



Predictors and outcomes of new-onset atrial fibrillation in patients with acute myocardial infarction

Prediktori i ishod novonastale atrijske fibrilacije kod bolesnika sa akutnim infarktomiokarda

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Abstract

Background/Aim. The onset of atrial fibrillation (AF) in the acute phase of myocardial infarction (MI) may be a predictor of poor prognosis. The aim of our study was to examine this relationship. **Methods.** Six hundred patients were enrolled in the study and divided into two groups. The first group included 48 patients with new-onset AF and the second group of 552 patients without this arrhythmia. Patients with previously registered AF were excluded from the study. We investigated the correlation between new-onset AF and intra-hospital mortality as well as mortality during the follow-up period of 48 months. We also analyzed predictors of this arrhythmia. **Results.** New-onset AF was registered in 48 (8%) patients. The independent predictors of this arrhythmia were older age, particularly more than 70 years [odds ratio 2.37; 95% confidence interval (CI) 1.23–4.58] and increased body mass index (odds ratio 1.17; 95% CI 1.04–1.33). Patients with new-onset AF had a higher mortality during the hospital course than patients without AF, but this difference was not statistically significant (10.4% *vs* 5.6%, $p = 0.179$). Patients with this arrhythmia had also a higher mortality after follow-up period of 48 months than patients without AF (33.3% *vs* 17.8%, $p = 0.009$). Major adverse cardiac and cardiovascular events (MACCE) defined as death, recurrent MI, revascularization, and stroke were more after registered in patients with new-onset AF than in those with no this arrhythmia after follow-up period of 48 months (52.1% *vs* 33.9%, $p = 0.011$). However, multivariate Cox's regression analysis demonstrated that new-onset AF was not an independent predictor of mortality during the follow-up period of 48 months (HR 0.68; 95% CI 0.38–1.20; $p = 0.182$). **Conclusion.** New-onset AF in patients with MI was associated with a higher mortality as well as MACCE after the follow-up period of 48 months but was not an independent predictor of mortality during this period.

Key words:

myocardial infarction; atrial fibrillation; risk factors; aged; obesity; prognosis; mortality; sensitivity and specificity.

Apstrakt

Uvod/Cilj. Pojava atrijske fibrilacije (AF) u akutnoj fazi infarkta miokarda (MI) može biti prediktor loše prognoze. Cilj naše studije bio je da ispitamo ovu povezanost. **Metode.** Ukupno, 600 bolesnika je uključeno u istraživanje i podijeljeno u dve grupe. Prva grupa je obuhvatila bolesnike sa novonastalom AF, dok je druga grupa obuhvatila bolesnike bez ove aritmije. Bolesnici sa ranije registrovanom AF isključeni bili su iz istraživanja. Ispitivana je korelacija između novonastale AF i intrahospitalnog odnosno mortaliteta u toku perioda praćenja od 48 meseci. Takođe, analizirani su prediktori novonastale AF. **Rezultati.** Novonastala AF registrovana je kod 48 (8%) bolesnika. Nezavisni prediktor novonastale AF bilo je životno doba, naročito preko 70 godina [odds ratio 2,37; confidence interval (CI) 1,23–4,58], a potom i povišeni indeks telesne mase (odds ratio 1,17; 95% CI 1,04–1,33). Bolesnici sa novonastalom AF imali su povišeni intrahospitalni mortalitet u odnosu na one bez tog poremećaja srčanog ritma, ali ova razlika nije bila statistički značajna (10,4% *vs* 5,6%; $p = 0,179$). Bolesnici sa novonastalom AF imali su povišeni mortalitet nakon perioda praćenja od 48 meseci (33,3% *vs* 17,8%; $p = 0,009$). Veliki neželjeni kardiovaskularni događaji (*major adverse cardiac and cardiovascular events* – MACCE) koji obuhvataju smrt, ponovni MI, odnosno revaskularizaciju i šlog, bili su češće prisutni kod bolesnika sa novonastalom AF (52,1% *vs* 33,9%; $p = 0,011$) tokom perioda praćenja od 48 meseci. Međutim, u multivarijantnom Cox regresionom modelu novonastala AF nije identifikovana kao nezavisni prediktor mortaliteta tokom perioda praćenja od 48 meseci (HR 0.68; 95% CI 0.38–1.20; $p = 0.182$). **Zaključak.** Novonastala AF kod bolesnika sa MI bila je povezana sa povišenim mortalitetom odnosno MACCE tokom perioda praćenja od 48 meseci, ali nije bila nezavisni prediktor mortaliteta tokom ovog perioda.

