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ORIGINAL RESEARCH

The Association Between Mitral Regurgitation and Long-Term Outcomes in Acute Myocardial Infarction Undergoing Percutaneous Coronary Intervention: A Retrospective Large Sample Cohort Study

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Background: The relationship between mitral regurgitation (MR) and long-term outcomes in Chinese patients with acute myocardial infarction (AMI) undergoing percutaneous coronary intervention (PCI) remains scarce. This study aimed to elucidate the connection between MR and long-term clinical outcomes following AMI treated with PCI.

Methods: In this retrospective study 6940 patients who were diagnosed with AMI were consecutively enrolled from General Hospital of Ningxia Medical University (2014–2019). The included AMI patients were divided into no MR, mild MR and moderate/serve MR according to MR occurred. All patients were clinically followed for 3-year to collect major adverse cardiac and cerebrovascular events (MACCEs), comprising all-cause death, nonfatal myocardial infarction (MI), rehospitalization for angina, rehospitalization for heart failure (RHF), and stroke. Cox regression models were employed to analyze the association between MR and 3-year clinical outcomes after adjusting for various confounding factors.

Results: Among the 6940 patients, 2871 (41.35%) exhibited no MR, 3681 (53.04%) had mild MR, and 388 (5.59%) had moderate/severe MR. The cumulative 3-year incidence of MACCEs was 19.21% overall, with rates of 15.26%, 20.37%, and 37.37% in the no MR, mild MR, and moderate/severe MR groups, respectively (log-rank $p < 0.001$). Kaplan–Meier survival curves of MR with all-cause death and RHF were also plotted (log-rank $p < 0.001$). After controlling confounding variables completely, we found that moderate/severe MR compared to none MR was found to be significantly associated with 3-year MACCEs [hazard ratio (HR) = 1.83; 95% confidence interval (CI) = 1.21–2.77; $p = 0.0042$], all-cause mortality (HR = 3.11; 95% CI = 1.75–5.50; $p=0.001$) and RHF (HR = 1.69; 95% CI = 1.09–2.62; p=0.019) through Cox proportional hazards regression models.

Conclusion: MR significantly predicted 3-year clinical outcomes in AMI patients undergoing PCI, highlighting the need for physicians to prioritize MR assessment in clinical practice.

Keywords: mitral regurgitation, acute myocardial infarction, percutaneous coronary intervention, major adverse cardiac and cerebrovascular events

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Introduction

Despite the marked progress in implementation of reperfusion strategies and medical management in the past decade, has significantly improved the survival rates of patients suffering from acute myocardial infarction (AMI),[1–3] however, AMI patients who receive percutaneous coronary intervention (PCI) still remain susceptible to long-term major adverse cardiac and cerebrovascular events (MACEEs), which can significantly affect their quality of life.[4] Valvular heart disease (VHD) may complicate clinical course of acute coronary syndromes (ACS).[5,6] Ischemic mitral regurgitation (MR) can occur following AMI due to reduced myocardial contraction at the site of papillary muscle insertion or papillary muscle displacement, resulting in leaflet tethering.

Up to 50% of patients with AMI exhibit any MR of varying degrees.[7,8] In the era before the widespread utilization of PCI and longer delays from symptom onset to treatment, MR was recognized as an adverse prognostic marker, correlating with increased mortality rates.[9–11] However, due to differences in population demographics, classification of MR severity, exclusion criteria for degenerative MR, and duration of follow-up, the impact of MR on AMI patients undergoing PCI has varied across studies. It is especially ambiguous whether MR was just an indicator of poor prognosis reflecting left ventricular dysfunction or if it exerts an independent adverse impact on clinical outcomes during long-term follow-up. The surgical treatment for ischemic MR in the presence of severe left ventricular dysfunction has often been hesitated despite a guideline recommendation. Nonetheless, there are currently fewer invasive transcatheter interventions for MR.[12] There is currently a shortage of Chinese studies exploring the connection between prognosis and MR in AMI patients who have undergone PCI. Utilizing data from a large sample Chinese retrospective cohort, we therefore aimed to study the prevalence of MR and examining how MR affects long-term outcomes in patients with AMI who have received PCI.

Methods

Study Design and Patients

This single-center, retrospective cohort study included 8485 consecutive patients diagnosed with acute myocardial infarction (AMI) at the General Hospital of Ningxia Medical University from January 2014 to December 2019. The study complied with the Declaration of Helsinki and was approved by the Ethics Committee of the General Hospital of Ningxia Medical University (approval number: 2020–774). This study was registered at the Chinese Clinical Trials Registry (registration number: ChiCTR2100043359). Because of the retrospective design of this study, the need for informed consent was waived by the institutional review board, and information related to patient identity was concealed. The exclusion criteria were as follows: patients who refused study participation (n = 90), unavailable transthoracic echocardiography (TTE) data including the grade of mitral regurgitation (MR) during hospitalization (n = 351), and missing follow-up information (n = 1104). Finally, 6940 patients (81.79%) provided verbal consent and completed the follow-up (Figure 1).

TTE data during the index hospitalization for AMI were obtained from the hospital charts or echocardiography database. For patients with multiple TTE evaluations during hospitalization, the data closest to the admission date was used. The severity of MR was assessed using an integrated approach, and MR was classified into four grades: none, mild, moderate, and severe, based on current guidelines.[13] Due to the small number of patients with severe MR, the grades "moderate" and "severe" were combined into a single category "moderate/severe". Additionally, we gathered data on other echocardiographic parameters, such as left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), and left ventricular end-systolic diameter (LVESD). Thus, 6940 patients were included in the final analysis and categorized into three groups based on MR grades.

