J Chin Med Assoc

ORIGINAL ARTICLE

Predischarge oxygen uptake efficiency slope has short and long-term value in the prognosis of patients after acute myocardial infarction

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Abstract

Background: Patients who survive an acute myocardial infarction (AMI) have a higher risk of having a major cardiovascular event (MACE). Cardiopulmonary exercise testing (CPET) could develop prognostic stratification and prescribing exercise prescription. Patients after AMI frequently terminate CPET early with submaximal testing results. We aimed to look at the characteristics of patients' predischarge CPET variables after AMI intervention and find potential CPET variables with prognostic value.

Methods: Between July 2012 and August 2017, we recruited patients who survived first AMI after primary percutaneous coronary intervention and received predischarge CPET retrospectively in a tertiary medical center of Taiwan. Patients were followed-up on a MACE or administrative censoring occurred (up to 5 years). To identify significant predictors of a MACE, a Cox regression model was used.

Results: One hundred thirteen patients (103 men and 10 women) were studied, with an average age of 58.32 ± 12.49. MACE over 3 months, 2-years, and 5-years was 17.70%, 53.10%, and 62.83%, respectively. The oxygen uptake efficiency slope during the whole during of CPET (OUES 100) divided by body surface area (OUES 100/BSA) was found to be a significant event predictor for MACE at 3-month, 2- and 5-years. Cox regression analysis revealed that those with OUES 100/BSA <0.722 (p = 0.004), OUES 100/BSA <0.859 (p = 0.002), and OUES 100/BSA <0.829 (p = 0.002) had a 7.14-fold, 3.47-fold, and 2.72-fold increased risk of 3-month, 2-year, and 5-year MACE, respectively.

Conclusion: It is critical to identify a submaximal predictor during CPET for patients who survive AMI. Our findings suggested that OUES could be a significant prognostic indicator in patients after first AMI in both the short and long term.

Keywords: Acute myocardial infarction; Cardiopulmonary exercise testing; Oxygen uptake efficiency slope; Phase I rehabilitation

1. INTRODUCTION

Acute myocardial infarction (AMI) is a major cause of morbidity and mortality around the world. AMI causes fatal conditions such as heart failure and sudden cardiac death, and it has become the leading contributor to disease burden.[1] In Taiwan, despite the overall age- and gender-adjusted AMI incidence maintaining at approximately 50 per 100 000 people in the past decade, a noteworthy rise of 30.3% in young males and 24.4% in young females under 55 has been observed.[2] Survivors of AMI confront an elevated risk of major cardiovascular events (MACE) following discharge. MACEs typically includes heart failure, nonfatal reinfarction, rehospitalization for cardiovascular-related concerns, repeat percutaneous coronary intervention (PCI), coronary artery bypass grafting, and all-cause mortality.[3] The incidence of MACE varies from 4.2% to 51%, depending on the definition and duration of follow-up.[3] Therefore, implementing lifestyle changes, ensuring quality care, and administering guideline-directed medical therapy are pivotal for secondary prevention of MACE.

The European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery advocate a postrevascularization imaging examination 6 months later for high-risk patients.[4] However, echocardiography and coronary computed tomography offer limited long-term prognostic value. Stress

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Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2024) 87: 414-421.

Received December 21, 2023; accepted January 18, 2024.

