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Optimal timing of invasive intervention for high-risk non-ST-segment-elevation myocardial infarction patients

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ABSTRACT

OBJECTIVE To compare the immediate, early, and delayed percutaneous coronary intervention (PCI) strategies in non-ST-segment-elevation myocardial infarction (NSTEMI) patients with high-risk.

METHODS Medical records of patients treated at the Daping Hospital, Third Military Medical University, Chongqing, China between 2011 and 2021 were retrospectively reviewed. Only patients with complete available information were included. All patients assigned into three groups based on the timing of PCI including immediate (< 2 h), early (2–24 h) and delayed (≥ 24 h) intervention. Multivariable Cox hazards regression and simpler nonlinear models were performed.

RESULTS A total of 657 patients were included in the study. The median follow-up length was 3.29 (interquartile range: 1.45–4.85) years. Early PCI strategy improved the major adverse cardiac event (MACE) outcome compared to the immediate or delayed PCI strategy. Early PCI, diabetes mellitus, and left main or/and left anterior descending or/and left circumflex stenosis or/and right coronary artery ≥ 99% were predictors for MACE outcome. The optimal timing range for PCI to reduce MACE risk is 3–14 h post-admission. For high-risk NSTEMI patients, early PCI reduced primary clinical outcomes compared to immediate or delayed PCI, and the optimal timing range was 3–14 h post-admission. Delayed PCI was superior for NSTEMI with chronic kidney injury.

CONCLUSIONS Delayed invasive strategy was helpful to reduce the incidence of MACE for high-risk NSTEMI with chronic kidney injury. An immediate PCI strategy might increase the rate of MACE.

Non-ST-segment-elevation myocardial infarction (NSTEMI) represents a life-threatening manifestation with considerable risk of morbidity and mortality worldwide.[1] Along with the generation of high-sensitive cardiac necrotic biomarkers, patients previously diagnosed with unstable angina were considered as NSTEMI in fact. The 2020 European Society of Cardiology guidelines state that for patients with NSTEMI who do not have persistent ST-segment elevation, it is suggested to perform coronary angiography and percutaneous coronary intervention (PCI) within 24 h after arrival. For the very high-risk NSTEMI (complicated with hemodynamic instability such as cardiogenic shock, life-threatening ventricular arrhythmia, and overt congestive heart failure), PCI is recommended within 2 h post-admission.[2]

However, except for the very high-risk NSTEMI, the optimal timing of PCI within 24 h for ordinary NSTEMI (high-risk) is still being debated. Most of the previous clinical studies targeted on non-ST-segment-elevation acute coronary syndrome (NSTE-ACS) which includes both unstable angina and NSTEMI. A meta-analysis of NSTE-ACS found that there was not enough evidence to support either an early (≤ 20 h) or late (20.5–86 h) invasive strategy in the NSTE-ACS population.[3] Several randomized trials indicated that a reduction of mortality, new myocardial infarction or refractory angina was found in patients undergoing earlier PCI, compared with selected intervention.[4] Furthermore, a meta-analysis of randomized trials demonstrated that an early invasive

strategy did not reduce mortality when compared with a delayed invasive strategy in patients with NSTE-ACS. However, implementing an early intrusive technique could potentially reduce the mortality rate among individuals at high risk.[5] A recent study focused on patients with "high-risk" NSTEMI who had a GRACE (Global Registry of Acute Coronary Events) score more than 140. The study examined three different techniques for performing PCI: extremely early (< 2 h), early (2–24 h), and delayed (≥ 24 h). It determined that PCI within the initial 12 h of admission was linked to a lower risk of ischemic outcomes at 180 days (about 6 months) for these "high-risk" NSTEMI patients.[6]

The exact definition of early, late, or delayed PCI varies across different studies, making it difficult to draw firm conclusions. Nonetheless, several clinical trials have examined different time periods within 24 h. For instance, the RIDDLE-NSTEMI trial found that early angiography within a median time of 1.4 h was linked to reduced mortality or recurring myocardial infarction at both 30 days (about 4 and a half weeks) and 1 year when compared with a delayed strategy with a median time of 61 h (about 2 and a half days).[7] Some recent meta-analysis also found similar points.[8,9] Nevertheless, the outcomes of individual studies assessing the optimal timing of invasive strategies in patients with diverse baseline risk profiles are inconclusive.

