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The influence of severe mitral regurgitation on major adverse cardiac and cerebrovascular events after myocardial infarction in 1-year follow-up: Data from PL-ACS registry

Short title: The influence of mitral regurgitation on outcomes after MI

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WHAT'S NEW?

The present study showed that in the patients with acute myocardial infarction (non-ST-segment elevation myocardial infarction [NSTEMI] and ST-segment elevation myocardial infarction [STEMI]) severe mitral regurgitation is strongly associated with increased mortality and major adverse cardiac and cerebrovascular events occurrence in 12-month follow-up.

Moreover, it is an independent risk factor of all-cause death. Taking into consideration these results, early echocardiographic assessment of mitral regurgitation becomes a crucial element in determining the prognosis of patients after myocardial infarction and enables appropriate treatment implementation.

ABSTRACT

Background: Mitral regurgitation (MR) is frequently observed in patients with myocardial infarction (MI). However, the incidence of severe MR in contemporary population is unknown.

Aims: The study evaluates the prevalence and prognostic impact of severe MR in contemporary population of patients with ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI).

Methods: The study group consists of 8062 patients enrolled in the Polish Registry of Acute Coronary Syndromes over the years 2017–2019. Only the patients with full echocardiography performed during the index hospitalization were eligible. Primary composite outcome was 12-month major adverse cardiac and cerebrovascular events (MACCE) (death, non-fatal MI, stroke and heart failure [HF] hospitalization) compared between patients with and without severe MR.

Results: 5561 NSTEMI patients and 2501 STEMI patients were enrolled into the study. Severe MR occurred in 66 (1.19%) NSTEMI patients and 30 (1.19%) STEMI patients. Multivariable regression models revealed that severe MR is an independent risk factor of all-cause death in 12-month observation (odds ratio [OR], 1.839; 95% confidence interval [CI], 1.012–3.343; $P = 0.046$) in all MI patients. Patients with NSTEMI and severe MR had higher mortality (22.7% vs. 7.1%), HF rehospitalization rate (39.4% vs. 12.9%) and MACCE occurrence (54.5% vs. 29.3%). Severe MR was associated with higher mortality (20% vs. 6%) and higher HF rehospitalization (30% vs. 9.8%), stroke (10% vs. 0.8%) and MACCE rates (50% vs. 23.1%) in STEMI patients.

Conclusions: Severe MR is associated with higher mortality and MACCE occurrence in patients with MI in 12-month follow-up. Severe MR is an independent risk factor of all-cause death.

Key words: mitral regurgitation, mortality, myocardial infarction

INTRODUCTION

Cardiovascular diseases, especially ischemic heart disease, remain among the most prevalent causes of mortality and morbidity, being responsible for 19%–20% of deaths in Europe [1]. Valvular heart disease (VHD) may complicate clinical course of acute coronary syndromes (ACS) [2, 3]. Mitral regurgitation (MR) of any severity is frequently observed in patients with acute myocardial infarction (MI) [3–23], affecting up to 50% of patients [13, 17]. In the era before widespread use of primary percutaneous coronary interventions (PCI) and longer delays from symptoms onset to treatment the MR has been reported as a poor prognostic factor [4–6, 8, 10–19], associated with an increase in mortality rate [4–6, 8, 12–19]. Most studies assess this association in the mild and moderate stage of MR [4, 10, 12, 13, 16] in both the acute [11, 16] and the chronic [4–6, 8, 10–17] phase after MI. It is less clear how severe MR affects the outcomes in contemporary population of non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI) patients treated invasively in all-comer nationwide registry.

The aim of the present study was to evaluate specifically the prevalence and prognostic implication of severe MR in patients with acute MI in relation to in-hospital and 12-month outcomes. In this registry we assessed both STEMI and NSTEMI patients. The study group includes patients enrolled in the nationwide Polish Registry of Acute Coronary Syndromes (PL-ACS).

METHODS

Registry design

We used data from the PL-ACS Registry Database which is an ongoing nationwide registry since 2003. It collects specific data on clinical characteristics, in-hospital management and discharge treatment of all patients with ACS. The registry was established as a cooperative initiative of the Silesian Center for Heart Diseases in Zabrze and the Polish Ministry of Health. Design, methods and logistic aspects of the PL-ACS were published previously [24, 25]. According to the protocol, all patients admitted with the initial diagnosis of ACS were evaluated for eligibility to enter the registry, but they were not enrolled until ACS had been confirmed. Patient data were gathered and analyzed by experienced physicians and set directly in an appropriate web-based form.

Data collection and study group profile

Till the beginning of 2021 the PL-ACS included almost 783 000 patients. To obtain 12-month

follow-up all patients discharged till the end of 2019 were considered. Then, the patients with the diagnosis of unstable angina were excluded. For the reason that follow-up data was available only from the regional Silesian branch of National Health Fund and only from the years 2017–2019, 466 642 patients were excluded. 12 different hospitals from Silesia region provide follow-up data. Only one additional patient was excluded due to the lacks in the EF measurements. The echocardiographic evaluation was performed during the index hospitalization. Only the patients with detailed echocardiographic description of the valvular diseases were included. After that, the patients with severe aortic stenosis, severe aortic regurgitation or severe mitral stenosis and those who did not survive primary hospitalization were excluded. After excluding patients in whom coronary angiography was not performed, final study group consisted of 8062 individuals (Figure 1). Supplementary material, *Figure S1* presents the study population flowchart.

