Original Article

Prognostic relevance and clinical features of papillary muscle infarction with mitral regurgitation in patients with ST segment elevation myocardial infarction

Dazhou Lei[1], Jun Xie[2], Qing Dai[2], Yinhao Huang[1], Xuan Wei[1], Dan Mu[2], Xue Bao[2], Jianhui Li[1], Biao Xu[1,2]

[1]Department of Cardiology, Nanjing Drum Tower Hospital Clinical College of Nanjing Medical University, Nanjing, China; [2]Department of Cardiology, Drum Tower Hospital, Medical School of Nanjing University, Nanjing, China

Contributions: (I) Conception and design: D Lei, B Xu; (II) Administrative support: B Xu; (III) Provision of study materials or patients: J Xie, Q Dai, J Li, X Bao, D Mu; (IV) Collection and assembly of data: D Lei, Y Huang, X Wei; (V) Data analysis and interpretation: D Lei, B Xu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Biao Xu. Department of Cardiology, Nanjing Drum Tower Hospital Clinical College of Nanjing Medical University No. 321 Zhongshan Road, Nanjing 210008, China. Email: xubiao62@nju.edu.cn.

Background: Papillary muscle infarction (PapMI) combined with mitral regurgitation (MR) is a severe complication of ST-segment elevation myocardial infarction (STEMI). The features detected by cardiac magnetic resonance (CMR) imaging in PapMI have not been characterized. The aim of the present study was to assess the incidence, determinants, and the prognostic significance of PapMI with MR at 1-year follow-up in a study of patients with STEMI after primary percutaneous coronary intervention (pPCI).

Methods: We enrolled 209 patients with STEMI reperfused by pPCI (<12 hours after symptom onset) at 2 centers. CMR and echocardiography were performed within 1 week after infarction using a standardized protocol. According to the results of CMR and echocardiography, patients were divided into PapMI with MR, PapMI (PapMI without MR), and non-PapMI groups. The primary clinical endpoint of the study was the occurrence of major adverse cardiovascular events (MACE).

Results: PapMI with MR was found in 27 patients (13%). The existence of PapMI with MR was associated with age (P<0.001), impaired left ventricular ejection fraction (LVEF) (P=0.005), higher SYNTAX score (P=0.002), concentration of troponin I (P<0.001), longer time to reperfusion (P<0.001), more diabetics (P<0.001), and microvascular occlusion (MVO) (P<0.001). Binary logistic regression with stepwise backward selection analysis showed that advanced age, MVO, and impaired LVEF were independent risk factors for PapMI with MR. Patients in the PapMI with MR group had significantly more MACE compared with the PapMI and non-PapMI groups [PapMI with MR, 23 (85.2%) *vs.* PapMI, 21 (55.3%) *vs.* non-PapMI, 29 (20.1%)] at 1-year follow-up (P<0.001). However, there were no pronounced differences in mortality rates among the 3 groups (P=0.071).

Conclusions: The presence of PapMI with MR in patients with STEMI is associated with advanced age, MVO, and impaired LVEF, which can increase the rates of MACE.

Keywords: Cardiac magnetic resonance (CMR); ST-segment elevation myocardial infarction (STEMI); papillary muscles; mitral regurgitation (MR); prognosis

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Introduction

pPCI is the first treatment in patients with STEMI, despite advances in coronary reperfusion, papillary muscle infarction (PapMI) can result in dysfunction of the papillary muscles and subsequent ischemic functional mitral valve regurgitation (MR). MR occurs in 30–50% of cases after ST-segment elevation myocardial infarction (STEMI) and is independently associated with increased mortality, few reports assessed the Prognostic relevance and clinical features of patients with PapMI only (1-3). However, the precise clinical characteristics of PapMI with MR in patients with STEMI after primary percutaneous coronary intervention (pPCI) are currently under debate, and data on the prognostic significance of PapMI are not clear, partly because PapMI is difficult to verify or exclude by traditional imaging techniques such as echocardiography or myocardial perfusion imaging (SPECT). Late gadolinium-enhanced (LGE) cardiac magnetic resonance (CMR) imaging, typically using an inversion-recovery gradient echo sequence 10–30 min after intravenous injection of a gadolinium-based contrast agent (4-6), allows for the identification and accurate quantitative analysis of MI (7,8). Thus, our aims of this study were to determine the clinical features and prognosis of PapMI with MR in patients with STEMI detected by CMR. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jtd-20-3476).