Consequently, the ideal timing for performing PCI in patients with NSTEMI remains unknown, despite the utilization of high-sensitive cardiac necrotic biomarkers. This retrospective study sought to assess the clinical outcomes of patients with NSTEMI who underwent PCI at different time intervals, with the goal of identifying the most favorable timing for the procedure.

METHODS

Study Population

This study was a retrospective analysis conducted at Daping Hospital, Third Military Medical University, Chongqing, China involving 675 inpatients diagnosed with acute NSTEMI between 2011 and 2021. Acute NSTEMI diagnosed according to 2015 European Society of Cardiology guideline for NSTEMI[10]: the detection of an increase and/or decrease of a cardiac biomarker, preferably high-sensitivity cardiac troponin T or I, with at least one value above the 99th percentile of the upper reference limit and at least one of the following: (1) symptoms of myocardial ischemia; (2) new ischemic electrocardiogram (ECG) changes (persistent or transient ST-segment depression, T-wave inversion, flat T waves or pseudo-normalization of T wave); (3) development of pathological Q waves on ECG; and (4) imaging evidence of loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology. Exclusion criteria were included: (1) age < 18 years and > 90 years; and (2) very high-risk patients (hemodynamic instability, cardiogenic shock, life-threatening ventricular arrhythmias). Based on the PCI timing after hospitalization, all patients were divided into three groups: immediate PCI group (< 2 h after admission, n = 249), early PCI group (2–24 h after admission, n = 210) and delayed PCI group (≥ 24 h after admission, n = 216). The study was performed according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Daping Hospital (No.2024266), Third Military Medical University, Chongqing, China.

The length of follow-up, enrolment period, the time needed from admission to angiography in each group, angiographic characteristics, patient demographics, risk factors for coronary artery disease, cardiac diseases history, coronary angiography result, medical therapy on admission were recorded. Diseased vessels were defined as ≥ 50% coronary artery stenosis. According to the current guidelines and previous reported, the GRACE risk score and Gensini score were calculated.[11,12]

Clinical Outcomes

The trial measured several clinical outcomes, including death from any cause (including cardiovascular and non-cardiovascular death), the need for unplanned revascularization, the occurrence of new myocardial infarction (heart attack), the development of new heart failure, the occurrence of stroke, and rehospitalization for unstable angina. Major adverse cardiac events (MACE) were defined as all-cause death, new myocardial infarction, repeat intervention. All patients were followed up until reaching one of the endpoint events, or until March 8, 2022. A telephone survey was conducted after permission obtained from participants or their legally authorized representatives. The rate of loss to follow-up after 11 years was 7.8%.

Statistical Analysis

Statistical analyses performed using SPSS 19.0 (SPSS

Inc., IBM, Chicago, IL, USA). Baseline clinical characteristics and medications at discharge were compared across the three groups. All continuous data are presented as medians (interquartile range, IQR) (IQR: 25th, 75th percentiles) and compared with Wilcoxon rank sum test. Categorical variables are summarized as counts (percentages) and compared using the Pearson's chi-squared test. Time to event was defined as the time from admission to the endpoint. Kaplan-Meier cumulative incidence rates were compared using the log-rank test for primary outcomes based on timing of PCI. Hazard ratio (HR) for the MACE events were performed using multivariable Cox hazards regression model analyses. The 1-β value for MACE events in this study was calculated to be 0.963. All patients were divided into male and female subgroup, age ≤ 65 years and age > 65 years subgroup, body mass index (BMI) ≤ 30 kg/m^2 and BMI > 30 kg/m^2 subgroup, respectively. MACE based on the timing of intervention for the subgroups were also assessed by comparison of Kaplan-Meier analysis. Simpler nonlinear models were fitted for MACE outcomes to quantify associations. A two-sided *P*-value < 0.05 was considered statistically significant.