Endpoints and definitions

The major adverse cardiac and cerebrovascular events (MACCE), assessed within the 12-month follow-up, were defined as all-cause death, non-fatal MI, stroke and rehospitalization due to heart failure (HF). Non-fatal MI was defined per European Society of Cardiology (ESC) MI criteria [26]. Stroke was defined as an acute neurological deficit that lasted over 24 hours and was confirmed by neurologist. The study involved only the patients with a confirmed diagnosis of STEMI or NSTEMI, meeting the ESC MI criteria [26]. The data collection period was from 2017 to 2019. The definition of severe MR during that time did not change, despite the publication of new ESC Guidelines for the management of valvular heart disease in the end of 2017 [27, 28]. The co-morbidities definitions which changed during that time were updated due to the European Scientific Societies recommendations.

Study hypothesis and objectives

In this study it is hypothesized that presence of severe MR significantly influences prognosis of patients with MI. The study group was divided into two subgroups depending on whether patients were admitted with STEMI or NSTEMI. Each group was then further split into two subgroups: with or without severe MR (Figure 1). We compared the differences in terms of demographic data, clinical characteristics, treatment strategy, drugs prescribed at discharge, in-hospital and 12-month outcomes including the number of MACCE.

Statistical analysis

Baseline demographic and clinical characteristics, angiographic findings, in-hospital adverse events, drugs at discharge, and events in the 12-month follow-up were compared depending on the diagnosis of severe MR and type of MI. Continuous variables were summarized using the arithmetic mean with standard deviation (SD) for normal distribution or median with interquartile range (IQR) for non-normal distribution. Normality of distribution was verified using the Shapiro–Wilk test. Continuous variables with normal distribution were compared using Student's t-test, whereas variables with skewed distribution were compared using the Mann–Whitney U test. Categorical variables were summarized using frequency tables. The chi-squared test with Yates's modification was used for the comparison of categorical data, if applicable. Long-term survival was compared using the log-rank test and the Kaplan–Meier model was used to present cumulative survival probability. The multivariable analyses of factors affecting 12-month mortality and MACCE occurrence were performed. Forward stepwise logistic regression with cross validation was used. The multivariable models for 12-month mortality and MACCE occurrence included over 20 variables. Statistical significance was defined as P <0.05. All statistical analyses were performed using Statsoft Statistica software.

RESULTS

Population characteristics

As shown in Supplementary material, *Figure S1*, the final analysis included 8062 patients with known echocardiographic findings related to VHD. Figure 1. illustrates distribution of patients with MR depending on the diagnosis of STEMI (31%; n = 2501) or NSTEMI (69%; n = 5561). Those two subgroups were then further divided into severe MR+ and severe MR- subgroups.

In NSTEMI subgroup, the patients with severe MR were more often previously diagnosed with coronary artery disease (CAD), HF, atrial fibrillation (AF), and chronic kidney disease and had more often coronary artery bypass graft (CABG) and peacemaker (PM) implantation done in the history. In STEMI subgroup, the patients with severe MR were older and had a greater prevalence of AF. Table 1 shows the baseline demographic data.

Supplementary material, *Table S1* presents clinical characteristics. Regardless of MI type, in the echocardiography examination, patients with severe MR had lower left ventricular ejection fraction (LVEF) and larger left ventricular (LV) systolic and diastolic diameters. Heart rate (HR) was also higher in the subgroups with severe MR in STEMI and NSTEMI subgroups. In NSTEMI subgroup, patients with severe MR also had lower systolic blood

pressure (SBP). Higher Killip class at admission was also statistically significant for the severe MR+ subgroup in NSTEMI subgroup. In patients with both MI types, a higher NYHA class at discharge was typical for patients with severe MR.

With regard to concomitant VHD (Supplementary material, *Table S2*), moderate and severe tricuspid regurgitation (TR) was significantly more often identified in severe MR subgroups, regardless of MI type. Moderate aortic regurgitation (AR) was more frequent in patients with severe MR in NSTEMI subgroup.

In hospital management

As shown in Supplementary material, *Table S3* in NSTEMI subgroup, use of radial access was significantly lower in severe MR+ vs. severe MR- patients. Severe MR was associated with higher number of stenoses in coronary arteries in both STEMI and NSTEMI subgroup. There was also a significant difference in terms of distribution of coronary lesions between severe MR+ and severe MR- patients with NSTEMI. In the subgroup with NSTEMI, PCI was done more often in the severe MR- subgroup.

During index hospitalization (Table 2), equally in STEMI and NSTEMI subgroups, patients with severe MR had pulmonary edema more often. A tendency for more frequent shock diagnosis could be seen in the severe MR+ subgroup in NSTEMI subgroup.

