

# Predictive value of cardiopulmonary fitness parameters in the prognosis of patients with acute coronary syndrome after percutaneous coronary intervention

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## Abstract

**Objectives:** We aimed to determine the predictive value of cardiopulmonary exercise testing (CPX) in the prognosis of patients with acute coronary syndrome (ACS) treated with percutaneous coronary intervention (PCI).

**Methods:** We conducted a retrospective study including patients who underwent CPX within 1 year of PCI between September 2012 and October 2017. Patients were followed-up until the occurrence of a major adverse cardiac event (MACE) or administrative censoring (September 2019). A Cox regression model was used to identify significant predictors of a MACE. Model performance was evaluated in terms of discrimination (C-statistic) and calibration (calibration-in-the-large).

**Results:** In total, 184 patients were included and followed-up for a median 51 months (interquartile range: 36–67 months) and 32 events occurred. Multivariable analysis revealed that body mass index and Gensini score were significant predictors of a MACE. Four CPX-related variables

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were found to be predictive of a MACE: premature CPX termination, peak oxygen uptake, heart rate reserve, and ventilatory equivalent for carbon dioxide slope. The final prediction model had a C-statistic of 0.92 and calibration-in-the-large 0.58%.

**Conclusion:** CPX-related parameters may have high predictive value for poor outcomes in patients with ACS who undergo PCI, indicating a need for appropriate treatment and timely management.

### Keywords

Acute coronary syndrome, percutaneous coronary intervention, prediction, prognosis, body mass index, Gensini score, cardiopulmonary exercise testing

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## Introduction

Percutaneous coronary intervention (PCI) is an important treatment modality in coronary artery disease (CAD). In 2017, up to 753,142 patients with CAD underwent interventional therapy in mainland China.<sup>1</sup> Although most of these patients have good long-term prognosis after regular drug therapy, some still experience poor disease progression, such as revascularization, sudden cardiac death, or other adverse events. Early identification of patients at risk of these poor outcomes after PCI is important, for caregivers to provide sufficient monitoring and timely management.

Despite of the existence of several non-invasive assessment schemes for the evaluation of disease prognosis in patients with CAD treated by PCI, which method to use in clinical practice in a given context remains uncertain. The 2018 European Society of Cardiology and the European Association for Cardio-Thoracic Surgery guidelines on myocardial revascularization suggest that high-risk patients should undergo a routine noninvasive imaging examination 6 months after revascularization.<sup>2</sup> Nonetheless, noninvasive echocardiography has little value in predicting

long-term prognosis. Frequent coronary computed tomography or coronary angiography is not only expensive but also substantially increases the risk of radiation exposure. As such, routine imaging screening is not recommended for predicting long-term cardiovascular events. Noninvasive stress imaging, such as stress echocardiography, is another option for risk assessment.<sup>2</sup> However, stress echocardiography requires extensive professional training and demands extremely high standards for operators; thus, it cannot be widely used in China at this time. On the contrary, cardiopulmonary exercise testing (CPX) is a non-invasive method for the objective and quantitative evaluation of cardiac reserve function and exercise tolerance.<sup>3</sup> It is reported that CPX has significantly higher sensitivity and specificity than traditional tests, such as the electrocardiogram (ECG) exercise test in detecting myocardial ischemia in patients with chest pain.<sup>4</sup> Moreover, CPX indices such as peak oxygen consumption (peak  $\text{VO}_2$ ), anaerobic threshold, oxygen pulse ( $\text{VO}_2/\text{heart rate}$ ), and work efficiency (i.e., ratio of the change in oxygen uptake to the change in work rate [ $\Delta\text{VO}_2/\Delta\text{work rate}$ ]) are strongly correlated with cardiac function.<sup>5-7</sup>

Acute coronary syndrome (ACS) is the main cause of death in patients with CAD. However, most existing studies have either focused on the severity of coronary atherosclerosis and the degree of revascularization or have solely studied CPX variables. Data exploring the effect of CPX parameters in the existence of other relevant clinical variables are scarce. As such, the present study was proposed to examine the additional prognostic value of CPX variables, while taking into account other recognized clinical predictors of a major adverse cardiac event (MACE). The findings have the potential to guide clinicians in making management decisions for patients treated with PCI.