Data Measurement and Definitions

Three experienced data inspectors collected information from medical records based on standardized definitions. After carefully examination of patients' electronic health records, we are starting to gather essential data included demographic information [age, gender, body mass index (BMI), admission diagnosis, cardiovascular risk [diabetes mellitus (DM), hypertension, prior cerebrovascular disease (CVD), prior peripheral vascular disease and prior coronary artery disease (CAD), current smoking and current drinking], data related to angiography and basic cardiovascular medication information [antiplatelet drugs, statins, beta-blockers, angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB)]. Systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), Killip grade, Door to balloon (D to B) time and Length of hospitalization on hospital

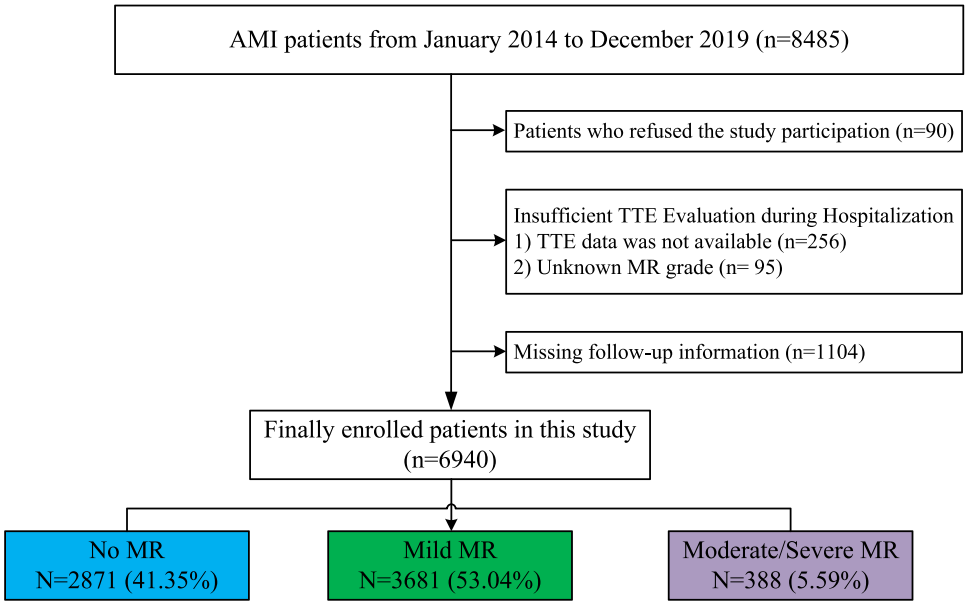

Figure 1 Flowchart illustrating the selection process of study participants.
Abbreviations: MR, mitral regurgitation; AMI, acute myocardial infarction; TTE, transthoracic echocardiogram.

admission were recorded. Blood samples were collected from the cubital vein after fasting for at least eight hours for testing high-sensitivity C-reactive protein (hs-CRP), peak pro-BNP, peak cardiac troponin I (cTNI), serum creatinine (Scr), uric acid (UA) and D-D dimer (D-D). cTNI levels was measured using chemiluminescent immunoassay (VITROS5600, Johnson & Johnson, USA), and hs-CRP, Scr, UA, and D-D levels were analyzed using ADVIA® Chemistry XPT system (SIEMENS, Germany) at the central laboratory of General Hospital of Ningxia Medical University.

AMI encompassed conditions such as ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI), with diagnoses made in accordance with respective guidelines.[14] The identification of diabetes mellitus[15] was based on either the self-reported use of antidiabetic medications or elevated blood glucose readings, characterized by casual blood glucose levels of 11.1mmol/L or higher, fasting blood glucose levels of 7.0 mmol/L or higher, or 2-hour postprandial levels exceeding 11.1mmol/L following a 75 g oral glucose tolerance test. Hypertension was identified through a consistent record of blood pressure readings of 140/90mmHg or above, or the ongoing use of antihypertensive medication.[16] According to coronary angiography results, the severity of CAD was evaluated by the Gensini Score,[17] and multivessel disease was defined as ≥50% diameter stenosis in at least 2 major coronary arteries. Smoking was defined as individuals who had engaged in smoking within the past ten years.

Follow-up and Endpoints

Following discharge, patients were required to attend follow-up evaluations at 1, 6, 12, 18, 24, 36 months, with additional annual appointments scheduled either via phone calls or in-person visits to the clinic. The major adverse cardiac and cerebrovascular events (MACCEs), assessed within the 3 years follow-up, were defined as all-cause death, nonfatal myocardial infarction (MI), rehospitalization for angina, rehospitalization for heart failure (RHF) and stroke. The study endpoint was evaluated based on the time taken for the occurrence of the first event. All-cause mortality referred to death regardless of the cause. Non-fatal MI was defined per the European Society of Cardiology (ESC) MI criteria.[18] Rehospitalization for angina and heart failure define as admission for treatment due to a recurrence of angina or heart failure. Nonfatal stroke was defined as disabling vascular brain injury caused by cerebral ischemia or hemorrhage. The stroke was defined as an acute neurological deficit that lasted over 24 hours and was confirmed by a neurologist.

Statistical Analysis

For continuous variables, mean ± standard deviation (SD) was used for statistical description if they met normal distribution; independent samples *t*-test was used for inter-group comparison. The median (25–75%) was used for description if the variables

did not meet normal distribution; and the rank sum test was used for inter-group comparison. For counting data, the number of cases (%) was used to describe it, the chi-square test was used for comparison between groups, and Fisher's exact probability was used when the chi-square test was not satisfied. Continuous data were compared using the Kruskal–Wallis's test or one-way analysis of variance, and categorical data were compared using the chi-squared test. A multivariable Cox proportional hazards regression models were used to calculate hazard ratios (HRs) between MR grade and MACCEs. We used three levels of adjustment: Model 1 was adjusted for age, sex, BMI; Model 2 was adjusted for age, sex, BMI, DM, hypertension, prior CVD, peripheral vascular disease, prior CAD, current smoking, current drinking, Killip classification; and Model 3 was adjusted for Age, Sex, BMI, DM, Hypertension, Prior CVD, Peripheral vascular disease, Prior CAD, current smoking, current drinking, Killip classification, LVEF, Pro-BNP, CTNI, Scr, Primary PCI, β-blocks, Gensini score, Radial access. All clinical events were analyzed by time to the first event for Kaplan–Meier analysis, and the differences were assessed with the Log rank test. All statistical analyses were performed with R (the R Foundation, Vienna, Austria) and EmpowerStats (X & Y Solutions, Boston, MA, USA). All tests were 2-sided, and a $p < 0.05$ was considered statistically significant.

