

Early Cardiac Rehabilitation Improved Prognosis in Patients with Heart Failure Following Acute Myocardial Infarction

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Abstract

Background: Cardiac rehabilitation (CR) has been shown to improve exercise intolerance and QoL, and minimize re-hospitalizations in patients with congestive heart failure (CHF). However, studies on early CR in patients with acute myocardial infarction (AMI) who developed CHF following percutaneous coronary intervention (PCI) are rare. The purpose of this study is to evaluate the effectiveness of early CR on patients with CHF after AMI following PCI.

Methods: Two hundred thirty-seven patients who developed heart failure after AMI following PCI were enrolled. Patients were divided into heart failure with reduced ejection fraction (HFrEF) group and heart failure with mid-range ejection fraction (HFmrEF) group. Of which, 78 patients who accepted a two-week CR were further divided into two subgroups based on major adverse cardiovascular events (MACE). Key cardio-pulmonary exercise testing (CPX) variables that may affect the prognosis were identified through the comparison of the cardio-respiratory fitness (CRF).

Results: Early CR significantly reduced cardiac death in patients with HFrEF, and reduced re-hospitalization in patients with HFmrEF after AMI ($P < 0.01$). Serum potassium and CR ratio were independent risk factors for MACE in patients with both HFrEF and HFmrEF after AMI. In the CR group who developed MACE, there were more diabetics ($P=0.035$), with higher serum potassium ($P=0.043$), and lower $P_{ET}CO_2$ at VT ($P=0.016$). $P_{ET}CO_2$ at VT was an independent risk factor for re-hospitalization. The incidence of re-hospitalization was significantly lower when the $P_{ET}CO_2$ at VT was greater than 33.5mmHg ($P=0.03$).

Conclusions: Early CR reduced the incidence of MACE in patients with heart failure after AMI following PCI. The $P_{ET}CO_2$ at VT is an independent risk factor for re-hospitalization, and could be used as a key evaluating hallmark for early CR in patients who developed heart failure after AMI.

Background

Congestive heart failure (CHF) is a major cause of mortality and morbidity and the end pathophysiological condition of many cardiovascular diseases [1]. One of the leading causes of CHF is myocardial infarction. Percutaneous coronary intervention (PCI) significantly decreased the mortality in patients with acute myocardial infarction (AMI) [2]. However, CHF continues to develop in some patients before or soon after PCI.

Exercise intolerance, represented as decreased capacity to perform physical activities with symptoms of severe fatigue and/or dyspnea, is a characteristic of CHF and associated with increased mortality and reduced quality of life (QoL) [3]. The pathophysiological mechanisms of exercise intolerance in CHF are multifactorial, involving impaired cardiac and pulmonary reserve as well as decreased respiratory and peripheral skeletal muscle function [4]. In addition to conventional treatment, many researchers have shown that cardiac rehabilitation (CR) can improve exercise intolerance and QoL, and minimize re-hospitalizations in patients with CHF [5, 6]. However, studies on early CR in patients who developed CHF soon after AMI following PCI are scarce. A pilot study done by Houchen L et al. indicated that early CR could significantly reduce depression, enhance exercise tolerance and decrease CHF-associated hospital admission [7]. However, the study population was small and no control group was presented for comparison. In view of this, this study evaluated patients with CHF after AMI following PCI with

and without CR, and compared biochemical parameters and cardio-respiratory fitness (CRF), as well as long-term prognosis at 4 years follow-up.

Methods

Patient population:

From January 2015 to January 2016, patients admitted for acute ST elevation myocardial infarction with CHF following PCI were identified in the Department of Cardiology at the First Hospital of Jilin University. The study protocol was approved by the Institutional Review Board of the hospital.

Patients' baseline characteristics and biochemical parameters were collected from medical records. According to the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure^[8], patients were divided into heart failure with reduced ejection fraction (HFrEF) group and heart failure with mid-range ejection fraction (HFmrEF) group. In each group, patients were further divided into CR and non-CR subgroups. CR consisted 2 weeks exercise including 3 supervised regular exercise sessions per week on a bicycle^[9] and 4 supervised electrical stimulation sessions per week for no regular exercise day^[10]. Regular exercise session lasted for 20 minutes including warm-up and cool-down, and included three 3-minute intervals aiming at Borg 11–13 by subjective sensation separated by 2-minute recovery periods of 0 watt intensity^[9]. Electrical stimulation was performed 30 min/day, 4 days per week, using a dual-channel battery-powered stimulator Elpha-II 3000 (DANMETER® A/S, Odense, Denmark). The stimulator delivered a biphasic current of 25 Hz frequency. The electrical current characteristics were set up as follows: "on-off" mode stimulus (3 s stimulation, 6 s rest), pulse width 300us, rise and fall time 1 s. The intensity of the stimulation was adjusted to produce a visible muscle contraction but not too strong to make the patients uncomfortable^[10]. Adhesive electrodes were placed on both legs over the upper and lower aspects of gastrocnemius muscles, and over the upper-lateral and lower-medial portions of the quadriceps muscles. After the 2 weeks CR, patients were advised to continue individualized exercise at home for 3–4 sessions per week. Individualized exercise prescription was created based on each patient's CRF from cardio-pulmonary exercise testing (CPX) before discharge^[11]. Patients who accepted the 2-weeks CR were subsequently reassigned into two subgroups based on the major adverse cardiac events (MACE), namely the MACE group and the non-MACE group. The parameters of CRF between the two subgroups were compared, and the main CPX variables that may predict the prognosis of patients with CHF were identified.