Ključne reči:

infarkt miokarda; fibrilacija pretkomora; faktori rizika; stare osobe; gojaznost; prognoza; mortalitet; osetljivost i specifičnost.

Introduction

New-onset atrial fibrillation (AF) frequently complicates acute phase of myocardial infarction (MI) with the incidence of 6–21%^{1,2}.

The large epidemiological studies demonstrated that new-onset AF is associated with high mortality and adverse events in patients with MI^{1–7}. However, the outcome of this association is still unclear. Thromboembolic complications are one of the known mechanisms^{1–7}. Patients with new-onset AF are older as well as with higher rate of hypertension (HTA) and heart failure (HF) which may contribute to worse outcome^{1–7}. AF may precipitate the occurrence of severe ventricular arrhythmias which may lead to sudden death in these patients⁸. A large number of research have been done in patients with ST elevation myocardial infarction (STEMI), but some studies have also included patients with non-ST elevation myocardial infarction (NSTEMI)^{3,7,9}. However, there are a small number of studies that examined association between new-onset AF and clinical outcomes among patients with both STEMI and NSTEMI².

Furthermore, some studies showed a higher mortality in patients with new-onset AF, but this arrhythmia was not an independent predictor of mortality^{10–12}. This was the reason why we performed this research.

Its aim was to assess the impact of new-onset AF on mortality during the hospital period as well as mortality after a follow-up of 48 months in patients with MI, both STEMI, and NSTEMI, as well as predictors of new-onset AF.

Methods

This prospective study enrolled 600 patients with both STEMI and NSTEMI admitted to the Coronary Care Unit (CCU) of the Department of Cardiology, Clinical Center of Montenegro, between January 2009 to December 2010, after the approval by the local Ethics Committee.

Inclusion criteria involved patients aged 18 or older with MI both STEMI and NSTEMI, and in sinus rhythm on admission. Patients were divided into two groups: the first group which included patients with new-onset AF, i.e. developed during the hospital period, and the second group which included patients without AF registered previously as well as during the hospital period.

Permanent AF on admission or AF registered before, age < 18 years, congenital cardiac disease, severe valvular disease and healed endocarditis were exclusion criteria. Diagnosis of acute MI was determined according to the European Society of Cardiology Clinical Practical Guidelines for STEMI and NSTEMI^{13,14}.

The irregular rhythm on electrocardiography (ECG) with the lack of discernible P waves and duration more than 30 seconds not presented at hospital admission defined AF. All patients were continuously monitored by ECG during the whole period in the CCU. In patients with palpitations after the CCU period, permanent ECG monitoring was performed to confirm or exclude AF.

Echocardiography also was performed but with a delay of least 5 days of admission due to minimizing the impact of myocardial stunning^{15–17}. Simpson's method was used to assess left ventricular ejection fraction (LV-EF). Mitral regurgitation (MR) was estimated as mild when the jet area was under than 20%, moderate in patients in whom the jet area was between 20–40% and severe with the jet area more than 40% of the left atrial (LA) area¹⁸. LA diameter was determined by parasternal long axis view using a systolic frame in M-mode imaging.

Thrombolytic therapy was applied or primary percutaneous coronary intervention (PCI) was performed within 24 hours of the onset of symptoms in patients with STEMI as well as other therapy such as aspirin, heparin, angiotensin converting enzyme (ACE) inhibitors, β -blockade, and statins which was also performed in NSTEMI patients.

Patients were followed-up 48 months after being discharged from the hospital. The assessment was made 1 month after discharge and thereafter every 6 months until the study was completed.

Follow-up data were obtained for 99% of patients.

Statistical analysis

Continuous variables were presented as either means (\pm SD) or median values and categorical variables as numbers or percentages. Unpaired *t*-test was used for comparing continuous variables, and χ^2 and Fisher's and Mann-Whitney's test for categorical variables of baseline characteristics. The relationship between patient's variables and new-onset AF was determined by univariate and multivariate logistic analysis. The crude cumulative incidence of mortality according to the AF status was illustrated by Kaplan-Meier plot and survival rate was assessed by Log Rank test. The prognostic effect of new-onset AF on mortality during the follow-up period of 48 months was examined using Cox's proportional hazards models. *P* value < 0.05 was considered as significant. Statistical analysis was performed using IBM SPSS Statistics 22 (SPSS Inc., Chicago, IL, USA).