Methods

Population

The population was composed of consecutive patients with first STEMI enrolled in a prospective study between June 2018 and February 2020 at Drum Tower Hospital affiliated to Medical School of Nanjing University and Xinxiang Central Hospital. We used the Sample size formula to calculate the Sample size required for the study before it stared. The definition of STEMI was based on the ESC/ACCF/AHA/WHF consensus document, and was established by the presence of typical chest pain lasting >30 minutes, sustained 1.0 mm ST-segment elevation in at least 2 contiguous leads on ECG, and cardiac enzyme elevation. According to the results of CMR and echocardiography, patients were divided into PapMI with MR, PapMI (PapMI without MR), and non-PapMI groups. All patients underwent emergency coronary angiography and coronary intervention. The exclusion criteria were as follows: aged >85 years, renal insufficiency, cardiac shock, patients with contraindications for CMR, cardiomyopathy, and mitral valve disease history. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent was taken from all the patients. The ethics committee of Drum Tower Hospital affiliated to Medical School of Nanjing University and Xinxiang Central Hospital approved the study protocol (No.2019-190-03). Bias control through multicenter study and reduce the rate of loss to follow-up. Study profile see *Figure 1*.

Intervention

Coronary angiography was performed by the radio or femoral approach. All patients underwent P-PCI and stenting according to standard techniques. Stent implantation was successfully completed in all patients.

CMR protocol and analysis

All imaging was performed on a 1.5 T Philips Achieva Cardiac MR scanner (Philips HealthCare, Best, NL, USA). Breath-hold LGE short-axis images were acquired ~15 minutes after injection of 0.2 mmol/kg Gd-DTPA (GE Pharmacy, Shanghai, China). Imaging parameters for the 2D LGE were: TR/TE, 6/3; FA, 25°; TI 260–350 ms; voxel, 1.6×1.9×8 mm^3; and shot duration 100–125 ms. CMR was performed 4.8±1.9 days after PCI. The CMR images were analyzed by a cardiac radiologist blinded to patient history and clinical outcome, using commercially available software (Extended MR WorkSpace 2.6.3.5, Philips Medical Systems, Best, The Netherlands). The MR exam included assessment of cardiac function, flow, anatomy, and viability. Left ventricular (LV) ejection fraction (EF), mitral regurgitation (MR) fraction, and LV dimensions as measured by cardiac MR were obtained. The typical PapMI of images of CMR see *Figure 2*.

Echocardiography

Based on the standard clinical practice in accordance with the American Society of Echocardiography recommendations (9) , transthoracic Doppler echocardiography was performed with a commercially available ultrasound machine (Vivid-7, General Electric, Horten, Norway). The severity of MR was scored as mild (regurgitant orifice area <0.2 cm^2), moderate (regurgitant

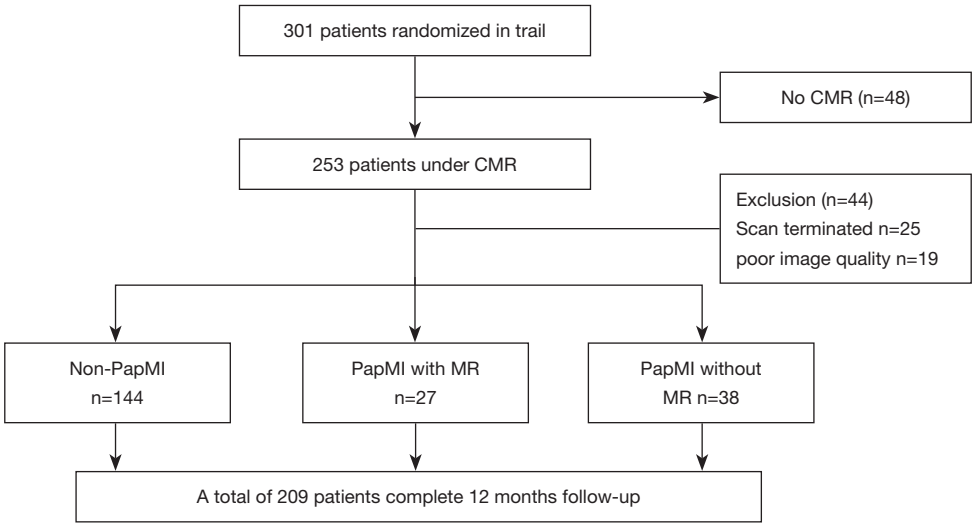

Figure 1 Study profile. CMR, cardiac MRI; PapMI, papillary muscle infarction MR, mitral regurgitation.