doi: 10.1097/JCMA.0000000000001081

Table 1

Participant characteristics according to outcome group

Variables	Within 3 mo			Within 2 y			Within 5 y		
	Adverse event-free group (n = 93)	Adverse event group (n = 20)	*p*[a]	Adverse event-free group (n = 53)	Adverse event group (n = 60)	*p*[a]	Adverse event-free group (n = 42)	Adverse event group (n = 71)	*p*[a]
Sex-female, %	9 (9.7%)	1 (5.0%)	0.688	7 (13.2%)	3 (5.0%)	0.185	5 (11.9%)	5 (7.0%)	0.496
Age, y	58.3 ± 12.3	57.8 ± 13.5	0.869	59.2 ± 12.9	57.4 ± 12.2	0.433	58.5 ± 12.8	58.1 ± 12.4	0.881
BMI, kg/m^2	24.9 ± 2.8	25.0 ± 2.3	0.887	24.8 ± 2.5	25.0 ± 2.8	0.708	24.8 ± 2.8	25.0 ± 2.7	0.758
Smoker, %	59 (63.4%)	14 (70.0%)	0.578	32 (60.4%)	41 (68.3%)	0.377	24 (57.1%)	49 (69.0%)	0.202
ACS type									
STEMI	78	18	0.733	43	53	0.285	35	61	0.711
Non-STEMI	15	2		10	7		7	10	
Comorbidities									
Hypertension	60 (64.5%)	10 (50.0%)	0.132	37 (69.8%)	36 (60.0%)	0.276	28 (66.7%)	45 (63.4%)	0.724
Diabetes	29 (31.2%)	8 (40.0%)	0.446	16 (30.2%)	21 (35.0%)	0.587	12 (28.6%)	25 (35.2%)	0.467
Dyslipidemia	55 (59.1%)	15 (75.0%)	0.185	30 (56.5%)	40 (66.7%)	0.272	24 (57.1%)	46 (64.8%)	0.419
Biochemistry data									
Cr, μmol/L	75.4 ± 16.1	77.1 ± 11.7	0.655	73.2 ± 14.3	77.9 ± 13.6	0.079	72.2 ± 12.9	77.8 ± 18.6	0.088
TC, mmol/L	5.0 ± 0.6	5.2 ± 0.5	0.130	4.9 ± 0.8	5.1 ± 0.6	0.161	5.0 ± 0.6	5.1 ± 0.7	0.407
LDL, mmol/L	2.7 ± 0.6	2.9 ± 0.5	0.198	2.7 ± 0.7	2.8 ± 0.6	0.258	2.7 ± 0.7	2.8 ± 0.7	0.444
HbA1C, %	6.2 ± 1.4	6.4 ± 1.6	0.532	6.1 ± 1.3	6.3 ± 1.4	0.399	6.1 ± 1.4	6.3 ± 1.6	0.415
Echocardiography									
LVEF, %	48.3 ± 7.4	43.3 ± 10.1	0.011*	49.6 ± 7.1	45.6 ± 8.6	0.009*	50.2 ± 7.3	45.8 ± 8.3	0.006*
Numbers of stenotic coronary arteries confirmed by initial angiography									
1 vessel	44 (47.3%)	2 (10.0%)	0.002*	27 (50.9%)	19 (31.7%)	0.038*	22 (52.4%)	24 (33.8%)	0.079
2 vessels	29 (31.2%)	7 (35.0%)		17 (32.1%)	19 (31.7%)		13 (31.0%)	23 (32.4%)	
3 vessels	20 (21.5%)	11 (55.0%)		9 (17.0%)	22 (36.6%)		7 (16.6%)	24 (33.8%)	
Medications									
Ticagrelor	20 (21.5%)	6 (30.0%)	0.396	14 (26.4%)	12 (20.0%)	0.419	11 (26.2%)	15 (21.1%)	0.537
Aspirin	89 (95.7%)	19 (95.0%)	1.00	50 (94.3%)	58 (96.7%)	0.664	39 (92.9%)	69 (97.2%)	0.359
Beta-blocker	75 (80.7%)	17 (85.0%)	0.762	43 (81.1%)	49 (81.7%)	0.942	34 (81.0%)	58 (81.7%)	0.922
Clopidogrel	71 (76.3%)	14 (70.0%)	0.574	37 (69.8%)	48 (80.0%)	0.211	29 (69.1%)	56 (78.9%)	0.242
ACEI/ARB	78 (83.9%)	15 (75.0%)	0.345	47 (88.7%)	46 (76.7%)	0.095	38 (90.5%)	55 (77.5%)	0.080
Statins	61 (65.6%)	16 (80.0%)	0.210	34 (64.2%)	43 (71.7%)	0.392	28 (66.7%)	49 (69.0%)	0.796

Data are the mean ± SD or No. (percentage).

ACEI = angiotensin converting enzyme inhibitor; ACS = acute coronary syndrome; ARB = angiotensin receptor blocker; BMI = body mass index; Cr = creatinine; HbA1C = glycated hemoglobin; LDL = low-density lipoprotein cholesterol; LVEF = left ventricular ejection fraction; STEMI = ST-elevation myocardial infarction; TC = total cholesterol.

[a]All the comparisons between two groups were done by independent *t* test except that comparisons of categorical variables between the two groups were done by Fisher exact test for gender, ACS type, medications (Ticagrelor, Aspirin, Beta-blocker, Clopidogrel, ACEI/ARB) or Chi-square test for smoker, comorbidities, numbers of stenotic coronary arteries confirmed by initial angiography and medications (Statin).

* $p < 0.05$.

echocardiography requires extensive training and adherence to high interoperator consistency standards.[5] In contrast, cardiopulmonary exercise testing (CPET) excels in providing comprehensive insights into cardiovascular, pulmonary, and musculoskeletal integration, offering valuable assessments of functional aerobic capacity in various populations, both healthy and diseased, making it a gold standard for prognostic stratification.[6,7]

Among all CPET indices, maximal oxygen consumption (max VO_2) is the most consistent with predicted values in patients with various diseases.[8] However, challenges such as peripheral muscle fatigue, dyspnea, and significant cardiac alterations impede cardiac patients from achieving maximal exercise effort.[9] Consequently, submaximal CPET parameters prove more suitable for assessing patients with cardiovascular disorders. Indices such as anaerobic threshold (AT), the slope of the relationship between minute ventilation and carbon dioxide production (VE/VCO_2 slope), work efficiency, and oxygen uptake efficiency slope (OUES) exhibit strong correlations with cardiac function.[10,11] Furthermore, the OUES, which estimates ventilator efficiency in relation to oxygen consumption,[12] is now a well-established substitute for max VO_2 in submaximal exercise effort in adults,[13] older children,[12] and AMI survivors.[14] The OUES has a high correlation with peak VO_2, good test-retest reliability, and relatively stable during the incremental exercise test.[15]

Per the American College of Cardiology/American Heart Association guidelines,[16] AMI patients should undergo predischarge CPET for risk stratification and subsequent cardiac rehabilitation prescription. However, due to safety concerns, limited resources, and inadequate equipment, few hospitals, including tertiary ones, conduct predischarge CPET for AMI patients.[17] Additionally, the prognostic significance of OUES in the predischarge status of AMI patients remains unknown. This study aims to investigate the short and long-term prognostic value of predischarge CPET variables, particularly OUES, providing valuable insights for physicians in managing post-AMI patients.

