International Journal of Cardiology 287 (2019) 27–31

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Myocardial infarction with non-obstructive coronary arteries (MINOCA) in Chinese patients: Clinical features, treatment and 1 year follow-up

Fuad A. Abdu [a,1], Lu Liu [a,1], Abdul-Quddus Mohammed [a,1], Yanru Luo [a], Siling Xu [a], Ranshaka Auckle [a], Yawei Xu [a], Wenliang Che [a,b,*]

[a] Department of Cardiology, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai, China
[b] Department of Cardiology, Shanghai Tenth People's Hospital Chongming Branch, Shanghai, China

ARTICLE INFO

Article history:
Received 4 August 2018
Received in revised form 12 February 2019
Accepted 18 February 2019
Available online 20 February 2019

Keywords:
MINOCA
Clinical features
Treatment
1 year follow-up

ABSTRACT

Background: Myocardial infarction with non-obstructive coronary arteries (MINOCA) is characterised by clinical evidence of myocardial infarction with normal or near-normal coronary arteries on angiography (stenosis<50%). We investigated clinical features among Chinese MINOCA patients and one-year follow-up on medication management and cardiovascular events.

Methods: The data of 2029 patients with acute myocardial infarction were consecutively collected. MINOCA patients were identified with coronary angiography (<50% stenosis). Clinical features, medication management and cardiovascular events were assessed.

Results: One hundred and twenty-eight patients (6.3%) were diagnosed as MINOCA. Compared with the myocardial infarction with obstructive coronary arteries (MI-CAD) patients, the prevalence of traditional risk factors of CAD was lower in MINOCA patients. The levels of TG, LDL-C, cTnT, CK-MB and myoglobin in the MINOCA group were significantly lower, whereas LVEF was higher. MINOCA patients are less likely to receive secondary prevention medication for MI, and use of all recommended drugs decreased at one-year follow-up. MACE in the MINOCA group was lower. After adjusting related risk factors, logistic analysis showed MINOCA was independently associated with lower risk of MACE. Independent predictors for MACE in MINOCA patients were older age (≥60 years), females, atrial fibrillation and reduced LVEF.

Conclusion: Compared with MI-CAD, MINOCA was accompanied by fewer traditional risk factors of CAD, less likely to be discharged upon secondary prevention medication of MI and the occurrence of MACE during 1 year follow-up was lower. Older age (≥60 years), females, atrial fibrillation and reduced LVEF were independent risk factors for MACE in MINOCA patients within one year.

© 2019 Elsevier B.V. All rights reserved.

1. Introduction

Myocardial infarction with non-obstructive coronary arteries (MINOCA) is a group of syndromes with multiple causes characterised by clinical evidence of myocardial infarction with normal or near-normal coronary arteries on angiography (stenosis<50%) [1,2].

The prevalence of MINOCA in the myocardial infarction population was reported to be 2.6%–15% [3–11]. The underlying pathological mechanisms are poorly understood, although several different mechanisms have been proposed, including epicardial origin (eccentric plaque, coronary dissection and coronary artery spasm) or microvascular origin (Takotsubo cardiomyopathy, myocarditis, microvascular coronary artery spasm, coronary microvascular embolism and type 2 myocardial infarction) [1–3,12,13]. It is paramount to ascertain whether MINOCA is a distinct clinical entity with specific pathophysiological mechanisms, clinical features, outcomes and to determine the appropriate management strategy for these patients. The secondary prevention therapy of myocardial infarction with obstructive coronary arteries (MI-CAD) may not always be effective in MINOCA patients. One study [14] has reported that dual antiplatelet therapy and β-blockers seemed less likely to reduce the risk of new cardiovascular events in MINOCA patients, while renin-angiotensin system blockers and statins may be beneficial. Although patients with MINOCA appear to have a slightly better long-term prognosis compared to MI-CAD patients, it is not always benign [3,10,11].

In May 2016, the European Society of Cardiology (ESC) [1] has formally laid recommendations specifically for the diagnosis and treatment of MINOCA, which have progressively expanded our ability to understand this heterogeneous clinical entity. However, there is no published data concerning MINOCA patients in China to date.