Quantification of cardio-respiratory fitness

CPX, which is a widely accepted evaluation tool in both the United States and Europe^[12, 13], was used for the assessment of CRF. The measurement of ventilatory gas exchange was used to predict prognosis of death and re-hospitalization^[13–15]. In CR patients, the oxygen consumption (VO_2), carbon dioxide production (VCO_2), minute ventilation (VE), partial pressure of end-tidal carbon dioxide (PETCO_2), respiratory exchange ratio (RER) and other key CPX variables were measured with submaximal graded exercise test using Cardio-respiratory instrumentation Medisoft (Made in Belgium, Model:E100000011000001 N:130619–05-1470,) after 2-week CR. The exercise load was determined via a cycle ergometer work rate. The progressive load was 10 watts per minute during the graded exercise test. The exercise test was terminated if the patient developed any of the following subjective or objective conditions: abnormal hemodynamic or electrocardiographic exercise response, or other causes such as dyspnea, angina or lower extremity muscle fatigue.

Clinical follow-up

Follow-up data was acquired through hospital records and telephone interviews which were conducted every 3 months from discharge until cardiac death or July 2019, whichever came first. MACE including cardiac death and re-hospitalization were documented. Patients with cardiac death who lost telephone interviews were identified from the population registry bureau. The average duration of follow-up was 4 years.

Statistical analysis

Continuous variables were expressed as means \pm standard deviation, and non-normally distributed variables were presented as medians (interquartile range). Categorical variables were expressed as numbers and percentages. Variable parameters between the groups were compared with means of one-way analysis of variance, or Mann-Whitney U test for continuous variables and chi-square test for dichotomous variables, as appropriate. In all analyses, a two-tailed $p < 0.05$ was considered as statistical significance.

Cox multivariate regression analysis, in which test indices and variables showing $p < 0.05$ in the univariate analysis were included, was used to determinate independent risk factors for MACE. A receiver operating characteristic (ROC) curve was used to predict the prognosis for MACE. All statistical analysis data were performed using the SPSS 19 software (IBM Corp., Armonk, NY, USA).

Results

A total of 274 patients of AMI with CHF following PCI were identified, after excluding 21 patients who were lost to follow-up and 16 patients who were not able to participate cardiopulmonary exercise testing (CPX) (Table 1), 237 patients were included in the final analyses. Of which, 55 patients had HF_rEF ($n = 22$ in CR and $n = 33$ in non-CR group) and 182 had HF_mrEF ($n = 56$ in CR and $n = 126$ in non-CR group).

Table 1
The reason of not administering exercise prescriptions for the 16 patients

	Number of patients
Multiple organ failure	2
Uremia	2
Ankylosing spondylitis	6
Diabetic ketosis	1
Diabetic foot	1
Systemic lupus erythematosus	1
Tumours	1
After aortic stent implantation	1
Left ventricular apical thrombosis	1
Total	16

In HFrEF group, there were no significant differences in baseline characteristics between CR and non-CR groups except that the non-CR group patients were older with fewer smokers. In HFmrEF group, there were more male patients in non-CR group otherwise there were no significant differences in baseline characteristics between CR and non-CR groups (Table 2).

Table 2
Comparison of MACE (4 years) in two groups.

	HFrEF group(n = 55)			HFmrEF group(n = 182)		
	CR (n = 22)	NCR (n = 33)	P	CR (n = 56)	NCR (n = 126)	P
Sex, male (%)	17(77.3%)	26(78.8%)	1.000	36(64.3%)	99(78.6%)	0.046
Age (years)	57.09 ± 9.17	64.94 ± 7.81	0.001	58.84 ± 10.37	59.63 ± 12.47	0.677
History of hypertension, n (%)	13(59.1%)	15(45.5%)	0.412	29(51.8%)	60(47.6%)	0.633
History of diabetes, n (%)	6(27.3%)	12(36.4%)	0.565	14(25%)	36(28.6%)	0.720
Smoking history, n (%)	16(72.7%)	14(42.4%)	0.032	28(50%)	79(62.7%)	0.142
History of stroke, n (%)	2(9.1%)	2(6.1%)	1.000	1(1.8%)	9(7.1%)	0.285
WBC (10 ⁹ /L), median (IQR)	9.13 ± 3.22	10.36 ± 3.73	0.212	9.88 (7.70,12.89)	9.84 (7.83,12.44)	0.913
Platelet (10 ⁹ /L), median (IQR)	217.45 ± 67.00	197.42 ± 75.13	0.317	228.5 (186,271.75)	216.5 (180.5,245.25)	0.128
HGB (g/l)	139 ± 22.31	133.39 ± 20.31	0.339	141.68 ± 17.316	142.24 ± 18.165	0.846
Blood potassium (mmol/l)	4.06 ± 0.40	4.22 ± 0.53	0.229	3.92(3.66,4.14)	4.03(3.77,4.28)	0.123
Urea nitrogen (mmol/l), median (IQR)	6.19 ± 1.57	5.76 ± 2.30	0.451	5.27(4.20,6.27)	5.57(4.80,6.91)	0.136
Creatinine (umol/L), median (IQR)	76.70 (64.25,92.85)	80.00 (63.65,95.35)	0.904	63.80 (56.53,82.80)	70.65 (57.50,81.55)	0.541
AST (U/L), median (IQR)	108.3 (22.05,353.72)	120.4 (27.75,420.25)	0.327	71.65 (34.43,198.98)	94.60 (41.73,224.08)	0.151
ALT (U/L), median (IQR)	44.05 (25.33,76.45)	51.4 (20.7,93.8)	0.624	45.15 (24.20,67.63)	44.70 (28.68,69.00)	0.536

HFrEF: Heart failure with reduced ejection fraction, HFmrEF: Heart failure with mid-range ejection fraction, CR: Cardiac rehabilitation, NCR: Non cardiac rehabilitation, WBC: White blood cell, HGB: Hemoglobin, AST: Glutamic pyruvic transaminase, ALT: Glutamic pyruvic aminotransferase, HDL-C: High density lipoprotein cholesterol, non- HDL-C: non-High density lipoprotein cholesterol, TC: total cholesterol, FBS: Fasting blood sugar, EDLV: End diastolic diameter of left ventricle, EF: Ejection fraction, LM: The left main coronary artery, LAD: Left anterior descending branch, LCX: Left circumflex branch, RCA: Right coronary artery, MACE: major cardiac events, IQR: Interquartile range.