RESULTS

Study Population

The flow chart for this study is depicted (supplemental material, Figure 1S). The final analysis included 716 patients and 43 patients were lost to follow-up.

Baseline characteristics of study population are shown in Table 1. The median age of the three groups were 67 years, 65 years, and 67 years, respectively. And the proportion of male in the three groups were 76.7%, 70.0%, and 76.4%, respectively. Established risk factors for NSTEMI (smoking, drinking, diabetes mellitus, hypertension, hyperlipoidemia, and stroke, cardiac biomarkers and NT-proBNP elevated, ischemic ECG changes) were well-matched among the three groups. The number of diseased vessels, Killip class, Gensini score, the use of evidence-based standard therapies: aspirin, anticoagulant agents, angiotensin converting-enzyme inhibitors, beta-receptor inhibitors and statins were similar among the three different treatment strategy groups (all $P > 0.05$). GRACE risk score and heart rate were slightly lower in immediate PCI group (both $P < 0.05$). The proportion of 1 stent was significantly higher, and the proportion of more than 3 stents was significantly lower in immediate PCI group ($P = 0.022$).

Clinical Outcomes

The median duration of follow-up for all patients was 3.29 years (IQR: 1.45–4.85 years). The median follow-up durations for the immediate PCI group, early PCI group, and delayed PCI group were 3.30 years (IQR: 1.60–4.78 years), 3.31 years (IQR: 1.82–4.70 years), and 3.23 years (IQR: 1.14–5.20 years), respectively. During a follow-up period up to 11 years, the endpoint rate of all-cause death (9.2% *vs.* 4.3% *vs.* 10.2%), unplanned revascularization (20.1% *vs.* 9.5% *vs.* 17.1%), new heart failure (2.4% *vs.* 1.4% *vs.* 2.3%) were significantly lower in early PCI group and the rate of stroke (10.4% *vs.* 4.8% *vs.* 4.6%) was significantly lower in delayed PCI group compared with immediate PCI group. There was no significant difference among the three groups in cardiovascular death (7.2% *vs.* 4.3% *vs.* 10.2%, $P = 0.052$), rehospitalization for unstable angina (18.5% *vs.* 17.1% *vs.* 15.7%, $P = 0.738$), and new myocardial infarction (1.6% *vs.* 1.9% *vs.* 3.2%, $P = 0.458$) (supplemental material, Table 1S).

The Kaplan–Meier curves for the prevalence of MACE of the study groups are reported in Figure 1. Early PCI treatment improved the MACE outcome compared to the immediate and delayed PCI treatment strategy (both $P < 0.05$). Multivariate analysis found that early PCI treatment was a protective factor compared to immediate PCI treatment and a strong predictor for MACE (HR = 0.452, 95% CI: 0.286–0.716, $P = 0.01$). Furthermore, diabetes mellitus (HR = 1.424, 95% CI: 1.012–2.003, $P = 0.042$), and left main or/and left anterior descending or/and left circumflex stenosis or/and right coronary artery ≥ 99% (HR = 1.733, 95% CI: 1.234–2.434, $P = 0.002$) both were predictors for MACE outcome (Figure 2).

Nonlinear spline models were employed to demonstrate the estimated connections between the delay to PCI and the rate of MACE in patients with NSTEMI. Our estimation indicates that the risk of MACE is lowest at the time of PCI within a 6-hour period. For high-risk patients with NSTEMI, the ideal timing for invasive intervention may be 3–14 h after admission, as shown in Figure 3. The survival curve of subgroups MACE shows that early PCI treatment was beneficial to reduce MACE in male, middle-aged, elderly subgroup, obese and non-obese patients (all $P < 0.05$). In female subgroup, early invasive treatment also tends to lower MACE (Figure 4). In NSTEMI without chronic kidney injury subgroup, early PCI

Table 1 Baseline characteristics of study population.