* Corresponding author at: Department of Cardiology, Shanghai Tenth People's Hospital, Tongji University School of Medicine, 301 Yanchang Road, Shanghai 200072, China.
E-mail address: chewenliang@tongji.edu.cn (W. Che).
[1] Contributed equally to this work.

https://doi.org/10.1016/j.ijcard.2019.02.036
0167-5273/© 2019 Elsevier B.V. All rights reserved.

This study aimed to investigate the clinical features, treatment in Chinese patients with MINOCA and one-year follow-up on the cardiovascular events.

2. Methods

2.1. Study population

Our study complied with the Declaration of Helsinki and was approved by the hospital's ethical review board (Shanghai Tenth People's Hospital, Tongji University, Shanghai, China). Informed written consent was obtained from all patients enrolled in this study.

This is a prospectively-planned observational study on patients with acute myocardial infarction (AMI) admitted to Shanghai Tenth People's Hospital from July 2014 to December 2017 who underwent coronary angiography. The patients were divided into two groups according to the results of coronary angiography, namely, the MI-CAD group (≥50% stenosis) and the MINOCA group (<50% stenosis). The inclusion criteria were: (1) conforms to the diagnostic criteria of the AMI guidelines [15]; and (2) age >18 years old. The exclusion criteria were: (1) types 3–5 myocardial infarction; (2) thrombolytic therapy had been received prior to coronary angiography; (3) women at pregnant or breastfeeding stage; (4) severe liver and kidney diseases; and (5) a malignant tumour with an expected survival time of less than one year.

The basic information (such as age, gender, height, weight, heart rate, blood pressure) and past medical history (such as diabetes, hypertension, hyperlipidaemia, previous heart failure, previous atrial fibrillation, previous acute coronary syndrome (ACS), body mass index, smoking history) were recorded in detail. Fasting blood within 24 h of admittance was collected for assessing blood cardiac troponin-T (cTnT), creatine kinase-MB (CK-MB), N-terminal pro-brain natriuretic peptide (NT-proBNP), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG) and C-reactive protein (CRP). The data of electrocardiogram, echocardiography and coronary angiography were collected. To determine the ultimate aetiology of MINOCA patients, left ventriculography and echocardiography were performed to assess wall motion, intravascular ultrasound (IVUS) or optical coherence tomography (OCT) was used to identify atherosclerotic plaque disruption or plaque erosion in selected patients due to its poor cost-effectiveness and insurance unfeasibility.

2.2. Diagnosis of MINOCA

The MINOCA was diagnosed according to recent Position Paper of the ESC [1] as follows. (1) The diagnostic criteria involve the criteria for AMI [15]: (a) a continuous increase and (or) decrease in cardiac biomarkers, with at least one item exceeding 99% of the upper limit of the reference value; (b)at least one evidence related to infarction: (i) ischemic symptoms; (ii)new or suspicious ST section raising, or new left bundle branch block; (iii) the pathological Q wave in the electrocardiogram; (iv)imaging evidence of new surviving myocardium loss or new local ventricular wall dysfunction; (v)angiography or autopsy hints a thrombus in the coronary artery. (2) The angiography hinted non-obstructive coronary artery. Angiography showed no coronary artery occlusion in any infarct-related coronary artery (coronary artery stenosis<50%), including normal coronary artery (stenosis ≤30%) and mild coronary atherosclerosis (30% ≤stenosis <50%). (3) For acute presentation, no clear cause has been clinically established: (a) the aetiology and diagnosis of clinical symptoms were unclear in the angiography; and (b) the potential causes of MINOCA in patients must be examined.

2.3. Follow-up

After discharge, all patients were followed up for one year by trained cardiologists in Shanghai Tenth People's Hospital. All patients were contacted by a doctor's office visit or telephone contact to assess their clinical status. In case of failure to contact the patient, information was collected through family members or the doctor of the patient. We asked our patients to maintain a log or diary and record their daily medication intake and visit physician's clinic at 1, 3, 6 and 12 months to evaluate their status on adherence and persistence. We also asked them to contact us immediately, if they develop any symptoms or feel uncomfortable taking drugs.

