of dyslipidemias.[16] All patients had access to echocardiography at hospital admission and prior to discharge, and we also investigated whether patients underwent CMR. CMR was considered of diagnostic value when it enabled the identification of MINOCA etiology or determined an ischemic cause of MINOCA (detection of subendocardial or transmural scarring), even when the mechanism of infarction could not be completely elucidated.

The final diagnosis of MINOCA was established by the investigators after revision of clinical data and results of complementary tests. Cardioembolic stroke was defined as the presence of a predisposing factor (atrial fibrillation without hypocoagulation, thrombophilia, heart valve disease), combined with an image suggestive of intracoronary thrombus that was not adherent to the plaque, or subendocardial or transmural delayed contrast enhancement. Diagnosis of spasm was defined based on documentation of previous spontaneous episodes of rest angina, associated with ST-segment changes that responded promptly to short-acting nitrates.[8] Plaque disruption and spontaneous coronary dissection were confirmed by intracoronary imaging (intravascular ultrasound or optical coherence tomography).[8] Cases where CMR revealed a contrast enhancement pattern compatible with subendocardial or transmural infarction were classified as of ischemic cause with uncertain mechanism. The final diagnosis of MINOCA was classified as unknown when patients did not meet the criteria described above.

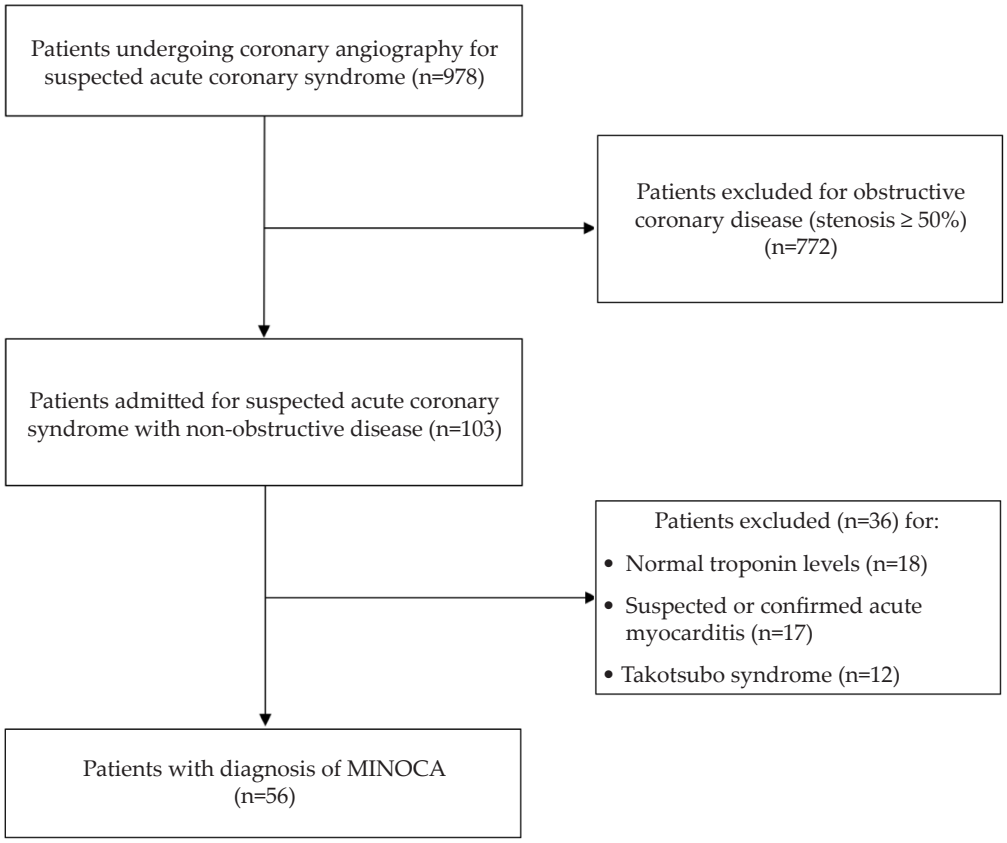

Figure 1 – Flowchart of patient selection process.