Variables	Immediate PCI group (*n* = 249)	Early PCI group (*n* = 210)	Delayed PCI group (*n* = 216)	*P*-value
Demographics				
Age, yrs	67 (58–74)	65 (55–71)	67 (60–73)	0.110
Male	191 (76.7%)	147 (70.0%)	165 (76.4%)	0.194
Body mass index, kg/m^2	24.2 (22.2–26.7)	23.6 (21.5–26.0)	24.4 (22.5–26.7)	0.194
Medical history				
Smoking	155 (62.2%)	113 (53.8%)	127 (58.8%)	0.187
Drinking	83 (33.3%)	67 (31.9%)	68 (31.5%)	0.904
Diabetes mellitus	107 (43.0%)	95 (45.2%)	104 (48.1%)	0.535
Hypertension	157 (63.1%)	128 (61.0%)	117 (54.2%)	0.133
Hyperlipoidemia	140 (56.2%)	113 (53.8%)	117 (54.2%)	0.851
Stroke	36 (14.5%)	33 (15.7%)	33 (15.3%)	0.929
Heart failure	6 (2.4%)	6 (2.9%)	8 (3.7%)	0.710
Prior history of PCI	28 (11.2%)	31 (14.8%)	31 (14.4%)	0.471
Chronic renal insufficiency	20 (8.0%)	16 (7.6%)	24 (11.1%)	0.375
Baseline risk variables				
Elevated cardiac biomarkers	98 (41.5%)	68 (34.3%)	72 (35.8%)	0.275
Elevated NT-proBNP	129 (79.1%)	117 (81.3%)	145 (81.0%)	0.873
Ischemic electrocardiogram changes	120 (48.2%)	93 (44.3%)	94 (43.5%)	0.550
GRACE risk score	139 (111–159)	144 (116–171)	145 (120–171)	0.039
Inspection indicators				
Systolic blood pressure, mmHg	132 (120–144)	136 (120–148)	1231 (119–144)	0.077
Diastolic blood pressure, mmHg	75 (69–84)	78 (69–89)	74 (66–80)	0.068
Heart rate, beats/min	72 (66–81)	78 (67–86)	76 (68–85)	0.003
Left ventricular ejection fraction, %	66 (60–71)	67 (60–73)	64 (58–71)	0.018
Killip class				0.240
1	162 (65.1%)	124 (59.0%)	113 (52.3%)	
2	72 (28.9%)	73 (34.8%)	87 (40.3%)	
3	13 (5.2%)	11 (5.2%)	14 (6.5%)	
4	2 (0.8%)	2 (1.0%)	2 (0.9%)	
Coronary angiography				
Number of diseased vessels				0.931
≤ 1	105 (42.2%)	87 (41.4%)	88 (40.7%)	
2–3	113 (45.4%)	101 (48.1%)	100 (46.3%)	
> 3	31 (12.4%)	22 (10.5%)	28 (13.0%)	
Culprit vessel				
Left main > 50%	8 (3.2%)	12 (5.7%)	13 (5.9%)	0.247
Left anterior descending > 50%	194 (77.3%)	169 (79.3%)	171 (78.8%)	0.395
Circumflex > 50%	153 (61.0%)	141 (68.1%)	147 (67.4%)	0.367
Right coronary artery > 50%	157 (64.1%)	127 (63.2%)	144 (67.3%)	0.410
Number of stents				0.022
1	125 (50.2%)	83 (39.5%)	86 (39.8%)	
2	67 (26.9%)	60 (28.6%)	53 (24.5%)	
≥ 3	57 (22.9%)	67 (31.9%)	77 (35.6%)	
Gensini score	54 (37–84)	56 (35–88)	51 (30–84)	0.594