The primary follow-up endpoint was major adverse cardiac events (MACE), defined as cardiovascular death, nonfatal MI, stroke, heart failure and cardiovascular-related rehospitalization. Cardiovascular death, was defined as death in the presence of ACS, significant cardiac arrhythmia, or refractory congestive heart failure. The diagnosis of MI was made if patients had any elevated levels of cardiac troponin in conjunction with symptoms suggestive of myocardial ischemia. The existence of new pathological Q wave was considered as a manifestation of acute MI. Stroke was defined as an ischemic cerebral infarction caused by thrombotic or an embolic occlusion of any major intracranial artery. Diagnosis of heart failure (HF) was established according to the current guidelines for the management of HF [16]. The follow-up data were available for 1839 patients (91%), which consisted of 109 follow-up patients in the MINOCA group (85.2% follow-up) and 1730 patients in the MI-CAD group (91% follow-up) (Fig. 1). In MINOCA group, 19 patients were lost to follow-up: 8 patients refused to follow up, 6 patients never responded to any phone calls, and 5 patients had incorrect contact information.

2.4. Statistical analysis

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) v.22 software for Windows 10. Numerical variables with a normal distribution were presented as the mean ± SE, numerical variables with a skewed distribution were presented as the median, and categorical variables were presented as percentages. For numerical variables, an independent sample *t*-test and the Mann-Whitney *U* test were used for intergroup comparisons. The chi-square test and Fisher's exact tests were used for comparisons of categorical variables. The association between variables was evaluated with the Pearson rank correlation. To quantify the relative risk of outcomes in the MINOCA and MI-CAD patient groups, logistic regression models were used to derive adjusted OR for MACE events. Covariates in the models were age, sex, hypertension, diabetes, smoking, atrial fibrillation, heart failure, cerebral infarction, TC, cTnT and LVEF. Cox regression analysis was used to identify independent risk factors for MACE of MINOCA patients. A two-tailed $P < 0.05$ was considered statistically significant for all analyses.

3. Results

3.1. Baseline characteristics of patients

The study objects included 2029 patients with AMI (STEMI 39.9%, NSTEMI 60.1%), of which 128 patients (6.3%) were having MINOCA. NSTEMI was more common in MINOCA patients than those with MI-CAD (69.5% vs 59.5%).

The baseline characteristics of the patients are shown in Table 1.

Compared with MI-CAD patients, MINOCA patients were younger, had a higher proportion of females and presented lower proportions of a history of smoking, diabetes, hypertension, hyperlipidaemia and previous ACS. The levels of TG, LDL-C, cTnT, CK-MB and myoglobin in the MINOCA group were significantly lower. Echocardiography revealed that the left ventricular ejection fraction (LVEF) in the MINOCA group was higher. Angiography displayed a high proportion of the MINOCA patients showed no stenotic vessels, however, in MINOCA patients with minor stenosis, the rate of the three-vessel lesions was much lower than that of the MI-CAD group.

A final diagnosis for MINOCA group was found in 55(43%). The final diagnoses were Takotsubo cardiomyopathy (10.9%), hypertrophic cardiomyopathy (7.8%), coronary dissection (6.3%), myocarditis (4.7%), severe valvular disease (3.9%), tachyarrhythmia-related chest pain (3.9%), coronary embolism (3.1%), and vasospasm (2.3%).

3.2. Medication use at hospital discharge and 1 year follow-up

At the time of discharge, MINOCA patients were less likely to be discharged on statins, aspirin, clopidogrel, angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blockers (ARB) and β-blocker. However, the proportion of patients using calcium channel blockers (CCB) in the MINOCA group was slightly higher than that in the MI-CAD group (Table 2). At 1 year follow-up, the use of statins, aspirin, clopidogrel, ACEI/ARB and β-blocker were still significantly lower on MINOCA patients, whereas there was no difference on CCB (Table 2). For MINOCA patients the use of all recommended medications decreased for 1 year after admission, and the most marked reductions were clopidogrel (27.3%), aspirin (24.9%) and statins (23.3%).

3.3. Clinical outcomes during 1 year follow-up

At 1 year follow-up, a total of 622 MACE had occurred. In the MINOCA group, 22 MACE occurred (4 cardiovascular deaths, 2 strokes, 1 heart failure, and 15 cardiovascular-related rehospitalizations). In the MI-CAD group, 600 MACE occurred (116 cardiovascular deaths, 66 nonfatal MI, 38 strokes, 41 heart failures, and 339 cardiovascular-related rehospitalizations).The occurrence of MACE was lower in the MINOCA group compared to the MI-CAD group ($P = 0.002$). The data are shown in Table 3. Further analysis to explore the type of MINOCA (non-Takotsubo versus Takotsubo) showed no significant difference in the outcome between non-Takotsubo and Takotsubo MINOCA, with no significative differences in rate of MACE (20.8% vs 15.4%, P =

Table 1
Baseline characteristics of the study population.

