



Original Article

Examination of the appropriate timing of reperfusion therapy for recent myocardial infarction: a Japanese single-center retrospective study^{☆,☆☆}



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ABSTRACT

Background: The various guidelines clearly mention the treatment strategies for in patient of acute myocardial infarction (MI) presenting more than 24 h from symptom onset (recent myocardial infarction, RMI). However, the appropriate timing of reperfusion for RMI is unclear.

Methods: We retrospectively evaluated 525 consecutive MI patients who underwent percutaneous coronary intervention (PCI) in our hospital between January 2008 and December 2012.

Results: Sixty RMI patients were more frequently associated with cardiac complications such as myocardial rupture (3.3% vs. 0%; $p < 0.01$), ventricular septal rupture (3.3% vs. 0.4%; $p < 0.05$), and congestive heart failure (15% vs. 2.6%; $p < 0.001$) than 272 consecutive ST-elevation myocardial infarction (STEMI) patients. Of the 60 RMI patients, 33 (55.0%) underwent PCI within 7 days (early-PCI group) and 27 (45.0%) underwent PCI after 7 days (late-PCI group). Left ventricular ejection fraction measured by echocardiography at second hospital day was similar between the groups. The early-PCI group was more significantly associated with cardiogenic shock and heart failure and more frequently required intra-aortic balloon pumping (24.2% vs. 3.7%; $p < 0.05$) than the late-PCI group. There were no significant differences in 30-day mortality, cardiac complications, and major cardiac events during long-term follow-up (12–36 months) between the groups.

Conclusion: RMI patients had a higher incidence of cardiac complications than AMI patients. Clinical outcomes were similar between patients undergoing early revascularization and those undergoing late revascularization, although the former group included a higher proportion of patients with severe cardiac failure.

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1. Introduction

Prognosis in ST-elevation myocardial infarction (STEMI) is reportedly inversely related to delay in reperfusion, and current guidelines recommend an early invasive strategy for high-risk non-ST-elevation acute coronary syndrome (NSTEMI) patients.^{1–4} The various guidelines clearly mention the treatment strategies for in patient of acute myocardial infarction (MI) presenting more than

24 h from symptom onset (recent myocardial infarction, RMI).^{5,6} However, the appropriate timing of reperfusion for RMI is unclear. So, we retrospectively investigated the difference of clinical outcome between the RMI patients underwent PCI within 7 days after admission and those who underwent PCI after more than 7 days after admission.

2. Methods

2.1. Study population

We retrospectively collected data from 525 consecutive MI patients in our hospital between January 2008 and December 2012. MI patients complicated with cardiopulmonary arrest out of the hospital ($n = 33$) and having the left main trunk culprit lesion ($n = 23$) and chronic total occlusion (CTO) lesions in a non-infarct-

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related artery ($n = 28$) were excluded. MI was defined according to the “third universal definition of myocardial infarction” proposed by the Writing Group on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction.⁷ Acute MI (AMI) was defined as MI diagnosed within 24 h from symptom onset, and recent MI (RMI) was defined as MI diagnosed after 24 h from symptom onset. Diagnostic ST-elevation is defined as new ST-elevation at the J point in at least 2 contiguous leads ≥ 2 mm (0.2 mV) in men or ≥ 1.5 mm (0.15 mV) in women in leads V_2 – V_3 and/or of ≥ 1 mm (0.1 mV) in other contiguous chest or limb leads. This study included 381 AMI patients (including 272 STEMI patients) and 60 RMI patients. All RMI patients were Q wave MI.

The demographic, clinical, and angiographic characteristics of the patients as well as in-hospital and 30-day outcomes were investigated. Cardiogenic shock on admission was defined according to the following clinical criteria used in the SHOCK trial⁸: hypotension was defined as a systolic blood pressure of <90 mmHg for at least 30 min or the need for supportive measures to maintain the systolic blood pressure at ≥ 90 mmHg, and end-organ hypoperfusion was defined as cold extremities or a urine output of <30 mL/h and a heart rate of ≥ 60 beats/min.