Continued

Variables	Immediate PCI group (n = 249)	Early PCI group (n = 210)	Delayed PCI group (n = 216)	P-value
Medications at discharge				
Aspirin	220 (88.7%)	193 (91.9%)	183 (84.7%)	0.070
Anticoagulant agents	225 (90.4%)	190 (90.5%)	197 (91.2%)	0.946
Angiotensin-converting enzyme inhibitor	106 (42.6%)	101 (48.1%)	79 (36.6%)	0.055
Beta-receptor inhibitor	145 (58.2%)	124 (59.0%)	127 (58.8%)	0.983
Statin	230 (92.4%)	199 (94.8%)	201 (93.1%)	0.581

Data are presented as median (interquartile range) or n (%). PCI: percutaneous coronary intervention.

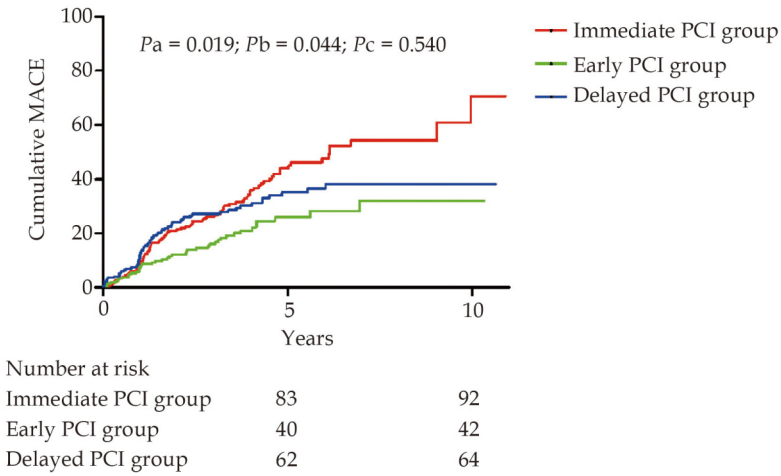

Figure 1 The Kaplan–Meier curves for the prevalence of MACE and stroke among immediate PCI group, early PCI group and delayed PCI group. *P*a refers to immediate PCI group compared with early PCI group; *P*b refers to immediate PCI group compared with delayed PCI group; and *P*c refers to early PCI group compared with delayed PCI group. MACE: major adverse cardiac event; PCI: percutaneous coronary intervention.

treatment can reduce the incidence of MACE more, but delayed PCI was an optimal treatment option in NSTE-MI with chronic kidney injury subgroup (supplemental material, Figure 2S).

DISCUSSION

The routine invasive technique is advantageous in patients with acute coronary syndrome when compared to the selective invasive strategy. However, the ideal timing for the invasive intervention has not been definitively determined.[10] Early invasive approach may reduce the incidence of ischemic events while patients are waiting for a selected procedure.[13] Alternatively, delaying the procedure for several days with prolonged antithrombotic pretreatment may be more conducive to plaque stabilization and avoid procedure-related complications.[14] Several randomized trials have investigated the issue of optimal timing for an invasive strategy in NSTE-ACS patients.[15–17] A prospective, randomized controlled trial has shown that without pre-treatment, invasive performed within 2 h was associated with a significant reduction in ischemic events compared to 12–72 h in patients with intermediate and high-risk NSTE-ACS.[15]

This cohort study of high-risk NSTEMI patients who underwent PCI based on more detailed timing of intervention (< 2 h *vs.* 2–24 h *vs.* ≥ 24 h) showed that 68% of patients underwent PCI within the guideline recommended 24-hour window and 32% of patients underwent PCI outside 24 h. The principal findings of present study are that among high-risk NSTEMI patients, an immediate PCI strategy was not superior to an early or a delayed PCI strategy in reducing MACE in the 11 follow-up years. On the contrary, an immediate PCI strategy was associated with a higher rate of MACE compared to the other two groups. The multivariate Cox model analysis showed that immediate PCI was likelihood with a worse MACE outcome compared to early PCI. Early PCI may be a protective factor for MACE.