	MINOCA (n = 128)	MI-CAD (n = 1901)	P value
Demographics			
Age (years)	61.94 ± 13.07	65.47 ± 12.05	0.001
Female, n (%)	60 (46.9)	433 (22.8)	<0.001
Risk factors			
BMI (kg/m^2)	24.48 ± 3.50	24.69 ± 3.81	0.544
Smoking history, n (%)	51 (39.8)	935 (49.2)	0.049
Diabetes, n (%)	14 (10.9)	563 (29.6)	<0.001
Hypertension, n (%)	67 (52.3)	1186 (62.4)	0.029
Hyperlipidaemia, n (%)	26 (20.3)	667 (35.1)	0.001
Previous stroke, n (%)	17 (13.3)	293 (15.4)	0.630
Atrial fibrillation, n (%)	13 (10.2)	115 (6.0)	0.087
Previous heart failure, n (%)	3 (2.3)	80 (4.2)	0.412
Previous ACS, n (%)	3 (2.3)	208 (10.9)	0.003
Obstructive airways disease, n (%)	7 (5.5)	106 (5.6)	0.880
Vital signs			
Systolic blood pressure (mm Hg)	142.50 ± 25.12	134.78 ± 22.00	<0.001
Diastolic blood pressure (mm Hg)	81.33 ± 13.45	78.73 ± 12.70	0.026
Mean heart rate, beats per minute	80.91 ± 19.39	80.31 ± 18.97	0.729
Biochemical parameters and LVEF			
CRP (mg/L)	13.96 ± 8.08	14.49 ± 6.60	0.387
TC (mmol/L)	4.35 ± 0.96	4.46 ± 1.02	0.236
TG (mmol/L)	1.40 ± 0.71	1.68 ± 1.00	0.002
HDL-C (mmol/L)	1.18 ± 0.36	1.02 ± 0.29	<0.001
LDL-C (mmol/L)	2.54 ± 0.85	2.76 ± 0.90	0.007
cTnT (ng/mL)	0.40 ± 0.12	2.48 ± 0.36	<0.001
CK-MB (ng/mL)	21.20 ± 5.85	74.60 ± 9.25	<0.001
Myoglobin (ng/ml)	145.17 ± 71.59	355.38 ± 80.20	<0.001
NT-proBNP (pg/mL)	2537.60 ± 5277.99	1838.70 ± 3751.26	0.048
LVEF (%)	53.24 ± 13.05	50.82 ± 10.23	0.011
Diagnosis			
STEMI, n (%)	39 (30.5)	770 (40.5)	0.032
NSTEMI, n (%)	89 (69.5)	1131 (59.5)	0.032
Angiographic data			
Normal-appearing vessels, n (%)	71 (55.5)	0	
Vessel with any stenosis			
1-vessel disease, n (%)	31 (54.4)	788 (41.5)	0.051
2-vessel disease, n (%)	17 (29.8)	540 (28.4)	0.815
3-vessel disease, n (%)	9 (15.8)	573 (30.1)	0.019

BMI, body mass index; ACS, acute coronary syndrome; CRP, C reactive protein; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein; LDL-C, high-density lipoprotein; cTnT, cardiac troponin T; CK-MB, creatine kinase isoenzyme; NT-proBNP, N-terminal pro-brain natriuretic peptide; LVEF, left ventricular ejection fraction; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; MINOCA, myocardial infarction with no obstructive coronary artery disease (<50% stenosis); MI-CAD, myocardial infarction with obstructive coronary artery disease.

1.000) and cardiovascular death (4.2% vs 0) (see Supplementary table). Among all patients with AMI, the MINOCA patients had an unadjusted OR of 0.542 (95% CI 0.336 to 0.874, P = 0.012) for the MACE, when compared with obstructive MI-CAD patients. After adjusting for age, sex, hypertension, diabetes, smoking, atrial fibrillation, heart failure, cerebral infarction, TC, cTnT and LVEF, the OR for those with MINOCA was 0.466 (95% CI 0.232 to 0.935, P = 0.032) compared with those with MI-CAD (Table 4).