	HFrEF group(n = 55)			HFmrEF group(n = 182)		
HDL-C(mmol/l)	1.09 ± 0.23	1.16 ± 0.33	0.380	1.19(1.00,1.38)	1.21(1.00,1.52)	0.306
non-HDL-C (mmol/l)	3.58 ± 0.95	3.46 ± 1.28	0.707	3.60 ± 0.93	3.48 ± 1.07	0.467
TC (mmol/L), median (IQR)	1.46(1.07,2.03)	1.31(0.93,2.18)	0.525	1.33(1.00,2.02)	1.40(1.02,2.07)	0.832
FBS (mmol/L), median (IQR)	6.14 (5.51,7.39)	7.08 (5.84,11.04)	0.071	6.60(4.93,8.37)	6.59(5.37,9.50)	0.350
EDLV (mm)	58.09 ± 5.52	54.88 ± 6.13	0.053	52.04 ± 5.30	51.19 ± 5.02	0.304
EF (%), median (IQR)	34(31,37)	35(30,38)	0.938	46(42,48)	46(44,49)	0.050
Target lesion location						
LAD, n (%)	10(45.5%)	17(51.5%)	0.790	41(73.2%)	88(69.8%)	0.730
LCX, n (%)	2(9.1%)	3(9.1%)	1.000	2(3.6%)	6(4.8%)	1.000
RCA, n (%)	10(45.5%)	13(39.4%)	0.782	13(23.2%)	32(25.4%)	0.853
KILLIP class						
I, n (%)	0(0.0%)	0(0.0%)	-	0(0.0%)	0(0.0%)	-
II, n (%)	7(31.8%)	12(36.4%)	0.780	31(55.4%)	73(57.9%)	0.750
III, n (%)	12(54.5%)	10(30.3%)	0.100	13(23.2%)	28(22.2%)	1.000
IV, n (%)	3(13.6%)	11(33.3%)	0.130	12(21.4%)	25(19.8%)	0.840
Cardiogenic death, n (%)	0(0.0%)	11(33.3%)	0.002	0(0.0%)	9(7.1%)	0.059

HFrEF: Heart failure with reduced ejection fraction, HFmrEF: Heart failure with mid-range ejection fraction, CR: Cardiac rehabilitation, NCR: Non cardiac rehabilitation, WBC: White blood cell, HGB: Hemoglobin, AST: Glutamic pyruvic transaminase, ALT: Glutamic pyruvic aminotransferase, HDL-C: High density lipoprotein cholesterol, non- HDL-C: non-High density lipoprotein cholesterol, TC: total cholesterol, FBS: Fasting blood sugar, EDLV: End diastolic diameter of left ventricle, EF: Ejection fraction, LM: The left main coronary artery, LAD: Left anterior descending branch, LCX: Left circumflex branch, RCA: Right coronary artery, MACE: major cardiac events, IQR: Interquartile range.

	HFrEF group(n = 55)			HFmrEF group(n = 182)		
Rehospitalization, n (%)	4(18.2%)	9(27.3%)	0.528	2(3.6%)	27(21.4%)	0.002
	1(4.5%)	6(18.2%)	0.223	1(1.8%)	7(5.6%)	0.438
Myocardial infarction, n (%)	3(13.6%)	3(9.1%)	0.674	1(1.8%)	18(14.3%)	0.008
	0(0.0%)	0(0.0%)	-	0(0.0%)	2(1.6%)	1.000
Heart failure, n (%)						
Stroke, n (%)						
MACE, n (%)	4(18.2%)	20(60.6%)	0.002	2(3.6%)	36(28.6%)	< 0.001
HFrEF: Heart failure with reduced ejection fraction, HFmrEF: Heart failure with mid-range ejection fraction, CR: Cardiac rehabilitation, NCR: Non cardiac rehabilitation, WBC: White blood cell, HGB: Hemoglobin, AST: Glutamic pyruvic transaminase, ALT: Glutamic pyruvic aminotransferase, HDL-C: High density lipoprotein cholesterol, non- HDL-C: non-High density lipoprotein cholesterol, TC: total cholesterol, FBS: Fasting blood sugar, EDLV: End diastolic diameter of left ventricle, EF: Ejection fraction, LM: The left main coronary artery, LAD: Left anterior descending branch, LCX: Left circumflex branch, RCA: Right coronary artery, MACE: major cardiac events, IQR: Interquartile range.						

Incidence of major cardiovascular events

In the HFrEF group, non-CR patients had higher MACE rate ($P = 0.002$) due to higher incidence of cardiac death ($P = 0.002$) as compared to CR patients (Table 2, Fig. 1). In the HFmrEF group, non-CR patients had higher MACE rate ($P < 0.001$) due to higher incidence of heart failure (HF) re-hospitalization ($P = 0.008$) as compared to CR patients (Table 2, Fig. 1).

