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ORIGINAL ARTICLE

Impact of sex on the follow-up course and predictors of clinical outcomes in patients hospitalised due to myocardial infarction with non-obstructive coronary arteries: a single-centre experience

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Abstract

Background: Myocardial infarction with non-obstructive coronary arteries (MINOCA) occurs more often in women.

Aim: We sought to assess the relationship between sex and clinical outcomes during follow-up in patients after MINOCA and to identify predictors of major adverse cardiac and cerebrovascular events (MACCE).

Methods: The study comprised 134 patients (78 women) at the mean age of 61.6 years, who were diagnosed with MINOCA at the Department of Cardiology between January 2015 and June 2018. The mean follow-up duration was 609.5 ± 412.2 days. Primary study endpoints were MACCE, which included all-cause death, myocardial infarction, reintervention, and cerebral stroke. Secondary endpoints were recurrent chest pain during follow-up and rehospitalisation for reasons other than MACCE.

Results: Kaplan-Meier survival curve analysis did not reveal any significant differences in the frequency of MACCE (p = 0.63) or mortality rate (p = 0.29) between men and women. There was no significant impact of sex on secondary study endpoints either. Sex was not identified as a predictor of primary or secondary study endpoints in univariate or multivariate analysis. Troponin index (risk ratio [RR] 1.002; 95% confidence interval [CI] 1.0005–1.0026, p = 0.004), age (RR 1.04; 95% CI 1.008–1.065, p = 0.01), serum creatinine level (RR 1.01; 95% CI 1.001–1.01, p = 0.02), hyperlipidaemia (RR 0.26; 95% CI 0.07–0.75, p = 0.01), and prior venous thromboembolic disease (RR 8.28; 95% CI 1.15–38, p = 0.04) were found to be predictors of MACCE in multivariate analysis.

Conclusions: Sex was not found to be significantly associated with clinical outcomes during the follow-up period in patients with MINOCA.

Key words: clinical outcomes, follow-up, myocardial infarction with non-obstructive coronary arteries, predictors, sex

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INTRODUCTION

Symptomatic coronary artery disease (CAD) presenting as chest pain does not always coexist with obstructive CAD. In some patients various forms of the disease (stable CAD or acute coronary syndrome) coincide with non-obstructive CAD [1, 2]. Several mechanisms have been found to be responsible for different clinical presentation of CAD in those patients. In patients with myocardial infarction with non-obstructive coronary arteries (MINOCA), the aetiology of the disease is very heterogeneous, and atherosclerosis is

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not the most prevalent cause, in contrast to patients with typical risk factors for atherosclerosis or those with myocardial infarction (MI) with obstructive CAD. In a large proportion (up to 25%) of patients with MINOCA, the aetiology is linked to hypercoagulable states. This especially concerns women who, in many of the published studies, make up the vast majority the population and in whom blood clotting disorders may be due to menopause, pregnancy, or childbirth [2, 3]. Recently published studies performed in patients with ST-segment elevation myocardial infarction (STEMI) and MINOCA diagnosed with intravascular ultrasound increased the significance of coronary atherosclerotic lesions, which are often assessed as mild via regular coronary angiography [4]. It was also shown that plaque burden was the most powerful predictor of future acute coronary events [5]. Large registry studies revealed that the incidence of MINOCA is higher in women compared to men and that MINOCA patients more often present with non-ST-segment elevation myocardial infarction (NSTEMI) than STEMI [6].

The aim of the current study was to assess the relationship between sex and clinical outcomes during follow-up in patients after MINOCA and to identify predictors of major adverse cardiac and cerebrovascular events (MACCE) in this group.

METHODS

We retrospectively analysed 1984 consecutive patients admitted to our catheterisation laboratory and to our Department of Cardiology due to MI from January 2015 until June 2018. From this group we extracted 134 (6.75%) patients with MINOCA (56 [41.8%] men). Both MI and MINOCA were diagnosed according to the previous definition of MI [2, 3]. Due to the fact that the troponin level was estimated using different assays, we calculated the troponin index from the maximal troponin value measured during hospitalisation in order to unify the results. The troponin index was calculated by dividing the troponin concentration by the upper limit of the reference range for the particular assay. Glomerular filtration rate (GFR) was estimated according to the Cockroft-Gault formula. Kidney failure was diagnosed when the GFR level was lower than 60 mL/min. Coronary slow-flow phenomenon was diagnosed on the basis of grade 2 on the Thrombolysis in Myocardial Infarction (TIMI) scale [7]. Slow flow was assumed as an indirect indicator of microcirculatory dysfunction.

This study complies with the Declaration of Helsinki. All subjects gave informed consent to participate before the investigation began.

Study endpoints

This was an observational follow-up study. Primary endpoints were main MACCE, which included cerebral stroke, MI, death, percutaneous coronary reintervention, and coronary artery bypass grafting. Secondary study endpoints were recurrent chest pain as well as rehospitalisation for reasons other than MACCE, such as anaemia, gastrointestinal bleedings, infections (e.g. pneumonia), and any other conditions that could possibly lead to the onset of type 2 MI. Data regarding primary and secondary endpoints were obtained on the basis of medical records gathered during follow-up visits at the outpatient clinic or by telephone.

Statistical analysis

Continuous variables are expressed as means and standard deviations or median and interquartile range, and categorical variables are shown as numbers and percentages. The investigated groups were analysed using the Shapiro-Wilk test to assess continuous data distribution. We compared men and women with the Mann-Whitney U-test, Student t test, Welch's t test, Person's χ^2 test, Fisher's exact test, and the Cochrane-Armitage test for trends when appropriate. Kaplan-Meier analysis was used for primary endpoint assessment. Mantel-Cox analysis was used for comparison between Kaplan-Meier survival curves for death and MACCE. In order to identify factors influencing the primary study endpoints, univariate and multivariate Cox regression proportional hazard models were constructed. Univariate Cox regression analysis was also adjusted for sex. To identify factors influencing secondary study endpoints, logistic regression analysis was performed along with adjustment for sex. Statistical significance was accepted at a p-value of 0.05. The statistical analyses were performed using the Statistica 10.0 software (Dell Software, Inc., Round Rock, TX, USA) and the SPSS STATISTICS 24 (IBM, SPSS Inc., Chicago, IL, USA).