Table 3
One-year follow-up data of patients.

	MINOCA (n = 109)	MI-CAD (n = 1730)	P value
MACE, n (%)	22 (20.2)	600 (34.7)	0.002
Cardiovascular death, n (%)	4 (3.7)	116 (6.7)	0.213
Nonfatal MI, n (%)	0	66 (3.8)	0.037
Stroke, n (%)	2 (1.8)	38 (2.2)	0.801
Heart failure, n (%)	1 (0.9)	41 (2.4)	0.325
Cardiovascular-related rehospitalization, n (%)	15 (13.8)	339 (19.6)	0.134

MACE, major adverse cardiovascular events; MINOCA, myocardial infarction with no obstructive coronary artery disease (<50% stenosis); MI-CAD, myocardial infarction with obstructive coronary artery disease.

3.4. Predictive factors of endpoint events in MINOCA patients

Univariate analysis showed older age (≥60 years old) (3.124; 1.051–9.287), females (3.587; 1.300–9.894), hypertension (3.543; 1.192–10.536), atrial fibrillation (3.843; 1.279–11.551), reduced LVEF (0.947; 0.921–0.974), and lower level of TC (0.520; 0.301–0.899) were significant predictors of MACE (Table 5).After excluding confounding factors, multivariate analysis showed older age (≥60 years old) (5.638;1.098–28.953), females (5.907; 1.497–23.313), atrial fibrillation (6.184; 1.174–32.585) and reduced LVEF (0.948;0.917–0.980) were independent risk factors for MACE in patients with MINOCA within one year (Table 6).

4. Discussion

Our study investigated the clinical features, treatment, and one-year follow-up of cardiovascular events among Chinese patients with MINOCA. The major findings were (1) Clinical diagnosis of MINOCA is relatively common in Chinese patients with MI, (2) MINOCA was accompanied by fewer traditional risk factors of CAD, (3) MINOCA patients were less likely to be discharged upon conventional secondary prevention medication of MI, (4) Occurrence of MACE during 1 year follow-up was lower in the MINOCA group compared to MI-CAD patients, (5) MINOCA was independently associated with lower risk of MACE, (6) Older age (≥60 years old), females, atrial fibrillation and reduced LVEF were independent risk factors for MACE in MINOCA patients within one year.

The precise prevalence of MINOCA varies among different studies [3–11], which have stated that in MI patients is approximately 2.6%–15%. In the present study, the prevalence of MINOCA was 6.3%. Moreover, NSTEMI was more common in patients with MINOCA, which was in line with the previous results [3,17]. Compared with MI-

Table 2
Use of medication at hospital discharge and at 1 year follow-up.

Medication	At discharge			One-year follow-up		
	MINOCA (n = 128)	MI-CAD (n = 1901)	P value	MINOCA (n = 109)	MI-CAD (n = 1730)	P value
Statins	112 (87.5)	1817 (95.6)	<0.001	70 (64.2)	1310 (75.7)	0.010
Aspirin	107 (83.6)	1803 (94.8)	<0.001	64 (58.7)	1562 (90.3)	<0.001
Clopidogrel	62 (48.4)	1758 (92.5)	<0.001	23 (21.1)	1406 (81.2)	<0.001
ACEI/ARB	67 (52.3)	1380 (72.6)	<0.001	48 (44.0)	1131 (65.4)	<0.001
β-BLOCK	73 (57.0)	1455 (76.5)	<0.001	54 (49.5)	1214 (70.2)	<0.001
CCB	42 (32.8)	428 (22.5)	0.010	23 (21.1)	351 (20.3)	0.937

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blockers; MINOCA, myocardial infarction with no obstructive coronary artery disease (<50% stenosis); MI-CAD, myocardial infarction with obstructive coronary artery disease.

Table 4
Risk of MACE in patients with MINOCA compared with patients with MI-CAD.