The one-year follow-up was conducted by means of review of medical records for the occurrence of the following outcomes – all-cause mortality and MACE (a composite of all-cause mortality and hospitalization due to cardiovascular disease, namely AMI, stroke, acute limb ischemia, or heart failure). The causes of readmission were determined according to medical records.

The GRACE 2.0 risk score was calculated at admission using a validated algorithm.[13]

Statistical analysis

Statistical analysis was performed using the IBM SPSS-statistics, version 25. The level of significance was set at 5%. The sample was described using descriptive statistics. Categorical variables were described as percentage. Normality of quantitative variables was verified by the Kolmogorov-Smirnov test with Lilliefors correction. These variables showed a non-Gausssian distribution and were described as median and interquartile range (IQR). Using a non-parametric analysis, the quantitative variables were analyzed using the Mann-Whitney test. The discriminatory power of the GRACE score for the prediction of cardiovascular events was assessed by ROC curve analysis. The maximum Youden index was used to determine the cutoff points for GRACE score that would best predict the occurrence of primary and secondary outcomes.

Results

Study sample and characteristics at admission

A total of 56 AMI patients that met the inclusion criteria were studied. This corresponded to 7% of admissions for AMI to our center during the study period. Clinical parameters evaluated at admission are described in Table 1. Median age of patients was 67 (IQR 60.5 – 76.3) years, and 55.4% were female. The

Table 1 – Clinical characteristics of patients admitted for acute myocardial infarction with non-obstructive coronary artery disease (MINOCA)

Total, n	**56**
Demographic data	
Median age, years (IQR)	67 (60.5 – 76.3)
Female sex, % (N)	55.4 (31)
Cardiovascular risk factors, % (n)	
Arterial hypertension	69.6 (39)
Type 2 diabetes mellitus	17.9 (10)
Dyslipidemia	71.4 (40)
Smoking habits (previous or current)	16.1 (9)
Obesity	26.8 (15)
Family history of early cardiovascular disease	10.7 (6)
Comorbidities, % (n)	
Atrial fibrillation/flutter	12.5 (7)
Previous stroke	1.8 (1)
Previous AMI	1.8 (1)
Symptoms and vital signs	
Chest pain, % (N)	94.6 (53)
Systolic blood pressure, mmHg (IQ)	144 (132-165)
Heart rate, bpm (IQ)	75 (61-85)
Electrocardiographic changes, % (n)	
Normal electrocardiogram	46.4 (26)
ST elevation	10.7 (6)
ST depression	8.9 (5)
T-wave inversion	30.4 (17)
Pathological q wave	8.9 (5)
Left bundle branch block	3.6 (2)
Laboratory data at admission	
Creatinine, mg/ml (IQ)	0.90 (0.78 – 1.06)
Cholesterol LDL, mg/dl (IQ)	111 (97 – 136)
GRACE score[11]	
Median (IQ)	113.5 (93 – 136)

IQR: Interquartile range; GRACE: Global Registry of Acute Coronary Events

most prevalent risk factors were arterial hypertension (69.6%) and dyslipidemia (71.4%). Only 1.8% of patients had previous AMI. Initial electrocardiogram was normal in 46.4% of patients and 10.7% had ST-segment elevation.

Clinical course during hospitalization

Patients' clinical data during hospitalization, including complementary diagnostic tests and therapy prescribed at discharge are described in Table 2.

During hospitalization, 5.4% of patients had heart failure; 30.9% of patients had abnormal echocardiographic findings of segmental contractility, and 8.2% had reduced ejection fraction (<50%). At discharge, most patients were prescribed angiotensin converting enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers (ARBs) (72.7%), combined with a betablocker (58.2%), statins (83.6%) or acetylsalicylic acid (61.8%), while 27.3% of patients received double antiplatelet therapy.