2.2. In-hospital management

Coronary angiography (CAG) was performed immediately after the diagnosis of MI in all patients. PCI was performed as soon as possible in all AMI patients. In RMI patients, PCI for the culprit lesion was performed at the operator's discretion, depending on patient consent, the requirement for evaluation of coexisting diseases, and cardiac failure treatment before PCI. PCI in all patients was performed using intravascular ultrasound (IVUS). If attenuated plaques or massive thrombi were detected by IVUS or CAG, we performed thrombus aspiration and distal protection before stent implantation. A thrombus was defined as an intraluminal lobulated mass with evidence of blood flow (micro-channels) within the mass, mobility, and a sparkling or scintillating appearance.⁹ An attenuated plaque was defined as a hypochoic plaque with deep ultrasound attenuation without calcification or a very dense fibrous plaque.¹⁰

CTO was defined as total occlusion of the artery lumen without antegrade flow or with flow (anterograde or retrograde) through collateral vessels in an artery other than the culprit artery. Door-to-balloon time was defined as the time between patient arrival at our hospital and the beginning of the mechanical reperfusion procedure. Door time was defined as the time of patient arrival at our hospital, indicated by the moment they took a number to be evaluated (before the patient was checked-in in that hospital area), which was automatically recorded by the information system. Balloon time was defined as the time of the first angioplasty balloon inflation or the first aspiration with an aspiration thrombectomy device. After the intervention, all patients were admitted to a coronary care unit. The patients underwent transthoracic echocardiography on day 1 after admission, and left ventricular ejection fraction (LVEF) was measured using the biplane method of discs (modified Simpson's rule). Left ventricular (LV) volume was measured in the apical 4-chamber and 2-chamber views. Serum creatine kinase isoenzyme levels were measured at baseline and at 3, 6, 9, 12, and 24 h after PCI.

2.3. Medications

All AMI and RMI patients received a loading dose of aspirin (200 mg) and clopidogrel (300 mg). During the procedure, intravenous unfractionated heparin was administered to maintain an activated clotting time of 250–300 s, and the postprocedural use of intravenous unfractionated heparin was left to the operator's

discretion in AMI patients. In all RMI patients, unfractionated heparin was administered as an intravenous bolus of 60 IU/kg (maximum, 4000 IU), followed by an infusion of 12 IU/kg/h (initial maximum, 1000 IU/h) that was adjusted to maintain an activated partial thromboplastin time of 1.5–2.0 times the control value. The intravenous infusion was administered for at least 48 h. All AMI and RMI patients took the statins, β -blockers and angiotensin converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) as soon as possible after emergency CAG and primary PCI. There were no patients treated with fibrinolysis before primary PCI in the current study.

After discharge, aspirin was used indefinitely, clopidogrel was continued for at least 12 months, and other medications (e.g., statins, β -blockers, angiotensin-converting enzyme inhibitors) were used according to the current guidelines.²

2.4. Statistical analysis

All data were analyzed retrospectively. Categorical variables were expressed as numbers and percentages, and continuous variables were expressed as mean \pm standard deviation. After testing for normal distribution, differences were compared using the unpaired Student's *t*-test, χ^2 test, or Fisher's exact test, as appropriate. Time-to-survival outcomes were analyzed using the Kaplan–Meier method. Cases were censored when death was observed. In order to compare time-to-survival outcomes between STEMI and RMI groups, *P*-values were calculated using the Cox regression stratified by matched pairs. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Japan),¹¹ which is a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0). More precisely, it is a modified version of R commander (version 1.6–3) designed to add statistical functions frequently used in biostatistics. A two-tailed *p*-value of <0.05 was considered statistically significant.

3. Results

3.1. RMI vs. STEMI

The 381 AMI patients included 272 STEMI patients and 109 non-STEMI patients. After propensity matching the remaining population ($n = 120$ [$n = 60$ RMI and $n = 60$ STEMI]), peak creatinine kinase level, creatinine clearance, and LVEF measured by echocardiography at second hospital day were significantly lower in the RMI group than in the STEMI groups (Table 1). However, there were no significant differences in 30-day mortality and the frequency of requiring intra-aortic balloon pumping (IABP) and cardiogenic shock between the RMI group and STEMI group. Moreover, there were no significant differences in the puncture site after PCI between the RMI group and STEMI group. After propensity score matching, prognosis during 5-year follow up of RMI patients was significantly poorer than STEMI patients (hazard ratio, 4.04; 95% confidence intervals, 1.76–9.26) (Fig. 1).