RESULTS

Epidemiology, frequency, and aetiology of MINOCA

The overall frequency of MINOCA among all the patients admitted to our department was estimated at 6.75% and it was higher in women than in men (11.3% vs. 4.7%, $p < 0.001$) (Fig. 1). On admission, 104 (77.6%) patients with MINOCA were diagnosed with NSTEMI, whereas 30 (22.4%) patients had STEMI. Upon discharge from hospital, 68 (50.7%) patients were diagnosed with NSTEMI, 11 (8.2%) had myocarditis, 17 (12.7%) had takotsubo cardiomyopathy, five (3.7%) had tachyarrhythmia, 12 (8.9%) had STEMI, there were six (4.5%) cases of heart failure, nine (6.7%) patients had type 2 MI, two (1.5%) had hypertrophic cardiomyopathy, and there were single cases of thromboembolic disease, arterial hypertension, myocardial bridge, and cerebral stroke (0.7% of patients each). The following aetiologies of MINOCA were revealed: unknown aetiology in 50 (37.3%) patients, takotsubo cardiomyopathy in 20 (14.9%) patients, tachyarrhythmia in 16 (11.9%) patients, myocarditis in 11 (6.7%) patients, slow-flow phenomenon in nine (6.7%) patients, arterial hypertension in five (3.7%) patients, myocardial bridge in four (3%) patients, arterial spasm, hypertrophic cardiomyopathies, and tumour embolisations in three

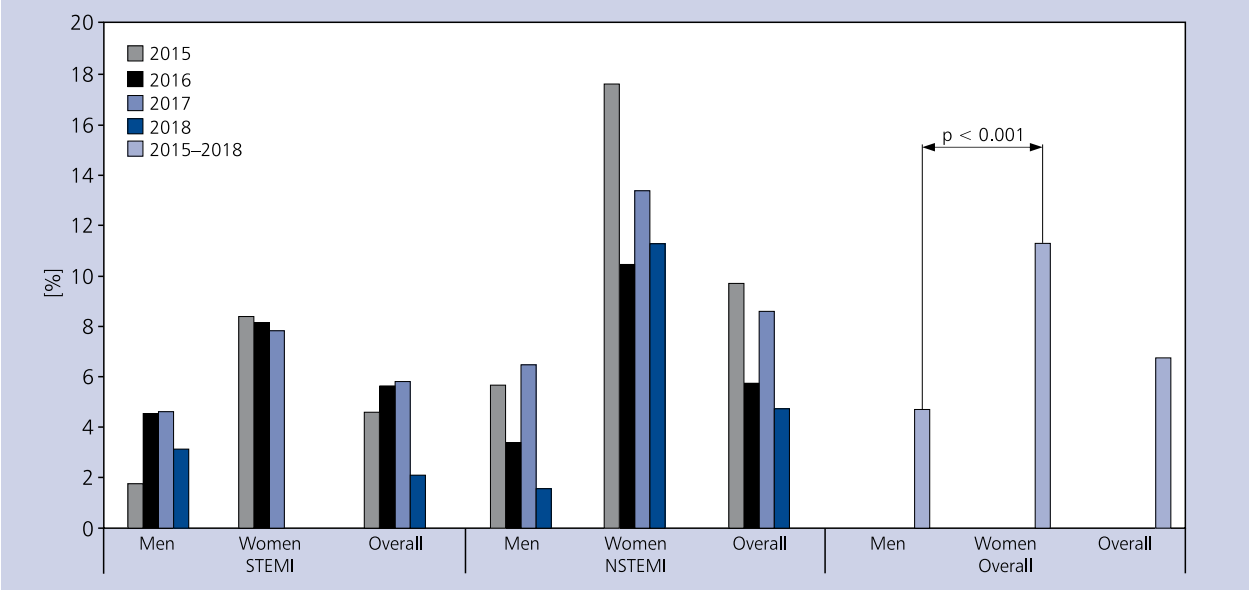


Figure 1. The rate of myocardial infarction with non-obstructive coronary arteries diagnosed at the Cardiology Department of the University Hospital in Krakow in the years 2015–2018, according to sex and the type of myocardial infarction; STEMI — ST-segment elevation myocardial infarction; NSTEMI — non-ST-segment elevation myocardial infarction

(2.2%) patients each, anaemia in two (1.5%) patients, as well as atrioventricular block, aortic dissection, muscular dystrophy, cerebral stroke, alcohol-induced cardiomyopathy, aortic valve stenosis, and antiphospholipid syndrome in one (0.7%) patient each.

General characteristics

In the group of patients included in the study, women were significantly older than men (66.6 ± 13.7 years vs. 56 ± 41.8 years, $p < 0.001$). The mean body mass index (BMI) was significantly lower in women compared to men (26.4 ± 5.8 kg/m^2 vs. 28.1 ± 4.4 kg/m^2, $p = 0.02$). Cardiac arrest on admission occurred only in men (six cases, $p = 0.002$), whereas women, in comparison to men, more often suffered from hyperlipidaemia (24.5% vs. 42.3%, $p = 0.03$), hypertension (59.2% vs. 75.6%, $p = 0.04$), and chronic kidney failure (11.8% vs. 32.8%, $p = 0.007$) (Table 1).

Pharmacotherapy

Women with MINOCA were numerically more often treated with acetylsalicylic acid before admission to hospital, but without statistical significance (16% vs. 29.8%, $p = 0.08$). However, statins were significantly more often used in women compared to men (16% vs. 32.8%, $p = 0.03$) (Table 2).