2. METHODS

2.1. Study design and participants

This follow-up study enrolled patients admitted for their first AMI at a tertiary center in southern Taiwan from December 2012 to November 2017. Patients were eligible if they were (1) aged 20 or older, (2) first diagnosed with AMI, (3) received

primary PCI (PPCI), and (4) underwent CPET before discharge, (5) had completed record of transthoracic echocardiographic examination and standard 12-lead electrocardiogram (ECG). Patients were excluded from the study if they had a history of acute coronary syndrome, or if they were deemed too frail for CPET or cardiac rehabilitation. This frailty criterion included those with cognitive impairment, neuromuscular disorders, ventilator dependence, severe pulmonary disorders requiring oxygen, and those who had been bedridden for more than 3 months. Additionally, patients with missing data or incomplete CPET records, as well as those who did not have regular medical follow-ups for at least 5 years following the onset of their AMI, were also excluded from the study. Cardiologists provided the PPCI and medications for the patients. Cardiologists would refer patients to physiatrists for phase I cardiac rehabilitation if there were no immediate complications following treatments. The phase I cardiac rehabilitation protocol was modified from the American College of Sports Medicine (ACSM) guidelines[18] and has been used as a standard operating procedure in this medical center with evidence to improve exercise capacity in patients after AMI.[19] Physiotherapists with at least 3 years of cardiopulmonary rehabilitation experience performed phase I cardiac rehabilitation for AMI patients. The study was approved by the Kaohsiung Veterans General Hospital's Institutional Review Board (VGHKS17-CT11-11) and we obtained informed consent from participants after explaining the CPET purpose and study objectives.

We retrospectively retrieved demographic, clinical, and angiographic data from patients' medical records. Clinical data encompassed medical history, medications, smoking history, and body mass index (BMI). Follow-up extended from PPCI to the first occurrence of a MACE or administrative censoring. Continuous medical care was provided by the medical center's Department of Cardiology outpatient clinic. MACEs, defined as repeat coronary revascularization, recurrent myocardial infarction, cerebral vascular accident, or cardiovascular death, were assessed at 3 months, 2 years, and 5 years post-AMI intervention. Cardiologists confirmed MACEs through medical records. Patients with MACE constituted the adverse event group, while those without MACE at each follow-up (within 3 months, 2 years, and 5 years) comprised the adverse event-free group.

2.2. Cardiopulmonary exercise testing

A symptom-limited, progressive exercise test was performed on each patient, which included leg ergometer, a flow module, a gas analyzer, and an ECG monitor (Metamax 3B, Cortex Biophysik GmbH Co., Germany). The exercise testing was carried out with an incremental workload of 10 W/min.[18] We stopped the test when the patients experienced subjectively unbearable symptoms (severe shortness of breath, chest pain, severe dizziness, excessive fatigue, physical instability, and excessive pallor as indicated by ACSM[18]), were unable to continue, or reached the submaximal endpoint, which was defined as work ≥75 W/min, peak oxygen consumption ≥5 metabolic equivalents (MET), peak heart rate ≥70% of the age-predicted value, or respiratory exchange rate ≥1.1. All patients underwent CPET under the supervision of a physiatrist with more than 10 years of experience (K.-L. L.).

During the CPET, we measured oxygen consumption (VO_2) and carbon dioxide production (VCO_2) on a breath-by-breath basis. Furthermore, the AT, respiratory rate, and several derived variables such as respiratory exchange ratio (RER) and VE/VCO_2 slope were determined. AT determination is commonly used when the VCO_2-VO_2 slope abruptly increases.[20] Peak VO_2 was the absolute value of peak oxygen uptake measured throughout the test, whereas peak MET was the relative value of peak VO_2 divided by a constant 3.5 Ml/kg/min. The percent of peak VO_2 to predicted value (predicted peak VO_2%) was calculated by comparing the measured peak MET to the predicted peak MET using Taiwan's normal standards.[21] The slope of the VE/VCO_2 ratio was measured from the start to just after the AT.[22] The OUES was calculated using the graphic slope (a) of the equation VO_2 = a log(VE) + b. The OUES was calculated using the total exercise time (OUES 100).[13] Due to the anthropometric variation, the OUES was normalized by body surface area (BSA).[23] Haycock formula was used to calculate the BSA.[24]

2.3. Statistical analysis

Before each analysis, normality and homoscedasticity were checked. To compare the outcomes of the adverse event group and adverse-free group, we used the Chi-square test or Fisher Exact test for categorical variables, independent *t* test for normally distributed variables and the Mann-Whitney *U*-test for nonnormally distributed variables. We plotted the receiver operating characteristic (ROC) curves and determined the optimal threshold values for each CPET variables for predicting 3-month, 2-year, and 5-year MACEs by selecting the point with the highest summation value of sensitivity and specificity. We used Kaplan-Meier survival analysis and the log-rank test to compare MACEs between the adverse event group and the adverse event-free group. To estimate the hazard ratio (HR) of each potential prognostic factors of CPET, we used univariate and multivariate Cox regression analysis. Because age and gender might be associated to poorer prognosis in AMI,[25,26] we used a multivariable Cox regression model adjusted for age and gender to mitigate potential biases associated with these variables. To indicate statistical significance, a two-tailed $p < 0.05$ was used. For all analyses, we used Statistical Package for the Social Sciences for Windows, version 21.0 (IBM Corp., Armonk, NY).