3.2. Early reperfusion vs. late reperfusion

Of 60 RMI patients, 33 (55.0%) underwent PCI within 7 days (early-PCI group) and 27 (45.0%) underwent PCI after 7 days (late-PCI group). The LVEF measured by echocardiography at second hospital day was similar between the groups. The early-PCI group was more significantly associated with cardiogenic shock and heart failure and more frequently required IABP (24.2% vs. 3.7%; $p < 0.05$) than the late-PCI group. Blood transfusion was performed more frequently in the early-PCI group than in the late-PCI group, although this difference was not significant (21.2% vs. 11.1%;

Table 1
Comparison of the baseline clinical characteristics, procedures, and complications between the RMI and STEMI groups in the pre and post propensity score matched model.

	Pre-match			Post-match		
	RMI (n = 60)	STEMI (n = 272)	p-value	RMI (n = 60)	STEMI (n = 60)	p-value
Age (years)	69.4 ± 14.0	67.2 ± 12.7	NS	69.4 ± 14.0	68.9 ± 13.3	NS
Sex (men/women), n	39/21	197/75	NS	39/21	41/19	NS
Cardiovascular risk factors						
Hypertension, n (%)	34 (56.7%)	159 (58.5%)	NS	34 (56.7%)	35 (58.3%)	NS
Diabetes mellitus, n (%)	17 (28.3%)	94 (34.6%)	NS	17 (28.3%)	22 (36.7%)	NS
Dyslipidemia, n (%)	27 (45.0%)	100 (36.8%)	NS	27 (45.0%)	13 (21.7%)	NS
Current smoking, n (%)	25 (41.7%)	110 (40.4%)	NS	25 (41.7%)	27 (45.0%)	NS
30-day mortality, n (%)	2 (3.3%)	9 (3.3%)	NS	2 (3.3%)	1 (1.7%)	NS
In-hospital mortality, n (%)	2 (3.3%)	12 (4.0%)	NS	2 (3.3%)	1 (1.7%)	NS
Cardiogenic shock, n (%)	5 (8.3%)	33 (12.1%)	NS	5 (8.3%)	3 (5.0%)	NS
Cardiac complications during or after PCI, n (%)	8 (13.3%)	23 (8.5%)	NS	8 (13.3%)	5 (8.3%)	NS
Myocardial rupture, n (%)	2 (3.0%)	0 (0%)	<0.01	2 (3.0%)	0 (0%)	<0.01
Ventricular septal rupture, n (%)	2 (3.0%)	1 (0.4%)	<0.05	2 (3.0%)	0 (0%)	<0.01
Ventricular fibrillation or ventricular tachycardia, n (%)	2 (3.0%)	16 (5.9%)	NS	2 (3.0%)	4 (6.7%)	NS
Acute stent thrombosis, n (%)	2 (3.0%)	6 (2.2%)	NS	2 (3.0%)	1 (1.7%)	NS
Congestive heart failure, n (%)	9 (15.0%)	7 (2.6%)	<0.001	9 (15.0%)	0 (0%)	<0.001
Peak CK (U/L)	1011 ± 1066	2474 ± 2284	<0.001	1011 ± 1066	2296 ± 2104	<0.001
CCr (mL/min)	68.1 ± 40.0	82.6 ± 39.6	<0.01	68.1 ± 40.0	79.4 ± 47.2	<0.01
Ejection fraction (day 1 after PCI) (%)	50.1 ± 13.6	54.7 ± 12.5	<0.01	50.1 ± 13.6	55.0 ± 11.8	<0.01
Culprit lesion						
LAD, n (%)	28 (47.0%)	135 (49.6%)	NS	28 (47.0%)	28 (46.7%)	NS
LCX, n (%)	8 (13.0%)	23 (8.5%)	NS	8 (13.0%)	3 (5.0%)	NS
RCA, n (%)	24 (40.0%)	121 (44.5%)	NS	24 (40.0%)	29 (48.3%)	NS
Number of stenosed vessels						
1, n (%)	29 (48.3%)	132 (48.5%)	NS	29 (48.3%)	27 (45.0%)	NS
2, n (%)	19 (31.7%)	101 (37.1%)	NS	19 (31.7%)	26 (43.0%)	NS
3, n (%)	13 (21.7%)	39 (14.3%)	NS	13 (21.7%)	7 (11.7%)	NS
PCI approach site						
Radial artery, n (%)	59 (98.3%)	257 (94.5%)	NS	59 (98.3%)	58 (96.7%)	NS
Brachial artery, n (%)	1 (1.6%)	4 (1.5%)	NS	1 (1.6%)	0	NS
Femoral artery, n (%)	0	12 (4.4%)	NS	0	2 (3.3%)	NS
Door-to-balloon (first device used) time, (min)	6192 ± 7920	44.0 ± 19.2	<0.0001	4462 ± 2952	44.1 ± 16.2	<0.0001
IABP, n (%)	9 (15.0%)	47 (17.3%)	NS	9 (15.0%)	5 (8.3%)	NS
ECMO, n (%)	1 (1.7%)	7 (2.6%)	NS	1 (1.7%)	0	NS
Final TIMI grade flow <3, n (%)	0	3 (1.0%)	NS	0	0	NS
Blood transfusion, n (%)	10 (16.7%)	43 (15.8%)	NS	10 (16.7%)	10 (16.7%)	NS
Minimum hemoglobin level (mg/dL)	10.2 ± 1.9	10.4 ± 2.0	NS	10.2 ± 1.9	10.2 ± 2.1	NS