Supplementary material, *Table S4* presents drugs prescribed at discharge. Diuretics and aldosterone receptor antagonists (MRA) were given more frequently to patients with severe MR, in both MI type subgroups. Furthermore, in NSTEMI subgroup, anticoagulants were prescribed more frequently in severe MR subgroup. At the same time, ASA was given less often in the same subgroup.

Follow-up

12-month follow-up is presented in Table 2. The median follow-up was 19.5 (12.9–27.1) months. In the subgroup of patients with NSTEMI, individuals with severe MR had higher mortality, were more often rehospitalized due to HF and had higher MACCE occurrence. Furthermore, they had more often ICD and CRT implantation. Similarly in the STEMI subgroup, patients with severe MR had a higher mortality rate and were more often rehospitalized because of HF and had more frequently CRT implanted. Additionally, in this subgroup, stroke occurred significantly more often. Rate of composite MACCE was also significantly higher. Kaplan–Meier estimators (Figures 2–5, Supplementary material, *Figures S2–S4*) present the distribution of events over time during follow-up period.

Analysis of multivariable models for 12-month mortality (Table 3) and MACCE (Supplementary material, *Table S5*) occurrence reveals that in the population after MI, severe MR is an independent risk factor of all-cause death in 12-month observation. At the same time, severe MR is not an independent risk factor of MACCE occurrence during 12-month follow-up.

DISCUSSION

The present study shows that severe MR is infrequent in contemporary population of patients with acute MI treated invasively. It is associated with statistically significant increase in mortality rate and composite MACCE occurrence in patients diagnosed with STEMI and NSTEMI, during 12-month follow-up. It also proves that severe MR is an independent risk factor of all-cause death.

When considering the impact of MR on patients with MI there are several factors which can have a significant influence on obtained results. Therefore, they had to be taken into consideration when analysing each study concerning subject-matter. Despite the importance of the problem the number of reliable studies analysing this matter is limited. It is also worth mentioning that in a few studies [10, 14, 17] analysed group do not exceed 350 patients. Consequently, the absolute number of patients with MR is relatively low. Nevertheless, one general conclusion is common to almost all of them [4–6, 8, 12–18] — MR has a significant influence on mortality in the group of patients after MI.

The worse prognosis for the patients with MR may come from worse in-hospital characteristics, which appears to be typical for all analysed studies [10, 12–17], including the present study. Among others, factors listed most often are advanced age [10, 12–16], CAD diagnosed in history [10, 12, 14], and diabetes mellitus [10, 14].

Despite the fact that etiology and the mechanisms in which MR evolves may play an important role in order to properly analyse current population it is hard to distinguish ischemic mitral regurgitation (IMR) from MR caused by factors other than MI. IMR is defined as MR directly associated with CAD. IMR occurs due to ischemic myocardial changes despite unaltered mitral leaflets and chordae. LV remodelling and papillary muscle displacement are usually listed as those playing an important role in its development [18, 29–32].

In this study, worse echocardiography results regarding LV systolic and diastolic diameters, as well as LVEF can be seen in the subgroup with severe MR, in both STEMI and NSTEMI subgroup. In connection with this, it is highly possible that most patients with severe MR

from our study could be diagnosed with IMR, however it is not possible to definitely confirm that assumption.

There are some differences between the present study and others accessible research concerning subject-matter. Most studies in their analysis include both MI types in one group [12, 15, 16], some including also UA [13, 14]. Due to relevant differences in clinical course between STEMI and NSTEMI, in the present study those two subgroups were analysed separately. In most studies concerning subject matter the group diagnosed with MR is not divided, including MR from mild to severe [10] or subgroups include moderate and severe MR together [12, 13, 15, 16]. In several studies demarking a subgroup with severe MR only would probably create a group composed of just a few patients, not big enough to obtain reliable results. In this study, in order to obtain transparent results only the patients with severe MR were taken into consideration. MI treatment methods is another factor which differentiates compared studies. Several of them [4, 6–9, 12] counts thrombolysis, whereas in the present study coronary angioplasty and CABG were the only methods considered.

Study limitations

Several potential limitations should be bear in mind when interpreting presented data. First, despite its high probability, we can not confirm without fail that index MI was the factor inducing MR. This is the limitation common to almost all studies concerning subject matter [10–13, 15, 16]. Second, data used in this study were gathered retrospectively. Because different physicians did echocardiography examinations and the MR was operator-assessed, that may lead to interpretation bias. Third, echocardiography was done only once during the index hospitalization. Because grade of the MR may change in time, an echocardiography assessment during follow-up would have provided important data. Fourth, because it was not possible to obtain follow-up data from all National Health Fund departments, all analyzed follow-up data comes from the regional Silesian branch of National Health Fund.

Clinical implications

The present study confirms the importance of echocardiography assessment of MR in patients after MI. Taking into consideration statistical significance regarding mortality in this population, special emphasis shall be placed on early clinical and echocardiography control and appropriate treatment implementation.