Results

A total of 600 patients with MI were enrolled in this study. AF was registered in 48 (8%) patients during the hospital course. The baseline characteristics of patients in regards to the presence or absence of new-onset AF are listed in Table 1.

During the hospital course, 212 (73.1%) patients with STEMI as well as 140 (45.2%) patients with NSTEMI underwent PCI (*p* < 0.001).

Predictors of new-onset atrial fibrillation during the hospital course

The strongest predictors of new-onset AF during the hospital course were older patients, particularly more than 70 years, and with increased body mass index (BMI) (Table 2). The other parameters such as heart rate above more than 80 bpm on admission and Killip class after adjustment by logistic analysis were not independent.

Table 1

Baseline characteristics in regards to the presence or absence of new-onset atrial fibrillation (AF)			
Characteristics	AF group	No AF group	p
	n = 48	n = 552	
Age (years), $\bar{x} \pm SD$	69.9 \pm 9.4	63.1 \pm 11.4	< 0.001
Gender, n (%)			
male	32 (66.7)	393 (71.2)	0.508
female	16 (33.3)	159 (28.8)	
MI, n (%)			
STEMI	26 (54.2)	264 (47.8)	0.399
NSTEMI	22 (45.8)	288 (52.2)	
Previous MI, n (%)	14 (29.2)	120 (21.7)	0.236
Previous CABG, n (%)	4 (8.3)	48 (8.7)	1.000
Killip class, n (%)			
I	35 (72.9)	486 (88.0)	
II	9 (18.8)	55 (10.0)	0.002
III	3 (6.3)	7 (1.3)	
IV	1 (2.1)	4 (0.7)	
Previous HF, n (%)	6 (12.5)	33 (6.0)	0.116
Diabetes mellitus, n (%)	15 (31.3)	152 (27.5)	0.582
Diabetic neuropathy, n (%)	15 (31.3)	119 (21.6)	0.122
COPD, n (%)	14 (29.2)	166 (30.1)	0.889
CKD, n (%)	17 (35.4)	170 (30.8)	0.507
BMI (kg/m ²), $\bar{x} \pm SD$	28.0 \pm 2.6	26.7 \pm 2.6	0.001
Dyslipidemia, n (%)	17 (35.4)	180 (32.6)	0.691
Smoking, n (%)	23 (47.9)	273 (49.5)	0.838
Previous CVI, n (%)	3 (6.3)	24 (4.3)	0.469
HTA, n (%)	26 (54.2)	268 (48.6)	0.455
LV-EF (%), $\bar{x} \pm SD$	41.7 \pm 4.6	43.9 \pm 4.9	0.003
LA (mm), $\bar{x} \pm SD$	43.6 \pm 3.9	40.4 \pm 3.6	< 0.001
MR, n (%)			
none	8 (16.7)	303 (55.0)	< 0.001
mild	28 (58.3)	208 (37.7)	
moderate-severe	12 (25.0)	40 (7.3)	
Heart rate on admission (bpm), median (range)	85.5 (55.0–122.0)	77.0 (43.0–125.0)	< 0.001
HTA on admission (mmHg), median (range)			
systolic blood pressure	158 (201–85)	154 (194–87)	0.657
diastolic blood pressure	81 (132–47)	80 (128–50)	
Localization of STEMI, n (%)			
anterior	14 (53.8)	113 (42.8)	0.279
inferior	12 (46.2)	151 (57.2)	
PCI during the hospital course, n (%)	30 (62.5)	322 (58.3)	0.574
Thrombolytic therapy, n (%)	17 (65.4)	192 (72.7)	0.930
Primary PCI, n (%)	4 (15.4)	49 (18.6)	0.720
VT during the hospital course, n (%)	9 (18.8)	42 (7.6)	0.014

MI – myocardial infarction; STEMI – ST elevation myocardial infarction, NSTEMI – Non-ST elevation myocardial infarction; CABG – coronary artery bypass graft; HF – heart failure; COPD – chronic obstructive pulmonary disease; CKD – chronic kidney disease; BMI – body mass index; CVI – cerebrovascular insult; HTA – hypertensio arterialis; LV-EF – left ventricle ejection fraction; LA – left atrium; MR – mitral regurgitation; PCI – percutaneous coronary intervention; VT – ventricular tachycardia.