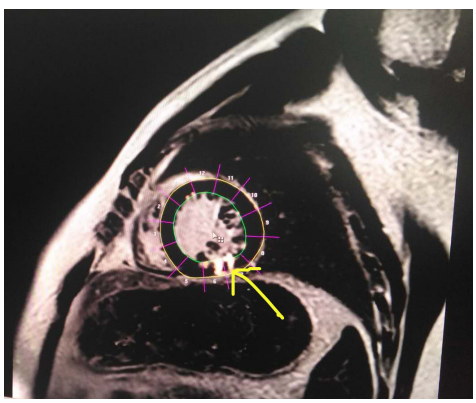

Figure 2 The typical PapMI of images of CMR, the yellow arrow show inferior of PapMI. CMR, cardiac MRI; PapMI, papillary muscle infarction MR, mitral regurgitation.

orifice area, 0.2 to 0.4 cm^2), or severe (regurgitant orifice area >0.4 cm^2). In this study, MR was defined as greater than moderate grade.

Cardiovascular events

The primary clinical endpoint was defined as a composite of cardiovascular death, reinfarction, in-stent restenosis (ISR), readmission, and heart failure within 12 months after infarction. A blinded independent clinical events committee adjudicated all potential cardiovascular events based on prospectively defined guidelines (10,11). All patients received follow-up in outpatient clinics, or by telephone and email. Follow-up was performed every 3 months.

Statistical analysis

Data were statistically evaluated using dedicated software (SPSS version 24.0 SPSS Inc., CA, USA). Comparisons of continuous variables were performed with 1-way ANOVA analysis. Categorical variables were compared with the Wilcoxon signed-rank test. The Chi-squared test was used to compare proportions. Binary logistic regression with stepwise backward selection was used to screen the independent variables, and odds ratio (OR) and confidence intervals (CI) were calculated. All statistical tests were 2-sided. $P<0.05$ indicated a statistically significant difference.

Results

Clinical characteristics of the study population

A total of 209 patients were enrolled in the current study. Clinical characteristics of the patients are presented in *Table 1*. A total of 27 patients with a median age of 66.8 years showed PapMI with MR after PCI (PapMI with MR group) and 38 patients with a median age of 61.2 years showed PapMI without MR after PCI (PapMI group), whereas 144 patients did not develop PapMI after PCI (non-PapMI group), with a median age of 57.0 years. Compared with the non-PapMI and PapMI group, the PapMI with MR group had more advanced age (P=0.001), higher troponin I