	Unadjusted			Adjusted for A		
	OR	95% CI	P value	OR	95% CI	P value
MINOCA	0.542	0.336–0.874	0.012	0.466	0.232–0.935	0.032
MI-CAD	1.845	1.145–2.973	0.012	2.145	1.069–4.303	0.032

A = age, sex, hypertension, diabetes, smoking, atrial fibrillation, heart failure, cerebral infarction, TC, cTnT, LVEF. MACE, major adverse cardiovascular events; MINOCA, myocardial infarction with no obstructive coronary artery disease (<50% stenosis); MI-CAD, myocardial infarction with obstructive coronary artery disease; CI, confidence interval; OR, odds ratio.

CAD patients, the proportion of MINOCA patients suffering from risk factors was relatively lower, indicating that the mechanism of MINOCA was not utterly due to atherosclerosis and thrombosis caused by traditional risk factors. In view of the lower levels of cardiac biomarkers and the higher LVEF value, the degree of myocardial damage in MINOCA patients can be presumed lower than that in MI-CAD patients.

MINOCA is a group of syndromes involving one or more causes. In the recent few years, physicians have witnessed a huge leap towards our understanding of MINOCA, suggesting a slight better clinical prognosis and reduced rate of MACE compared to MI-CAD. The most common causes of MINOCA are plaque rupture or erosion [1,2,12,13], coronary artery spasm [1–3,12,13,18], thromboembolism [1,2], coronary dissection [1,2,12,13], Takotsubo cardiomyopathy [1–3,10,12,13,19], unrecognized myocarditis [1–3,12,13,19,20], and other forms of type-2 myocardial infarction [1]. However, MINOCA remains potentially challenging with multiple pathogenic mechanisms with various causes and inconclusive management therapy to effectively treat patients. Additional studies are still mandatory to further explore the mechanism of MINOCA. Currently, ESC [1] has proposed the following diagnostic tests to be useful in diagnosing MINOCA, including left ventriculography or echocardiography, cardiac magnetic resonance imaging (CMR), IVUS, OCT and coronary CT angiography. In our study , we excluded patients presenting with a classical myocarditis presentation at enrollment according to ESC 2013 Myocarditis Task Force criteria [21]. However, at 1-month follow up, we found that the serum troponin levels in 6 patients were elevated for over 3 weeks and remained persistent and constantly high. Combined with series of serological tests including elevated C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR), and increased IgM (serology) against viruses known to affect the myocardium, the diagnosis of suspected myocarditis was made in these 6 patients. A low proportion of myocarditis patients without CMR may constitute a discrepancy in the diagnosis of MINOCA. We sought to imitate real-world practice by using the information available at hand.

Given that MINOCA may have diverse possible pathological mechanisms, the conventional secondary prevention strategy for MI may not be suitable for all patients with MINOCA. Some studies [9,22] demonstrated that patients with no obstructive coronary artery disease were less likely to be discharged on the conventional secondary prevention therapy. In our study, the results showed a relatively lower prescription rate and premature discontinuation of secondary prevention medications in the MINOCA group. The most possible reason was underdiagnosis and undertreatment of MINOCA by physicians due to their lack of knowledge in such cases. Some MINOCA patients were treated as usual benign CAD patients due to an insignificant obstructive coronary artery. In addition, no optimal pharmacotherapy has been certified to effectively combat MINOCA, which has left the physicians baffled all around the world including China. Previous studies [14] have shown that β-blockers and dual antiplatelet therapy seemed less likely to reduce the risk of new cardiovascular events in MINOCA patients, whereas statins and renin-angiotensin system blockers may be beneficial. Other studies [23] showed that low-dose aspirin might not reduce future cardiovascular events in coronary vasospastic angina patients with non-significant stenosis. Currently, limited data are available in the management of patients with MINOCA in China. In our study, despite secondary prevention therapy, MINOCA patients after one-year follow-up demonstrated an increased incidence of unfavorable clinical outcome, and there is no tangible evidence that this adjuvant therapy can be beneficial in the long-term management of MINOCA.