Some recent trials demonstrate a similar phenomenon

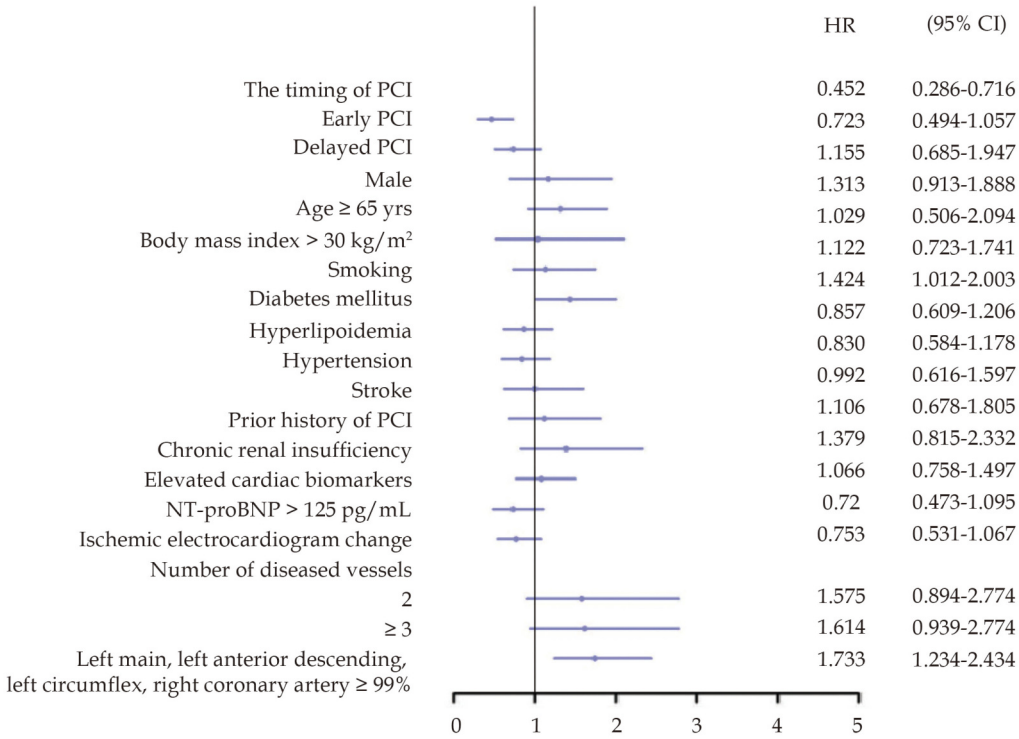

Figure 2 Using multivariable Cox hazards regression model analyses the hazard ratio for the MACE outcome. MACE: major adverse cardiac event; PCI: percutaneous coronary intervention.

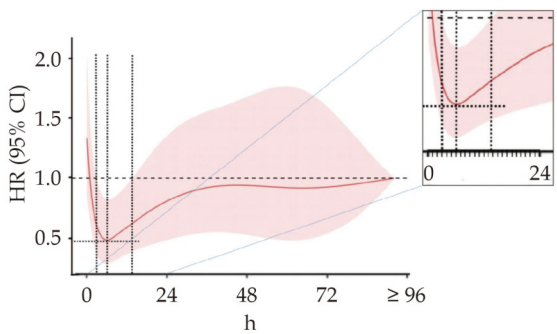

Figure 3 Restrictive cubic spline to fit the nonlinear relationship between the timing of PCI and the incidence of MACE to find the optimal range to reduce the incidences of MACE. MACE: major adverse cardiac event; PCI: percutaneous coronary intervention.