In HFrEF group, patients who developed MACE had higher serum potassium level ($P = 0.001$), lower left ventricular end diastolic diameter ($P = 0.018$) and CR ratio ($P = 0.002$) compared to patients who did not have MACE (Table 3). Serum potassium (OR = 2.793, 95%CI: 1.207–6.465, $P = 0.016$) and CR ratio (OR = 0.298, 95%CI: 0.099–0.902, $P = 0.032$) were independent risk factors for MACE of HFrEF patients, as shown in Table 5. In HFmrEF group, patients who developed MACE tended to be female ($P = 0.013$), older ($P < 0.001$), with history of stroke ($P = 0.035$), with lower hemoglobin ($P = 0.012$), higher serum potassium ($P = 0.009$), and lower the CR ratio ($P < 0.001$) (Table 4). Sex (OR = 2.411, 95%CI: 1.150–5.054, $P = 0.020$), age (OR = 1.039, 95%CI: 1.008–1.071, $P = 0.014$), history of stroke (OR = 3.628, 95%CI: 1.288–10.219, $P = 0.015$), serum potassium (OR = 3.054, 95%CI: 1.739–5.362, $P < 0.001$), CR ratio (OR = 0.115, 95%CI: 0.028–0.482, $P = 0.003$) were independent risk factors for MACE of HFmrEF patients, as shown in Table 6.

Table 3
Comparison of baseline data in the HFrEF group

	Non-MACE(n = 31)	MACE(n = 24)	P
Sex, male (%)	26(83.9%)	17(70.8%)	0.328
Age (years)	59.90 ± 8.24	64.25 ± 9.87	0.081
History of hypertension, n (%)	18(58.1%)	10 (41.7%)	0.282
History of diabetes, n (%)	7(22.6%)	11(45.8%)	0.087
Smoking history, n (%)	18(58.1%)	12(50.0%)	0.594
History of stroke, n (%)	4(12.9%)	0(0.0%)	0.123
WBC (10 ⁹ /L)	9.43 ± 3.16	10.43 ± 4.00	0.306
Platelet (10 ⁹ /L)	209.97 ± 69.14	199.58 ± 76.70	0.601
HGB (g/l)	140.39 ± 19.80	129.50 ± 21.57	0.057
Blood potassium(mmol/l)	3.97 ± 0.33	4.40 ± 0.54	0.001
Urea nitrogen(mmol/l)	6.26 ± 1.82	5.53 ± 2.33	0.196
Creatinine (umol/L), median (IQR)	80.90(66.70,92.90)	73.30(61.93,95.83)	0.524
AST (U/L), median (IQR)	89.70(25.20,363.70)	144.75(28.43,380.45)	0.333
ALT (U/L), median (IQR)	49.20(26.10,70.10)	55.15(22.33,126.3)	0.297
HDL-C (mmol/l)	1.13 ± 0.23	1.14 ± 0.36	0.936
non-HDL-C (mmol/l), median (IQR)	3.31(2.93,4.79)	3.29(2.36,3.88)	0.135
TC (mmol/L), median (IQR)	1.57(1.07,2.14)	1.23(0.82,2.00)	0.133
FBS (mmol/L), median (IQR)	6.14(5.43,8.74)	7.19(6.00,10.41)	0.058
EDLV (mm)	57.84 ± 5.67	54.00 ± 5.96	0.018
EF (%), median (IQR)	33.48 ± 4.96	33.58 ± 4.71	0.940
CR, n (%)	18(58.1%)	4(16.7%)	0.002
WBC: white blood cell, HGB: Hemoglobin, AST: Glutamic pyruvic transaminase, ALT: Glutamic pyruvic aminotransferase, HDL-C: High density lipoprotein cholesterol, non- HDL-C: non-High density lipoprotein cholesterol, TC: Total cholesterol, FBS: Fasting blood sugar, EDLV: End diastolic diameter of left ventricle, EF: Ejection fraction, CR: cardiac rehabilitation, MACE: major cardiac events, IQR: Interquartile range.			

Table 4
Comparison of baseline data in the HFmrEF group

	Non-MACE(n = 144)	MACE(n = 38)	P
Sex, male (%)	113(78.5%)	22(57.9%)	0.013
Age (years)	57.69 ± 11.64	65.84 ± 10.41	< 0.001
History of hypertension, n (%)	70(48.6%)	19(50%)	1.000
History of diabetes, n (%)	41(28.5%)	9(23.7%)	0.684
Smoking history, n (%)	90(62.5%)	17(44.7%)	0.063
History of stroke, n (%)	5(3.5%)	5(13.2%)	0.035
WBC (10 ⁹ /L)	10.53 ± 3.44	9.73 ± 2.64	0.184
Platelet (10 ⁹ /L)	218(181.75,250)	231.5(186.5,262.25)	0.365
HGB (g/l)	143.76 ± 17.38	135.63 ± 18.44	0.012
Blood potassium (mmol/l), median (IQR)	3.98(3.66,4.17)	4.12(3.89,4.41)	0.009
Urea nitrogen (mmol/l), median (IQR)	5.52(4.65,6.74)	5.57(5.03,6.38)	0.942
Creatinine (umol/L), median (IQR)	67.85(57.20,79.40)	74.40(58.40,85.88)	0.213
AST (U/L), median (IQR)	73.45(37.50,212.43)	101.40(47.58,243.68)	0.279
ALT (U/L), median (IQR)	44.50(25.95,68.13)	52.95(31.28,74.47)	0.158
HDL-C (mmol/l)	1.24 ± 0.34	1.27 ± 0.38	0.551
non-HDL-C(mmol/l), median (IQR)	3.48(2.95,4.08)	3.43(2.66,4.30)	0.783
TC (mmol/L), median (IQR)	1.40(1.04,2.00)	1.36(0.97,2.49)	0.753
FBS (mmol/L), median (IQR)	6.54(5.21,9.18)	6.62(5.88,9.61)	0.162
EDLV (mm)	51.52 ± 5.10	51.18 ± 5.19	0.719
EF (%), median (IQR)	46(44,49)	46(42,47)	0.095
CR, n (%)	54(37.5%)	2(5.3%)	< 0.001
WBC: white blood cell, HGB: Hemoglobin, AST: Glutamic pyruvic transaminase, ALT: Glutamic pyruvic aminotransferase, HDL-C: High density lipoprotein cholesterol, non- HDL-C: non-High density lipoprotein cholesterol, TC: Total cholesterol, FBS: Fasting blood sugar, EDLV: End diastolic diameter of left ventricle, EF: Ejection fraction, CR: cardiac rehabilitation, MACE: major cardiac events, IQR: Interquartile range.			