For the calculation of the minimum sample size required for our study, we used the online calculator designed by the University of California, San Francisco, based on the HR regression model (URL: https://sample-size.net/sample-size-survival-analysis/). The calculator considers the type I error set at 0.05 and a test power set at 0.8. The ratio of the exposed group (with MACEs) to the non-exposed group (without MACEs) is set at 1:4, based on past literature. The relative hazard is estimated to be 2.0, referring to previous studies.[3,27] The calculated minimum sample size is 102.

3. RESULTS

3.1. Study population

A total of 122 patients underwent predischarge CPET following the first AMI. Six patients were excluded (three with missing ECG data, three with incomplete echocardiography data). After thorough review, 116 patients remained, with 3 lost to follow-up within 5 years (1 at 6 months, 2 at 1 year after PPCI). Table 1 displays the baseline characteristics of participants categorized by outcome group. The analysis included the remaining 113 patients, with a mean Killip class of 1.82 ± 1.02. The interval between PPCI and CPET was 5.70 ± 3.23 days. Most patients were on dual antiplatelet therapy after PPCI. Demographics and clinical data were compared between AMI survivors with and without MACEs at 3 months, 2 years, and 5 years. No significant differences were observed in age, BMI, smoking status, AMI type, gender, comorbidities, basic biochemistry profile (including serum creatinine, total cholesterol, low density lipoprotein cholesterol, and glycated hemoglobin), or medications. Throughout follow-up, the group without MACEs exhibited higher left ventricular ejection fraction (*p* values: 0.011, 0.009, 0.006, respectively). Additionally, this group had fewer stenotic coronary arteries at 3-month and 2-year follow-up (*p* values: 0.002, 0.038).

3.2. Parameters of CPET

Among the 123 participants, 41 (36.3%) of them terminated CPET earlier. The reasons included fatigue (n = 20), dyspnea (n = 13), pallor (n = 5), chest tightness (n = 2), and dizziness (n = 1). Table 2 shows CPET parameter comparisons between the adverse event group and the adverse event-free group at each follow-up period. Patients in the adverse event-free group had higher OUES 100 (p = 0.004) and OUES 100/BSA (p = 0.002) within 3 months of the onset of AMI than those in the adverse event group. Patients without MACEs had higher peak systolic blood pressure (SBP) (p = 0.006), predicted peak VO_2% (p = 0.016), OUES 100 (p = 0.002) and OUES 100/BSA (p < 0.001), and lower VE/VCO_2 slope (p = 0.044) within 2 years of the onset of AMI than those with MACEs. Patients in the adverse event-free group had higher peak SBP (p = 0.031), OUES 100 (p = 0.003), and OUES 100/BSA (p = 0.001) than those in the adverse event group after 5 years.

3.3. Univariate and multivariate analyses for identification of predictors and the survival probability

ROC curves for LVEF and OUES 100/BSA were analyzed to predict 3-month MACEs. The area under curve (AUC) values for LVEF and OUES 100/BSA were 0.656 (p = 0.029) and 0.721 (p = 0.002), respectively. Optimal cutoff points for predicting 3-month MACEs were 43.5% for LVEF and 0.7226 for OUES 100/BSA, determined by the maximum sum of sensitivity and specificity (Table 3, Fig. 1A).

For 2-year MACEs, ROC curves for LVEF, peak SBP, predicted peak VO_2%, and OUES 100/BSA were examined. In descending order, AUC values for OUES 100/BSA were 0.676 (p = 0.001), LVEF and peak SBP both 0.640 (p = 0.010 and 0.011), and predicted peak VO_2% 0.629 (p = 0.018). Optimal cutoff points for predicting 2-year MACEs were 0.8589 for OUES 100/BSA, 48.5% for LVEF, 138.5 mmHg for peak SBP, and 38.815% for predicted peak VO_2%, determined by maximum sum of sensitivity and specificity (Table 3, Fig. 1B).

For 5-year MACEs, ROC curves for LVEF, peak SBP, and OUES 100/BSA were analyzed. In descending order, AUC values were 0.671 (p = 0.002) for OUES 100/BSA, 0.659 (p = 0.005) for LVEF, and 0.603 (p = 0.069) for peak SBP. Optimal cutoff points for predicting 5-year MACEs were 0.829 for OUES 100/BSA, 48.5% for LVEF, and 153 mmHg for peak SBP, determined by maximum sum of sensitivity and specificity (Table 3, Fig. 1C).