Cardiac magnetic resonance and definite diagnosis of MINOCA

Results of CMR are described in Table 2. The causes of MINOCA and values of GRACE score of the patients are described in Table 3. Only 12 patients (21.4%) underwent CMR, which added a diagnostic value in 50% of these patients. In most cases, CMR was performed in outpatient regimen, with a median waiting time of 3.3 months since MINOCA (IQR 1.5 – 10.7).

The cause of MINOCA was determined in 17.9% of the 56 patients. The most common etiology was ischemic disease with unknown etiology (10.7%), followed by vasospasm (5.4%). One case of cardioembolic stroke was detected. No patient underwent intravascular ultrasound or optical coherence tomography, and hence the presence of plaque disruption or spontaneous coronary dissection could not be confirmed.

Events

One patient was lost to follow-up. Among the other 55 patients, the one-year mortality rate was 5.5% and 9.1% developed MACE. Rehospitalization for cardiovascular event occurred in 7.3% of patients. Most events were seen in patients without a definite diagnosis of MINOCA.

Table 2 – Clinical course during hospitalization (including complementary diagnostic tests and drugs prescribed at discharge) of patients admitted for acute myocardial infarction with non-obstructive coronary artery disease (MINOCA)

Clinical course during hospitalization	
Length of hospital stay (median days, IQR)	4 (3-5)
Development of heart failure, % (N)	5.4 (3)
Laboratory data	
Highest troponin I level, ng/mL (IQ)	5.02 (1.55 – 11.09)
Echocardiogram, % (n)	
Changes in segmental contractility	30.9 (17)
Ejection fraction < 40%	4.1 (2)
Ejection fraction 40-50%	4.1 (2)
Ejection fraction >50%	91.8 (45)
Results of coronary angiography, % (n)	
Coronary stenosis	58.9 (33)
Stenosis <50%	41.1 (23)
Myocardial bridging	7.1 (4)
Intracoronary thrombus	3.6 (2)
Slow coronary flow (TIMI-2)	8.9 (5)
Coronary ectasia	3.6 (2)
Results of cardiac magnetic resonance, % (n=12)	
No pathological changes	41.7 (5)
Late gadolinium enhancement pattern suggestive of infarction	50.0 (6)
Myocardial edema	8.3 (1)
Drugs prescribed at discharge, % (n)	
ACE inhibitor/ARBs	72.7 (40)
Spironolactone	1.8 (1)
Betablocker	58.2 (32)
AAS	61.8 (34)
Dual antiplatelet therapy	27.3 (15)
Statin	83.6 (46)

IQR: Interquartile range; ACEI: angiotensin-converting-enzyme inhibitor; ASA: acetylsalicylic acid; ARB: angiotensin receptor blockers

Table 3 – Causes of acute myocardial infarction with non-obstructive coronary artery disease (MINOCA) and respective GRACE score

	% (n)	GRACE score
Cardioembolic stroke	1.8 (1)	138
Vasospasm	5.4 (3)	131 (127 – 147)
Plaque disruption	0 (0)	
Spontaneous coronary dissection	0 (0)	
Ischemic etiology (unknown mechanism)	10.7 (6)	110 (91 – 126)
Without a definite diagnosis	82.1 (46)	112 (93 – 136)

GRACE score

GRACE score at admission was associated with overall mortality (p=0.019) and occurrence of MACE at one year (p=0.034). Higher scores were observed in patients with MACE (Figure 2).

Figure 3 shows the ROC curves for GRACE score in predicting the outcomes studied. The GRACE score showed a high discriminatory power for overall mortality (area under the curve [AUC] of 0.907; 95% confidence interval [CI] of 0.812 – 1.000), and a cut-off of 138 showed high sensitivity and high specificity (maximum Youden index of 0.560) (Figure 3).

The frequencies of occurrence of outcomes according to the GRACE score cut-off points are described in Table 4. Among the patients with GRACE score <114, no patient had MACE after one year of follow-up. Among the patients with GRACE score of 114-137, 13.3% had MACE after one-year follow-up, but the mortality rate was 0%. Among the patients with a GRACE score ≥138, 25% had MACE, with a one-year mortality rate of 25%.