## Methods

### *Study design and population*

We conducted a retrospective study including patients with ACS age over 18 years from a tertiary center in Beijing, China. Patients were enrolled if they had undergone PCI and received CPX within 1 year after PCI in the Division of Cardiology, Peking University People's Hospital, between September 2012 and October 2017. Patients with previous coronary artery bypass grafting (CABG), other heart diseases, chronic lung diseases, or cancer were excluded.

For each included patient, we retrospectively reviewed the hospital records to obtain their demographic, clinical, and angiographic data. Clinical information including body mass index (BMI), past medical history, drug use, and smoking history were collected from the medical records. All enrolled patients underwent PCI using standard techniques. The Gensini score was calculated to assess the severity of coronary atherosclerosis, as previously described.<sup>8</sup> All interventional strategies, including the completeness

of revascularization, use of stents, choice of stent type, and use of periprocedural antithrombin and antiplatelet therapy, were at the operator's or cardiac team's discretion.

### *Ethics approval and consent to participate*

The study was approved by the ethics committee of Peking University People's Hospital (approval no. 2018PHB124-01, issued on 18 September 2018; approval no. 2019PHB146-01, issued on 20 August 2019). Patient follow-up was conducted by telephone, and the process was approved by the ethics committee, which waived the need for informed consent. Data were anonymized before use.

### *Cardiopulmonary exercise testing*

All patients were clinically stable on a regular pharmacologic regimen, as evaluated by a cardiologist and exercised infrequently. Patients underwent symptom-limited treadmill testing on a cardiopulmonary apparatus (COSMED QUARK PFT 4 ERGO; COSMED, Rome, Italy). To ensure patient safety, all tests were supervised by an experienced physician, with the assistance of an experienced nurse. All testing in this study was performed in the same laboratory and at the same room temperature (20–25°C). Before each test, the equipment was calibrated according to the manufacturer's specifications, using reference gases. The following variables were expressed as 30-s averages: oxygen uptake ( $\text{VO}_2$ ;  $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ), ventilatory equivalent for carbon dioxide ( $\text{VE}/\text{VCO}_2$ ), and end-tidal carbon dioxide pressure ( $\text{PETCO}_2$ ; mmHg). Heart rate was recorded using a 12-lead ECG to detect any potential arrhythmias or signs of ischemia, which would indicate that the test should be stopped. Blood pressure was obtained via auscultation at rest, every

2 to 3 minutes during exercise, and regularly during recovery. The VE/VCO<sub>2</sub> slope (minute ventilation to carbon dioxide production slope) was calculated using least squares linear regression with the use of data from the entire exercise period. The test was finished when patients reached physical exhaustion: achieving 85% of the predicted maximum heart rate for the patient's age or a respiratory exchange ratio (RER)  $\geq 1.1$ .<sup>3,5</sup> Tests were stopped before these endpoints as premature CPX termination when one of the following criteria were met<sup>5</sup>: 1) presence of chest pain, dyspnea, dizziness, palpitations, leg pain, or fatigue; 2)  $\geq 2$  mm ST depression in at least two leads; 3) hypertension ( $>250$  mmHg systolic;  $>120$  mmHg diastolic); 4) a drop in systolic blood pressure  $>20$  mmHg; 5) serious rhythm disturbances (second or third degree heart block).

### Prognosis

Patients were followed from the date of the PCI to the occurrence of an adverse event or administrative censoring (September 2019), whichever came earlier. The study endpoint was defined as the occurrence of a MACE, including myocardial infarction, repeat coronary revascularization during follow-up, stent thrombosis, stroke, or sudden cardiac death. Revascularization was defined as repeated revascularization for ischemic symptoms and events driven by the PCI or surgery of any vessel.