CONCLUSIONS

Mitral regurgitation is a frequent comorbid condition in patients after MI, both STEMI and NSTEMI. It is strongly associated with increased HF diagnosis, higher mortality and MACCE

occurrence in long 12-month follow-up. In the population after MI, severe MR is an independent risk factor of all-cause death in 12-month observation. Thus, assessment of MR becomes a crucial element in determining the prognosis of patients after MI.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska

Article information

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Table 1. Demographic data

	NSTEMI (n = 5561)			**STEMI (n = 2501)**		
	Severe MR+ (n = 66)	**Severe MR– (n = 5495)**	***P*-value**	**Severe MR + (n = 30)**	**Severe MR – (n = 2471)**	***P*-value**
Age, years, mean (SD)	70.2 (10.5)	68.6 (10.5)	0.22	73.0 (11.6)	64.9 (13.9)	<0.001
Female sex, n (%)	20 (30.3)	1927 (35.1)	0.51	18 (60.0)	813 (32.9)	0.01
Hypertension, n/n (%)	52/59 (88.1)	4190 (80.5)	0.53	18/26 (69.2)	1530 (66.8)	0.10
Hyperlipidemia, n/n (%)	33/58 (56.9)	2995 (61.5)	0.92	13/27 (48.1)	1118 (52.5)	0.98
Smoker, n/n (%)	30/44 (68.2)	2809 (59.9)	0.74	14/21 (66.7)	1501 (68.8)	0.10
Diabetes, n/n (%)	24/59 (40.7)	1698 (33.1)	0.68	6/26 (23.1)	543 (23.8)	1.00
Obesity, n/n (%)	18/50 (36.0)	1110 (23.1)	0.20	3/20 (15.0)	461 (21.2)	0.93
CAD, n/n (%)	30/64 (46.9)	1323 (26.1)	0.003	3/28 (10.7)	300 (13.0)	0.99
MI, n/n (%)	28/64	1609	0.20	2/29 (6.9)	344 (14.8)	0.70

	(43.8)	(31.2)				
PCI, n/n (%)	29/64 (45.3)	1638 (31.8)	0.15	3/30 (10.0)	342 (14.7)	0.92
CABG, n/n (%)	15/62 (24.2)	514 (10.1)	0.004	0/30 (0)	57 (2.5)	0.86
HF, n/n (%)	23/61 (37.7)	610 (12.0)	<0.001	1/30 (3.3)	119 (5.1)	0.98
AF, n/n (%)	24/63 (38.1)	796 (15.6)	<0.001	10/29 (34.5)	168 (7.2)	<0.001
Stroke, n/n (%)	3/61 (4.9)	327 (6.5)	0.97	0 (0)	82 (3.5)	0.78
CKD, n/n (%)	17/62 (27.4)	608 (12.0)	0.003	3/30 (10.0)	128 (5.5)	0.77
PAD, n/n (%)	10/60 (16.7)	561 (11.2)	0.62	0 (0)	127 (5.5)	0.64
COPD/asthma, n/n (%)	2/61 (3.3)	346 (6.9)	0.74	2/29 (6.9)	121 (5.3)	0.99
History of malignancy, n/n (%)	3/61 (4.9)	182 (3.7)	0.97	1/29 (3.4)	83 (3.6)	1.00
PM, n/n (%)	6/63 (9.5)	153 (3.0)	0.03	1/30 (3.3)	10 (0.4)	0.14
ICD, n/n (%)	3/63 (4.8)	77 (1.5)	0.22	0 (0)	11 (0.5)	0.99
CRT-D, n/n (%)	1/63 (1.6)	42 (0.8)	0.93	0 (0)	5 (0.2)	0.10

Obesity defined as BMI (body mass index) >30 kg/m^2

Abbreviations: AF, atrial fibrillation; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy defibrillator; HF, heart failure; ICD, implantable cardioverter-defibrillator; MI, myocardial infarction; MR, mitral regurgitation; NSTEMI, non-ST-segment elevation myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PM, pacemaker; STEMI, ST-segment elevation myocardial infarction