Discussion

Characteristics of our patients with diagnosis of MINOCA are similar to those described in several international studies.[2-4,6,17-19] A recent systematic review of records of patients with MINOCA reported a mean age of 55 years,[6] and higher prevalence of female

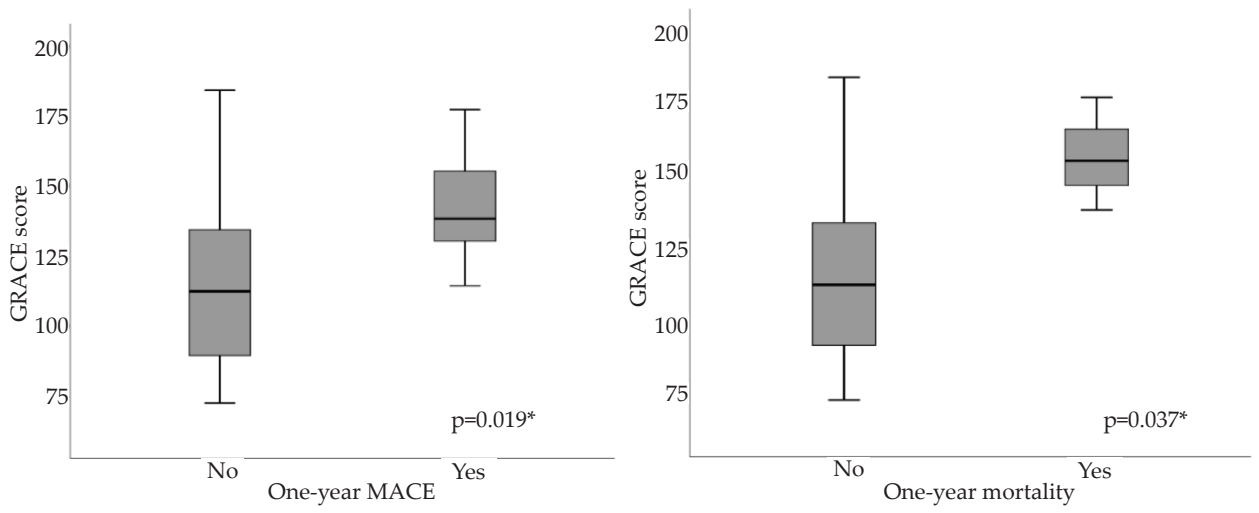

Figure 2 – Boxplot of the distribution of GRACE score for patients who had (or not) major adverse cardiovascular event (MACE) and patients who died (or survived) in one year * Mann Whitney test