### Statistical analysis

Continuous variables are expressed as mean  $\pm$  standard deviation (SD). CPX parameters were compared between groups using one-way analysis of variance or the nonparametric Kruskal–Wallis test. Categorical variables were compared between groups using the Pearson's

chi-square or Fisher's exact test. Candidate risk factors that were associated with the outcome in univariate analysis ( $p < 0.05$ ) were entered into a multivariable Cox model using a backward elimination algorithm, and the model with the minimum Akaike information criterion (AIC) was selected as the final prediction model.<sup>9</sup> Statistical power was calculated using PASS 11 (NCSS LLC, East Kaysville, Utah, USA) at a 0.05 significance level for the Cox proportional hazards model.<sup>10,11</sup>

The predictive performance of the prediction model was evaluated in terms of discrimination and calibration. Discrimination indicates the proportion of all pairs of patients who were correctly ordered such that the patient with the highest predicted survival was the one who survived the longest, represented by Harrell's C-statistic. To assess independent contributions of the identified predictors to the final model, we constructed three models that added different sets of predictors in a step-by-step manner. In addition to the C-statistic, we also recorded the net reclassification index (NRI) and integrated discrimination improvement (IDI), which were used to measure the added utility offered by new predictors included in the risk prediction models. Given that an a priori defined cut-off point did not exist in our case, we used continuous NRI.<sup>12</sup> We also calculated the calibration, which ascertained the extent of agreement between the predicted and observed outcomes. Calibration was evaluated by assessing calibration-in-the-large, which compares the Kaplan–Meier estimate of the complete sample to the average predicted probabilities and indicates the extent to which the predictions were systemically too high or too low. Analyses were conducted using IBM SPSS 22 (IBM Corp., Armonk, NY, USA) and R 3.4.1 (The R Project for Statistical Computing, Vienna, Austria).

## Results

### Study population

A total of 209 patients underwent PCI and subsequently received CPX within 1 year during the study period. Six patients were excluded from the study because of previous CABG surgery, 1 because of severe valve dysfunction, 3 were excluded owing to cardiomyopathy, 11 owing to chronic lung

disease, and 4 patients were lost to follow up. The remaining 184 patients were enrolled in the study, including 29 patients with ST-elevation myocardial infarction (STEMI), 65 with non-STEMI, and 58 patients with unstable angina pectoris (UAP).

Patients in the adverse event-free group ( $n = 152$ ) were age  $55.86 \pm 10.07$  years and 88.8% were male (135/152); in the adverse event group ( $n = 32$ ), participants were age

**Table 1.** Participant characteristics according to outcome group.

Variable	Adverse event-free group ( $n = 152$ )	Adverse event group ( $n = 32$ )	p value	
Sex: male	135 (88.8)	28 (87.5)	1.000	
Age (years), mean (SD)	55.86 (10.07)	55.16 (10.22)	0.722	
BMI ( $\text{kg}/\text{m}^2$ ), mean (SD)	25.58 (2.70)	27.76 (2.47)	<0.001	
CAD family history	39 (26.5)	9 (28.1)	1.000	
Smoker	89 (59.3)	18 (56.2)	0.901	
ACS type			0.377	
	STEMI	29 (19.1)	9 (28.1)	
	non-STEMI	65 (42.8)	10 (31.2)	
	UAP	58 (38.2)	13 (40.6)	
Comorbidities				
	Hypertension	100 (65.8)	20 (62.5)	0.880
	Diabetes	63 (41.4)	10 (31.2)	0.383
	Anemia	0 (0.0)	1 (3.1)	0.388
	Hyperlipidemia	70 (46.1)	19 (59.4)	0.240
	Chronic kidney disease	7 (4.6)	3 (9.4)	0.514
	Hyperuricemia	15 (9.9)	2 (6.2)	0.759
	Cerebral vascular disease	5 (3.3)	1 (3.1)	1.000
Echocardiographic variable				
	LVEF (%), mean (SD)	62.93 (10.89)	61.79 (8.75)	0.594
	LVEDd ( $\text{mm}/\text{m}^2$ ), mean (SD)	4.96 (0.49)	5.02 (0.44)	0.570
	Revascularization or incomplete revascularization	55 (37.7)	18 (58.1)	0.058
Multi-level lesions on coronary arteriography	109 (71.7)	29 (90.6)	0.043	
Gensini score, mean (SD)	54.57 (25.97)	87.25 (30.66)	<0.001	
Medications				
	Aspirin	139 (93.9)	29 (96.7)	0.872
	Clopidogrel	128 (85.9)	24 (80.0)	0.586
	Statins	146 (97.3)	31 (96.9)	1.000
	Beta blockers	126 (83.4)	28 (87.5)	0.761
	ACEI/ARB	87 (57.6)	19 (59.4)	1.000
	Nitrates	39 (25.8)	11 (34.4)	0.443

\*Number (percentage) unless otherwise specified.