Table 1 Baseline characteristics of the study population

Variables	PapMI with MR (n=27)	PapMI (n=38)	Non-PapMI (n=144)	P
Age, years	66.8±7.9	61.2±8.1	57.0±10.6	0.001
Male, n (%)	16 (59.3)	26 (68.4)	97 (67.3)	0.689
DM, n (%)	19 (70.4)	18 (47.4)	54 (37.5)	0.006
Current smoker, n (%)	19 (70.4)	20 (52.6)	84 (58.3)	0.350
Hypertension, n (%)	15 (55.6)	18 (47.4)	81 (56.3)	0.616
Aspirin, n (%)	27 (100.0)	38 (100.0)	142 (98.6)	0.634
Clopidogrel, n (%)	1 (3.7)	4 (10.5)	6 (4.2)	0.274
Ticagrelor, n (%)	26 (96.3)	34 (89.5)	138 (95.8)	0.274
Statins, n (%)	26 (96.3)	34 (89.5)	127 (88.2)	0.453
ACEI/ARB, n (%)	11 (40.7)	15 (39.5)	47 (32.6)	0.583
β-blocker, n (%)	23 (85.2)	30 (78.9)	104 (72.2)	0.300
GPIIb/IIIa, n (%)	6 (22.2)	9 (23.7)	27 (18.8)	0.672
WBC (10^{-9}/L)	9.7±2.3	10.3±3.1	10.5±2.9	0.480
N (%)	69.6±16.0	71.2±14.4	72.5±14.9	0.665
HbA1c (%)	6.2±1.2	6.2±1.2	6.3±1.5	0.936
C-RP (mg/L)	8.8±8.3	9.6±8.6	11.7±11.7	0.345
CREA (μmol/L)	66.7±22.6	67.6±11.1	70.4±16.9	0.611
TG (μmol/L)	4.2±0.9	4.4±0.8	4.1±0.9	0.266
LDL (μmol/L)	2.4±0.9	2.5±0.7	2.6±0.9	0.537
HGB (g/L)	141.1±14.3	138.1±14.2	137.7±15.5	0.551
PLT (10^{-9}/L)	195.3±60.6	205.7±61.3	208.5±76.6	0.684
Troponin I (ng/mL)	9.9±1.9	8.2±2.6	6.7±3.8	<0.001
NT-BNP (pg/mL)	204.1±253.9	229.6±307.8	151.7±235.8	0.216
CK-MB (μ/L)	161.3±119.3	141.0±84.9	165.0±94.6	0.397
BMI (kg/m^2)	24.2 ±1.8	25.8 ±3.5	25.1 ±3.4	0.165
SO to B (h)	12.1±5.0	10.3±4.4	8.1±5.6	0.001
SYNTAX score	15.2±6.5	18.8±5.6	19.2±4.2	<0.001

Data is presented as number of patients. Age, WBC, N, HbA1c, C-RP, CREA, TG, LDL, HGB, PLT, troponin I, NT-BNP, CKMB, BMI, SO to B, and SYNTAX score at presentation are presented as mean ± SD. PapMI, papillary muscle infarction; MR, mitral regurgitation; DM, current smoker, n (%), hypertension, and medication are expressed in terms of frequency with percentage. DM, diabetes mellitus; ACEI, ACE, angiotensin-converting enzyme; AT-1, angiotensin II type 1 receptor; WBC, white blood cell; N, neutrophile granulocyte; HbA1c, glycated hemoglobin; C-RP, C reactive protein; CREA, creatinine; TG, triglyceride; LDL, low density lipoprotein; HGB hemoglobin; PLT, platelet; NT-BNP brain natriuretic peptide; CK-MB, creatine kinase-MB; BMI, body mass index; SO to B, symptom onset-to-balloon. MR, mitral regurgitation.

(P<0.001), higher SYNTAX score (P<0.001), more diabetics (P=0.006), and longer time to reperfusion [symptom onset-to-balloon (SO to B), P=0.001] at presentation. There were no differences in clinical parameters including gender, BMI, smoking status, hypertension, medication history, and other baseline characteristics among the 3 groups.

Table 2 Cardiovascular magnetic resonance imaging results

Variables	PapMI with MR (n=27)	PapMI (n=38)	non-PapMI (n=144)	P
Infarct size (%)	13.4±5.5	12.1±5.1	14.0±5.8	0.174
LVEF (%)	46.8±9.6	45.3±11.0	50.7±8.7	0.002
MVO, n (%)	16 (59.3)	21 (55.3)	47 (32.6)	0.004
LVSDV (mL)	78.1±23.3	89.0±28.4	91.0±29.5	0.103
LVEDV (mL)	124.9±15.2	128.1±16.7	124.5±23.5	0.662
LAD (cm)	3.6±0.5	3.5±0.4	3.5±0.4	0.185

Continuous data are presented as median and interquartile range. PapMI, papillary muscle infarction; LVEF, left ventricular ejection fraction; MVO, microvascular occlusion; LVSDV, left ventricular end-systolic volume; LVEDV, left ventricular end-diastolic volume; LAD, left atrium diameter.