Biochemical indices

With regard to biochemical indices, there was a significantly greater mean value of troponin index in men compared to women (243.3 ± 302 vs. 167 ± 265.1, $p = 0.03$), whereas the mean N-terminal pro–B-type natriuretic peptide (NT-proBNP) concentration was significantly higher in women (2671.0 [692.5–5102.0] pg/mL) than in men (485.6 [156.0–1393.3] pg/mL); $p = 0.02$. The mean haemoglobin concentration was significantly lower in women compared to men (12.5 ± 1.5 g/dL vs. 13.5 ± 2.2 g/dL, $p < 0.001$). The mean high-density lipoprotein cholesterol concentration was higher in women compared to men (1.4 ± 0.4 mmol/L vs. 1.1 ± 0.3 mmol/L, $p < 0.001$), and the mean serum creatinine concentration was significantly greater in men (86.2 ± 37.4 μmol/L vs. 76 ± 42.8 μmol/L, $p < 0.001$). The mean GFR was significantly lower in women compared to men (83 ± 41 mL/min vs. 120 ± 52.3 mL/min, $p < 0.001$; Table 3).

Electrocardiography, cardiac echocardiography, and coronary angiography

There were no significant differences in electrocardiographic signs of myocardial ischaemia, except for the T-wave inversion, which occurred significantly more often in women compared to men (24.3% vs. 8.9%, $p = 0.02$). Also, echocardiographic parameters did not differ significantly between these two groups, despite the fact that there were numerically more female than male patients with impaired left ventricular ejection fraction (LVEF) below 40% (28.2% vs. 18.2%, $p = 0.18$), left ventricular akinesis (33.3% vs. 24.4%, $p = 0.08$), and pericardial effusion (11.7% vs. 5.9%, $p = 0.26$). Conversely, left ventricular hypertrophy tended to be observed more often in men compared to women (29.4% vs. 17.9%, $p = 0.12$).

In terms of coronary angiography findings, there were numerically more cases of muscular bridges (12.5% vs. 5.1%, $p = 0.12$), arterial spasms (5.3% vs. 1.3%, $p = 0.17$), contrast slow-flows (19.6% vs. 14.1%, $p = 0.39$), and atherosclerotic

Table 1. Clinical characteristics of MINOCA patients

	Men (n = 56)	Women (n = 78)	p	Overall (n = 134)
Age [years]	54.5 ± 17.4	66.6 ± 13.7	< 0.001	61.6 ± 16.4
BMI [kg/m^2]	28.1 ± 4.4	26.4 ± 5.8	0.02	27.1 ± 5.3
Hospitalisation time [days]	6 ± 3.1	7.1 ± 3.5	0.055	6.7 ± 3.4
Second episode of MINOCA	5 (8.9)	7 (9.1)	0.97	12 (9)
Chest pain on admission	23 (44.2)	27 (34.6)	0.26	50 (38.5)
Cardiac arrest during MI	6 (11)	0 (0)	0.002	6 (4.5)
NSTEMI on admission	42 (75)	62 (79.5)	0.53	104 (77.6)
Diabetes	11 (20.4)	18 (23.1)	0.71	29 (22)
Hyperlipidaemia	13 (24.5)	33 (42.3)	0.03	46 (35.1)
Hypertension	32 (59.2)	59 (75.6)	0.04	91 (68.9)
Smoking	19 (35.2)	17 (22.1)	0.09	36 (27.5)
COPD/Bronchial asthma	3 (5.5)	7 (9)	0.46	10 (7.6)
Chronic kidney failure	6 (11.8)	22 (32.8)	0.007	28 (23.7)
Venous thromboembolic disease	1 (1.8)	0 (0)	0.23	1 (0.8)
Prior MI	7 (12.7)	13 (16.7)	0.53	20 (15)
Prior PCI	7 (12.7)	7 (9)	0.48	14 (10.5)
Prior TIA/cerebral stroke	1 (1.9)	7 (9)	0.08	8 (6)
Pacemaker/ICD/CRT	1 (1.9)	4 (5.2)	0.31	5 (3.8)
Autoimmune diseases	2 (3.8)	2 (2.6)	0.71	4 (3.1)
Cancer	1 (1.9)	2 (2.7)	0.77	3 (2.3)
Alcohol abuse	2 (3.8)	1 (1.4)	0.38	3 (2.4)

Data are presented as arithmetic mean ± standard deviation or number (percentage). BMI — body mass index; COPD — chronic obstructive pulmonary disease; CRT — cardiac resynchronisation therapy; ICD — implantable cardioverter-defibrillator; MI — myocardial infarction; MINOCA — myocardial infarction with non-obstructive coronary artery; NSTEMI — non-ST-segment elevation myocardial infarction; PCI — percutaneous coronary intervention; TIA — transient ischaemic attack

Table 2. Pharmacotherapy before admission to hospital

	Men	Women	P	Overall
Acetylsalicylic acid	8 (16)	20 (29.8)	0.08	28 (23.9)
Anticoagulant	6 (12.2)	8 (11.9)	0.96	14 (12.1)
Statin	8 (16)	22 (32.8)	0.03	30 (25.6)
DAPT	3 (6)	3 (4.4)	0.69	6 (5.1)
β-blocker	11 (22)	23 (34.3)	0.14	34 (29)
Glucocorticosteroids	1 (2)	4 (5.9)	0.3	5 (4.2)
Hormonal contraception	0 (0)	1 (1.4)	0.38	1 (0.8)
HRT	0 (0)	1 (1.4)	0.38	1 (0.8)
Amphetamine	2 (3.6)	0 (0)	0.09	2 (1.5)

Data are presented as numbers (percentages). DAPT — dual antiplatelet therapy; HRT — hormone replacement therapy

plaques (85% vs. 71.8%, p = 0.11) in men compared to women, but without statistical significance (Table 4).