ACEI, angiotensin converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; LVEDd, left ventricular end-diastolic diameter; STEMI, ST-elevation myocardial infarction; SD, standard deviation; ST-elevation myocardial infarction; UAP, unstable angina pectoris.

55.16 ± 10.22 years and 87.5% were male (28/32), as shown in Table 1.

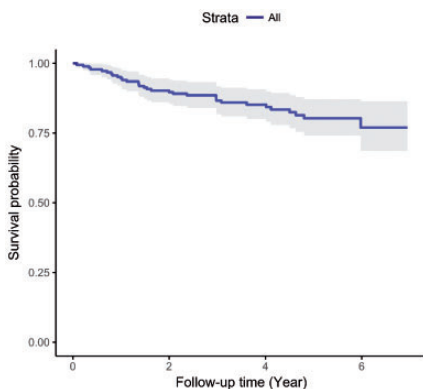
All CPX was performed within 1 year after PCI (range 2–12 months, mean ± SD, 7.27 ± 3.68 months). During a median follow-up period of 51 months (interquartile range [IQR]: 36–67 months), there were 32 cases of an adverse event (prevalence: 17.39%), including 1 case of cardiac death, 8 cases of stroke or myocardial infarction, and 26 cases of repeat revascularization (including 3 cases of myocardial infarction).

### Survival probability

The survival probabilities declined significantly in the first 5 years after PCI (Figure 1): 95.1% (95% confidence interval [CI]: 92.0%–98.3%) at 1 year, 89.7% (95% CI: 85.4%–94.2%) at 2 years, 86.6% (95% CI: 81.7%–91.8%) at 3 years, 85.2% (95% CI: 80.0%–90.6%) at 4 years, and 80.3% (95% CI: 74.1%–87.1%) at 5 years.

### Univariate analyses for identification of predictors

Results of univariate analyses for all candidate predictors are shown in Tables 1 and 2.



**Figure 1.** Kaplan–Meier curve for survival probability after percutaneous coronary intervention.

Patients with adverse events had a significantly higher BMI ( $p < 0.001$ ) and more serious coronary heart disease (higher Gensini score,  $p < 0.001$ ; greater number of lesion vessels,  $p = 0.043$ ) than did patients with no adverse events. However, there were no significant differences in sex, age, or conventional coronary risk factors such as a family history of CAD, smoking, CAD type, revascularization degree, major comorbidities, and medications between patients with and without a MACE.

Key CPX variables are presented in Table 2. There were no significant differences in resting heart rate, resting blood pressure, peak blood pressure, RER, VE, peak metabolic equivalent ( $\text{MET}_{\text{peak}}$ ), anaerobic threshold metabolic equivalent ( $\text{MET}_{\text{AT}}$ ), or change in end-tidal carbon dioxide ( $\delta\text{PetCO}_2$ ) between groups. Patients with adverse events had significantly lower heart rate reserve values ( $p < 0.001$ ), lower peak  $\text{VO}_2$  ( $p = 0.002$ ), and higher  $\text{VE}/\text{VCO}_2$  slope ( $p < 0.001$ ) than did adverse event-free patients. In addition, premature CPX termination occurred in 84.4% ( $n = 27$ ) of patients in the adverse events group and 25.7% ( $n = 39$ ) in the adverse event-free group. Among patients with and without a MACE, tests were stopped in 55.6% ( $n = 15$ ) and 46.2% ( $n = 18$ ) owing to the presence of chest pain, dyspnea, dizziness, palpitations, leg pain, or fatigue; in 29.6% ( $n = 8$ ) and 33.3% ( $n = 13$ ) owing to ECG changes ( $\geq 2$  mm ST depression in at least two leads); in 14.8% ( $n = 4$ ) and 17.9% ( $n = 7$ ) owing to hypertension ( $> 250$  mmHg systolic;  $> 120$  mmHg diastolic); and in none ( $n = 0$ ) and 2.6% ( $n = 1$ ) owing to a drop in systolic blood pressure ( $> 20$  mmHg) or serious rhythm disturbances (second or third degree heart block), respectively. The difference in the distribution of reasons for CPX termination was not significant between groups. Most instances in which patients had their test terminated early were owing to clinical