RMI, recent myocardial infarction; STEMI, ST-elevation myocardial infarction; CK, creatinine kinase; PCI, percutaneous coronary intervention; CCr, creatinine clearance; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; IABP, intra-aortic balloon pumping; ECMO, extracorporeal membrane oxygenation; TIMI, thrombolysis in myocardial infarction; NS, not significant.

Data are presented as numbers (%) or mean ± standard deviation.

$p = 0.30$). There were no significant differences in 30-day mortality and cardiac complications between the groups (Table 2). Moreover, major cardiac events during long-term follow-up (12–36 months) did not differ between the groups (Table 3).

4. Discussion

In this study, we report our clinical experience with RMI patients who underwent revascularization within or after 7 hospital day. The main findings of this study are as follows: (1) RMI patients had a higher incidence of cardiac complications than STEMI patients; (2) LV pump function was significantly lower in RMI patients than in STEMI patients; (3) there were no significant differences in the incidence of cardiac complications and mortality between the early-PCI and late-PCI groups; (4) the degrees of LV remodeling and dysfunction were similar between the early-PCI and late-PCI groups at long-term follow-up.

Previous studies have reported the benefits of early coronary intervention for NSTEMI/ACS.^{4,12–14} Katritsis et al.⁴ conducted a meta-analysis of randomized trials addressing the optimal timing (early vs. delayed) of coronary angiography in NSTEMI/ACS and suggested

that early catheterization followed by coronary intervention on the first day of hospitalization was safe and superior in terms of a lower risk of recurrent ischemia (–41%) and shorter hospital stay (–28%). Although some observational studies have suggested that early intervention, compared to delayed intervention, may reduce events,^{12,13} others have reported similar outcomes between the 2 approaches.¹⁴ On the other hand, some studies have suggested that an invasive strategy, compared to a selectively invasive (or conservative) strategy, may increase the risk of events in women with acute coronary syndrome.^{15,16} Thus, there is no consensus on whether early or delayed intervention is superior for NSTEMI/ACS.

The ESC¹⁷ and ACCF/AHA¹⁸ guidelines recommend reperfusion therapy within the first 12 h of symptom onset in all STEMI patients. Reperfusion therapy is also recommended in STEMI patients with evidence of ongoing ischemia within 12–24 h of symptom onset. However, routine PCI of a totally occluded artery >24 h after symptom onset is not recommended in stable patients without signs of ischemia, according to the ESC guidelines. On the other hand, a meta-analysis of 5 nonrandomized studies^{19–23} and 1 randomized trial²⁴ comparing immediate with delayed stenting in patients undergoing primary PCI with early invasive

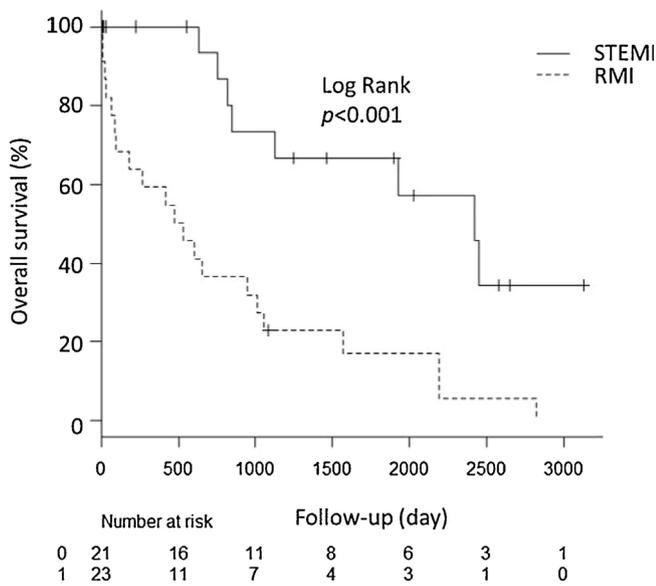


Fig. 1. Adjusted Cox proportional hazards of mortality compared between RMI group and STEMI group.