Results

Participants' Characteristics

In 6940 analyzed patients, mild MR was identified in 3681 patients (53.04%), and moderate/severe MR in 388 patients (5.59%), whereas 2871 patients (41.35%) did not have MR (Figure 1).

In total patients, the mean age of the study population was 60.99 ± 11.84 years, and 5314 (76.57%) patients were male. In terms of general conditions, patients with greater severity of MR were older, more often women, STEMI patients and Killip II–IV patients and had lower BMI, SBP and DBP than those with no MR. As the severity of MR increased, HR became incrementally quicker, leading to prolonged D to B time and hospitalization periods. Patients with greater severity of MR also had more cardiovascular disease risks such as DM, Hypertension, Prior CVD, Peripheral vascular disease, Prior CAD and current smoking. Regarding the laboratory and TTE data, patients with higher grade of MR had higher hs-CRP, peak-cTNI, peak-Pro-BNP, SCR, UA, D-D, LVEED and LVESD, but lower LVEF level. Patients with greater severity of MR had lower prescription rates of guideline-directed medications including antiplatelet, statins and ACEI/ARB. Meanwhile, those with moderate/severe MR had lower primary PCI and radial approach than those with no MR. Also, the rate of beta-blockers use was not different between mild MR and moderate/severe MR groups. Patients with greater severity of MR more often had higher prevalence of LCX and RCA infarction artery, CTO, stent length and number of stents. But the mild MR group patients with higher Gensini score and Lesion vessel number than other groups (Table 1).

Table 1 Baseline Characteristics of Study Population (N = 6940)

MR Grade	Overall n = 6940	None n = 2871	Mild n = 3681	Moderate/serve n = 388	*P*-value
General conditions					
Age(years)	60.99 ± 11.84	58.08 ± 11.92	62.60 ± 11.34	67.28 ± 10.55	<0.001
Male, n (%)	5314 (76.57%)	2325 (80.98%)	2734 (74.27%)	255 (65.72%)	<0.001
BMI(Kg/m^2)	24.31 ± 4.48	24.73 ± 4.16	24.05 ± 4.74	23.70 ± 4.02	<0.001
HR (bpm)	79.94 ± 16.16	78.78 ± 15.00	80.22 ± 16.41	85.94 ± 20.15	<0.001
SBP (mmHg)	122.17 ± 22.18	123.54 ± 21.66	121.65 ± 22.33	116.86 ± 23.62	<0.001
DBP (mmHg)	75.92 ± 14.20	76.72 ± 14.12	75.69 ± 14.16	72.13 ± 14.58	<0.001
STEMI, n (%)	5074 (73.12%)	2047 (71.30%)	2778 (75.49%)	249 (64.18%)	<0.001
D-B time (mins)	70.62 ± 109.21	77.89 ± 129.29	64.79 ± 91.75	78.45 ± 106.23	<0.001
Length of hospitalization (days)	9.06 ± 4.47	8.62 ± 3.97	9.30 ± 4.61	9.98 ± 6.04	<0.001
Killip classification					<0.001
I	5305 (76.44%)	2429 (84.60%)	2694 (73.19%)	182 (46.91%)	
II	1029 (14.83%)	298 (10.38%)	638 (17.33%)	93 (23.97%)	
III	223 (3.21%)	37 (1.29%)	138 (3.75%)	48 (12.37%)	
IV (cardiogenic shock)	383 (5.52%)	107 (3.73%)	211 (5.73%)	65 (16.65%)	

(*Continued*)

Table 1 (Continued).