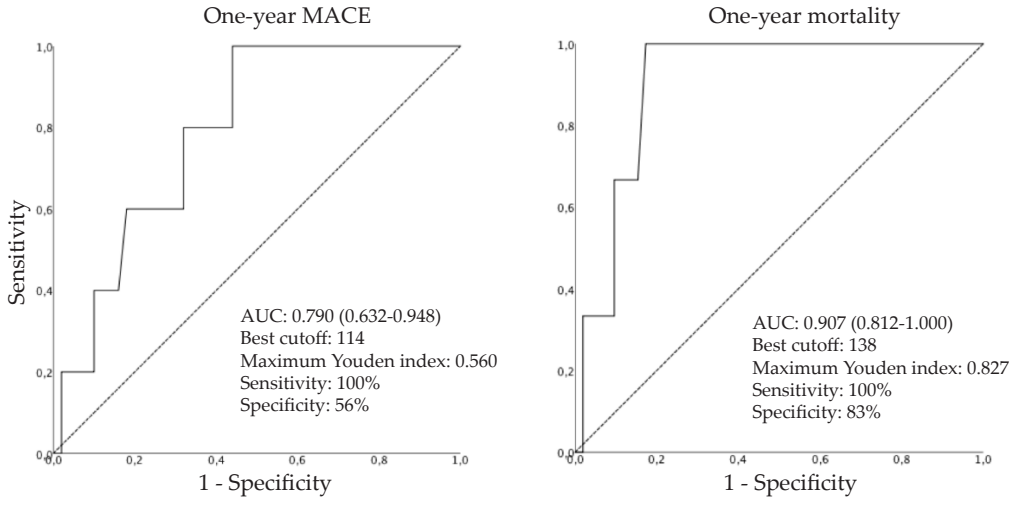

Figure 3 – ROC curves of GRACE score in predicting overall mortality and major adverse cardiovascular events (MACE) in one year; AUC: area under the curve.

Table 4 – One-year rates of major adverse cardiovascular events stratified according to GRACE score

	GRACE score			Total
	<114	114-137	≥138	
Number of patients	28	15	12*	55*
Mortality (n)	0% (0)	0% (0)	25.0% (3)	5.5% (3)
MACE (n)	0% (0)	13.3% (2)	25.0% (3)	9.1% (5)

** One lost to follow-up (% of follow up: 98%)*

patients, [2-4,6,17-19] suggesting sex-related or hormone effects on the pathophysiology of the disease.[8] However, contrary to our findings, some international studies have described a lower frequency of classical cardiovascular risk factors in these patients.[18,19] Our study showed a high prevalence of dyslipidemia and arterial hypertension in our sample, which was already reported in a previous Portuguese study.[17] As compared with the population of the Portuguese Registry of Acute Coronary Syndromes,[20] our sample shows some similarities, such as mean age (66 ±13 years), and prevalence of arterial hypertension (66.9%) and dyslipidemia (57.2%), and differed especially in sex distribution and prevalence of smoking (28.5%), diabetes mellitus (31.9%), and history of AMI (17.9%). These findings may reflect a higher prevalence of MINOCA associated with atherosclerotic disease in the Portuguese population, which is difficult to be confirmed in our study due to the small proportion of patients whose cause of MINOCA could be confirmed, despite similar mortality rates to other series.[21]

In our sample, the prognosis was similar to that previously described in other observational studies. Kang et al.[10] also reported an annual MACE rate of 7.8%, which was comparable to that observed in the comparative sample of acute coronary syndrome patients with one or two-vessel disease. Pasupathy et al.,[6] in a systematic review of studies on MINOCA patients, described a 12-month all-cause mortality rate of 4.7%. More recently, the COAPT study[22] presented even more worrying results – an all-cause mortality rate of 3.9% and 12.6% likelihood of occurrence of the composite endpoint of cardiac death and cardiovascular rehospitalization within one year.

A variable clinical course has been reported in previous studies; while most patients have a favorable course, without myocardial function sequelae, a significant proportion of patients develop MACE in short term. In light of the difficulty in establishing an etiological diagnosis in all patients, and the clinical dilemma in identifying which patients would require a closer follow-up and more aggressive secondary prevention therapy, the prognostic stratification is crucial. Numerous studies have proposed several prognostic markers, but with heterogeneous results – female sex, history of smoking, atrial fibrillation, previous AMI, ST-segment elevation at admission,[18,23] age, diabetes, previous stroke, peripheral arterial disease, chronic obstructive pulmonary disease, neoplasms, reduced ejection fraction, levels of LDL, creatinine and C-reactive protein,[18] and number of coronary arteries with stenosis less than 50%.[24]

The GRACE score is an ideal prognostic stratification tool in these patients. The instrument allows an objective quantification of the risk, making it more practical for clinicians when compared with a wide range of markers difficult to be integrated. Also, there is ample scientific evidence on the use of this risk stratification score in acute coronary syndrome.[11-13] Also, it has been widely use in clinical practice even for risk stratification of patients with MINOCA, before being submitted to catheterization.[12] Our study showed that the GRACE score is associated with one-year MACE. The cut-off points revealed by our statistical analysis are similar to those suggested by the ESC guidelines on the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation.[12] The authors suggest that MINOCA patients with a GRACE score < 109 would be classified as "low risk", a GRACE score of 109-139 would indicate an "intermediate risk" (already at a high risk of one-year MACE) and those with a GRACE score ≥140 would be classified as "high risk" (at high risk of one-year mortality). Therefore, an AMI patient, regardless of the presence of obstructive coronary artery disease, would be categorized into a risk group (low, intermediate, or high). However, independent of such classification, the active investigation for the etiologic diagnosis and appropriate therapy is always indicated.