The incidence of MACEs at 3 months, 2 years, and 5 years was 17.7%, 53.1%, and 62.8%, respectively. After adjusting for age and gender, Kaplan-Meier analysis and the log-rank test indicated statistically significant differences: (1) 3-month MACEs in AMI survivors with high and low OUES 100/BSA (p = 0.002) and LVEF (p = 0.007); (2) 2-year MACEs in AMI survivors with high and low OUES 100/BSA (p = 0.001), LVEF (p = 0.002), peak SBP (p = 0.007), and predicted peak VO_2% (p = 0.004); (3) 5-year MACEs in AMI survivors with high and low OUES 100/BSA (p = 0.001), LVEF (p < 0.001), and peak SBP (p = 0.014). Multivariate Cox regression analysis, adjusted for age and gender, revealed that lower OUES was associated with higher MACE risk at 3 months (HR = 7.435, p = 0.002), 2 years (HR = 3.026, p = 0.005), and 5 years (HR = 2.882, p < 0.001). Compared to other prognostic predictors, including LVEF, peak SBP, and predicted peak oxygen consumption percentage, OUES 100/BSA emerged as a significantly superior predictor for both short and long-term MACEs in AMI survivors (Table 4 and Fig. 2).

4. DISCUSSION

Our study indicates that OUES 100/BSA is a significant prognostic indicator for short and long-term outcomes in AMI patients. Notably, we are the first to demonstrate the utility of

Table 2

Comparisons of variables of cardiopulmonary exercise testing according to outcome group

	Within 3 mo			Within 2 y			Within 5 y		
Variables	Adverse event-free group (n = 93)	Adverse event group (n = 20)	p^a	Adverse event-free group (n = 53)	Adverse event group (n = 60)	p^a	Adverse event-free group (n = 42)	Adverse event group (n = 71)	p^a
Resting heart rate, bpm	75.6 ± 11.7	78.7 ± 14.7	0.314	76.9 ± 11.4	75.5 ± 13.1	0.542	78.4 ± 11.5	74.8 ± 12.	0.127
Peak heart rate—AT heart rate, bpm	10.0 ± 6.7	10.6 ± 6.1	0.722	10.0 ± 6.3	10.3 ± 6.8	0.829	9.5 ± 6.0	10.5 ± 6.9	0.404
AT heart rate—resting heart rate, bpm	17.7 ± 8.2	17.2 ± 10.2	0.822	17.6 ± 7.1	17.6 ± 9.8	0.955	17.7 ± 7.5	17.5 ± 9.2	0.926
Resting systolic BP, mmHg	116.3 ± 16.1	113.3 ± 16.0	0.437	117.0 ± 16.4	114.8 ± 15.8	0.471	114.1 ± 15.0	116.8 ± 16.7	0.383
Resting diastolic BP, mmHg	71.0 ± 11.0	67.8 ± 9.2	0.227	70.5 ± 9.9	70.3 ± 11.4	0.933	69.8 ± 9.5	70.7 ± 11.4	0.665
Peak systolic BP, mmHg	144.6 ± 24.2	136.5 ± 19.6	0.163	149.6 ± 25.3	137.6 ± 20.5	0.006*	149.4 ± 26.4	139.5 ± 21.0	0.031*
Peak diastolic BP, mmHg	78.2 ± 15.5	74.1 ± 12.2	0.268	78.6 ± 15.1	76.5 ± 15.0	0.467	79.7 ± 16.1	76.2 ± 14.3	0.242
Peak respiratory exchange ratio	1.05 ± 0.12	1.04 ± 0.12	0.620	1.05 ± 0.13	1.05 ± 0.11	0.891	1.05 ± 0.14	1.05 ± 0.11	0.991
Peak MET	3.4 ± 0.8	3.1 ± 1.0	0.272	3.4 ± 0.8	3.2 ± 0.9	0.287	3.4 ± 0.8	3.3 ± 0.9	0.391
Maximal watt	53.6 ± 18.6	49.3 ± 17.5	0.349	53.4 ± 18.2	52.3 ± 18.7	0.750	54.0 ± 18.0	52.1 ± 18.7	0.597
Predicted peak VO_2%	40.8 ± 10.7	37.7 ± 13.2	0.266	42.9 ± 11.2	37.9 ± 10.7	0.016*	42.3 ± 11.6	39.0 ± 10.8	0.144
Minute ventilation, L/min	25.4 ± 7.7	26.5 ± 10.8	0.592	25.1 ± 7.6	26.0 ± 8.9	0.561	25.4 ± 8.2	25.7 ± 8.4	0.877
VE/VCO_2 slope	31.0 ± 8.0	32.5 ± 10.4	0.488	30.6 ± 7.3	32.8 ± 9.4	0.086	29.7 ± 5.4	32.2 ± 9.9	0.091
Peak rate pressure product	15 030 ± 3619	15 101 ± 4162	0.938	15 723 ± 3781	14 443 ± 3553	0.066	15 883 ± 3991	14 564 ± 3452	0.063
OUES 100	1.4 ± 0.4	1.1 ± 0.4	0.004*	1.5 ± 0.4	1.2 ± 0.4	0.002*	1.5 ± 0.4	1.3 ± 0.40	0.003*
OUES 100/BSA	0.8 ± 0.2	0.6 ± 0.2	0.002*	0.8 ± 0.2	0.7 ± 0.2	<0.001*	0.8 ± 0.3	0.7 ± 0.2	0.001*

Data are the mean ± SD.