MR Grade	Overall n = 6940	None n = 2871	Mild n = 3681	Moderate/serve n = 388	*P*-value
Risk factor, n (%)					
DM	1663 (23.97%)	625 (21.78%)	912 (24.78%)	126 (32.47%)	<0.001
Hypertension	3688 (53.14%)	1416 (49.32%)	2032 (55.20%)	240 (61.86%)	<0.001
Prior CVD	773 (11.14%)	249 (8.67%)	451 (12.25%)	73 (18.81%)	<0.001
Peripheral vascular disease	295 (4.25%)	127 (4.42%)	133 (3.61%)	35 (9.02%)	<0.001
Prior CAD	1024 (14.76%)	343 (11.95%)	581 (15.78%)	100 (25.77%)	<0.001
Current smoking	4146 (59.74%)	1815 (63.22%)	2141 (58.16%)	190 (48.97%)	<0.001
Current drinking	1345 (19.38%)	623 (21.70%)	678 (18.42%)	44 (11.34%)	<0.001
Laboratory test					
hs-CRP (mg/L)	28.98 ± 44.93	23.05 ± 38.03	31.12 ± 47.57	43.29 ± 51.79	<0.001
Peak cTNI (ng/L)	16.59 ± 19.70	14.35 ± 17.62	18.38 ± 21.04	15.94 ± 19.27	<0.001
Peak Pro-BNP (ng/mL)	2127.99 ± 4597.70	1159.37 ± 3009.13	2310.83 ± 4575.55	7010.40 ± 8638.28	<0.001
SCR (mmol/L)	78.17 ± 48.48	74.53 ± 33.61	78.21 ± 51.57	103.57 ± 86.00	<0.001
UA (mmol/L)	340.43 ± 101.47	337.65 ± 95.61	338.00 ± 100.44	382.67 ± 136.31	<0.001
D-D (μg/mL)	0.77 ± 1.99	0.57 ± 1.37	0.83 ± 2.24	1.55 ± 2.70	<0.001
LVEDD (mm)	37.61 ± 7.03	35.58 ± 6.15	38.54 ± 6.78	43.81 ± 9.56	<0.001
LVESD (mm)	36.99 ± 5.01	35.58 ± 4.35	37.66 ± 4.97	41.05 ± 6.18	<0.001
LVEF (%)	52.77 ± 10.66	55.96 ± 10.04	51.10 ± 10.25	45.09 ± 11.39	<0.001
HBA1C	6.53 ± 1.58	6.49 ± 1.55	6.54 ± 1.60	6.67 ± 1.54	0.22
Medications, n (%)					
DAPT, n (%)	6816 (98.21%)	2834 (98.71%)	3607 (97.99%)	375 (96.65%)	0.005
Statins, n (%)	6857 (98.80%)	2843 (99.02%)	3636 (98.78%)	378 (97.42%)	0.024
Beta-blockers, n (%)	5154 (74.27%)	2169 (75.55%)	2695 (73.21%)	290 (74.74%)	0.098
ACEI/ARB, n (%)	3206 (46.20%)	1417 (49.36%)	1637 (44.47%)	152 (39.18%)	<0.001
Anticoagulation, n (%)	5628 (81.10%)	2372 (82.62%)	2983 (81.04%)	273 (70.36%)	<0.001
Thrombolytic therapy, n (%)	425 (6.12%)	172 (5.99%)	237 (6.44%)	16 (4.12%)	0.181
Angiographic characteristics					
Radial approach, n (%)	6008 (86.57%)	2585 (90.04%)	3177 (86.31%)	246 (63.40%)	<0.001
Primary PCI, n (%)					<0.001
0	3248 (46.80%)	1365 (47.54%)	1631 (44.31%)	252 (64.95%)	
1	3692 (53.20%)	1506 (52.46%)	2050 (55.69%)	136 (35.05%)	
Gensini score	64.78 ± 48.54	61.28 ± 45.94	67.79 ± 48.83	62.04 ± 61.13	<0.001
Left-domain, n (%)	394 (6.22%)	156 (5.78%)	218 (6.49%)	20 (7.27%)	0.405
Infarction related artery					
LM	52 (1.13%)	18 (0.96%)	29 (1.14%)	5 (3.03%)	0.054
LAD	2876 (53.09%)	1269 (55.58%)	1521 (51.86%)	86 (42.79%)	<0.001
LCX	904 (18.79%)	387 (19.59%)	465 (17.55%)	52 (28.11%)	<0.001
RCA	1934 (37.66%)	775 (36.71%)	1059 (37.51%)	100 (49.50%)	0.002
TIMI before PCI					<0.001
0	2999 (50.32%)	1191 (46.76%)	1661 (52.45%)	147 (59.76%)	
1	300 (5.03%)	127 (4.99%)	160 (5.05%)	13 (5.28%)	
2	594 (9.97%)	283 (11.11%)	290 (9.16%)	21 (8.54%)	
3	2067 (34.68%)	946 (37.14%)	1056 (33.34%)	65 (26.42%)	

(*Continued*)

Table 1 (Continued).

MR Grade	Overall n = 6940	None n = 2871	Mild n = 3681	Moderate/serve n = 388	*P*-value
Thrombus aspiration, n (%)	452 (7.31%)	199 (7.59%)	232 (7.03%)	21 (7.95%)	0.655
TIMI after PCI					<0.001
0	107 (1.85%)	41 (1.67%)	60 (1.95%)	6 (2.51%)	
1	43 (0.74%)	11 (0.45%)	29 (0.94%)	3 (1.26%)	
2	81 (1.40%)	28 (1.14%)	41 (1.33%)	12 (5.02%)	
3	5541 (96.00%)	2377 (96.74%)	2946 (95.77%)	218 (91.21%)	
Lesion vessel number	1.98 ± 1.06	1.96 ± 1.00	2.03 ± 1.05	1.66 ± 1.34	<0.001
CTO, n (%)	344 (5.60%)	129 (4.97%)	202 (6.15%)	13 (4.94%)	0.132
Stent length, mm	44.53 ± 27.87	43.04 ± 26.96	45.06 ± 28.15	53.33 ± 31.63	<0.001
Number of stents in IRA	1.73 ± 0.97	1.70 ± 0.95	1.75 ± 0.98	1.99 ± 1.10	<0.001

Notes: Data are expressed as the means ± SD, median (interquartile ranges), or numbers (percentages).
Abbreviations: TG, triglyceride; HDL-C, high density lipoprotein cholesterol; BMI, body mass index; SBP, systolic blood pressure; CVD, Cerebrovascular Disease; DBP, diastolic blood pressure, CAD, coronary artery disease; STEMI, ST-segment elevation myocardial infarction; DAPT, Dual-anti platelet-therapy; LVEF, left ventricular ejection fraction; LM, left main coronary artery; LAD, left anterior descending. LCX, left circumflex coronary artery; RCA, right coronary artery; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor inhibitor; TIMI: Thrombolysis in Myocardial Infarction; DAPT, Dual-anti platelet-therapy.

Association Between MR Grade and 3-year Clinical Outcomes

Complete 3-year clinical follow-up rate was obtained in 81.79% of patients. The cumulative 3-year incidence of MACCEs was 19.21% in overall patients,15.26% in none MR, 20.37% in mild MR, and 37.37% in moderate/severe MR (log-rank $p < 0.001$) (Table 2 and Figure 2). Table 3 shows the three Cox regression models used to evaluate the correlation between MR grades and 3-year MACCEs, all-cause mortality and RHF. For MACCEs, the higher non-adjusted risk of both mild MR and moderate/severe MR relative to no MR was significant for MACCEs (HR: 1.38, 95% CI: 1.22–1.55, $p < 0.0001$, and HR:2.94, 95% CI: 2.44–3.55, $p < 0.0001$, respectively). Confounding factors (Age, Sex, BMI, DM, Hypertension, Prior CVD, Peripheral vascular disease, Prior CAD, current smoking, current drinking, Killip classification, LVEF, Pro-BNP, CTNI, Scr, Primary PCI, β-blocks, Gensini score, radial approach) were completely adjusted in Model 3, the increased risk of MACCEs from None MR to moderate/severe MR was statistically significant (p for trend < 0.001). Both mild MR and moderate/severe MR relative to no MR for MACCEs (HR: 1.04, 95% CI: 0.81–1.33, $p = 0.7485$, and HR 1.83, 95% CI: 1.21–2.77, $p = 0.0042$, respectively) (Table 3).