The prognosis of MINOCA and its related factors have attracted considerable attention, and different studies have found varying results. Systematic review [3] indicated that the total-cause mortality of MINOCA in the 1 year follow-up was 4.7%. A meta-analysis [24] showed that the yearly event rates(all-cause mortality, myocardial infarction, all-cause mortality plus myocardial infarction, cardiac death, and major cardiovascular events) in non-obstructive CAD were lower than that in obstructive CAD respectively. In a study on the long-term outcome of 2438 ACS patients with non-obstructive coronary arteries, MACE in patients with obstructive CAD was higher, and the rate of death, ACS leading to hospitalization, and stroke was similar in two groups [9]. Kang et al. [25] demonstrated no significant difference in the incidence of MACE at 12 months between patients with near-normal coronary arteries and 1–2 vessel lesion. Raparelli et al. [10] found that the recurrent nonfatal MI, nonfatal stroke, congestive heart failure, or cardiac-related mortality and all-cause readmission rate in MINOCA patients at 1 year was lower than that in the MI-CAD group. In the present study, MACE in MINOCA patients at 1 year follow-up was lower than that in MI-CAD patients. MINOCA patients had an unadjusted OR of 0.542 for the MACE, when compared with obstructive MI-CAD patients. Interestingly, after adjusting for related risk factors of cardiovascular disease, we found that the OR remained largely unchanged in MINOCA group demonstrating that MINOCA was independently associated with lower risk of MACE. However, the cardiovascular death was not significantly different between two groups, which indicated that MINOCA still inducted great harm and should be given the same attention as MI-CAD although the coronary artery had no obvious obstruction. Multi-factor survival analysis showed that older age (≥60 years old), female sex, atrial fibrillation and reduced LVEF are independent risk factors for MACE in patients with MINOCA within one year. The present results together with previous data [26,27] demonstrated that the prognostic determinants of MINOCA are different when compared to MI-CAD.

Several limitations need to be considered in the present study. First, the definition of MINOCA utilized in this study is generic and includes patients with suspected MINOCA (i.e. Tako-tsubo syndrome). The recently published 4th universal definition of myocardial infarction [28] will change the context of acute myocardial infarction on the MINOCA definition. Second, the present study is an observational single-center study. Consistent with contemporary practice, few patients with MINOCA underwent extensive investigations to identify the underlying cause of the acute MI presentation; i.e. provocative spasm testing and/or coronary hemodynamic studies. Third, lack of CMR may influence the accuracy of our findings in MINOCA patients. In addition, small sample size, short period of follow-up and loss of follow-up could contribute to a bias of the present result in our study.

5. Conclusion

Compared with MI-CAD, MINOCA was accompanied by fewer traditional risk factors of CAD, less likely to be discharged upon secondary prevention medication of MI and the occurrence of MACE during 1 year follow-up was lower. Older age (≥60 years old), females, atrial fibrillation and reduced LVEF were independent risk factors for MACE in MINOCA patients within one year. The findings of this study lay the foundation for further investigating and improving the diagnosis and treatment ability of MINOCA patients in China.

Conflicts of interest

The authors have no conflicts of interest to declare in relation to this article.

Sources of funding

This work was supported by the National Natural Science Foundation of China (81570436), Foundation of Shanghai Municipal Commission of Health and Family Planning (201640053), Shanghai Medical Guiding Project (124119a6900), and Foundation of Chongming (CKY2017-16, CKY2018-18).

Acknowledgments

Those who contributed to the work and meet the authorship criteria are listed as authors of the article. We also are indebted to the participants of this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.02.036.