revascularization revealed that delayed stent implantation was associated with better angiographic outcomes.

MI patients were usually treated in accordance with these ESC and ACCF/AHA guidelines in our hospital. In the present study, clinical outcomes after prompt or proper PCI were better in STEMI patients than in RMI patients. Therefore, we consider that early reperfusion using IVUS and distal protection devices is superior to delayed reperfusion in AMI patients. In several studies, the clinical outcomes of early reperfusion therapy were poorer than those of

delayed reperfusion therapy, possibly because of the low frequency of the use of IVUS as well as distal protection devices in primary PCI. Kawaguchi et al.²⁵ reported on the relationship between the measures of plaque composition and the frequency of post-PCI distal embolization in STEMI patients. It is noteworthy that lesions with a large necrotic core and thrombus burden have been detected using IVUS. Further, IVUS use for identifying the risk of distal embolization may lead to the selective use of adjunctive distal protection techniques.

Meanwhile, the ESC¹⁷ and ACCF/AHA¹⁸ guidelines suggest that primary PCI should be performed in patients with STEMI and cardiogenic shock or severe acute heart failure, irrespective of the time of MI onset. In the present study, RMI patients were more likely to be admitted to the hospital for congestive heart failure, and therefore, PCI was immediately performed in these patients. However, these guidelines could not identify the appropriate timing of reperfusion in RMI patients without cardiogenic shock and acute heart failure.

There were no significant differences in cardiac complications and LV pump function at long-term follow-up between the early-PCI and late-PCI groups in this study. However, 2 cases of ventricular septal rupture occurred in the early-PCI group and 2 cases of myocardial free-wall rupture occurred in the late-PCI group. To avoid cardiac complication: ventricular septal rupture, myocardial rupture, prompt revascularization of IRA is recommended by recent guidelines.^{17,18} In particular, these guidelines recommend that the goal should be to achieve a ‘door-to-balloon’ delay ≤60 min between presentation in the hospital and primary PCI in PCI-capable hospitals. In this study, the mean door-to-balloon time of STEMI group was 44.0 min. This early revascularization might lead to be significant low rate of ventricular rupture in STEMI group. The average delay between AMI and ventricular rupture is bimodal in distribution, occurring within the first day

Table 2
Comparison between the early-PCI and late-PCI groups.

	Early-PCI group (n = 33)	Late-PCI group (n = 27)	p-value
Age (years)	70.0 ± 15.4	68.7 ± 12.3	NS
Sex (men/women), n	20/13	19/8	NS
30-day mortality, n (%)	2 (6.6%)	0	NS
5-year mortality, n (%)	15 (45.5%)	6 (22.2%)	NS
Cardiogenic shock, n (%)	3 (9.1%)	2 (7.4%)	NS
Cardiac complications during or after PCI, n (%)	10 (30.0%)	6 (22.0%)	NS
Myocardial rupture, n (%)	0	2 (7.4%)	NS
Ventricular septal rupture, n (%)	2 (6.6%)	0	NS
Ventricular fibrillation or ventricular tachycardia, n (%)	1 (3.0%)	1 (3.7%)	NS
Acute stent thrombosis, n (%)	1 (3.0%)	1 (3.7%)	NS
Congestive heart failure, n (%)	6 (18.2%)	2 (7.4%)	NS
Peak CK (U/L)	1148 ± 1241	842 ± 793	NS
CCr (mL/min)	68.9 ± 39.7	67.2 ± 34.2	NS
Ejection fraction (day 1 after PCI) (%)	50.2 ± 14.4	49.9 ± 12.7	NS
TIMI grade flow before PCI	1.37 ± 1.38	1.09 ± 1.28	NS
TIMI grade flow after PCI	3.0 ± 0	3.0 ± 0	NS
Culprit lesion			
LAD, n (%)	15 (45.0%)	13 (48.0%)	NS
LCX, n (%)	4 (12.0%)	4 (15.0%)	NS
RCA, n (%)	14 (42.0%)	10 (37.0%)	NS
Number of stenosed vessels			
1, n (%)	14 (42.4%)	15 (55.6%)	NS
2, n (%)	12 (36.4%)	7 (25.9%)	NS
3, n (%)	8 (24.2%)	5 (18.5%)	NS
IABP, n (%)	8 (24.2%)	1 (3.7%)	<0.05
ECMO, n (%)	1 (3.0%)	0	NS
Blood transfusion, n (%)	7 (21.2%)	3 (11.1%)	NS
Minimum hemoglobin level (mg/dL)	9.9 ± 1.7	10.4 ± 2.1	NS