The cumulative 3-year incidence of all-cause mortality was 8.52% in overall patients, 5.22% in none MR, 9.26% in mild MR, and 25.77% in moderate/severe MR (log-rank $p < 0.001$) (Table 2 and Figure 3). For all-cause mortality, the higher non-adjusted risk of both mild MR and moderate/severe MR relative to no MR was significant for MACCEs (HR: 1.80, 95% CI: 1.49–2.19, $p < 0.0001$, and HR:5.62, 95% CI: 4.36–7.24, $p < 0.0001$, respectively). Confounding factors were completely

Table 2 3-year Clinical Outcome in Three Groups

3-year Clinical Outcome, n (%)					
Outcome	**Overall n = 6940**	**None n = 2871**	**Mild n = 3681**	**Moderate/serve N = 388**	***P*-value**
MACCEs	1333 (19.21%)	438 (15.26%)	750 (20.37%)	145 (37.37%)	<0.001
All-cause mortality	591 (8.52%)	150 (5.22%)	341 (9.26%)	100 (25.77%)	<0.001
Nonfatal myocardial infarction	198 (2.85%)	80 (2.79%)	106 (2.88%)	12 (3.09%)	0.934
Rehospitalization for angina	501 (7.22%)	194 (6.76%)	273 (7.42%)	34 (8.76%)	0.285
RHF	951 (13.70%)	228 (7.94%)	580 (15.76%)	143 (36.86%)	<0.001
Stroke	124 (1.79%)	37 (1.29%)	69 (1.87%)	18 (4.64%)	<0.001

Notes: Data are expressed as numbers (percentages).
Abbreviations: MACCEs, major adverse cardiac and cerebrovascular events; RHF, rehospitalization for heart failure.

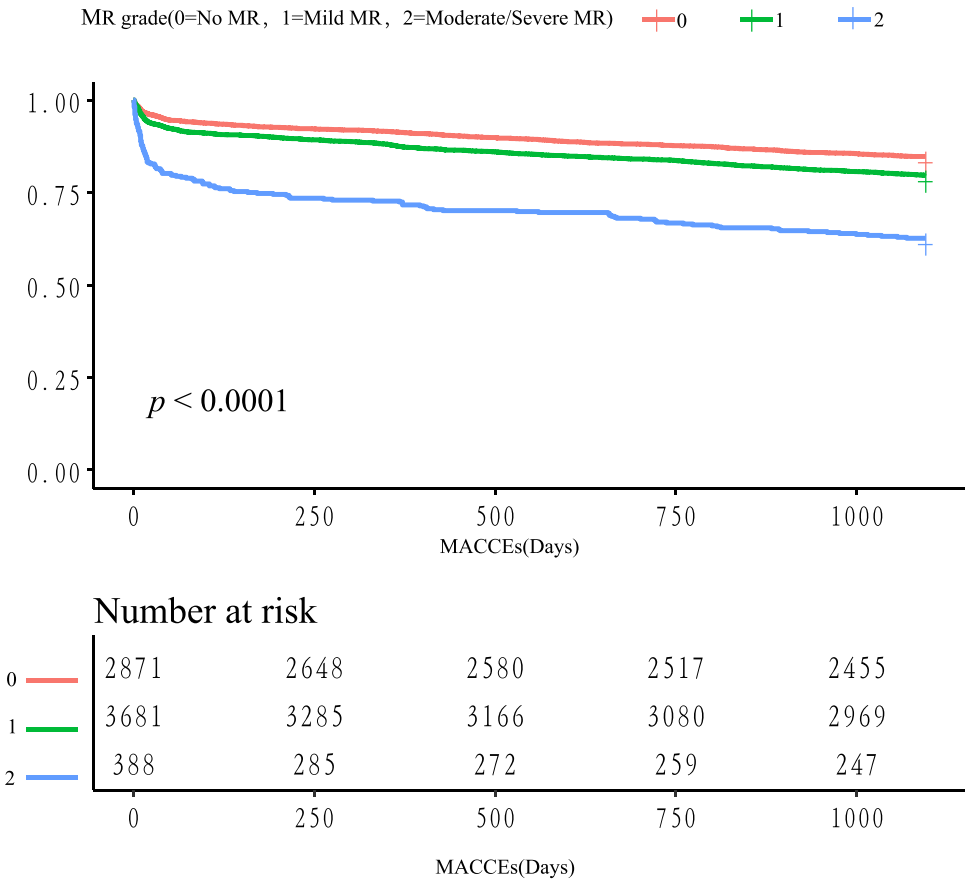

Figure 2 Kaplan-Meier event curves for MACCEs.
Abbreviations: MR, mitral regurgitation; MACCs, major adverse cardiac and cerebrovascular events.

adjusted in Model 3, the increased risk of all-cause mortality from none MR to moderate/severe MR was statistically significant (p for trend = 0.001). Both mild MR and moderate/severe MR relative to no MR for all-cause mortality (HR: 1.13, 95% CI: 0.87–1.39, $p = 0.5694$, and HR 3.11, 95% CI: 1.75–5.50, $p < 0.0001$, respectively) (Table 3).