AT = anaerobic threshold; BP = blood pressure; BSA = body surface area; MET = metabolic equivalent; predicted peak VO_2% = percentage of measured peak oxygen consumption to estimated peak oxygen consumption; OUES 100 = oxygen uptake efficiency slope calculated from data of the whole exercise duration; VE/VCO_2 slope = minute ventilation to carbon dioxide production slope.

[a]All the comparisons between two groups were done by independent t test.

* p < 0.05.

Table 3

Optimal cutoff points and related diagnostic value by receiver operating characteristic curve analysis

	Cutoff point	Sensitivity	Specificity	AUC	*p*	No. of MACE, % (<cutoff value)	No. of MACE, % (>cutoff value)	*p*
Within 3 mo								
LVEF	43.5	0.600	0.731	0.656	0.029	12 (32.4%)	8 (10.5%)	0.004
OUES 100/BSA	0.7226	0.850	0.559	0.721	0.002	41 (70.7%)	30 (54.6%)	0.076
Within 2 y								
LVEF	48.5	0.65	0.642	0.640	0.010	39 (67.2%)	21 (38.2%)	0.002
Peak systolic BP, mmHg	138.5	0.567	0.717	0.640	0.011	34 (69.4%)	26 (40.6%)	0.002
Predicted peak VO_2%	38.815	0.583	0.698	0.629	0.018	45 (77.6%)	26 (47.3%)	0.001
OUES 100/BSA	0.8589	0.850	0.434	0.676	0.001	51 (63.0%)	9 (28.1%)	0.001
Within 5 y								
LVEF	48.5	0.634	0.690	0.659	0.005	45 (77.6%)	26 (47.3%)	0.001
Peak systolic BP, mmHg	153	0.789	0.452	0.603	0.069	56 (70.9%)	15 (44.1%)	0.007
OUES 100/BSA	0.829	0.789	0.500	0.671	0.002	56 (72.7%)	15 (41.7%)	0.001

BP = blood pressure; BSA = body surface area; LVEF = left ventricular ejection fraction; MACE = major cardiac event; OUES 100 = oxygen uptake efficiency slope calculated from data of the whole exercise duration; predicted peak VO_2% = percentage of measured peak oxygen consumption to estimated peak oxygen consumption.

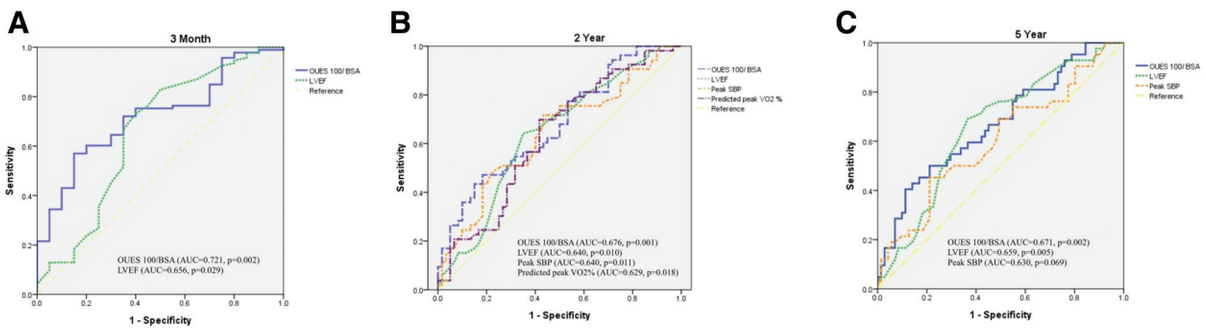

Fig. 1 The ROC curve of cardiopulmonary exercise testing variables in determination of MACE of patients survived acute myocardial infarction at 3-mo (a), 2-y (b), and 5-y (c). ROC curve analysis for 3-mo MACEs identified best cutoff points for LVEF and OUES 100/BSA with AUC values of 0.656 and 0.721, respectively (a). ROC curves for 2-y identified best cutoff points for OUES 100/BSA, LVEF, peak SBP, and predicted peak VO_2% with AUC values of 0.676, 0.640, 0.640, and 0.629, respectively (b). ROC curves for 5-y identified best cutoff points for OUES 100/BSA, LVEF, and peak SBP with AUC values of 0.671, 0.659, and 0.603, respectively (c). AUC = area under curve; BSA = body surface area; LVEF = left ventricular ejection fraction; OUES 100 = oxygen uptake efficiency slope calculated from data of the whole exercise duration; predicted peak VO_2% = percentage of measured peak oxygen consumption to estimated peak oxygen consumption; SBP = systolic blood pressure.

submaximal CPET variables, particularly OUES, in phase I cardiac rehabilitation as indicators for a 5-year prognosis.