**Table 2.** CPX variables according to outcome group.

Variable	Adverse event-free group (n = 152)	Adverse event group (n = 32)	p value
Time post-PCI (months), mean (SD)	7.12 (3.89)	7.97 (3.75)	0.264
Premature CPX termination (yes), n (%)	39 (25.7)	27 (84.4)	<0.001
Resting systolic BP (mmHg), mean (SD)	121.59 (17.99)	123.69 (14.26)	0.537
Resting diastolic BP (mmHg), mean (SD)	79.15 (7.34)	79.94 (10.05)	0.611
Peak systolic BP (mmHg), mean (SD)	161.10 (23.49)	154.78 (21.47)	0.165
Peak diastolic BP (mmHg), mean (SD)	85.82 (13.95)	86.34 (15.85)	0.853
RER, mean (SD)	1.09 (0.09)	1.08 (0.13)	0.559
VE (L/min), mean (SD)	62.01 (19.40)	57.72 (12.10)	0.231
VE/VCO <sub>2</sub> slope, mean (SD)	33.23 (4.62)	36.77 (3.47)	<0.001
Resting heart rate (bpm), mean (SD)	71.41 (11.12)	71.06 (11.77)	0.875
Heart rate reserve, mean (SD)	64.17 (17.30)	47.53 (11.20)	<0.001
Peak heart rate – anaerobic threshold heart rate (bpm), mean (SD)	31.70 (17.22)	25.56 (15.07)	0.063
Anaerobic threshold heart rate – resting heart rate (bpm), mean (SD)	32.34 (14.87)	30.06 (12.16)	0.420
Peak VO <sub>2</sub> (mL·kg <sup>-1</sup> ·min <sup>-1</sup> )	23.55 (4.89)	20.65 (4.05)	0.002
MET <sub>AT</sub> , mean (SD)	4.58 (1.08)	4.41 (1.03)	0.435
MET <sub>peak</sub>			0.274
MET <sub>peak</sub> ≤ 5, n (%)	21 (13.8)	9 (28.1)	
5 < MET <sub>peak</sub> < 7, n(%)	65 (42.8)	17 (53.1)	
MET <sub>peak</sub> ≥ 7, n (%)	66 (43.4)	6 (18.8)	
δPETCO <sub>2</sub> (mmHg), mean (SD)	7.95 (3.78)	8.20 (3.01)	0.730

AT, anaerobic threshold; BP, blood pressure; CPX, cardiopulmonary exercise testing; MET, metabolic equivalent; PCI, percutaneous coronary intervention; peak VO<sub>2</sub>, peak oxygen consumption; RER, respiratory exchange ratio; SD, standard deviation; VE, minute ventilation; VE/VCO<sub>2</sub> slope, minute ventilation to carbon dioxide production slope; δPETCO<sub>2</sub>, change in end-tidal carbon dioxide.

symptoms or ECG changes; in all patients with restrictive manifestations, these were relieved within 5 minutes of exercise cessation and rest, with no serious adverse events or complications.

### Derivation of the prediction model

Significant variables in univariate analyses were entered into the multivariable Cox regression model. With a sample size of 184 and an adverse event rate of 17.39%, the statistical power ranged from 68.44% to 99.50% for continuous variables including peak VO<sub>2</sub>, VE/VCO<sub>2</sub> slope, and heart rate reserve. The statistical power was relatively low for binary variables such as premature

CPX termination (12.67%). In the multivariable model, six covariates were identified as statistically significant predictors of the composite outcome: BMI, Gensini score, premature CPX termination, peak VO<sub>2</sub>, heart rate reserve, and VE/VCO<sub>2</sub> slope (Table 3). Of all predictors, premature CPX termination had the largest effect on the composite outcome, with a hazard ratio (HR) of 4.06 (95% CI: 1.43–11.54, p=0.01), followed by BMI (HR: 1.23, 95% CI: 1.07–1.40, p<0.001), peak VO<sub>2</sub> (HR: 1.18, 95% CI: 1.05–1.33, p=0.01), VE/VCO<sub>2</sub> slope (HR: 1.11, 95% CI: 1.02–1.20, p=0.01), and Gensini score (HR: 1.02, 95% CI: 1.00–1.03, p=0.01). A protective effect was noted for heart rate