The cumulative 3-year incidence of RHF was 13.70% in overall patients, 7.94% in none MR, 15.76% in mild MR, and 36.86% in moderate/severe MR (log-rank $p < 0.001$) (Table 2 and Figure 4). For RHF, the higher non-adjusted risk of both mild MR and moderate/severe MR relative to no MR was significant for RH (HR: 2.07, 95% CI: 1.78–2.41, $p <$

Table 3 Multivariate Cox Regression Analysis for 3-year Clinical Outcomes

End points	Non-adjusted		Model 1		Model 2		Model 3	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
MACCEs								
None	Reference		Reference		Reference		Reference	
Mild	1.38 (1.22, 1.55)	<0.0001	1.17 (1.04, 1.32)	0.0086	1.06 (0.94, 1.19)	0.4221	1.04 (0.81,1.33)	0.7485
Moderate/severe	2.94 (2.44, 3.55)	<0.0001	2.13 (1.76, 2.58)	<0.0001	1.49 (1.23,1.82)	<0.0001	1.83 (1.21,2.77)	0.0042
P for trend	<0.001		<0.001		<0.001		0.033	

(*Continued*)

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Table 3 (Continued).

End points	Non-adjusted		Model 1		Model 2		Model 3	
	HR (95% CI)	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
All-cause mortality								
None	Reference		Reference		Reference		Reference	
Mild	1.80 (1.49, 2.19)	<0.0001	1.32 (1.09, 1.61)	0.0046	1.11 (0.91, 1.35)	0.2976	1.13 (0.87,1.39)	0.5694
Moderate/severe	5.62 (4.36, 7.24)	<0.0001	3.01 (2.33, 3.90)	<0.0001	1.77 (1.36, 2.31)	<0.0001	3.11 (1.75,5.50)	0.0001
P for trend	<0.001		<0.001		<0.001		0.001	
RHF								
None	Reference		Reference		Reference		Reference	
None	2.07 (1.78,2.41)	<0.0001	1.71 (1.46, 1.99)	<0.0001	1.39 (1.19,1.63)	<0.0001	1.33 (1.00,1.75)	0.0497
Mild	5.65 (4.58, 6.96)	<0.0001	3.80 (3.07, 4.71)	<0.0001	2.02 (1.62,2.51)	<0.0001	1.69 (1.09,2.62)	0.019
Moderate/severe	<0.001		<0.001		<0.001		<0.001	

Notes: Non-adjusted model: No covariates were adjusted. Model 1 adjust for: Age, Sex, BMI. Model 2 adjust for: Age, Sex, BMI, STEMI, DM, Hypertension, Prior CVD, Peripheral vascular disease, Prior CAD, current smoking, current drinking, Killip classification. Model 3 adjust for: Age, Sex, BMI, DM, Hypertension, Prior CVD, Peripheral vascular disease, Prior CAD, current smoking, current drinking, Killip classification, LVEF, Pro-BNP, CTNI, Scr, Primary PCI, β-blocks, Gensini score, Radial approach.
Abbreviations: MR, mitral regurgitation; MACCEs: major adverse cardiac and cerebrovascular events, RHF: rehospitalization for heart failure.

0.0001, and HR:5.65, 95% CI: 4.58–6.96, $p < 0.0001$, respectively). Confounding factors were completely adjusted in Model 3, the increased risk of all-cause mortality from none MR to moderate/severe MR was statistically significant (p for trend < 0.001). Both mild MR and moderate/severe MR relative to no MR for all-cause mortality (HR: 1.33, 95% CI: 1.00–1.75, $p = 0.0497$, and HR 1.69, 95% CI: 1.09–2.62, $p = 0.019$, respectively) (Table 3).

The cumulative 3-year incidence of stroke was 1.79% in overall patients, 1.29% in none MR, 1.87% in mild MR, and 4.64% in moderate/severe MR ($p < 0.001$) (Table 2). But the nonfatal myocardial infarction and rehospitalization for angina were no statistical significance between the three groups.

Discussion

In this Chinese study, patients with AMI who were successfully treated with primary PCI but had MR were found to be significantly associated with a poor 3-year clinical outcome. The previous study,[7,19,20] MR although functional or ischemic, was a common finding after AMI, with an incidence as high as 57% according to echocardiographic studies. In our study, the incidence of MR was 58.63%: mild MR, 53.04%; moderate/severe MR, 5.59%. As a long-term outcome, ischemic MR following AMI was associated with an increased risk for MACCEs, all-cause mortality and rehospitalization for heart failure, with a magnitude that was correlated with the severity of MR.[19–22] Studies on MR support that the higher the severity of MR, the higher the incidence of in-hospital cardiac death.[8] As observed in our study, a mild degree of MR was also significantly related to higher incidence of outcomes (Table 3, Figures 2–4). Therefore, because even a mild degree of MR can be a risk factor for higher mortality among AMI patients, early detection, and close follow-up of patients with MR, if present after AMI, may be crucial, because its presence plays a crucial role in post-MI risk stratification.

Data regarding the prevalence of MR in patients suffering from ischemic heart disease are controversial because the method of quantification and the timing of MR evaluation are different across literature. In recent studies reporting the