Due to the escalating patient numbers and high mortality rates post-AMI without continuous standard treatment,[5] it is critical to identify high-risk patients surviving AMI. CPET, offering noninvasive, objective, and quantifiable assessments of cardiac reserve function and exercise tolerance, holds significant potential for risk stratification and tailored treatment. The 2016 European Association for Cardiovascular Prevention and Rehabilitation/American Heart Association scientific statement highlights the prognostic significance of peak VO_2, VO_2 at ventilator threshold, and the VE/VCO_2 slope in diverse populations.[28] Niu et al[5] discovered that premature CPET termination, peak VO_2, heart rate reserve, and VE/VCO_2 slope have a high predictive value for poor outcomes in patients with acute coronary syndrome following PCI. However, in their study, the median time from PCI to CPET was 7.27 ± 3.68 months, which was significantly longer than our data (5.70 ± 3.23 days). That is, participants in their study were mostly in phase II or even III cardiac rehabilitation, whereas those in our study were only in phase I. Patients who have recently survived an AMI may find it difficult to achieve maximal effort during CPET,[29] and compliance with further cardiac rehabilitation and CPET after the discharge was low.[30] It is critical to identify a submaximal predictor of CPET just before discharge. Cai et al[31] looked at the predischarge CPET on outcomes in patients with ST-elevation AMI after PCI. However, they evaluated the maximal CPET parameters rather than the submaximal ones. With an average 2.5-year follow-up time, they discovered that VO_2 at the AT with a cutoff value of 10.5 mL/kg/min could be an independent indicator for cardiovascular disease prognosis.[31] Our findings showed that OUES 100/BSA was a significantly better predictor in predicting of MACE in patients who survived AMI, whether followed for 3 months, 2 years, or 5 years.

OUES, which was first proposed in 1996, has been extensively studied in patients with heart failure.[28] Patients with heart failure who had a predischarge OUES of <1.25 were found to have a 4.87-fold higher risk of 1-year MACE. As a sensitive CPET marker to clinical change, OUES could also be measured before and after exercise training[32] and heart transplantation.[33] Tsai et al[19] discovered that OUES could be used to monitor the effect of phase I cardiac rehabilitation in patients who had just survived AMI. A lack of improvement in OUES after an exercise training program is proved to be associated with a worse prognosis in patients with coronary artery disease.[34] Our study is the first to look at the predictive value of predischarge OUES in predicting MACEs in AMI patients, revealing OUES 100/BSA as the most sensitive CPET parameter for up to 5 years.

Table 4

Predictive measures for 3-mo, 2-y, and 5-y major adverse cardiovascular event in patients survive acute myocardial infarction

Variable	No. of patients	No. of MACE	Univariate[a]		Multivariate[a]	
			Hazard ratio (95% CI)	*p*	Hazard ratio (95% CI)	*p*
Within 3 mo						
LVEF ≥43.5%	76	8 (10.5%)	1.000	0.007*	1.000	0.006*
LVEF <43.5%	37	12 (32.4%)	3.45 (1.41-8.46)		3.57 (1.45-8.78)	
OUES 100/BSA ≥0.7226	56	3 (5.4%)	1.000	0.002*	1.000	0.002*
OUES 100/BSA <0.7226	57	17 (29.8%)	7.14 (2.07-24.62)		7.38 (2.13-25.55)	
Within 2 y						
LVEF ≥48.5%	55	21 (38.2%)	1.000	0.002*	1.000	0.002*
LVEF <48.5%	58	39 (67.2%)	2.36 (1.38-4.04)		2.41 (1.38-4.20)	
Peak systolic BP ≥138.5 mmHg	64	26 (40.6%)	1.000	0.007*	1.000	0.443
Peak systolic BP <138.5 mmHg	49	34 (69.4%)	2.03 (1.21-3.39)		1.24 (0.71-2.16)	
Predicted peak VO_2% ≥38.815	62	25 (40.3%)	1.000	0.004*	1.000	0.150
Predicted peak VO_2% <38.815	51	35 (68.6%)	2.27 (1.31-3.94)		1.53 (0.86-2.73)	
OUES 100/BSA ≥0.8589	32	9 (28.1%)	1.000	0.001*	1.000	0.005*
OUES 100/BSA <0.8589	81	51 (63.0%)	3.47 (1.70-7.09)		3.03 (1.40-6.53)	
Within 5 y						
LVEF ≥48.5%	55	26 (47.3%)	1.000	<0.001*	1.000	<0.001*
LVEF <48.5%	58	45 (77.6%)	2.41 (1.47-3.93)		2.77 (1.68-4.57)	
Peak systolic BP ≥153 mmHg	34	15 (44.1%)	1.000	0.014*	1.000	0.050
Peak systolic BP <153 mmHg	79	56 (70.9%)	2.05 (1.16-3.63)		1.80 (1.00-3.22)	
OUES 100/BSA ≥0.829	36	15 (41.7%)	1.000	0.001*	1.000	<0.001*
OUES 100/BSA <0.829	77	56 (72.7%)	2.71 (1.52-4.83)		2.88 (1.607-5.20)	

BP = blood pressure; BSA = body surface area; LVEF = left ventricular ejection fraction; MACE = major cardiac event; OUES 100 = oxygen uptake efficiency slope calculated from data of the whole exercise duration; predicted peak VO_2% = percentage of measured peak oxygen consumption to estimated peak oxygen consumption.

[a]Adjusted for age and gender.