Table 3 Predictors of PapMI with MR in binary logistic regression analysis

Variables	Odds ratio (CI)	P
Age (years)	1.10 (1.03–1.17)	0.003
MVO	4.37 (1.19–16.0)	0.026
LVEF (%)	0.91 (0.86–0.97)	0.004

PapMI, papillary muscle infarction; MR, mitral regurgitation; MVO, microvascular occlusion; LVEF, left ventricular ejection fraction; CI, confidence interval.

CMR characteristics of the study population

The CMR characteristics of the subjects are presented in *Table 2*. Compared with the non-PapMI and PapMI groups, the PapMI with MR group had more microvascular occlusions (MVO) (P=0.004) and impaired left ventricular ejection fraction (LVEF) (P=0.002). There were no differences in LV volume parameters, including infarct size, left ventricular end-systolic volume (LVSDV), left ventricular end-diastolic volume (LVEDV), and left atrium diameter (LAD) among the 3 groups.

Predictors of PapMI with MR

Binary logistic regression with stepwise backward selection analysis were implemented to evaluate the independent prognostic factors for the incidence of PapMI with MR. Significant predictors are shown in *Table 3*. The independent predictors of the presence of PapMI with MR were age [OR, 1.10 (CI, 1.03–1.17); P=0.003), presence of MVO [OR, 4.37 (CI, 1.19–16.0); P=0.026], and impaired LVEF [OR, 0.91 (CI, 0.86–0.97); P=0.004].

Clinical outcomes at 1-year follow-up

Clinical outcomes were assessed at the 1-year follow-up visit for all patients. At 1-year follow-up, there were no significant differences in death [non-PapMI, 3 (2.1%) *vs.* PapMI, 2 (5.3%) *vs.* PapMI with MR, 3 (11.1%); P=0.071] and ISR [non-PapMI, 3 (2.1%) *vs.* PapMI, 2 (5.3%) *vs.* PapMI with MR, 2 (7.4%); P=0.284] among the 3 groups (*Table 4*, *Figures 3*,*4*). There were significantly higher occurrences of nonfatal reinfarctions (P=0.011), readmission (P=0.003) and heart failure (P=0.018) in the PapMI with MR group (*Table 4*; *Figure 3*). Accordingly, major adverse cardiovascular events (MACE) at 1-year follow-up were significantly higher in the PapMI with MR group (P<0.001; *Table 4*, *Figure 5*).

Discussion

It is well known that PapMI is associated with MR following myocardial infarction (1,12-16). To the best of our knowledge, however, no studies have shown the real-world prognostic significance of PapMI with MR in

Table 4 Occurrence of the individual components of the combined clinical endpoint and MACE

Variables	Non-PapMI (n=144)	PapMI (n=38)	PapMI with MR (n=27)	P
Combined study endpoint, n (%),	29 (20.1)	21 (55.3)	23 (85.2)	<0.001
Death, n (%)	3 (2.1)	2 (5.3)	3 (11.1)	0.071
Reinfarction, n (%)	5 (3.5)	3 (7.9)	5 (18.5)	0.011
ISR, n (%)	3 (2.1)	2 (5.3)	2 (7.4)	0.284
Readmission, n (%)	8 (5.6)	7 (18.4)	7 (25.9)	0.003
Congestive heart failure, n (%)	10 (3.4)	7 (3.4)	6 (22.2)	0.018

MACE, major adverse cardiovascular event; PapMI, papillary muscle infarction; MR, mitral regurgitation; ISR, in-stent restenosis.