**Table 3.** Results from multivariable analysis for the predictors of the composite outcome.

Variable	HR	95% CI	SD	R-squared (X1 vs. other Xs)	p value	Power (%)
BMI	1.23	1.07–1.40	2.7725	0.06872	<0.001	87.97
Premature CPX termination	4.06	1.43–11.54	0.4894	0.2335	0.01	12.67
VE/VCO <sub>2</sub> slope	1.11	1.02–1.20	4.5965	0.1914	0.01	68.44
heart rate reserve	0.94	0.90–0.97	18.1456	0.4901	<0.001	99.50
Peak VO <sub>2</sub>	1.18	1.05–1.33	4.8414	0.445	0.01	92.18
Number of lesion vessels on coronary arteriography	1.89	0.49–7.29	NA	NA	0.36	NA
Gensini score	1.02	1.00–1.03	29.415	0.2143	0.01	83.17

BMI, body mass index; HR, hazard ratio; NA, not applicable; CI, confidence interval; peak VO<sub>2</sub>, peak oxygen consumption; VE/VCO<sub>2</sub> slope, minute ventilation to carbon dioxide production slope.

**Table 4.** Goodness of fit and discriminatory capacity of each model for the outcome.

Model	C-statistic	AIC	NRI	IDI
Model 1	0.74	290.4	NA	NA
Model 2	0.86	264.4	0.88 (0.42, 1.01)	0.38 (0.11, 0.61)
Model 3	0.92	245.2	0.28 (–0.43, 0.84)	0.15 (–0.14, 0.39)

Model 1: age + sex + BMI + Gensini score; Model 2: age + sex + BMI + Gensini score + premature CPX termination; Model 3: age + sex + BMI + Gensini score + premature CPX termination + minute ventilation to carbon dioxide production slope + heart rate reserve + peak oxygen consumption).

AIC, Akaike information criterion; BMI, Body mass index; IDI, integrated discrimination improvement; NA, not applicable; NRI, net reclassification index.

reserve (HR: 0.94, 95% CI: 0.90–0.97,  $p < 0.001$ ).

### Prediction model performance

We constructed three models with different sets of predictors (Table 4). Model 1, including only demographic variables (age, sex, and BMI) and Gensini score, yielded a C-statistic of 0.74 for the outcome. Model 2 added premature CPX termination to Model 1 and improved the C-statistic by 0.12. The final prediction model (Model 3) included all predictors identified in the multivariable analyses and demonstrated a good C-statistic of 0.92 for the outcome. A continuously decreasing AIC was

observed from Model 1 to Model 3 for the outcome (290.4, 264.4, 245.2, respectively). Compared with Model 1, Models 2 and 3 showed improvements in NRI of 0.88 (0.42, 1.01) and 0.28 (–0.43, 0.84), respectively; accordingly, the increases in IDI were 0.38 (0.11, 0.61) and 0.15 (–0.14, 0.39), respectively. Good calibration was obtained for the primary outcome, with calibration-in-the-large of 0.58%.

### Discussion

Patients with ACS may experience poor disease progression after PCI, despite receiving regular drug therapy. In the present study, 17.39% of patients experienced MACE



during a median follow-up period of 51 months. Baseline characteristics including BMI and Gensini score, CPX-related parameters including premature CPX termination, peak  $\text{VO}_2$ , heart rate reserve, and  $\text{VE}/\text{VCO}_2$  slope were found to be important predictors of MACE. Based on this clinically available information, we constructed a prediction model to predict an individual's risk of a MACE, which showed good discrimination and calibration.

In the present study, we found a prevalence of MACE of 17.39%. This was consistent with the findings of Abhyankar et al.<sup>13</sup> who reported a prevalence of 12.5% for MACE during a median follow-up of 7 years based on a single-center study in 2018. In another study looking at prognosis and disease progression in patients under age 50 years who were undergoing PCI, survival was 97.8% after 5 years, and freedom from major adverse cardiac and cerebrovascular events was 74.1%.<sup>14</sup>