References

[1] Agewall, S., et al., *ESC working group position paper on myocardial infarction with non-obstructive coronary arteries.* European Heart Journal, 2016: p. ehw149.DOI:https://doi.org/10.1093/eurheartj/ehw149.
[2] G. Niccoli, G. Scalone, F. Crea, Acute myocardial infarction with no obstructive coronary atherosclerosis: mechanisms and management, Eur. Heart J. 36 (8) (2015) 475–481.
[3] S. Pasupathy, et al., Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries, Circulation 131 (10) (2015) 861–870.
[4] K.R. Bainey, 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. 264 (2018) 12–17.
[5] A.I. Larsen, et al., Characteristics and outcomes of patients with acute myocardial infarction and angiographically normal coronary arteries, Am. J. Cardiol. 95 (2) (2005) 261–263.
[6] E.R. Gehrie, 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. 158 (4) (2009) 688–694.
[7] P. Widimsky, et al., Prevalence of normal coronary angiography in the acute phase of suspected ST-elevation myocardial infarction: experience from the PRAGUE studies, Can. J. Cardiol. 22 (13) (2006) 1147–1152.
[8] Safdar, B., et al., Presentation, Clinical Profile, and Prognosis of Young Patients With Myocardial Infarction With Nonobstructive Coronary Arteries (MINOCA): Results From the VIRGO Study. J. Am. Heart Assoc., 2018. 7(13).DOI:https://doi.org/10.1161/JAHA.118.009174.
[9] R. Rossini, et al., Long-term outcomes of patients with acute coronary syndrome and nonobstructive coronary artery disease, Am. J. Cardiol. 112 (2) (2013) 150–155.
[10] V. Raparelli, et al., Myocardial infarction with no obstructive coronary artery disease: angiographic and clinical insights in patients with premature presentation, Can. J. Cardiol. 34 (4) (2018) 468–476.
[11] P.R. Barr, et al., Myocardial infarction without obstructive coronary artery disease is not a benign condition (ANZACS-QI 10), Heart Lung Circ 27 (2) (2018) 165–174.
[12] N. Poku, S. Noble, Myocardial infarction with non obstructive coronary arteries (MINOCA): a whole new ball game, Expert. Rev. Cardiovasc. Ther. 15 (1) (2016) 7–14.
[13] S. Pasupathy, R. Tavella, J.F. Beltrame, The what, when, who, why, how and where of myocardial infarction with non-obstructive coronary arteries (MINOCA), Circ. J. 80 (1) (2016) 11–16.
[14] B. Lindahl, et al., Medical therapy for secondary prevention and long-term outcome in patients with myocardial infarction with nonobstructive coronary artery disease, Circulation 135 (16) (2017) 1481–1489.
[15] K. Thygesen, et al., Third universal definition of myocardial infarction, Circulation 126 (16) (2012) 2020–2035.
[16] P. Ponikowski, et al., ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC, Eur J Heart Fail, 2016. 18 (8) (2016) 891–975.
[17] N. Johnston, et al., Effect of gender on patients with ST-elevation and non-ST-elevation myocardial infarction without obstructive coronary artery disease, Am. J. Cardiol. 115 (12) (2015) 1661–1666.
[18] A. Da Costa, Clinical characteristics, aetiological factors and long-term prognosis of myocardial infarction with an absolutely normal coronary angiogram; a 3-year follow-up study of 91 patients, Eur. Heart J. 22 (16) (2001) 1459–1465.
[19] G.A. Lanza, et al., Clinical spectrum and outcome of patients with non-ST-segment elevation acute coronary syndrome and no obstructive coronary atherosclerosis, Circ. J. 80 (7) (2016) 1600–1606.
[20] P. Tornvall, et al., Myocarditis or "true" infarction by cardiac magnetic resonance in patients with a clinical diagnosis of myocardial infarction without obstructive coronary disease: a meta-analysis of individual patient data, Atherosclerosis 241 (1) (2015) 87–91.
[21] Caforio, A.L., 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): p. 2636–48, 2648a-2648d.DOI:https://doi.org/10.1093/eurheartj/eht210.
[22] V.S. Ramanath, et al., Receipt of cardiac medications upon discharge among men and women with acute coronary syndrome and nonobstructive coronary artery disease, Clin. Cardiol. 33 (1) (2010) 36–41.
[23] M. Ishii, et al., Impact of aspirin on the prognosis in patients with coronary spasm without significant atherosclerotic stenosis, Int. J. Cardiol. 220 (2016) 328–332.
[24] C. Pizzi, et al., Nonobstructive versus obstructive coronary artery disease in acute coronary syndrome: a meta-analysis, J. Am. Heart Assoc. 5 (12) (2016), e004185. .
[25] W.Y. Kang, et al., Are patients with angiographically near-normal coronary arteries who present as acute myocardial infarction actually safe? Int. J. Cardiol. 146 (2) (2011) 207–212.
[26] A.M. Nordenskjold, et al., Predictors of adverse outcome in patients with myocardial infarction with non-obstructive coronary artery (MINOCA) disease, Int. J. Cardiol. 261 (2018) 18–23.
[27] F. Montenegro Sa, et al., Myocardial infarction with nonobstructive coronary arteries: a single-center retrospective study, Coron. Artery Dis. (2018)https://doi.org/10.1097/MCA.0000000000000619.
[28] K. Thygesen, et al., Fourth universal definition of myocardial infarction (2018), J. Am. Coll. Cardiol. (2018)https://doi.org/10.1016/j.jacc.2018.08.1038.