Table 2. Events during hospitalization and 12-months follow-up

	NSTEMI	**STEMI**

	(n = 5561)			**(n = 2501)**		
	Severe MR + (n = 66)	**Severe MR – (n = 5495)**	***P*-value**	**Severe MR + (n = 30)**	**Severe MR – (n = 2471)**	***P*-value**
Events during hospitalization						
Shock, n (%)	2 (3.0)	31 (0.6)	0.08	2 (6.7)	49 (2.0)	0.35
Pulmonary edema, n (%)	3 (4.6)	45 (0.8)	0.009	2 (6.7)	21 (0.8)	0.02
MI, n (%)	1 (1.5)	22 (0.4)	0.57	0 (0)	9 (0.4)	0.99
Stroke/TIA, n (%)	1 (1.5)	11 (0.2)	0.16	0 (0)	6 (0.2)	0.10
Major bleeding, n (%)	2 (3.0)	78 (1.4)	0.74	0 (0)	44 (1.8)	0.91
SCA at hospital, n (%)	1 (1.5)	30 (0.5)	0.77	1 (3.3)	39 (1.6)	0.90
12-months follow-up events						
Death, n (%)	15 (22.7)	388 (7.1)	<0.001	6 (20.0)	148 (6.0)	0.02
MI, n (%)	9 (13.6)	819 (14.9)	0.99	3 (10.0)	273 (11.0)	0.10
Hospitalization due to HF, n (%)	26 (39.4)	709 (12.9)	<0.001	9 (30.0)	242 (9.8)	0.004
Stroke, n (%)	1 (1.5)	98 (1.8)	0.10	3 (10.0)	19 (0.8)	<0.001
MACCE, n (%)	36 (54.5)	1612 (29.3)	<0.001	15 (50.0)	570 (23.1)	0.007
PM implantation, n (%)	1 (1.5)	84 (1.5)	1.00	0 (0)	13 (0.5)	0.98
ICD implantation, n (%)	6 (9.1)	124 (2.3)	0.004	1 (3.3)	74 (3.0)	1.00
CRT implantation, n (%)	6 (9.1)	60 (1.1)	<0.001	1 (3.3)	7 (0.3)	0.03

Major bleeding was defined as bleeding (I) associated with >5 g/dl (0.5 g/l) decrease in the hemoglobin level or >15% (absolute) decrease in the hematocrit level, (II) the event that caused hemodynamic compromise, or (III) the requirement for blood transfusion

Abbreviations: CRT, cardiac resynchronization therapy; MACCE, major adverse cardiac and cerebrovascular events; SCA, sudden cardiac arrest; TIA, transient ischemic attack; other — see Table 1

Table 3. Multivariate analysis for death during 12-months follow-up

	OR	95% CI	P
EF, per 1% increase	0.968	0.958–0.978	<0.001
Age, per 1 year increase	1.055	1.043–1.068	<0.001
Diuretics at discharge, vs. no diuretics at discharge	1.761	1.361–2.278	<0.001
Killip class 2 at admission, vs. Killip class 1 at admission	1.545	1.159–2.059	0.003
Killip class 3 at admission, vs. Killip class 1 at admission	1.541	0.937–2.535	0.09
Killip class 4 at admission, vs. Killip class 1 at admission	1.185	0.545–2.578	0.67
CKD, vs. no CKD	1.438	1.086–1.904	0.01
COPD/asthma, vs. no COPD/asthma	1.684	1.184–2.395	0.004
NYHA II at discharge, vs. NYHA I at discharge	1.457	1.141–1.860	0.003
NYHA III at discharge, vs. NYHA I at discharge	1.729	1.189–2.515	0.004
NYHA IV at discharge, vs. NYHA I at discharge	1.317	0.395–4.387	0.65
ACEI/ARB/ARNI at discharge, vs. no ACEI/ARB/ARNI at discharge	0.661	0.508–0.860	0.002
PAD, vs. no PAD	1.584	1.169–2.147	0.003
HR, per 1 bpm increase	1.008	1.002–1.013	0.005
IABP, vs. no IABP	3.274	1.169–9.170	0.02
LVEDD, per 1 mm increase	0.990	0.982–0.999	0.03
Severe MR, vs. no severe MR	1.839	1.012–3.343	0.046

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; ARNI, angiontensin receptor neprilysin inhibitor; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; IABP, intra-aortic balloon pump; LVEDD, left ventricular end diastolic diameter; NYHA,

New York Heart Association Functional Classification; OR, odds ratio; PAD, peripheral artery disease; other — see Table 1

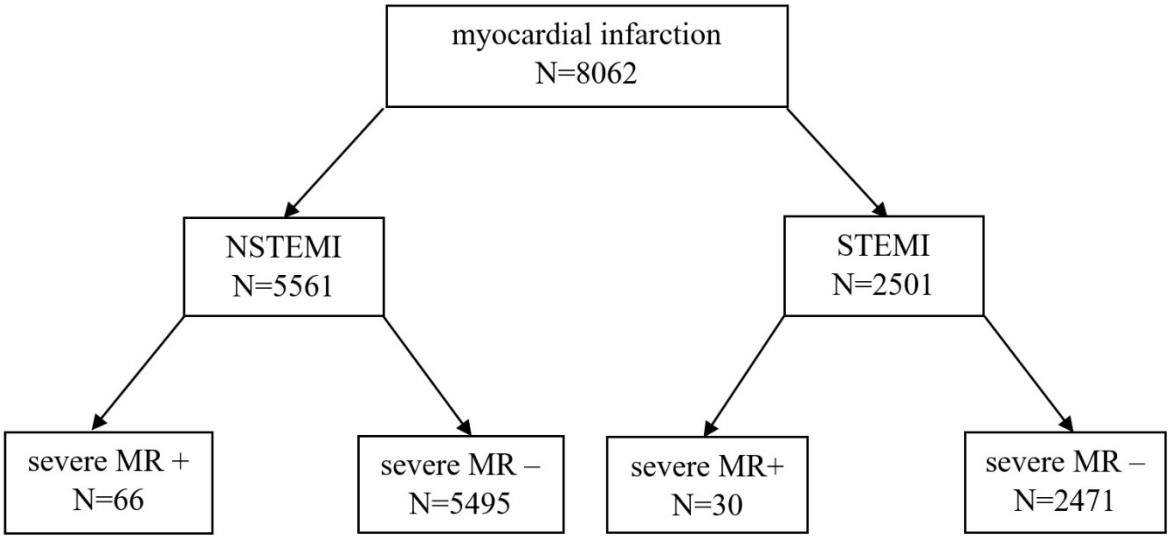

Figure 1. Study group division

Abbreviations: MR, mitral regurgitation; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction