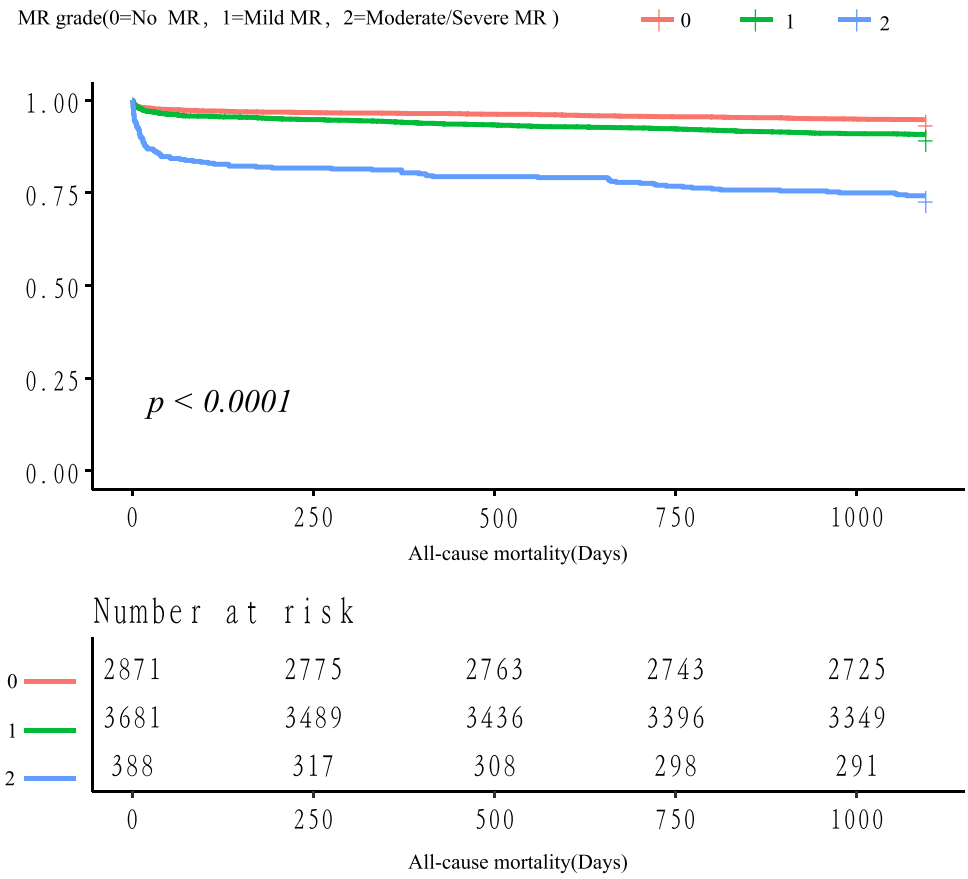

Figure 3 Kaplan-Meier event curves for All-cause mortality.
Abbreviation: MR, mitral regurgitation.

incidence of MR in patients with AMI by 3 grades (none, mild, and moderate/severe), mild MR and moderate/severe MR accounted for 11% to 44% and 3% to 15%, respectively.[20,22,23] Bursi et al1[6] reported ischemic mitral regurgitation in 50% of patients within 30 days following AMI, while other study evidenced a prevalence of up to 57% during the index hospitalization.[19] In our study, any degree of MR was detected in 58% of patients, which is consistent with the previous studies, although there were differences in study designs, including patient selection (inclusion of NSTEMI and previous MI patients), timing or methodology of TTE assessment (time elapsed post-admission for TTE and whether quantitative assessment was conducted), and treatment strategy (whether all enrolled patients underwent PCI). Compared to those without MR, greater severity of MR in our study was more likely to be old, more often female, had more co-morbidities, and condition more often worsened, similar to previous reports.[8,9,24] In addition, patients with severe MR exhibited echocardiographic features included a reduced LVEF, as well as enlarged LVEDD and LVESD, consistent with findings from previous studies.[25,26]

In recent times, the heightened adoption of drug-eluting stents and the aggressive use of medications such as ACE inhibitors, thienopyridines, β-blockers, and statins have resulted in a reduction in the complications and mortality rates associated with AMI. Tomasz Tokarek et al[27] observed a potential association between the use of radial access (RA) during PCI and decreased mortality in patients with ST-segment elevation myocardial infarction (STEMI) complicated by cardiogenic shock (CS). In our cohort, most percutaneous coronary interventions (PCI) were performed via the radial approach (RA), which is consistent with current guideline recommendations and the prevailing practice in our center during the study period. Specifically, approximately 86.57% of procedures utilized the radial access route, with the remainder performed via the femoral approach. It has been shown that MR is an independent risk factor of adverse outcome in a post-PCI population.[28] However, the impact of MR in AMI patients who have received PCI has shown

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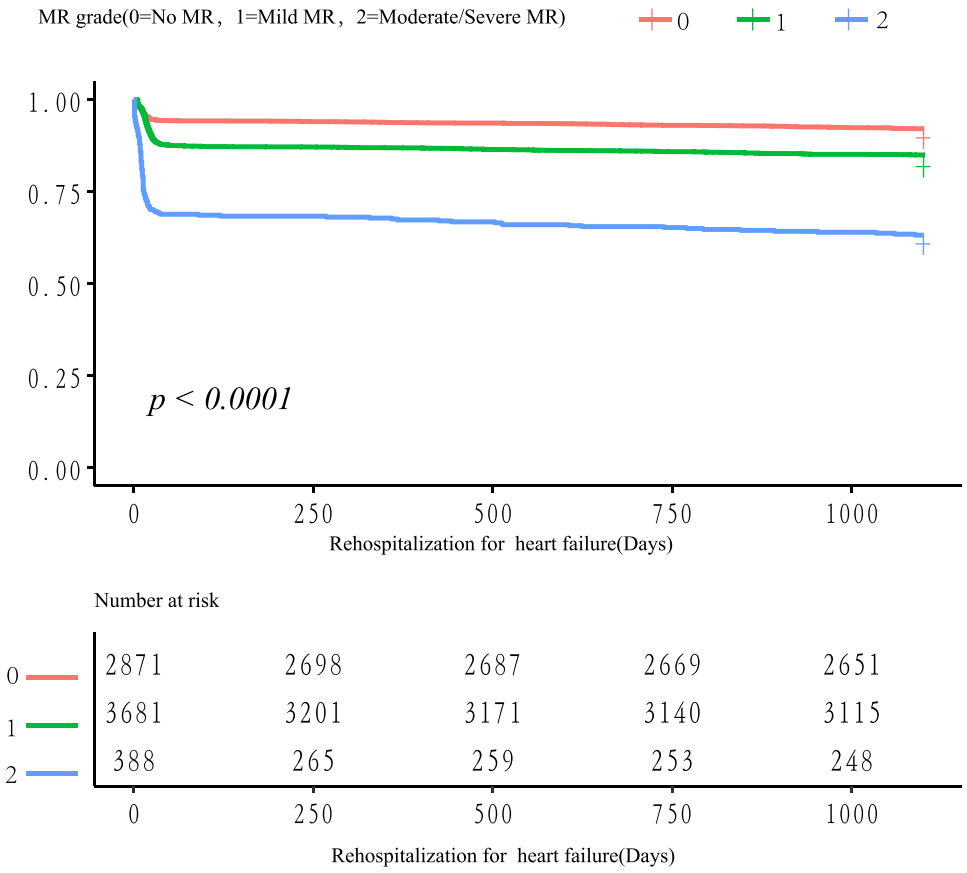