CMR is an essential tool in the diagnosis of MINOCA. When performed in the acute phase of the disease (ideally in the first seven days of presentation),[25] the test allows the diagnosis in up to 87% of patients, changes the diagnosis made by cardiologists in nearly 52% of patients, and contributes to the definition of the best therapeutic strategy for the patient.[26] In our study, CMR had a lower diagnostic value, since it was performed in outpatient regimen in most cases, and did not allow the detection of perilesional edema using T2-weighted sequences or changes in segmental contractility in acute phase.[8,27] The low percentage of patients who underwent CMR in our study may be explained by the low accessibility of this test in our center. Similarly, although intravascular ultrasound and optical coherence tomography are essential tools for diagnosis of plaque disruption and spontaneous coronary dissection,[8] these are not readily accessible in clinical practice in our institution.

In the present study, secondary prevention therapy was prescribed at discharge based on clinical suspicion of the disease and following the current ESC recommendations.[8] Most patients were prescribed ACE inhibitors, ARBs, betablocker, and statins. However, considering the lack of robust scientific evidence, the benefit of using traditional therapies in secondary prevention in this population, with different diagnosis, is questionable. The MINOCA BAT trial aims to randomly assign more than 5,600 MINOCA patients to receive ACE inhibitor/ARBs plus betablocker versus placebo and evaluate one-year mortality rate and other cardiovascular events in one year. The use of these medications in this population can be considered reasonable according to recent findings reported in an observational study of MINOCA patients recorded in the SWEDEHEART registry,[28] suggesting long-term beneficial effects of ACE inhibitors and ARBs, and possibly betablockers in preventing cardiovascular events in these patients.

Limitations

This was a single-center, retrospective study, and limitations inherent to this study design should be considered, including a possible selection bias of patients. The small sample size and the short study period may affect the strength of our findings. In addition, since this was a retrospective study based on clinical records, a possible underreporting of endpoints cannot be ruled out. The low rate of identification of the cause of MINOCA may also bias the results, since it is not possible to determine the number of patients whose MINOCA was not related to vessel disease (as in case of myocarditis and Takotsubo syndrome). Besides, the cause of death of patients with definite diagnosis of MINOCA was unknown, which may limit the interpretation of the results.

Conclusions

This study highlights the diversity of causes and heterogeneous prognosis of MINOCA, which depends on the etiology and, in most cases, is not benign. The GRACE score at admission was shown a useful tool to identify those patients with a less favorable prognosis, with a good discriminatory ability in predicting the occurrence of events during the follow-up of our sample.

Future perspectives

Due to the heterogeneity of patients with MINOCA, multicenter studies using specific protocols for the etiological diagnosis, prognosis and therapeutic guidance are needed to establish the best therapeutic strategies tailored to the prognosis of each patient.

Author contributions

Conception and design of the research: Carvalho P, Caçoilo M; Afreixo V; Bastos JM; Acquisition of data Carvalho P, Caçoilo M; Analysis and interpretation of the data Carvalho P, Caçoilo M; Afreixo V; Bastos JM; Statistical analysis Caçoilo M; Afreixo V; Writing of the manuscript Carvalho P; Caçoilo M; Critical revision of the manuscript for intellectual content Carvalho P, Caçoilo M, Afreixo V, Bastos JM, Ferraz L, Vieira M, Santos L, Gonzaga A, Ferreira R, Adrega T, Faustino A, Briosa A.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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