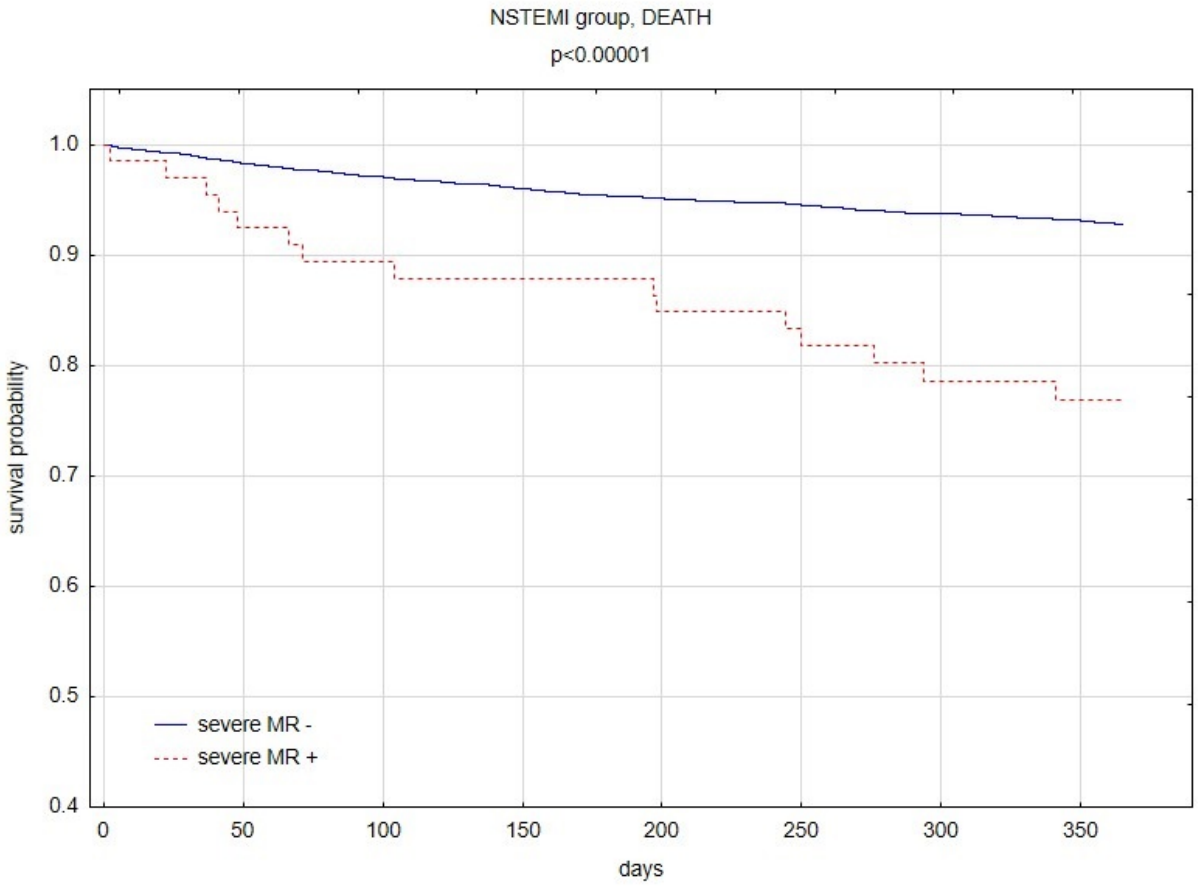

Figure 2. Kaplan-Meier estimator — NSTEMI group, mortality

Abbreviations: see Figure 1

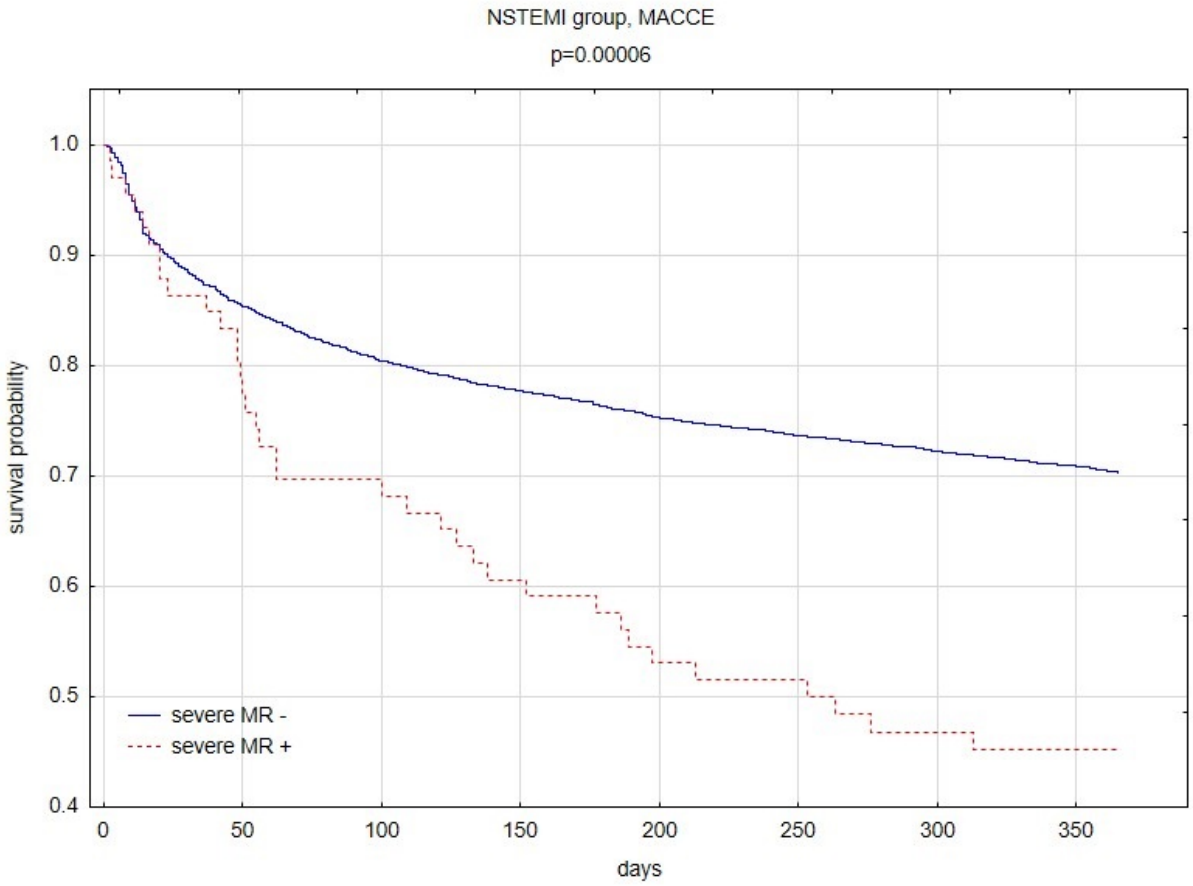

Figure 3. Kaplan-Meier estimator — NSTEMI group, MACCE occurrence

Abbreviations: MACCE, major adverse cardiac and cerebrovascular events; other — see Figure 1