to our findings in that there is no advantage to an immediate approach over an early invasive or selective invasive approach. Two meta-analyses of randomized controlled trials comparing early versus selected invasive strategies for NSTE-ACS patients indicated that an early invasive approach did not significantly reduce mortality, myocardial infarction, or revascularization rate when compared with a selected or delayed strategy.[5,18] In the TIMACS (Timing of Intervention in Acute Coronary Syndromes) trial, early coronary angiography (14 h) did not demonstrate superiority over late coronary angiography (50 h) in preventing death, myocardial infarction, or stroke.[11] However, the TIMACS study solely examined the effectiveness of an early versus a later invasive strategy, and early intervention was found to be advantageous for high-risk patients experiencing NSTE-ACS. As such, no conclusion can be drawn regarding the benefit of an immediate STEMI-like approach. Another randomized trial complemented this issue, in which patients with NSTEMI were randomized to an immediate (< 2 h after randomization), an early (10–48 h after randomization), or a selective invasive approach, and no advantage of immediate catheterization (1.1 h) over early catheterization (18.6 h) or selective catheterization (67.2 h) have shown in preventing death, myocardial infarction, refractory ischemia or rehospitalization during the 6-month follow-up period.[19] The TAO (Treatment of Acute coronary syndrome with Otamixaban) randomized trial also showed a parallel conclusion that in patients with high-risk NSTEMI (GRACE score > 140), undergoing coronary angiography within the initial 12 h (as opposed to 12–24 h or 24 h after admission) was associated with lower risk of ischemic outcomes at 180 days (about 6 months) without increase in bleeding risk.[20]