Table 5
Analysis of risk factors of MACE in patients with HFrEF (Cox multivariate regression analysis)

	OR	95% CI	<i>P</i>
EDLV (mm)	0.931	0.866–1.001	0.054
Blood potassium (mmol/l)	2.793	1.207–6.465	0.016
CR	0.298	0.099–0.902	0.032
EDLV:End diastolic diameter of left ventricle, CR: Cardiac rehabilitation.			

Table 6
Analysis of risk factors of MACE in patients with HFmrEF (Cox multivariate regression analysis)

	OR	95% CI	<i>P</i>
Sex, male (%)	2.411	1.150–5.054	0.020
Age(years)	1.039	1.008–1.071	0.014
HGB(g/l)	0.987	0.966–1.009	0.240
Blood potassium(mmol/l)	3.054	1.739–5.362	< 0.001
History of stroke (%)	3.628	1.288–10.219	0.015
CR	0.115	0.028–0.482	0.003
HGB: Hemoglobin, CR: Cardiac rehabilitation.			

The main CPX variables for prognosis prediction

The 78 patients who accepted the 2-weeks CR were subsequently reassigned into two subgroups based on the MACEs, namely the MACE group (n = 6) and the non-MACE group (n = 72) (Table 7).

Table 7
Comparison of baseline data in patients with cardiac rehabilitation

	Non-MACE(n = 72)	MACE(n = 6)	P
Sex, male (%)	49(68.1%)	4(66.7%)	1.000
Age (years)	58.93 ± 9.52	52.33 ± 6.95	0.103
History of hypertension, n (%)	39(54.2%)	3 (50.0%)	1.000
History of diabetes, n (%)	16(22.2%)	4(66.7%)	0.035
Smoking history, n (%)	40(55.6%)	4(66.7%)	0.691
History of stroke, n (%)	3(4.2%)	0(0.0%)	1.000
WBC (10 ⁹ /L), median (IQR)	9.55(7.55,12.35)	7.28(5.34,11.55)	0.195
Platelet(10 ⁹ /L)	230.4 ± 64.39	240.33 ± 73.55	0.721
HGB(g/l)	140.77 ± 18.53	134.00 ± 21.68	0.400
Blood potassium (mmol/l), median (IQR)	3.96(3.66,4.17)	4.31(3.96,4.63)	0.043
Urea nitrogen (mmol/l)	5.70 ± 1.57	5.30 ± 1.11	0.546
Creatinine (umol/L), median (IQR)	71.05(57.90,88.80)	73.80(62.03,129.95)	0.579
AST (U/L), median (IQR)	70.35(29.43,203.52)	70.50(33.60,167.83)	0.751
ALT (U/L), median (IQR)	41.40(23.30,65.30)	66.25(35.38,102.98)	0.111
HDL-C(mmol/l)	1.17 ± 0.25	0.99 ± 0.18	0.106
non-HDL-C (mmol/l), median (IQR)	3.48(3.01,4.18)	3.51(3.01,4.39)	1.000
TC (mmol/L), median (IQR)	1.40(1.08,2.00)	1.67(1.05,3.63)	0.559
FBS(mmol/L),median (IQR)	6.47(5.16,8.25)	6.20(5.26,7.77)	0.882
EDLV (mm)	53.66 ± 6.22	55.33 ± 5.28	0.526
EF (%), median (IQR)	42(39,46)	38.5(31.5,46.0)	0.179
HFrEF, n (%)	51(70.8%)	4(66.7%)	1.000

WBC: White blood cell, HGB: Hemoglobin, AST: Glutamic pyruvic transaminase, ALT: Glutamic pyruvic aminotransferase, HDL-C: High density lipoprotein cholesterol, non- HDL-C: non-High density lipoprotein cholesterol, TC: total cholesterol, FBS: Fasting blood sugar, EDLV: End diastolic diameter of left ventricle, EF: Ejection fraction, HFrEF: Heart failure with reduced ejection fraction, LM: The left main coronary artery, LAD: Left anterior descending branch, LCX: Left circumflex branch, RCA: Right coronary artery, R-HR: Rest heart rate, E-HR: Exercise Heart Rate, E-VE: Exercise Minute ventilation, Δ VE: Margin of Minute ventilation, VE/MVV%: The ratio of minute ventilation to the maximum expected value, VO_2 at VT: Oxygen consumption per kilogram of weight per minute at anaerobic threshold, E- VCO_2 : Exercise Carbon dioxide production, ΔVCO_2 : Margin of Minute ventilation Carbon dioxide production, VE/ VCO_2 slope: Minute ventilation/Carbon dioxide production, R- $P_{ET}CO_2$: Rest Partial pressure of end-tidal carbon dioxide, $P_{ET}CO_2$ at VT: Partial pressure of end-tidal carbon dioxide at anaerobic threshold, $\Delta P_{ET}CO_2$: Margin of Partial pressure of end-tidal carbon dioxide, MACE: major cardiac events, IQR: Interquartile range.