Table 2

The predictors of new-onset atrial fibrillation (AF) and echo parameters in patients with myocardial infarction (MI)

Independent variable	Univariate logistic regression		Multivariate logistic regression	
	OR (95% CI)	p	OR (95% CI)	p
Age (more than 70 years)	3.32 (1.82–6.04)	< 0.001*	2.37 (1.23–4.58)	0.010*
Body mass index	1.22 (1.09–1.37)	0.001*	1.17 (1.04–1.33)	0.012*
Heart rate on admission (bpm)				
up to 80	reference category		reference category	
81–100	2.33 (1.21–4.50)	0.012*	0.70 (0.28–1.72)	0.438
more than 100	6.37 (2.60–15.60)	< 0.001*	1.71 (0.40–7.29)	0.469
Killip class	1.97 (1.27–3.06)	0.003*	0.72 (0.34–1.51)	0.386
LV-EF	0.92 (0.87–0.97)	0.003*	1.06 (0.97–1.17)	0.205
Diameter of LA	1.26 (1.16–1.37)	< 0.001*	1.18 (1.03–1.33)	0.015*
MR				
none	reference category		reference category	
mild	5.10 (2.28–11.41)	< 0.001*	3.56 (1.25–10.32)	0.018*
moderate to severe	11.36 (4.38–29.48)	< 0.001*	3.32 (0.72–15.365)	0.124

*statistically significant predictors of new-onset AF; LV-EF – left ventricle ejection fraction; LA – left atrium; MR – mitral regurgitation; OR – odds ratio; CI – confidence interval.

predictors of new-onset AF. Echo parameters such as the enlarged diameter of LA as well as presentation of MR significantly correlated with new-onset AF, but LV-EF did not (Table 2). Nevertheless, the other parameters such as gender, STEMI, localization of MI, thrombolytic therapy, PCI as well as CABG during the initial hospital period, previous MI, HF and CVI, diabetes mellitus, diabetic neuropathy, COBP, CKD, dyslipidemia, smoking and HTA were not included in the multivariate logistic regression analyses because univariate logistic regression analyses showed no statistical significance.

A total of 43 (89.6%) patients with new-onset AF were recovered to sinus rhythm during the hospital period. Recurrent AF was registered in 37.5% of patients with new-onset AF during the follow-up period of 48 months.

Impact of atrial fibrillation on mortality during the hospital period

A total of 36 (6.0%) patients died during the hospital course. A total of 5 patients (10.4%) with AF died during the hospital course as well as 31 patients (5.6%) without AF, but this difference was not statistically significant ($p = 0.179$). A total of 3 (11.5%) patients with STEMI and AF died during the hospital course as well as 2 (9.1%) patients

with NSTEMI, but with no statistically significant difference ($p > 0.05$).

Impact of atrial fibrillation on mortality during the follow-up period of 48 month

A total of 486 (81.0%) patients survived after the follow-up period of 48 months. A total of 16 patients with new-onset AF died after this follow-up period, 8 (30.8%) patients with STEMI and 8 (36.4%) patients with NSTEMI ($p > 0.05$). A total of 16 (33.3%) patients with AF developed during the hospital period as well as 98 (17.8%) those without AF died after the follow-up period of 48 months ($p = 0.009$) (Figure 1).

The correlation between mortality and new-onset AF was assessed using unadjusted and adjusted Cox's proportional hazards model (Table 3).

Correlation between new-onset AF and major adverse cardiac and cardiovascular events after follow-up period of 48 months

MACCE defined as death, recurrent MI, revascularization and stroke were registered more often in patients with new-onset AF during the follow-up period of 48 months (Table 4 and Figure 2).