Primary and secondary study endpoints

The mean duration of the follow-up period was almost equal in men and women (609.5 ± 434.7 days vs. 609.5 ± 398.1 days, p = 0.99). The percentage of completed follow-ups (92.8% vs. 91%, p = 0.7) and MACCE rate (19.2% vs. 22.5%, p = 0.65) also did not differ significantly between these two groups. With regard to primary and secondary study endpoints, mortality was similar between the two groups (18.6% vs. 11.5%, p = 0.3) (Table 5).

Table 3. Biochemical parameters

	Men	Women	P	Overall
Maximum troponin index	243.3 ± 302	167 ± 265.1	0.03	198.8 ± 282.5
CK-MB on admission [IU/L]	50.2 ± 100.4	34.6 ± 36.4	0.12	41 ± 70.1
Maximum CK-MB [IU/L]	78.9 ± 253.3	39.4 ± 39.9	0.1	56.1 ± 167.5
Elevated C-reactive protein (> ULN)	27 (75)	35 (85.3)	0.25	60 (77)
C-reactive protein [mg/L]	33.6 ± 51.5	36.6 ± 41.1	0.99	35.3 ± 45.5
NT-proBNP [pg/mL]	485.6 [156.0–1393.3]	2671.0 [692.5–5102.0]	0.02	4170 ± 6779
D-dimer [mg/L]	3.73 ± 6.4	1.74 ± 5.64	0.6	2.49 ± 6
Leucocytes [$\times 10^3/\mu$L]	8.7 ± 2.6	9.6 ± 3.6	0.24	9.23 ± 3.3
Haemoglobin [g/dL]	13.5 ± 2.2	12.5 ± 1.5	< 0.001	12.9 ± 1.9
Platelet count [$\times 10^3/\mu$L]	205.3 ± 54.1	217.1 ± 73.4	0.37	221.3 ± 66.1
Total cholesterol [mmol/L]	4.5 ± 1	4.9 ± 1.2	0.08	4.74 ± 1.1
HDL-C [mmol/L]	1.1 ± 0.3	1.4 ± 0.4	< 0.001	1.3 ± 0.4
LDL-C [mmol/L]	2.7 ± 1	2.8 ± 1.1	0.62	2.8 ± 1.1
Triglycerides [mmol/L]	1.5 ± 0.8	1.4 ± 0.6	0.65	1.5 ± 0.7
Creatinine [μmol/L]	86.2 ± 37.4	76 ± 42.8	< 0.001	80.2 ± 40.8
GFR [mL/min]	120 ± 52.3	83 ± 41	< 0.001	99.4 ± 49.7

Data are presented as arithmetic mean ± standard deviation or median [interquartile range], or number (percentage); CK-MB — creatine kinase-MB; GFR — glomerular filtration rate; HDL-C— high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol; NT-proBNP — N-terminal pro–B-type natriuretic peptide; ULN — upper limit of normal

Table 4. Electrocardiography, cardiac echocardiography, and coronary angiography

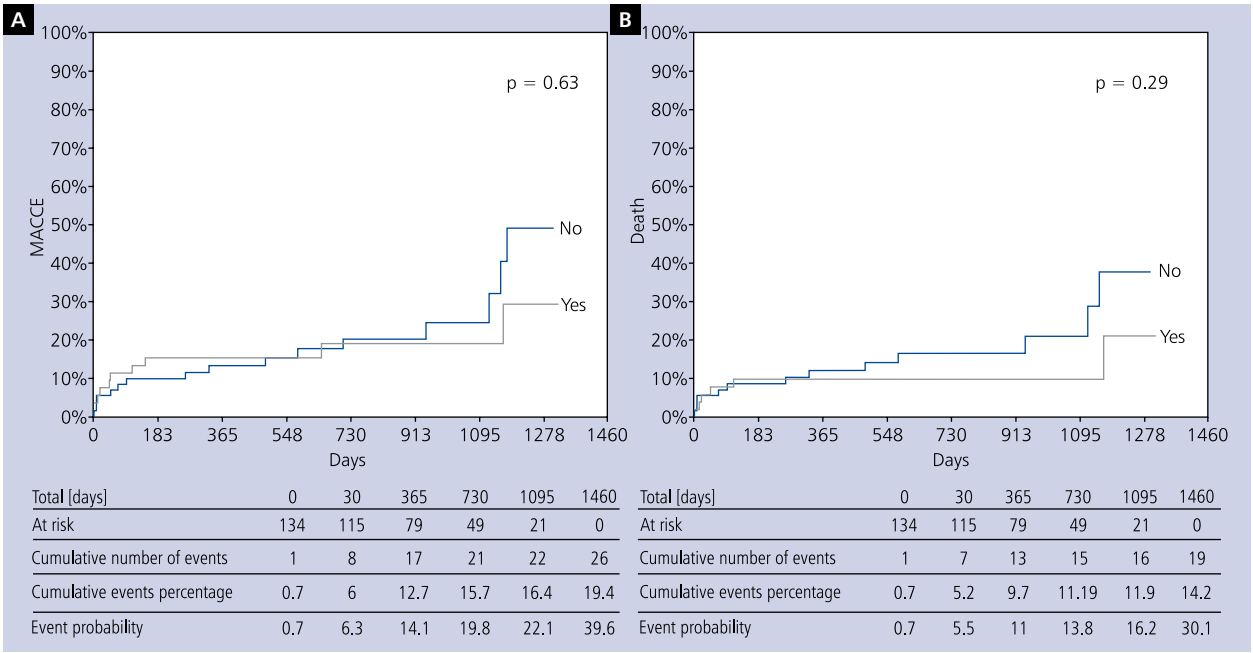
	Men	Women	P	Overall
Electrocardiography on admission:				
ST-segment elevation	14 (25)	15 (19.2)	0.42	29 (21.6)
ST-segment depression	8 (14.3)	15 (19.2)	0.45	23 (17.2)
T-wave changes	5 (8.9)	19 (24.3)	0.02	24 (17.9)
Other*	29 (51.8)	29 (37.2)	0.09	58 (43.3)
Echocardiography on admission:				
LVEF [%]	51.7 ± 15.7	50.3 ± 14.1	0.38	50.9 ± 14.7
LVEF < 40%	10 (18.2)	22 (28.2)	0.18	32 (24.1)
Wall motion disorders on admission:	34 (66.7)	60 (76.9)	0.2	94 (72.9)
Hypokinesis	24 (58.5)	34 (43.6)	0.69	58 (45)
Akinesis	10 (24.4)	26 (33.3)	0.08	36 (27.9)
Pericardial effusion	3 (5.9)	9 (11.7)	0.26	12 (9.4)
Left ventricular hypertrophy	15 (29.4)	14 (17.9)	0.12	29 (22.5)
Coronary angiography				
Plaques (> 0% stenosis < 50%)	34 (85)	56 (71.8)	0.11	90 (76.3)
Bridges	7 (12.5)	4 (5.1)	0.12	11 (8.2)
Arterial spasm	3 (5.3)	1 (1.3)	0.17	4 (3)
Contrast slow-flow	11 (19.6)	11 (14.1)	0.39	22 (16.4)