* $p < 0.05$.

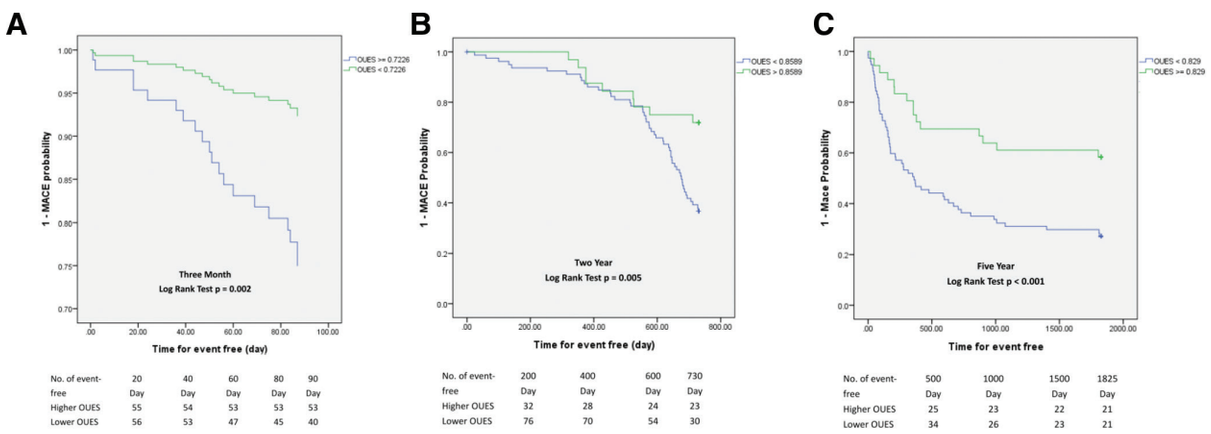

Fig. 2 Kaplan-Meier analysis of 3-mo (a), 2-y (b), and 5-y (c) MACE in patients survived acute myocardial infarction with high and low OUES. Patients survived acute myocardial infarction with low OUES showed significantly higher rate of 3-mo ($p = 0.002$), 2-y ($p = 0.005$), and 5-y ($p < 0.001$) MACE than those with high OUES. MACE = major adverse cardiovascular event; OUES = oxygen uptake efficiency slopes.

Predischarge CPET and phase I cardiac rehabilitation are not routinely performed for those just surviving AMI due to safety concerns and a lack of equipment and multidisciplinary well-trained professionals, even in developed countries.[17,30] All CPETs in our current study were performed 1 or 2 days before discharge of the AMI patients. Although 31 participants (27.43%) experienced unbearable symptoms and had to stop the CPET, they all recovered within 5 minutes and had no serious adverse events or complications. Our findings were consistent with those of Niu et al[5], who discovered that 39.13% of patients discontinued CPET prematurely.[5] Our results indicated the safety and feasibility of AMI patients undergoing CPET in well-prepared clinical settings.

Aside from the predictive value, the predischarge CEPT of AMI survivors is important for guiding the exercise prescription for cardiac rehabilitation. Cardiac rehabilitation reduces the risk of rehospitalization and all-cause mortality after AMI.[35] Early cardiac rehabilitation could significantly reduce cardiac death and rehospitalization.[36] Patients surviving AMI can benefit from phase I cardiac rehabilitation, including improvement of the prognosis[31] and the exercise capacity.[19] Our findings suggest that early-phase cardiac rehabilitation improves short and long-term outcomes for AMI patients. Individualized exercise prescriptions, based on cardiopulmonary fitness, should commence before AMI patient discharge.

Several limitations should be acknowledged in this study. First, the recruitment was confined to one medical center in southern Taiwan, impacting the generalizability to broader populations. Predominantly male patients were enrolled due to the center's characteristics. Second, while the sample size exceeded the minimal required size, it remained relatively small, potentially impacting the statistical power. Third, the study focused on survivors of the first AMI after successful PPCI, introducing selection bias and limiting the general applicability to those with more severe conditions. Fourth, we could not confirm the actual number of AMI patients admitted to our hospital or the specific count of patients with the first AMI after PPCI. Our database only contains the original number of first AMI patients referred for predischarge CPET, impacting the study's representativeness. Finally, our study included a significant proportion of smokers, and we acknowledge the potential impact of postoperative smoking cessation on their long-term outcomes. However, our current dataset does not encompass information regarding post-AMI smoking habits, including cessation. Future researches incorporate detailed information on smoking patterns on long-term outcomes should be warranted.

In conclusion, our study highlights OUES as a crucial prognostic marker at 3-month, 2-year, and 5-year follow-ups for AMI individuals. Identifying submaximal predictors, given the challenges AMI survivors face during CPET, underscores the importance of early post-AMI CPET for prognostic stratification and tailored exercise prescriptions in subsequent cardiac rehabilitation.

ACKNOWLEDGMENTS

The authors are grateful to all patients and their parents for participating in this study. The authors sincerely acknowledge department of Cardiology of Kaohsiung Veterans General Hospital for their kind patient referral and the help of statistical analysis from Professor Hui-Hsien Lin of Foo-Ying University, Kaohsiung, Taiwan.

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