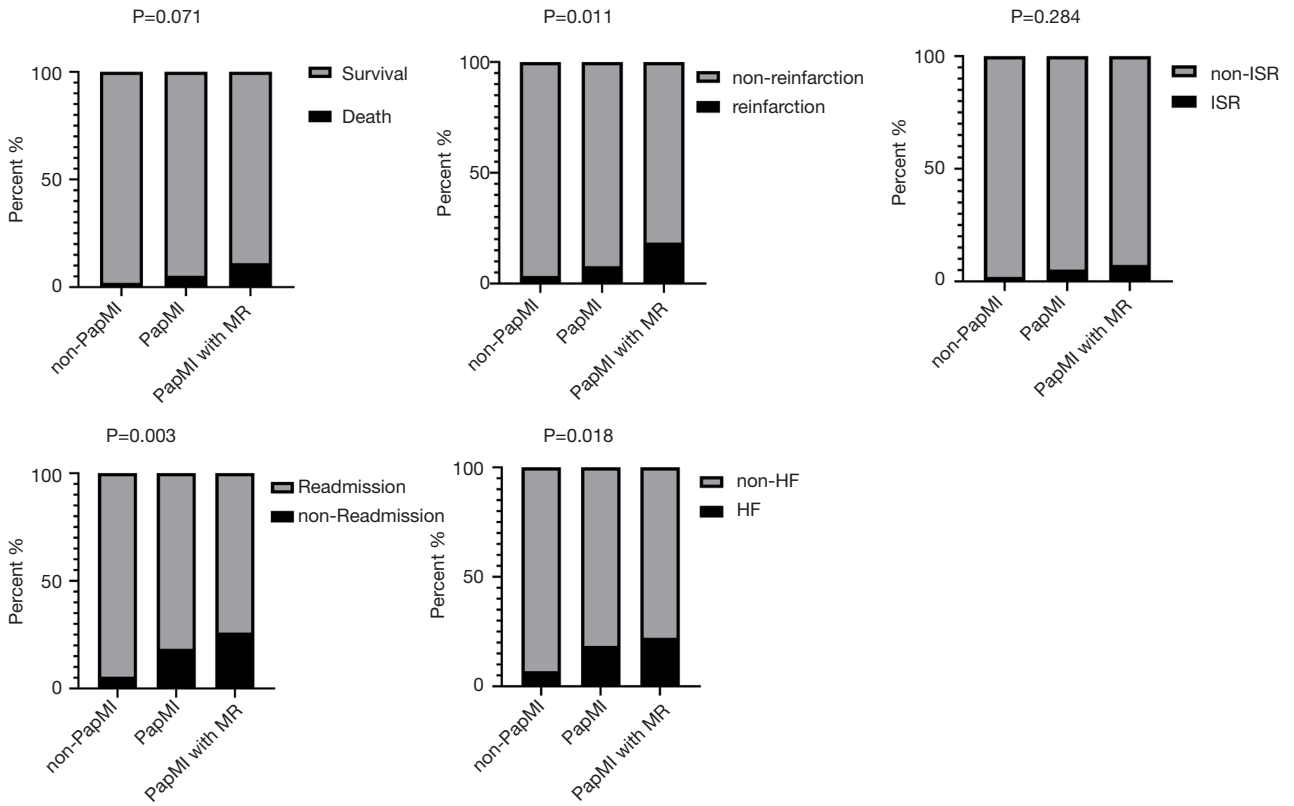

Figure 3 One sample *t*-test and Wilcoxon test analysis of the incidence of MACE 1 year after infarction. PapMI, papillary muscle infarction; MR, mitral regurgitation; MACE, major adverse cardiovascular events.

patients with STEMI diagnosed by CMR. In this study, we found that the incidence of PapMI with MR was 13%, indicating that the presence of PapMI with MR is not uncommon in the present day. Furthermore, the incidence of PapMI with MR was mainly related to advanced age, MVO detected by CMR, and impaired LV function. PapMI with MR had significantly more MACE compared with the PapMI and non-PapMI groups. However, mortality did not significantly increase at 1-year follow-up.

Compared to results published by Tanimoto *et al.* (1,12-16) reporting a prevalence of 40%, PapMI was observed more frequently in the present study with a prevalence of 45%. We detected 27 PapMI with MR cases among 209 STEMI patients (the incidence was 13%), and 65 PapMI patients (the incidence was 42%), suggesting that PapMI with MR is not so rare in STEMI and is common in PapMI. It's similar to the result of Chinitz *et al.* (17).

Advanced age is a traditional risk factor for STEMI. Our

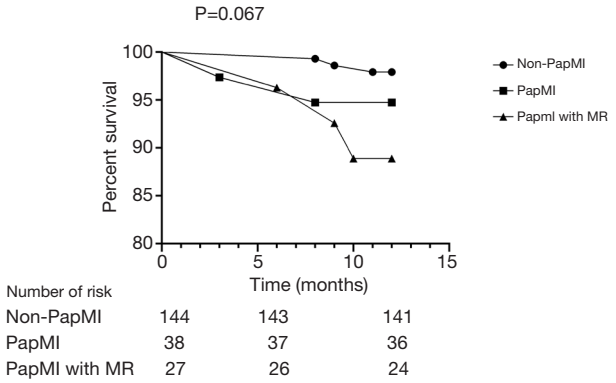

Figure 4 Cox regression analysis of mortality during 1-year follow-up. PapMI, papillary muscle infarction; MR, mitral regurgitation.