In the present study, all cardiopulmonary exercise tests were performed within 1 year of PCI. Premature termination of CPX occurred in 39.13% of patients. Because all patients recovered within 5 minutes with no serious adverse events or complications, we can conclude that CPX is safe and feasible to evaluate prognosis in patients with ACS following complete or incomplete revascularization. The present study showed that CPX parameters, such as peak  $\text{VO}_2$ , heart rate reserve, and  $\text{VE}/\text{VCO}_2$  slope are important predictors for long-term prognosis. Similar to our findings, a prospective study by Kavanagh et al.<sup>15</sup> evaluated 12,169 male patients with CAD who underwent cardiac rehabilitation over a median follow-up period of 7.9 years; the authors found that peak  $\text{VO}_2$  was a strong predictor of survival. The role of  $\text{VE}/\text{VCO}_2$  slope on MACE was confirmed in other studies where it was reported to be the most powerful predictor of heart failure prognosis.<sup>16,17</sup> Jae et al.<sup>18</sup>

found that heart rate reserve was negatively correlated with coronary artery calcification, an emerging marker of coronary atherosclerosis, which supports the hypothesis that a low heart rate reserve is related to the burden of atherosclerotic CAD.

The increasing number of patients with ACS and the associated high mortality rate make it crucial to identify high-risk patients who are likely to experience poor outcomes. However, most previous studies have addressed these responses in isolation, and the independent, additive value of numerous CPX variables with poor predictive value has largely been disregarded, especially in patients with ACS after PCI. Furthermore, there is growing awareness that statistical techniques should be applied to develop evidence-based multivariable models for the improvement of clinical decision making. CPX is an extremely important tool that is easy to perform in the assessment of patients with CAD, and related studies have confirmed that a composite risk score using numerous CPX variables outperforms the traditional single-variable approach in predicting outcomes among patients with heart failure.<sup>19,20</sup> As such, although no single exercise variable was shown to be superior to any other in the present study, a composite model that included basic prognostic factors alongside CPX parameters offered some additional value in predicting the prognosis of patients with ACS after PCI. In the final prediction model, we combined demographic variables (age, sex, and BMI) and Gensini score, which could reflect the severity of coronary atherosclerosis, and CPX-derived variables (premature CPX termination, peak  $\text{VO}_2$ ,  $\text{VE}/\text{VCO}_2$  slope, and heart rate reserve), to better predict long-term prognosis in patients with ACS treated by PCI. Our model showed good predictive performance, as indicated by a high C-statistic and good calibration-in-the-large value. Adding CPX parameters to the prediction

model led to improvements in the NRI and IDI, suggesting the important role of CPX in predicting poor prognosis in these patients. Because CPX is a noninvasive method for objective and quantitative evaluation of cardiac reserve function and exercise tolerance, it has great potential and application prospects for ensuring appropriate treatment and timely management.

## **Limitations**

This study had some limitations. First, this was a retrospective analysis and may be subject to information error. However, this misclassification bias is likely to be non-differential, leading to more conservative results. Second, we were limited by the sample size, leading to insufficient statistical power and a low event-per-variable rate ( $\approx 5$ ). However, our aim was to develop a prediction model rather than report the exact effect of a given risk factor on adverse outcomes. Third, we did not include all potential candidate predictors in our multi-variable prediction model, to avoid problems with overfitting. We may thus have missed some important variables. For example, pre-procedure CPX information would mostly be helpful to determine the predictive effects of CPX on the final outcomes but was unavailable in the current analyses. Future studies would be valuable, with the addition of pre-procedure CPX data. Finally, we used a composite outcome instead of a specific event, which assumes that the effect of a given predictor is constant across all components of the outcome. The relatively small number of patients did not allow us to conduct subgroup analyses for each MACE. However, we chose to err on the conservative side in interpreting our results; any bias from our study would be toward the null hypothesis. Our study can serve as a first step, on the basis of which future prospective studies with more

patients can verify the roles of the identified predictors in adverse outcomes.

## **Conclusions**

In this study, we developed a clinically-relevant model for patients with ACS who undergo PCI that included demographic variables (age, sex, BMI), Gensini score, and CPX-derived variables (premature CPX termination, peak  $VO_2$ ,  $VE/VCO_2$  slope, and heart rate reserve). This risk-stratification tool may help clinicians screen for high-risk groups and plan appropriate management for patients with ACS treated by PCI.