	Non-MACE(n = 72)	MACE(n = 6)	P
KILLIP class			
I, n (%)	0(0.0%)	0(0.0%)	-
II, n (%)	34(47.2%)	4(66.7%)	0.425
III, n (%)	23(31.9%)	2(33.3%)	1.000
IV, n (%)	15(20.8%)	0(0.0%)	0.590
Target lesion location			
LAD, n (%)	49(68.1%)	2(33.3%)	0.174
LCX, n (%)	3(4.2%)	1(16.7%)	0.279
RCA, n (%)	20(27.8%)	3(50.0%)	0.353
Rehospitalization, n (%)	0(0.0%)	6(100.0%)	< 0.001
Myocardial infarction, n(%)	0(0.0%)	2(33.3%)	0.005
Heart failure, n (%)	0(0.0%)	4(66.7%)	< 0.001
Stroke, n(%)	0(0.0%)	0(0.0%)	-
R-HR (bpm), median (IQR)	72(67,81)	79(56,90.5)	0.751
E-HR (bpm), median (IQR)	95(87,109)	105.5(89.75,118.25)	0.317

WBC: White blood cell, HGB: Hemoglobin, AST: Glutamic pyruvic transaminase, ALT: Glutamic pyruvic aminotransferase, HDL-C: High density lipoprotein cholesterol, non- HDL-C: non-High density lipoprotein cholesterol, TC: total cholesterol, FBS: Fasting blood sugar, EDLV: End diastolic diameter of left ventricle, EF: Ejection fraction, HFrEF: Heart failure with reduced ejection fraction, LM: The left main coronary artery, LAD: Left anterior descending branch, LCX: Left circumflex branch, RCA: Right coronary artery, R-HR: Rest heart rate, E-HR: Exercise Heart Rate, E-VE: Exercise Minute ventilation, Δ VE: Margin of Minute ventilation, VE/MVV%: The ratio of minute ventilation to the maximum expected value, VO_2 at VT: Oxygen consumption per kilogram of weight per minute at anaerobic threshold, E- VCO_2 : Exercise Carbon dioxide production, ΔVCO_2 : Margin of Minute ventilation Carbon dioxide production, VE/ VCO_2 slope: Minute ventilation/Carbon dioxide production, R- $P_{ET}CO_2$: Rest Partial pressure of end-tidal carbon dioxide, $P_{ET}CO_2$ at VT: Partial pressure of end-tidal carbon dioxide at anaerobic threshold, $\Delta P_{ET}CO_2$: Margin of Partial pressure of end-tidal carbon dioxide, MACE: major cardiac events, IQR: Interquartile range.

	Non-MACE(n = 72)	MACE(n = 6)	P
E-VE (L/min), median (IQR)	28.95(25.45,34.00)	30.95(22.88,35.42)	0.913
Δ VE (L/min), median (IQR)	16.80(13.73,21.20)	15.20(10.93,21.88)	0.586
VE/MVV (%), median (IQR)	28(25.25,31.75)	29.5(20.5,36.25)	0.992
VO ₂ at VT (ml/kg/min), median (IQR)	9(10,11)	9(7.5,11)	0.135
E-VCO ₂ (L/min), median (IQR)	0.70(0.61,0.85)	0.64(0.47,0.82)	0.383
Δ CO ₂ (L/min), median (IQR)	0.49(0.38,0.57)	0.39(0.25,0.56)	0.175
VE/VCO ₂ slope, median (IQR)	35.10(32.53,38.89)	36.34(35.98,42.86)	0.181
R-P _{ET} CO ₂ (mm Hg), median (IQR)	29(28,30)	28(26.25,30.25)	0.254
P _{ET} CO ₂ at VT (mm Hg), median (IQR)	33(32,34)	32(29,33)	0.016
Δ P _{ET} CO ₂ (mm Hg), median (IQR)	4(3,5)	3(1.25,4.25)	0.107
<p>WBC: White blood cell, HGB: Hemoglobin, AST: Glutamic pyruvic transaminase, ALT: Glutamic pyruvic aminotransferase, HDL-C: High density lipoprotein cholesterol, non- HDL-C: non-High density lipoprotein cholesterol, TC: total cholesterol, FBS: Fasting blood sugar, EDLV: End diastolic diameter of left ventricle, EF: Ejection fraction, HFrEF: Heart failure with reduced ejection fraction, LM: The left main coronary artery, LAD: Left anterior descending branch, LCX: Left circumflex branch, RCA: Right coronary artery, R-HR: Rest heart rate, E-HR: Exercise Heart Rate, E-VE: Exercise Minute ventilation, ΔVE: Margin of Minute ventilation, VE/MVV%: The ratio of minute ventilation to the maximum expected value, VO₂ at VT: Oxygen consumption per kilogram of weight per minute at anaerobic threshold, E-VCO₂: Exercise Carbon dioxide production, ΔVCO₂: Margin of Minute ventilation Carbon dioxide production, VE/VCO₂ slope: Minute ventilation/Carbon dioxide production, R-P_{ET}CO₂: Rest Partial pressure of end-tidal carbon dioxide, P_{ET}CO₂ at VT: Partial pressure of end-tidal carbon dioxide at anaerobic threshold, ΔP_{ET}CO₂: Margin of Partial pressure of end-tidal carbon dioxide, MACE: major cardiac events, IQR: Interquartile range.</p>			

Compared with non-MACE group, more patients in MACE group were diabetic (P = 0.035), had higher serum potassium (P = 0.043), higher incidence of heart failure re-hospitalization (P < 0.001) and myocardial infarction (P = 0.005), and lower P_{ET}CO₂ at VT (P = 0.016). P_{ET}CO₂ at VT was found to have predictive value for re-hospitalization. The area under the curve was 0.789 and the cut-off point was 33.5 mmHg (Fig. 3). P_{ET}CO₂ at VT was an independent risk factor for re-hospitalization (OR = 0.635, 95% CI: 0.463–0.871, P = 0.005), as shown in Table 8. The incidence of re-hospitalization was significantly lower when the P_{ET}CO₂ at VT was higher than 33.5 mmHg (P = 0.03) (Fig. 4).