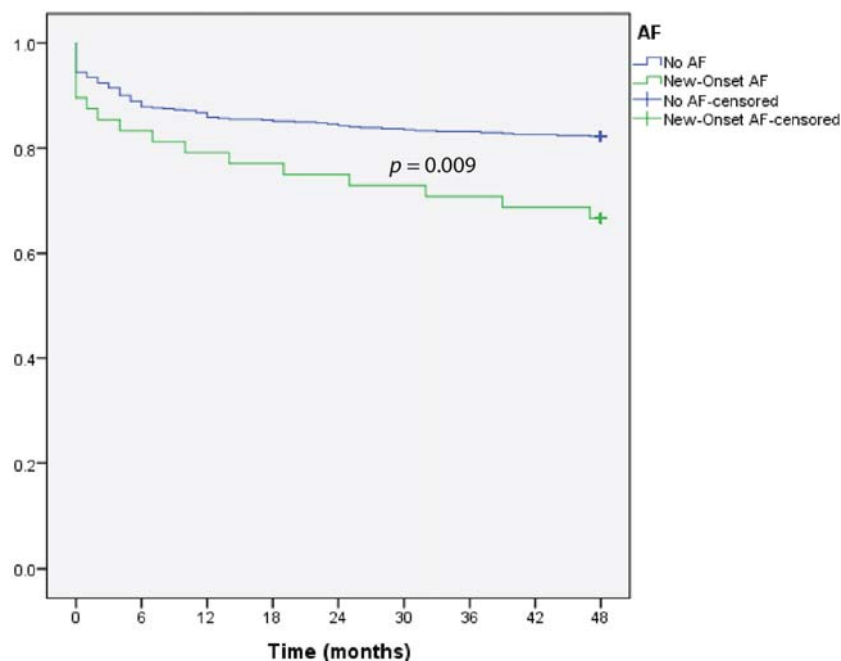


Fig. 1 – Crude cumulative incidence of mortality during the follow-up period of 48 months presented by Kaplan-Meier plots. AF – atrial fibrillation

Table 3

Predictors	Univariate Cox's regression model		Multivariate Cox's regression model	
	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
Age (more than 70 years)	2.06 (1.42–2.98)	< 0.001*	1.42 (0.96–2.08)	0.078
Killip class	3.71 (3.00–4.59)	< 0.001*	2.77 (2.13–3.61)	< 0.001*
Body mass index	1.45 (1.36–1.56)	< 0.001*	1.35 (1.26–1.45)	< 0.001*
Atrial fibrillation	1.97 (1.16–3.34)	0.012*	0.68 (0.38–1.20)	0.182

HR – hazard ratio; *statistically significant predictors; CI – confidence interval.

Table 4

Recurrent cardiovascular events	Recurrent cardiovascular events after follow-up period of 48 months		<i>p</i>
	AF group n (%)	No AF group n (%)	
MI	8 (16.7)	67 (12.1)	0.363
CABG	5 (10.4)	39 (7.1)	0.384
PCI	7 (14.6)	70 (12.7)	0.705
CVI	7 (14.6)	41 (7.4)	0.093
MACCE	25 (52.1)	187 (33.9)	0.011

AF – atrial fibrillation; MI – myocardial infarction; CABG – coronary artery bypass graft; PCI – percutaneous coronary intervention; CVI – cerebrovascular insult; MACCE – major adverse cardiac and cardiovascular events.