Figure 4 Kaplan-Meier event curves for RHF.
Abbreviations: MR, mitral regurgitation; RHF, rehospitalization for heart failure.

variability across studies due to differences in patient population, especially the evidence from China remains scare. Few studies have been conducted in which all the included AMI patients underwent PCI and the sample size was sufficient to examine the impact of MR on mortality through multivariable analysis. In a study by Sharma et al,[29] it was found that the presence of MR was linked to elevated mortality rates, even after adjusting for confounding factors in a cohort of 1000 consecutive patients admitted with AMI and treated with PCI. López-Pérez et al[30] reported that moderate/severe MR was independently associated with increased mortality in a study with a relatively small sample size of 1036 participants. Kim TH et al[22] reported that MR after AMI in a 1894 participants successfully treated with primary PCI was associated with poor long-term outcomes whether the patients had STEMI or NSTEMI. In addition, a larger cohort study (n = 4005) conducted by Mentias et al[25] revealed a notable increase in mortality rates associated with both mild MR and moderate/severe MR. However, it was a single-center study and a patient inclusion period of up to 20 years, the study's findings may not fully capture the advancements in medical and reperfusion therapies in more recent times. In our study had a larger sample of AMI patients (n = 6940) than these 4 studies, which allowed intensive adjustment by many clinically relevant factors affecting mortality, such as DM, previous stroke, Prior CAD, and medication at discharge, radial approach, cardiac function. We also included patients with NSTEMI into the study population and all the patients received PCI. Similar to previous reports,[21,31] this study adds to the literature by demonstrating that moderate/severe MR serves as a crucial independent predictor for 3-year MACCEs, all-cause mortality, and rehospitalization for HF following adjustment for multiple factors.

The relationship between MR and CVD outcomes may provide several potential explanations. Firstly, the analysis indicates that individuals with severe MR tended to be older, more co-morbidities, reduced LVEF, increased LVEDD, and a higher prevalence of female gender. Thus, MR could serve as an indicator of significant myocardial impairment or

a condition linked to a particular high-risk population.[32] On the other hand, the presence of MR may be directly correlated with ventricular remodeling caused by chronic volume overload, resulting in progressive myocardial function deterioration and the emergence of adverse events. Thus, the connection between moderate MR and a poorer outcome lends credence to this proposition. Furthermore, the left ventricular enlargement exacerbates ischemic MR, which could be called "MR begets MR".[21] Furthermore, those patients who develop at least moderate MR after AMI should be monitored closely and they may require specific treatments for MR, but there are currently no specific treatments for ischemic MR. Medical treatments such as angiotensin-converting enzyme inhibitors or β-blockers are widely used in the ischemic heart disease to prevent remodeling process; nevertheless, their effectiveness as a dedicated treatment for mitral regurgitation remains constrained. In our current investigation, the utilization of renin-angiotensin-aldosterone system inhibitors decreased as MR severity increased, partly due to patients with greater severity of MR had lower blood pressure and worse renal function. Nevertheless, it is imperative to maximize the administration of renin-angiotensin-aldosterone system inhibitors to mitigate heart failure risk. The debate surrounding the surgical intervention for secondary MR persists due to inconclusive results, primarily stemming from the lack of evident survival benefits and the notable recurrence of significant regurgitation within one year after surgery, even with the utilization of contemporary annuloplasty techniques.[33,34] Innovative approaches, such as cardiac resynchronization therapy leading to decreased mitral regurgitation through reverse left ventricular remodeling[35] or percutaneous edge-to-edge mitral valve repair may impact the prognosis in this pathology.[36] Hence, the most effective treatment for this high-risk patient group remains a subject of debate and necessitating further studies for clarification.

Our research has several limitations that should be acknowledged. In our study, the disparities in baseline characteristics and angiographic findings between patients with MR and those without MR were presented because this study was a nonrandomized, retrospective registry data analysis. Due to the potential influence of unmeasured variables, certain clinical factors may be confounded, necessitating a cautious interpretation of specific study results. To minimize the influence of these uneven risk factors, rigorous adjustments using a multivariate Cox hazard regression analysis were performed. Secondly, baseline echocardiographic data prior to the index PCI were not accessible in this study. Only echocardiograms from the index PCI were accessible, lacking previous baseline study data. Consequently, a clear differentiation between preexisting MR and newly developed ischemic MR could not be established. Third, because this study was not intended to be an echocardiographic study, it is important to note that morphological alterations of the mitral valve and structural changes in perivalvular structures and the myocardium (including leaflet tethering, chordal dysfunction, annular dilation, papillary muscle displacement, chamber deformation, and ventricular dilation) may contribute to adverse clinical outcomes independent of the presence of itself.[37,38] In the future, a well-defined standardized methods that distinguish between complicated dysfunctional MR may be advantageous for a more precise assessment of the effect of ischemic MR on clinical prognosis.

In summary, the data presented strongly indicate a notable association between MR and the clinical outcomes of AMI patients, emphasizing its prognostic significance for MACE and all-cause mortality. Noteworthy strengths of this Chinese study include its extensive cohort size and a prolonged 3-year follow-up period. Consequently, it is suggested that MR may serve as an efficacious and straightforward indicator for risk stratification for AMI patients.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are not publicly available due to the ongoing nature of this study but are available from the corresponding author on reasonable request.

Ethics Statement

The study complied with the Declaration of Helsinki and was approved by the Ethics Committee of the General Hospital of Ningxia Medical University (approval number 2020-774). As this was a retrospective study, and the requirement for informed consent was therefore waived.

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This paper has been uploaded to ResearchSquare as a preprint: (https://www.researchsquare.com/article/rs-4731069/v1).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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