Table 8
Analysis of risk factors of MACE in patients with rehabilitation (Cox multivariate regression analysis)

	OR	95% CI	P
P_{ET}CO₂ at VT (mmHg)	0.635	0.463–0.871	0.005
Blood potassium (mmol/l)	1.239	0.246–6.249	0.795
History of diabetes (%)	5.871	0.778–44.282	0.086
P _{ET} CO ₂ at VT: Partial pressure of end-tidal carbon dioxide at anaerobic threshold.			

Discussion

The present study is the first retrospective study evaluating early CR in patients with heart failure after AMI following PCI. The main findings of this study suggest that early CR was able to reduce cardiogenic death in patients with HFrEF, and reduce re-hospitalization in patients with HFmrEF after AMI. Furthermore, the intervention was safe; P_{ET}CO₂ at VT was an independent risk factor for re-hospitalization.

In patients with HF, research suggested that exercise-based CR could improve QoL, decrease all-cause hospital admissions and HF-dependent hospital admissions in the short term (up to 12 months) and potentially reduce mortality in the long term when compared to no exercise patients [16, 17]. Our study expands the previous research by showing that early rehabilitation program involving supervised regular exercise and electrical stimulation can reduce the incidence of cardiac death in patients with HFrEF, and heart failure re-hospitalization in patients with HFmrEF. Elevated serum potassium level and CR ratio were independent risk factors for cardiac death in HFrEF patients after AMI. Moreover, our study suggests that sex, age, history of stroke, and elevated serum potassium were independent risk factors for re-hospitalization in patients with HFmrEF after AMI. Thomsen et.al also reported that hyperkalemia was strongly associated with the degree of renal dysfunction and severe clinical outcomes as well as death in HF patients [18]. Houchen et.al found that a 6-week early rehabilitation program including exercise and self-management education, improved short-term exercise tolerance and depression [7]. However, the sample size was small in this study and there was no control group for comparison. With a larger study population and a non-CR control group, our results suggest that early CR was not only effective but also safe in patients with CHF soon after AMI.

Exercise intolerance is a major feature of CHF, and is associated with impaired QoL, reduced functional capacity and poor prognosis. In addition to reduced cardiac function, other causes such as reduced pulmonary reserve, impaired skeletal muscle function, etc can diversely and significantly contribute to the syndrome in CHF patients, and even turn into the dominant mechanisms of exercise intolerance [19]. Exercise can provide numerous benefits for CHF patients including decreased long-term morbidity and mortality [20], improved cardiac remodeling [21], increased neurovascular functional competency [22], reduced re-hospitalization and improved cardiorespiratory capacity and QoL [1, 23]. The benefits of electrical stimulation included improving blood supply and muscle strength, as well as exercise tolerance in severe CHF patients [24, 25], so it could be offered as an alternative to bicycle training as part of a home-based rehabilitation program [10]. In our study, the re-hospitalization in patients

who accepted the 2-week CR after PCI was only related to CRF, but not to serum potassium level or history of diabetes. The reason may be related to the protective effects of exercise on renal function and the improvement of glycolipid metabolism. Our previous research suggested that upregulation of nitric oxide synthases in the kidney and left ventricle may contribute, in part, to the renal and cardiac protective effects of exercise training in cardio renal syndrome in chronic heart failure rats ^[26]. Furthermore, exercise can reduce early diabetic nephropathy by upregulating nitric oxide synthases as well as ameliorating NADPH oxidase and α -oxoaldehydes in the kidneys of ZDF rats ^[27].

CRF is now being considered as an essential variable and should be assessed in health screenings ^[28]. The clinical values of CRF assessment include diagnosis, functional evaluation and prognosis prediction. CPX is the most precise tool to determine exercise tolerance and considered as the reference clinical procedure for assessing CRF by quantifying peak VO_2 which represents an individuals' capacity to generate energy for strenuous exercise ^[28]. CHF is a systemic syndrome with the reduction of functional reserve being the outstanding characteristic. The cardiovascular impairment has a direct negative effect on other systems and organs, including the respiratory, renal and neuromuscular systems. CPX is defined as "gold standard" for the CRF of patients with cardiovascular disease, the clinical diagnosis assessment and prognosis prediction can be achieved from direct measurement of VO_2 , VCO_2 and VE ^[29]. The characteristic of CPX data in patients with CHF are: decreased VO_2 at $\text{VT} < 40\%$ of the predicted $\text{VO}_{2\text{max}}$, O_2 pulse $< 85\%$ and as a plateau, increased VE/VCO_2 , wide breathing reserve and usually normal O_2 saturation ^[29, 30]. Weber et al. first published a classification for peak VO_2 results: class A, $\text{VO}_2 > 20 \text{ ml/kg/min}$; class B, $\text{VO}_2 16\text{-}20 \text{ ml/kg/min}$; class C, $\text{VO}_2 10\text{-}15 \text{ ml/kg/min}$; and class D, $\text{VO}_2 < 10 \text{ ml/kg/min}$ ^[31]. Arena et al. further proposed the classification based on ventilation/carbon dioxide production relationship (VE/VCO_2 slope) values: class I, $\text{VE}/\text{VCO}_2 \text{ slope} \leq 29.9$; class II, $\text{VE}/\text{VCO}_2 \text{ slope } 30\text{-}35.9$; class III, $\text{VE}/\text{VCO}_2 \text{ slope } 36\text{-}44.9$; class IV, $\text{VE}/\text{VCO}_2 \text{ slope} \geq 45$ ^[32]. Ferreira et al. noted that the cutoff point of $\text{VE}/\text{CO}_2 \text{ slope} \geq 43$ would be an appropriate hallmark for heart transplantation determination ^[33]. Chua et al. found that CHF patients with $\text{VE}/\text{VCO}_2 \text{ slope} > 34$ were at very high risk for death and re-hospitalization ^[34]. The 2012 EACPR/AHA scientific statement endorsed that peak VO_2 and VE/VCO_2 slope are the most studied CRF variables in CHF patients and both indicated significantly independent prognostic value ^[11]. For patients under medical treatment, a peak $\text{VO}_2 < 10.0 \text{ ml/kg/min}$ and a $\text{VE}/\text{VCO}_2 \text{ slope} \geq 45$ exist at the same time would indicate a very poor prognosis over the following 4-year ^[11]. It should be noted that, in order to achieve the prediction accuracy of peak VO_2 value on CHF, maximal exercise (at least $\text{RER} > 1.05$) should be achieved during the test ^[29]. Others evaluating the long term prognosis by VE/VCO_2 slope in CHF, and reported that it was an excellent independent value, even better than peak VO_2 , and could be achieved only from sub-maximal exercise ^[35, 36]. Similarly our results indicated that CR patients with $\text{VE}/\text{VCO}_2 \text{ slope} < 36$ had a good cardiovascular prognosis.