Additionally, we conducted a subgroup analysis to in-

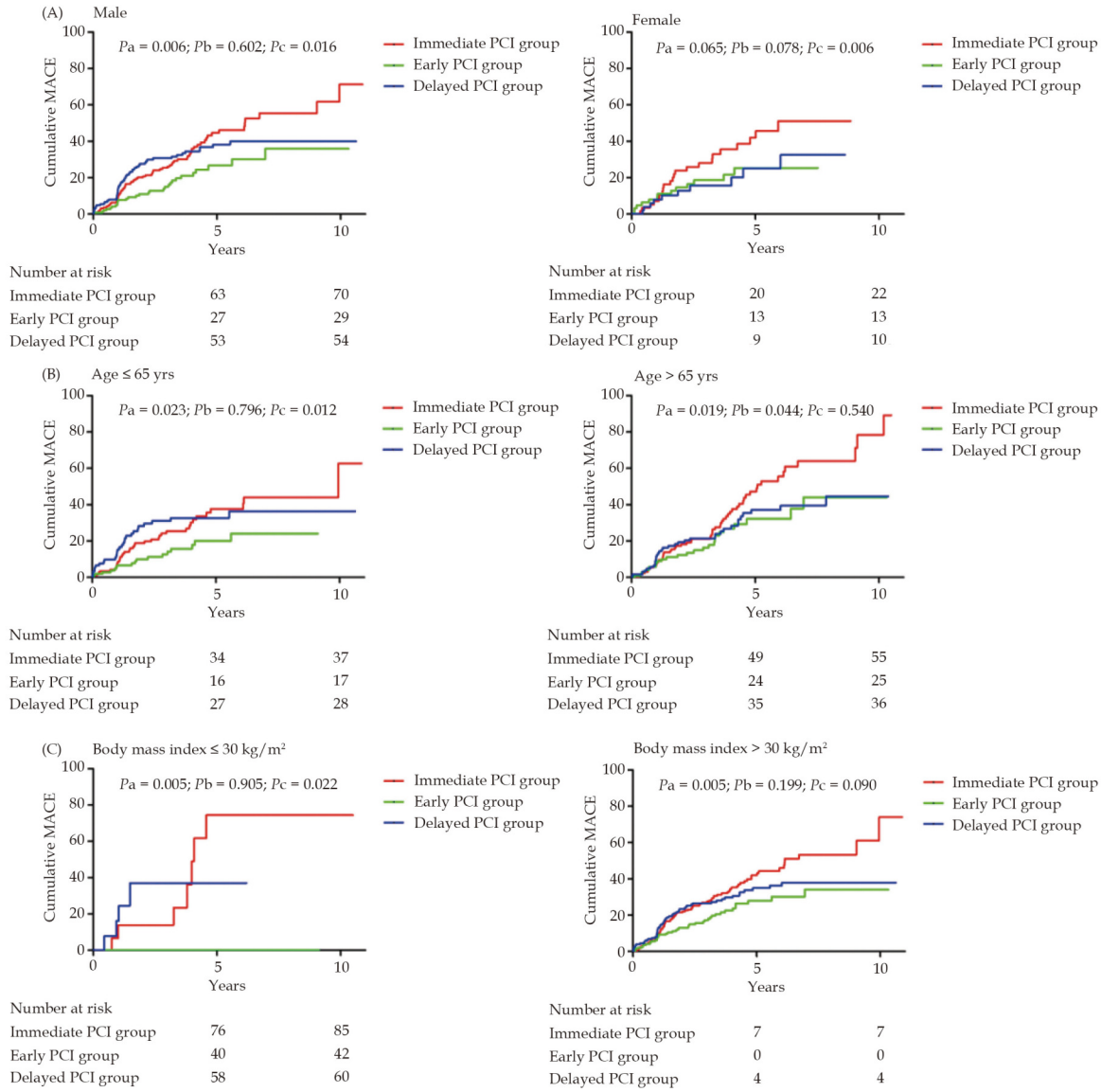

Figure 4 The Kaplan–Meier curves for the prevalence of MACE among immediate PCI group, early PCI group and delayed PCI group in male and female (A), middle-aged and elderly (B), and obese and non-obese subgroups (C). *P*a refers to immediate PCI group compared with early PCI group; *P*b refers to immediate PCI group compared with delayed PCI group; and *P*c refers to early PCI group compared with delayed PCI group. MACE: major adverse cardiac event; PCI: percutaneous coronary intervention.

vestigate the correlation between early PCI and the occurrence of MACE. Among several subcategories defined by gender, age, and BMI, the initial invasive method showed worse prognostic outcomes for MACE compared to early PCI. While the statistical significance of the difference was not observed in the female subgroup, the favorable trend remained obvious. Strikingly, our analysis on the subgroups revealed that early PCI was the most effective treatment for NSTEMI patients without chronic kidney injury. For NSTEMI patients with chronic kidney injury, a delayed invasive strategy was the preferred approach to minimize MACE. This could be attributed to the fact that delaying the invasive strategy resulted in better management of kidney function, thereby reducing risks such as contrast-associated kidney injury.[21,22]

Previous research has examined the effect of varying PCI timing on prognosis by categorizing participants into different treatment time groups. The research implemented a restrictive cubic spline method to model the nonlinear connection between PCI timing and the occurrence of MACE and identify the optimal range for redu-

cing MACE incidence. The MACE risk was at its lowest point 6 h after PCI intervention, and the recommended timing for high-risk NSTEMI patients undergoing PCI intervention falls within the range of 3–14 h.

LIMITATIONS

This study had several limitations. Firstly, it was a retrospective and observational study, which may contain some bias on patient selection. Secondly, the sample size was small and collected from a single center, which limits the statistical power of the study, but this can be improved by increasing the number of patients and the results should be verified in prospective cohort study in the future. Last but not least, we presented here a contemporary condition of real world, the timing of PCI was also affected by factors including patient preference, financial circumstances, and health insurance coverage, etc.

CONCLUSIONS

In high-risk NSTEMI patients, implementing an early PCI strategy is beneficial, and an invasive timing of 3–14 h after admission may be beneficial to reduce adverse prognostic events. Additionally, a delayed invasive strategy has shown efficacy in decreasing the incidence of MACE in high-risk NSTEMI patients with chronic kidney injury. However, an immediate PCI strategy may lead to increased MACE rates.

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