Data are presented as arithmetic mean ± standard deviation or number (percentage). LVEF — left ventricular ejection fraction; *e.g. tachyarrhytmias/bradyarrhytmias, atrial fibrillation/flagellation, repolarisation disorders, conduction disorders

Table 5. Primary and secondary study endpoints according to sex

	Men	Women	P	Overall
Follow-up time [days]	609.5 ± 434.7	609.5 ± 398.1	0.99	609.5 ± 412.2
Completed follow-up	52 (92.8)	71 (91)	0.7	123 (91.8)
MACCE	10 (19.2)	16 (22.5)	0.65	26 (21.1)
Myocardial infarction	2 (3.8)	1 (1.4)	0.38	3 (2.4)
Cerebral stroke	1 (1.9)	0 (0)	0.24	1 (0.8)
CABG	0 (0)	0 (0)	-	0 (0)
Death	6 (11.5)	13 (18.6)	0.3	19 (15.4)
Reintervention	1 (1.9)	2 (2.8)	0.75	3 (2.4)
Recurrent chest pain	10 (19.6)	13 (18.8)	0.91	23 (19.2)
Rehospitalisation not related to MACCE	10 (19.6)	11 (15.9)	0.6	21 (17.5)

Data are presented as arithmetic mean ± standard deviation or number (percentage). CABG — coronary artery bypass grafting; MACCE — major adverse cardiac and cerebrovascular events



Total [days]	0	30	365	730	1095	1460
At risk	134	115	79	49	21	0
Cumulative number of events	1	8	17	21	22	26
Cumulative events percentage	0.7	6	12.7	15.7	16.4	19.4
Event probability	0.7	6.3	14.1	19.8	22.1	39.6

Total [days]	0	30	365	730	1095	1460
At risk	134	115	79	49	21	0
Cumulative number of events	1	7	13	15	16	19
Cumulative events percentage	0.7	5.2	9.7	11.19	11.9	14.2
Event probability	0.7	5.5	11	13.8	16.2	30.1

Figure 2. **A.** Kaplan-Meier survival curves according to sex — days to major adverse cardiac and cerebrovascular events (MACCE) for male grouping variable. The log rank test p-value = 0.63; **B.** Kaplan-Meier survival curves according to sex — days to death for male grouping variable. The log rank test p-value = 0.29

Kaplan-Meier survival curves according to sex

Due to the low number of particular components of MACCE, except for death, which was the leading component, we limited the analysis to MACCE and death. The analysis of MACCE survival curves during the follow-up period revealed no significant differences between men and women (p = 0.63). However, the occurrence of MACCE tended to be higher in women compared to men (Fig. 2A, Table 5). The analysis of death survival curves during the follow-up period also did not demonstrate any significant difference between the sexes (p = 0.29). The frequency of deaths tended to be higher in women (Fig. 2B, Table 5).

Predictors of MACCE and death

Again, due to the low number of particular MACCE components, except for death, only the predictors of MACCE and death were analysed.

Univariate Cox regression analysis identified the following variables as predictors of death during the follow-up: chest pain on admission to hospital (hazard ratio [HR] 0.21; 95% confidence interval [CI] 0.03–0.7, p = 0.01), treatment with glucocorticosteroids (GCSs) (HR 14.2; 95% CI 4.29–43.05, p = 0.0001), smoking (HR 0.13; 95% CI 0.008–0.677, p = 0.009), pericardial effusion (HR 4.13; 95% CI 1.15–11.8, p = 0.03), serum C-reactive protein (CRP) level below upper

limit of normal (HR 0.000; 95% CI 0.00–0.63, p = 0.01), age (HR 1.8; 95% CI 1.26–2.7, p = 0.0007), BMI (HR 0.88; 95% CI 0.79–0.98, p = 0.02), serum creatinine level (HR 1.008; 95% CI 1.001–1.012, p = 0.02), GFR (HR 0.97; 95% CI 0.95–0.98, p < 0.001), LVEF (HR 0.96; 95% CI 0.94–0.99, p = 0.03), troponin index (HR 1.002; 95% CI 1.001–1.003, p = 0.004), creatine kinase-MB (CK-MB) on admission to hospital (HR 1.006; 95% CI 1.003–1.008, p = 0.002), maximal serum CK-MB (HR 1.002; 95% CI 1.001–1.003, p = 0.008), blood haemoglobin concentration (HR 0.665; 95% CI 0.53–0.82, p < 0.001), white blood cell count (HR 1.19; 95% CI 1.06–1.33, p = 0.003), total cholesterol level (HR 0.49; 95% CI 0.25–0.97, p = 0.04), and low-density lipoprotein cholesterol (LDL-C) level (HR 0.44; 95% CI 0.18–0.97, p = 0.04).