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## **Authors' contributions**

SN performed the study, acquired the data, performed the analysis, drafted the manuscript, and read and approved the final manuscript; FW participated in the analysis, contributed to drafting the manuscript, and read and approved the final manuscript; ZJ and SZ participated in data acquisition, and read and approved the final manuscript; SY and XH contributed to interpretation of the results, revised the manuscript, and read and approved the final manuscript; DG and CG participated in the design of the study and its coordination, supervised the analysis, contributed to result interpretation, revised the manuscript, and read and approved the final manuscript.

## **Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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## References

- Hu S, Gao R, Liu L, et al. Summary of the 2018 Report on Cardiovascular Diseases in China. *Zhongguo Xunhuan Zazhi* 2019; 3: 209–220.
- Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Kardiol Pol* 2018; 76: 1585–1664.
- Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *J Am Coll Cardiol* 2002; 40: 1531–1540.
- Belardinelli R, Lacalaprice F, Tiano L, et al. Cardiopulmonary exercise testing is more accurate than ECG-stress testing in diagnosing myocardial ischemia in subjects with chest pain. *Int J Cardiol* 2014; 174: 337–342.
- Keteyian SJ, Brawner CA, Savage PD, et al. Peak aerobic capacity predicts prognosis in patients with coronary heart disease. *Am Heart J* 2008; 156: 292–300.
- Al Rifai M, Patel J, Hung RK, et al. Higher Fitness Is Strongly Protective in Patients with Family History of Heart Disease: The FIT Project. *Am J Med* 2017; 130: 367–371.
- Bandera F, Generati G, Pellegrino M, et al. Role of right ventricle and dynamic pulmonary hypertension on determining  $\Delta\text{VO}_2/\Delta\text{Work}$  Rate flattening: insights from cardiopulmonary exercise test combined with exercise echocardiography. *Circ Heart Fail* 2014; 7: 782–790.
- Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. *Am J Cardiol* 1983; 51: 606.
- Ambler G, Brady AR and Royston P. Simplifying a prognostic model: a simulation study based on clinical data. *Stat Med* 2002; 21: 3803–3822.
- Hsieh FY and Lavori PW. Sample-Size Calculations for the Cox Proportional Hazards Regression Model with Nonbinary Covariates. *Control Clin Trials* 2000; 21: 552–560.
- Schoenfeld DA. Sample-Size Formula for the Proportional-Hazards Regression Mode. *Biometrics* 1983; 39: 499–503.
- Pencina MJ, D'Agostino RB Sr and Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med* 2011; 30: 11–21.
- Abhyankar A, Kaul U and Sinha SK. Seven-year clinical outcomes in patients undergoing percutaneous coronary intervention with biodegradable polymer coated sirolimus-eluting stent: Results from a single-center real-world experience. *Indian Heart J* 2018; 70: S280–S284.
- Lautamäki A, Airaksinen KE, Kiviniemi T, et al. Prognosis and disease progression in patients under 50 years old undergoing PCI: the CRAGS (Coronary aRtery disease in young adultS) study. *Atherosclerosis* 2014; 235: 483–487.
- Kavanagh T, Mertens DJ, Hamm LF, et al. Prediction of long-term prognosis in 12 169 men referred for cardiac rehabilitation. *Circulation* 2002; 106: 666–671.
- Arena R, Myers J, Aslam SS, et al. Peak  $\text{VO}_2$  and  $\text{VE}/\text{VCO}_2$  slope in patients with heart failure: a prognostic comparison. *Am Heart J* 2004; 147: 354–360.
- Bard RL, Gillespie BW, Clarke NS, et al. Determining the best ventilatory efficiency measure to predict mortality in patients with heart failure. *J Heart Lung Transpl* 2006; 25: 589–595.
- Jae SY, Kurl S, Laukkanen JA, et al. Relation of heart rate recovery after exercise

- testing to coronary artery calcification. *Ann Med* 2017; 49: 404–410.
19. Ingle L, Rigby AS, Sloan R, et al. Development of a composite model derived from cardiopulmonary exercise tests to predict mortality risk in patients with mild-to-moderate heart failure. *Heart* 2014; 100: 781–786.
20. Guazzi M, Boracchi P, Arena R, et al. Development of a cardiopulmonary exercise prognostic score for optimizing risk stratification in heart failure: the (P)e(R)i(O)dic (B)reathing during (E)xercise (PROBE) study. *J Card Fail* 2010; 16: 799–805.