CK, creatinine kinase; PCI, percutaneous coronary intervention; CCr, creatinine clearance; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; IABP, intra-aortic balloon pumping; ECMO, extracorporeal membrane oxygenation; TIMI, thrombolysis in myocardial infarction; NS, not significant. Data are presented as numbers (%) or mean ± standard deviation.

Table 3
Results at 30 days and 6 months.

	30 days			12–36 months		
	Early- PCI group (n = 33)	Late-PCI group (n = 27)	p-value	Early- PCI group (n = 33)	Late-PCI group (n = 27)	p-value
Death, n (%)	1 (3.0%)	2 (7.4%)	NS	10	6	NS
Cardiac complications, n (%)	10 (30.0%)	6 (22.0%)	NS	6 (18.2%)	5 (18.5%)	NS
Myocardial rupture, n (%)	0	2 (7.4%)	NS	0	0	NS
Ventricular septal rupture, n (%)	2 (6.1%)	0	NS	0	0	NS
Ventricular fibrillation or ventricular tachycardia, n (%)	1 (3.0%)	1 (3.7%)	NS	0	0	NS
Stent thrombosis, n (%)	1 (3.0%)	1 (3.7%)	NS	1 (3.0%)	0	NS
Myocardial infarction (non-culprit lesion), n (%)	0	0	NS	0	0	NS
Target vessel revascularization, n (%)	1 (3.0%)	2 (7.4%)	NS	5 (15.0%)	3 (11.1%)	NS
Congestive heart failure, n (%)	6 (18.2%)	2 (7.4%)	NS	1 (1.8%)	2 (7.4%)	NS
Echocardiographic parameters						
Ejection fraction (%)	61.9 ± 10.5	56.4 ± 9.4	NS	52.3 ± 11.6	54.3 ± 12.1	NS
Left ventricular diastolic dimension (mm)	48.1 ± 6.6	49.4 ± 4.2	NS	46.6 ± 6.2	51.3 ± 6.8	NS
Left atrial dimension (mm)	32.8 ± 13.4	37.8 ± 8.4	NS	35.6 ± 6.5	37.9 ± 6.9	NS

PCI, percutaneous coronary intervention; NS, not significant.
Data are presented as numbers (%) or mean ± standard deviation.

and another peak occurring between 3 and 5 days.^{26–28} The median time from the onset of symptoms of AMI to rupture is generally ≤24 h in patients receiving thrombolysis.²⁹ Without reperfusion, coagulation necrosis develops within the first 3–5 days after infarction, and the infarct lesion becomes fibrotic after several weeks. Although thrombolytic therapy reduces the size of the infarct, in some cases, it may promote hemorrhagic dissection in the myocardium, accelerating the onset of septal rupture.²⁸ On the basis of our study and several other reports, we suggest that PCI in RMI patients should be performed immediately if the patient is experiencing cardiac shock or acute heart failure; however, in other situations, it may be better to perform PCI at least 1–2 weeks after symptom onset.

The foremost limitation of this study is its nonrandomized retrospective observational design, which implies the absence of a data safety monitoring board and blinded core laboratory. Second, this study had a small sample size and short follow-up period. Therefore, additional larger studies with longer follow-up periods are required to clarify the adequate timing of invasive reperfusion therapy in RMI patients.

5. Conclusions

RMI patients had a higher incidence of cardiac complications than AMI patients. Clinical outcomes were similar between patients undergoing early revascularization and those undergoing late revascularization, although the former group included a higher proportion of patients with severe cardiac failure.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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