After adjustment for male sex, the following predictors remained significant: chest pain on admission, cardiac arrest on admission, treatment with GCSs, smoking, pleural effusion, CRP level on admission below upper limit of normal, age, serum creatinine concentration, GFR level, LVEF value, troponin index, CK-MB on admission, maximal CK-MB, haemoglobin concentration, and leucocyte count. Proportional hazard multivariate analysis confirmed that leucocyte count (risk ratio [RR] 1.23; 95% CI 1.08–1.4, p = 0.002), platelet count (RR 0.99; 95% CI 0.98–0.99, p = 0.02), troponin index (RR 1.001; 95% CI 1.0001–1.002, p = 0.029), blood haemoglobin concentration (RR 0.74; 95% CI 0.55–0.98, p = 0.03), ST-segment depressions on admission to hospital (RR 2.96; 95% CI 1.05–8.88, p = 0.04), and hyperlipidaemia (RR 0.06; 95% CI 0.01–0.27, p < 0.0001) were independent predictors of death.

Univariate Cox regression analysis revealed that predictors of MACCE during the follow-up included the following: cardiac arrest on admission to hospital (HR 6.84; 95% CI 1.58–20.7, p = 0.01), treatment with GCSs (HR 9.01; 95% CI 2.88–24.01, p = 0.0006), smoking (HR 0.3; 95% CI 0.07–0.87, p = 0.02), age (HR 1.42; 95% CI 1.08–1.93, p = 0.01), BMI (HR 0.91; 95% CI 0.84–0.99, p = 0.04), serum creatinine concentration (HR 1.006; 95% CI 1.000–1.011; p = 0.04), GFR (HR 0.98; 95% CI 0.97–0.99; p = 0.002), troponin index (HR 1.002; 95% CI 1.001–1.002, p = 0.006), CK-MB level on admission to hospital (HR 1.006; 95% CI 1.002–1.008, p = 0.002), maximal CK-MB level (HR 1.002; 95% CI 1.001–1.003, p = 0.01), blood haemoglobin concentration (HR 0.77; 95% CI 0.63–0.94, p = 0.01), leucocyte count (HR 1.16; 95% CI 1.05–1.28, p = 0.007), total serum cholesterol concentration (HR 0.57; 95% CI 0.34–0.97, p = 0.04), and LDL-C level (HR 0.42; 95% CI 0.21–0.78, p = 0.006). After adjustment for male sex, the following predictors remained significant: cardiac arrest on admission, treatment with GCSs, age, GFR value, troponin index, CK-MB level on admission to hospital, maximal CK-MB level, blood haemoglobin concentration, leucocyte count, and LDL-C level. Proportional hazard multivariate analysis confirmed the following to be independent predictors of MACCE: troponin index (RR 1.002; 95% CI 1.0005–1.0026, p = 0.004), age (RR 1.04; 95% CI 1.008–1.065, p = 0.01), serum creatinine level (RR 1.01; 95% CI 1.001–1.01, p = 0.02), hyperlipidaemia (RR 0.26; 95% CI 0.07–0.75, p = 0.01) and prior venous thromboembolic disease (RR 8.28; 95% CI 1.15–38, p = 0.04).

Predictors of chest pain and rehospitalisation

Univariate logistic regression analysis revealed the following to be among the predictors of recurrent chest pain during the follow-up period: chest pain on admission to hospital (odds ratio [OR] 2.77; 95% CI 1.08–7.08, p = 0.03), hyperlipidaemia (OR 2.95; 95% CI 1.17–7.41, p = 0.02), treatment with acetylsalicylic acid (OR 4.38; 95% CI 1.59–12.2, p = 0.005), treatment with statins (OR 2.96; 95% CI 1.08–8.08, p = 0.04), troponin index at baseline (OR 0.99; 95% CI 0.99–1.00, p = 0.008), CK-MB level on admission to hospital (OR 0.97, 95% CI 0.95–1.005, p = 0.03), maximal CK-MB during hospitalisation (OR 0.97; 95% CI 0.94–1.002, p = 0.01), leucocyte count (OR 0.76; 95% CI 0.62–0.94, p = 0.003), and platelet count (OR 0.99; 95% CI 0.98–0.99, p = 0.02). After adjustment for male sex, none of the predictors remained significant.

Maximal CK-MB level during hospitalisation (OR 0.98; 95% CI 0.94–1.00, p = 0.03) and NT-proBNP level (OR 1.02; 95% CI 1.01–1.05, p = 0.005) were identified as predictors of rehospitalisation during follow-up in univariate logistic regression analysis. After adjustment for male sex, chest pain on admission, dual antiplatelet therapy, and left ventricular contractility disorders significantly correlated with rehospitalisation rate during the follow-up period.

DISCUSSION

One of the main findings of the presented study was that the rate of MINOCA among the overall MI population in our centre was 6.75%, and it was significantly higher in women than in men. Secondly, the most common diagnosis, both on admission to hospital and at discharge, was NSTEMI, whereas STEMI was observed less often. The most common known aetiology of MINOCA was takotsubo cardiomyopathy, followed by tachyarrhythmias. Thirdly, the clinical outcomes during the follow-up period were not significantly different between men and women. Also, the rate of recurrent chest pain and rehospitalisation during follow-up did not differ between the sexes.