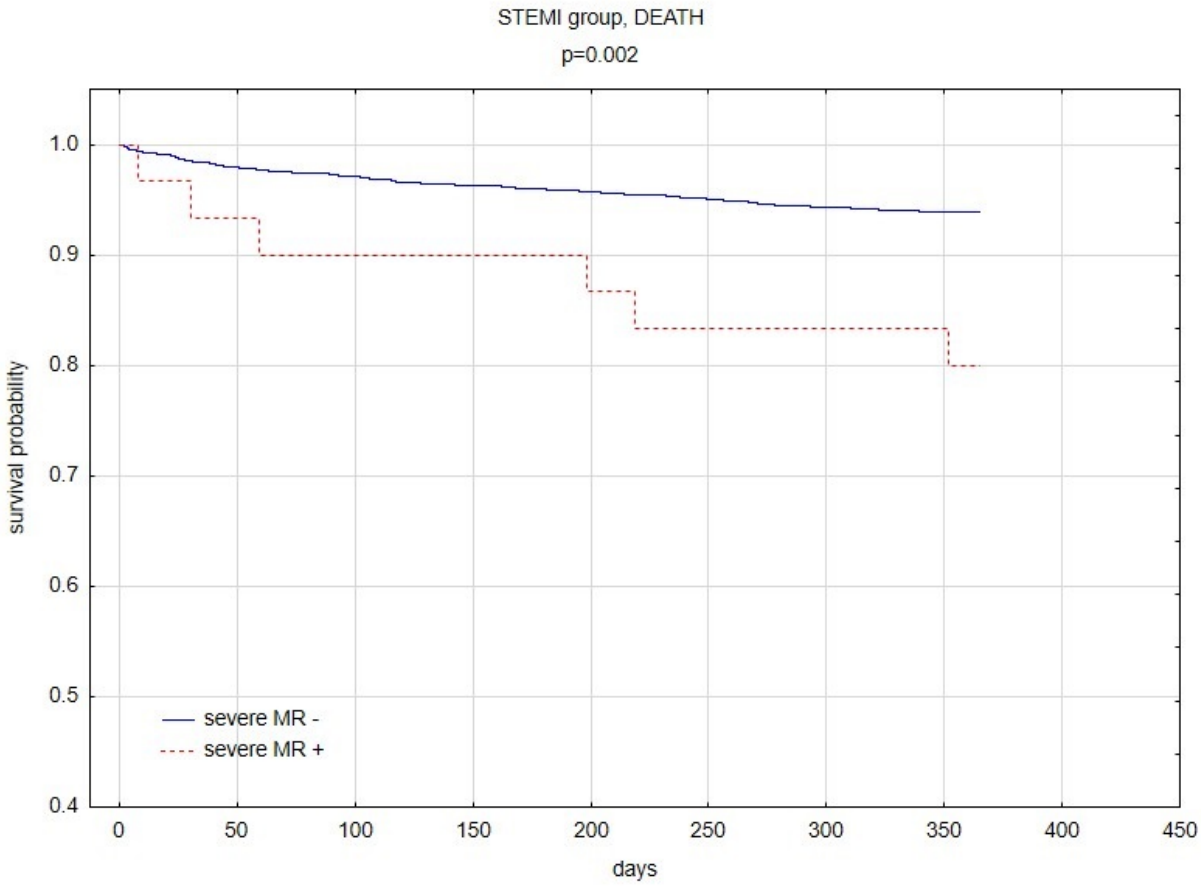

Figure 4. Kaplan-Meier estimator — STEMI group, mortality

Abbreviations: see Figure 1

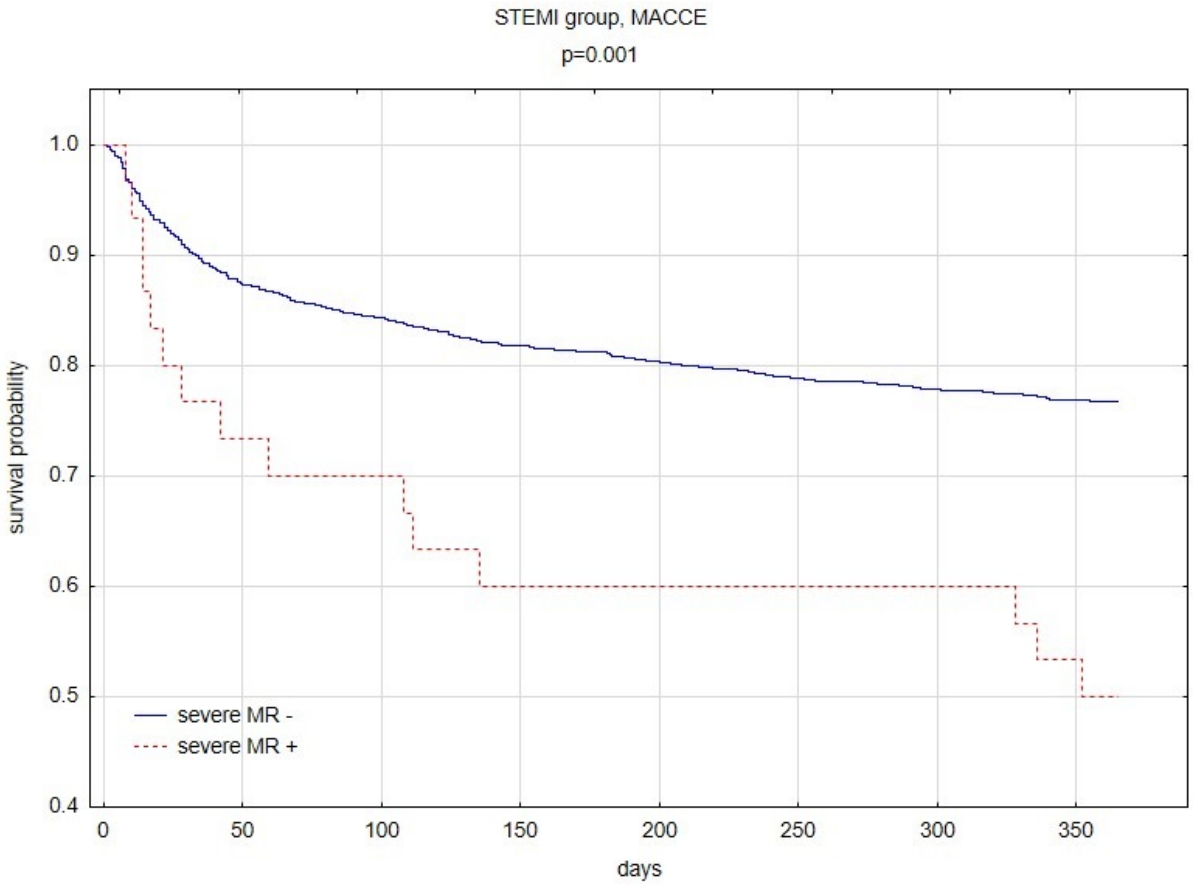

Figure 5. Kaplan-Meier estimator — STEMI group, MACCE occurrence

Abbreviations: see Figures 1 and 3