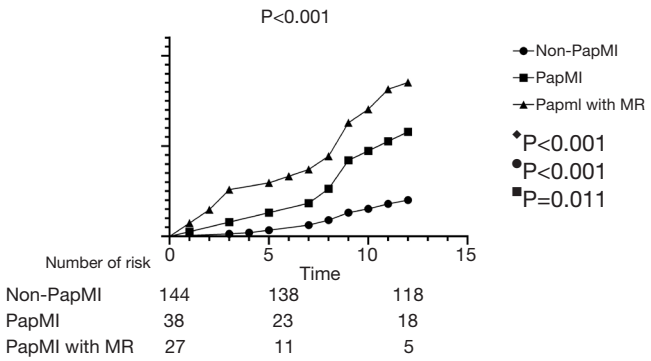

Figure 5 Cox regression analysis of the incidence of MACE defined by death, reinfarction, ISR, readmission, and new congestive heart failure during 1-year follow-up. PapMI, papillary muscle infarction; MR, mitral regurgitation; P◆, non-PapMI *vs.* PapMI; P●, non-PapMI *vs.* PapMI with MR; P■, non-PapMI *vs.* PapMI with MR. PapMI, papillary muscle infarction; MR, mitral regurgitation; MACE, major adverse cardiovascular events; ISR, in-stent restenosis.

study demonstrated that age [OR, 1.10 (CI, 1.03–1.17), P<0.001] was an independent predictor of PapMI with MR. This was also confirmed in a study by Bouma *et al.* (18).

MVO indicates a lack of adequate tissue perfusion within the infarcted myocardium, and is an independent risk factor for PapMI as visualized by CMR in previous studies. This conclusion is consistent with our study. PapMI was also related to obvious myocardial damage and MVO as detected by CMR. Others (19) have confirmed that PapMI was associated with severe reperfusion injury such as MVO and hemorrhage. However, our study is the first to use CMR to assess PapMI combined with MR including infarct extent and severe reperfusion injury such as MVO. Therefore, our results support previous findings by illustrating that MVO was an independent predictor for PapMI combined with MR [OR, 4.37 (CI, 1.19–16.0), P=0.028]. Grieve *et al.* (19). showed that impaired LV function was an independent risk factor for the presence of PapMI, and our study showed similar findings in the PapMI with MR group [OR, 0.91 (CI, 0.86–0.97), P=0.004].

Ischemic MR has been considered an independent risk factor of increased mortality in patients with PapMI (12,15,20-22). However, very few studies have reported on prognosis in PapMI with MR. Our study is the first to demonstrate that PapMI with MR has a poor prognosis. In our study, patients with PapMI with MR had significantly more MACE compared to the PapMI and non-PapMI groups [PapMI with MR, 23 (85.2%) *vs.* PapMI, 21 (55.3%) *vs.* non-PapMI, 29 (20.1%)] at 1-year follow-up (P<0.001, respectively). However, similar to previous results (23), there were no significant differences in mortality rates among the 3 groups (P=0.071).

In view of the relationship between PapMI and MR, we should pay attention to patients have suffered PapMI combined with MR, and beware patients with MR diagnosed by echocardiography caused by PapMI.

Conclusions

The incidence of PapMI with MR as determined by CMR imaging is not uncommon in STEMI patients after pPCI. Compared to the PapMI and non-PapMI groups, the PapMI with MR group had worse prognosis. Our data contributes to an improved understanding of the clinical characteristics of PapMI with MR, and may help aid in the prevention of MACE.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/jtd-20-3476

Data Sharing Statement: Available at http://dx.doi.org/10.21037/jtd-20-3476

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-20-3476). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent was taken from all the patients. The ethics committee of Drum Tower Hospital affiliated to Medical School of Nanjing University and Xinxiang Central Hospital approved the study protocol (No.2019-190-03).

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