According to current knowledge and recently published, large systematic reviews, the frequency of MINOCA is estimated at 6% with 95% CI 5%–7% [8]. However, a higher incidence of MINOCA (over 11%) was shown in a group of younger patients aged 18 to 55 years, consisting mostly of women [3]. In one of the recent large review articles, the ratio of men to women with MINOCA was different or even inverse (40% women) compared to our study, in which the percentage of women reached almost 60% [8]. Nevertheless, some publications support our results and report a higher incidence of MINOCA in women compared to men [9]. Similarly to our

analysis, the rate of MINOCA in a population-based registry study including patients with acute coronary syndromes without ST-segment elevation was more than twice as high in women as in men, although the overall rate of MINOCA was lower than reported herein (4.9%). Despite the fact that women included in our analysis were older and women included in the registry were more often hyperlipidaemic and former cigarette smokers, the frequency of diabetes and hypertension was comparable [10]. Similar findings have been confirmed in the analysis by Lansky et al. [11] performed in a group of patients with acute MI, in which women, despite being older and having more comorbid diseases, had less extensive CAD compared to men. Previously published studies revealed that the one-year mortality in MINOCA patients was 4.75%, while in our study, after almost two years of follow-up, it reached 15.4% in the overall group of patients [8]. Also, in the analysis performed on a large Swedish registry, which included over 12,000 patients with MINOCA, mortality rate during 2.6-year follow-up was 8% in STEMI patients and 5% in NSTEMI patients, which was significantly lower compared to our results [12].

In comparison to our analysis, studies in which the aetiology of MINOCA was determined based on magnetic resonance imaging (MRI) demonstrated greater rates of myocarditis (33%), arterial spasms (27%), and thrombophilia (14%) [8]. We were not able to compare these results due to the fact that MRI and blood tests for thrombophilia were performed only in a few of the analysed patients [13]. Young patients with suspected thrombophilia were referred to an outpatient clinic to be screened for hypercoagulable disorders. In the follow-up period, it turned out that almost none of the patients volunteered to perform the ordered tests. Therefore, it can be concluded that the most successful way to screen patients for this disease would be to perform the tests while they are at the clinic, although this is not recommended in the acute condition. Endovascular diagnostic tools, including optical coherence tomography and intravascular ultrasound (IVUS), were used in several patients. IVUS examination was performed in patients with suspected spontaneous coronary artery dissection and soft atherosclerotic plaque rupture. In the last year, the frequency of IVUS application significantly increased at our centre.

We did not observe significant differences in MACCE or death rate between men and women during the follow-up period; however, there was a tendency towards higher mortality in women. Similar results have been demonstrated for stable patients with non-obstructive CAD. It was shown that mortality in NSTEMI patients was higher in men, while in STEMI patients there was no significant difference in mortality between the sexes [6]. In the current study, the mean age of women who died during the follow-up period was 70.1 years (range, 40 to 90 years), while among male non-survivors it was 74.7 years (range, 51 to 90 years). This was significantly higher compared to patients who survived the follow-up period. Of the 19 patients who died in the follow-up period, four (21%) deaths occurred during hospitalisation. These patients were characterised by severe comorbidities such as sepsis, end-stage renal failure, cardiac tamponade in the course of hospitalisation, and the presence of sudden cardiac arrest on or before admission to hospital. However, the overall group of patients who died during the follow-up period was characterised by older age ($p < 0.001$), lower GFR value ($p < 0.001$), higher maximal CK-MB concentration ($p < 0.01$), lower haemoglobin concentration ($p < 0.001$), higher white blood cell count ($p = 0.03$), and higher levels of D-dimer ($p < 0.001$). What is more, the incidence of comorbidities was also higher in this group. It has been demonstrated that most of the predictors of adverse cardiovascular events following MINOCA are similar to the predictors of adverse events after regular acute MI with obstructive CAD. The WISE study identified hypertension, diabetes, and smoking as predictors of cardiovascular death and MI in women with signs of heart ischaemia during long-term follow-up, while in the current study, multivariate analysis did not confirm these factors as predictors of MACCE or death. Instead, the predictors identified in multivariate analysis were troponin level, age, serum creatinine level, and history of thromboembolic disease for MACCE, as well as leucocyte and platelet count, serum troponin level, blood haemoglobin concentration, and ST-segment depressions on admission to hospital for death [14]. In the current analysis, the increase in troponin and CK-MB levels at index procedure were found to be predictors of clinical outcomes expressed as the rate of MACCE and death, and troponin elevation was also associated with the occurrence of chest pain during the follow-up period, while the CK-MB level was associated with the rehospitalisation rate. The relationship between the extent of increase in markers of myocardial injury among patients with MINOCA and clinical outcomes expressed as the rate of MACE, all-cause mortality, cardiovascular mortality, and readmissions for heart failure during the follow-up period has been demonstrated in previously published studies [15]. However, the knowledge about the predictors of recurrent chest pains after MINOCA is smaller. It has been demonstrated that persistent chest pain after MINOCA is a predictor of adverse cardiovascular events [8]. Due to that reason and because of the unquestionable deterioration in quality of life that occurs after hospital discharge, we tried to identify potential predictors of recurrent chest pain on the basis of the information gathered during follow-up.

Available publications concerning the assessment of predictors of clinical outcomes after MINOCA are often based on large registries and do not include all biochemical data. Previously published studies, apart from the well-known predictors of MACCE such as older age, diabetes, hypertension, smoking, prior MI or cerebral stroke, chronic obstructive pulmonary disease, reduced LVEF or peripheral vascular disease,

and elevated serum creatinine level, identified a lower level of total cholesterol as a predictor, which was also confirmed in our study [10]. This finding was named "the cholesterol paradox" and it was observed in other populations of patients as well [11]. It was also shown that patients who did not receive statin therapy before an MINOCA incident and had low levels of cholesterol were at increased risk of MACCE during follow-up [16].

Due to manuscript length limitations we were not able to discuss all predictors of MACCE in the follow-up period, but attention was also paid to the influence of inflammatory markers, such as leucocyte count, and history of venous thromboembolism, on MACCE and mortality. The association of pro-inflammatory markers with clinical outcomes during follow-up is present in a great number of patients with myocarditis and other concomitant infectious diseases which are definitely more common in the MINOCA group than in patients with obstructive CAD. The association between clinical outcomes and thromboembolic diseases is undoubtedly connected to the fact that most of the MINOCA studies include a higher percentage of women, in whom hormonal changes are related to reproductive capacity.