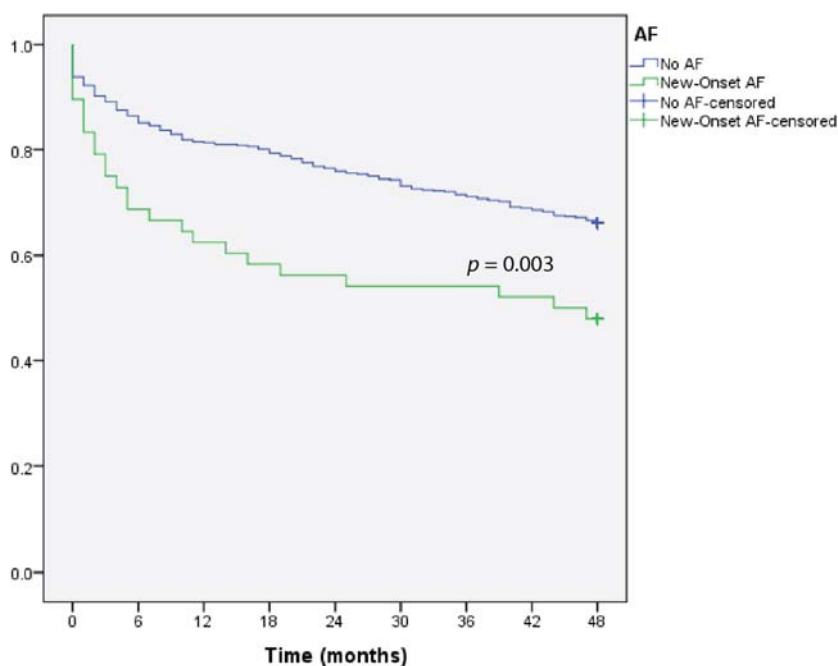


Fig. 2 – Composite end-point of death, recurrent myocardial infarction, revascularization and stroke during the follow-up period of 48 months presented by Kaplan-Meier plots, $p = 0.003$.
AF – atrial fibrillation.

Discussion

In our study, we presented the incidence of new-onset AF in STEMI and NSTEMI patients. In accordance with other previous studies, new-onset AF was more frequent in the STEMI group than in the NSTEMI one, but this difference was not statistically significant^{1,2}. The reason of higher incidence of AF in the STEMI population is still undetermined. The incidence of AF in MI with and without ST-segment elevation was also compared and published RICO study, but the result was also without statistical significance (7.6 vs 7.7%; $p = 0.334$)¹⁵.

We identified the several important baseline predictors of new-onset AF in the setting of MI. Namely, except for age, this study is one of the first which emphasized that the obesity is an independent predictor of new-onset AF in patients with both STEMI and NSTEMI. The correlation between obesity and new-onset AF in a patient with MI remains unclear. However, according to data from large German AF registry, obesity was present in 25% of patients with AF with BMI of 27.5 kg/m^{2,16}.

Recent data from a Danish cohort indicates that BMI is incrementally associated with the volume of left atrium which leads to more pronounced trigger activity provoked by a more profound stretching of the pulmonary veins¹⁷. The enlarged volume of left atrium also may lead to prolongation of ectopic signals with the easier perpetuation of AF^{17,18}. Higher BMI is associated with inflammation which is supported by a recent study demonstrating that gene coding for the interleukin-6 receptor polymorphism is related to AF¹⁹. Obesity is a major risk factor for obstructive sleep apnea which also may predispose to AF²⁰. MR in MI may also lead to both acute overload and enlargement volume of left atrium which through the described mechanisms may initiate and perpetuate AF^{17,21–24}. Unlike the previous study, we did not observe a positive association between MR severity and new-onset AF²⁵.

In our study we also presented the incidence of new-onset AF in STEMI patients according to the reperfusion regimens. In accordance with a recently published study, there

were no significant differences in the development of new-onset AF according to the reperfusion regimens (primary PCI vs thrombolysis)^{26, 27}.

In the present study we demonstrated a positive association between new-onset AF in patients with MI and complications developed during the hospital course such as HF and cardiogenic shock, but after adjustment for clinical and echo variables the risk associated with AF was attenuated. New-onset AF also was not an independent predictor of mortality during the hospital course. This finding was observed in both STEMI and NSTEMI patients for all of the studied outcomes. In spite of previous studies, there were significant differences in mortality during the hospital period according to the reperfusion regimens (primary PCI vs thrombolysis)²⁸⁻³².

New-onset AF was correlated with higher mortality after a follow-up period of 48 months. Furthermore, MACCE were more often registered in patients with new-onset AF after a follow-up period of 48 months. This finding was observed in both STEMI and NSTEMI groups. However, after multivariate Cox's regression analysis new-onset AF was not an independent predictor of mortality during the follow-up period of 48 months. This finding is in accordance with data of the study which included 4,108 patients hospitalized due to MI in 16 hospitals¹⁰. Namely, this study showed that patients with new-onset AF had higher long-term mortality than

patients without this arrhythmia, but independent effect of AF on long-term prognosis was not confirmed by using a multivariate analysis¹⁰.

Conclusion

New-onset AF was common in both patients with STEMI and those with NSTEMI and difference in its incidence between these two groups was not statistically significant. The strongest predictors of new-onset AF were older age and increased BMI. We also registered that echo parameters such as the enlarged diameter of left atrium as well as the presentation of MR were at the significant correlation with new-onset AF. There were no significant differences in mortality during the hospital period between MI patients with and without new-onset AF according to the reperfusion regimens. New-onset AF was associated with higher mortality as well as MACCE during the follow-up period of 48 months but was not an independent predictor of mortality during this period.

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