In conclusion, the current analysis confirmed the significantly greater occurrence of MINOCA among women compared to men. Sex was not associated with worse clinical outcomes expressed as MACCE and mortality in patients with MINOCA during the follow-up period. The frequency of recurrent chest pain and rehospitalisation during follow-up was not related to sex either. The following factors can be identified as the predictors of MACCE and mortality during the follow-up period in patients after MINOCA: leucocyte and platelet count, troponin index, blood haemoglobin concentration and ST-segment depressions on admission to hospital, age, serum creatinine level, and history of venous thromboembolic disease.

References

1. Jespersen L, Hvelplund A, Abildstrøm SZ, et al. Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. Eur Heart J. 2012; 33(6): 734–744, doi: 10.1093/eurheartj/ehr331, indexed in Pubmed: 21911339.
2. Agewall S, Beltrame JF, Reynolds HR, et al. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. Eur Heart J. 2017; 38(3): 143-15, doi: 10.1093/eurheartj/ehw149, index in Pubmed: 28158518.
3. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Eur Heart J. 2012; 33(20): 2551–2567.
4. Pasupathy S, Air T, Dreyer RP, et al. Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries. Circulation. 2015; 131(10): 861–870, doi: 10.1161/CIRCULATIONAHA.114.011201, indexed in Pubmed: 25587100.
5. Calvert PA, Obaid DR, O'Sullivan M, et al. Association between IVUS findings and adverse outcomes in patients with coronary artery disease: the VIVA (VH-IVUS in Vulnerable Atherosclerosis) Study. JACC Cardiovasc Imaging. 2011; 4(8): 894–901, doi: 10.1016/j.jcmg.2011.05.005, indexed in Pubmed: 21835382.
6. Pepine CJ, Ferdinand KC, Shaw LJ, et al. ACC CVD in Women Committee. Emergence of nonobstructive coronary artery disease: a woman's problem and need for change in definition on angiography. J Am Coll Cardiol. 2015; 66(17): 1918–1933, doi: 10.1016/j.jacc.2015.08.876, indexed in Pubmed: 26493665.
7. Gibson CM, Cannon CP, Daley WL, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. Circulation. 1996; 93(5): 879–888, indexed in Pubmed: 8598078.
8. Johnson BD, Shaw LJ, Pepine CJ, et al. Persistent chest pain predicts cardiovascular events in women without obstructive coronary artery disease: results from the NIH-NHLBI-sponsored Women's Ischaemia Syndrome Evaluation (WISE) study. Eur Heart J. 2006; 27(12): 1408–1415, doi: 10.1093/eurheartj/ehl040, indexed in Pubmed: 16720691.
9. Leipsic J, Taylor CM, Gransar H, et al. Sex-based prognostic implications of nonobstructive coronary artery disease: results from the international multicenter CONFIRM study. Radiology. 2014; 273(2): 393–400, doi: 10.1148/radiol.14140269, indexed in Pubmed: 25028784.
10. Safdar B, Spatz ES, Dreyer RP, 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): e009174, doi: 10.1161/JAHA.118.009174, indexed in Pubmed: 29954744.
11. Lansky AJ, Ng VG, Maehara A, et al. Gender and the extent of coronary atherosclerosis, plaque composition, and clinical outcomes in acute coronary syndromes. JACC Cardiovasc Imaging. 2012; 5(3 Suppl): S62–S72, doi: 10.1016/j.jcmg.2012.02.003, indexed in Pubmed: 22421232.
12. Nordenskjöld AM, Baron T, Eggers KM, et al. Predictors of adverse outcome in patients with myocardial infarction with non-obstructive coronary artery (MINOCA) disease. Int J Cardiol. 2018; 261: 18–23, doi: 10.1016/j.ijcard.2018.03.056, indexed in Pubmed: 29563017.
13. Januszek R, Bartuś S. Does the use of rotational atherectomy procedure during percutaneous coronary interventions influence the frequency of procedure-related myocardial injury assessed by cardiac magnetic resonance? J Thorac Dis. 2018; 10(Suppl 26): S3050–S3052, doi: 10.21037/jtd.2018.07.104, indexed in Pubmed: 30370075.
14. Sharaf B, Wood T, Shaw L, et al. Adverse outcomes among women presenting with signs and symptoms of ischemia and no obstructive coronary artery disease: findings from the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE) angiographic core laboratory. Am Heart J. 2013; 166(1): 134–141, doi: 10.1016/j.ahj.2013.04.002, indexed in Pubmed: 23816032.
15. Johnston N, Jönelid B, Christersson C, et al. Effect of gender on patients with ST-elevation and non-ST-elevation myocardial infarction without obstructive coronary artery disease. Am J Cardiol. 2015; 115(12): 1661–1666, doi: 10.1016/j.amjcard.2015.03.006, indexed in Pubmed: 25900352.
16. Cheng KH, Chu CS, Lin TH, et al. Lipid paradox in acute myocardial infarction — the association with 30-day in-hospital mortality. Crit Care Med. 2015; 43(6): 1255–1264, doi: 10.1097/CCM.0000000000000946, indexed in Pubmed: 25738856.

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WHAT IS NEW?

The present analysis confirmed that the occurrence of myocardial infarction with non-obstructive coronary arteries (MINOCA) is significantly greater among women compared to men. We showed that sex is not associated with clinical outcomes expressed as major cardiac and cerebrovascular events (MACCE) and death in patients with MINOCA during almost two years of follow-up. The study also demonstrated that the frequency of recurrent chest pains and rehospitalisations during the follow-up period is not significantly related to sex. White blood cell and platelet count, serum troponin index, haemoglobin concentration, ST-segment depressions on admission to hospital, age, serum creatinine level, hyperlipidaemia, and history of prior venous thromboembolic disease were identified as the predictors of MACCE and mortality during follow-up period in patients after MINOCA.