However, it is difficult to achieve a maximal test in most CHF patients due to the exercise intolerance. The 2016 EACPR/AHA updated the scientific statement, and felt that it is important to note that VO_2 at VT holds broad applicability in the context of assessing the capacity ^[37]. The VO_2 at VT has also been indicated as a hallmark for the prognosis prediction prior to surgery ^[38, 39]. Furthermore, we also showed that VO_2 at VT is a significant prognostic marker for AMI patients in whom a VO_2 at $\text{VT} < 10.5 \text{ ml/kg/min}$ indicated a poor long term prognosis ^[40]. The P_{ETCO_2} both at rest and in exercise have been found to be positively correlated with the prognosis of systolic heart failure ^[41]. Abnormalities in the VE/VCO_2 slope and P_{ETCO_2} in patients with HCM have been thought

to enhance pulmonary pressures^[31, 41]. In the present study, we noted that $P_{ET}CO_2$ at VT was also a predictor of re-hospitalization for patients with CHF after AMI, previous study showed that a lower $P_{ET}CO_2$ was associated with a poor prognosis^[40].

Our previous study demonstrated that VO_2 at VT was an independent risk factor for cardiovascular disease prognosis and could be used as an evaluating hallmark for Phase I cardiac rehabilitation in patients with STEMI after PCI^[40]. However, the $P_{ET}CO_2$ at VT is an independent risk factor for re-hospitalization in patients with heart failure after AMI. The reasons of the difference may be as follows: first, patients with STEMI after PCI may not have reduced ejection fraction and severe pulmonary dysfunction after PCI operation, a smaller amount of $P_{ET}CO_2$ is an indicator of less CO_2 production in the body and/or pulmonary arterial perfusion, or in other words, the cardiac output^[42]. The difference in $P_{ET}CO_2$ might be attribute to the difference in infarct location. VO_2 at VT is determined not only by the degree of the infarct area but also the peripheral oxygen utilization efficiency, and could be an independent risk factor for the prognosis in patients with STEMI after PCI. Second, ventilation is regulated by the sensitivity of respiratory chemo-receptors and the ergo reflex in skeletal muscles. The sensitivity of respiratory chemo-receptors increases when the sympathetic nerve is activated and/or acidosis occurs. These conditions often occur in HF patients^[43]. These subjects experience shortness of breath throughout mild to vigorous activity. While in insufficiently expansion and with increased dead space between artery and alveolus, diffusion of CO_2 is less, hence, $P_{ET}CO_2$ decreases. The re-hospitalization associated with exercise intolerance in patients with CHF are multifactorial, including impaired cardiac and pulmonary reserve, and decreased respiratory and peripheral skeletal muscle function, all of them can diversely and significantly contribute to the decrease in $P_{ET}CO_2$. The combined aerobic/resistance/inspiratory training in patients with CHF has been shown to produce positive changes in left ventricular structure and function, which provided additional benefits in both peripheral and diaphragmatic muscle function, dyspnea, cardiopulmonary exercise parameters and QoL^[44].

The limitations of this study include: 1) this is a retrospective study in which patients were not randomly assigned to CR or non-CR group, thus selective bias cannot be avoided; 2) patients in the non-CR group were not assessed for CRF using CPX before discharge; 3) the number of MACE in the early CR group was relatively small. Therefore, further research is needed to confirm the influence of CPF parameters on prognosis prediction and the accuracy of cut-off point value.

Conclusions

In conclusion, an early CR decreased the incidence of cardiovascular events in patients with CHF after AMI following PCI. Elevated serum potassium and CR ratio were independent risk factors for MACE in patients not only with HF_rEF but also with HF_mrEF after AMI. The $P_{ET}CO_2$ at VT was an independent risk factor for re-hospitalization, and could be used as a key evaluating hallmark for early CR in patients with CHF after AMI.

List Of Abbreviations

AMI: acute myocardial infarction

CHF: congestive heart failure

CR: cardiac rehabilitation

PCI: percutaneous coronary intervention

HFrEF: heart failure with reduced ejection fraction

HFmrEF: heart failure with mid-range ejection fraction

MACE: major adverse cardiovascular events

CPX: cardio-pulmonary exercise testing

CRF: cardio-respiratory fitness

QoL: quality of life

VO₂: oxygen consumption

VCO₂: carbon dioxide production

VE: minute ventilation

P_{ET}CO₂: partial pressure of end-tidal carbon dioxide

RER: respiratory exchange ratio

ROC: receiver operating characteristic

WBC: white blood cell

Cr: creatinine

AST: glutamic pyruvic transaminase

ALT: glutamic pyruvic aminotransferase

TC: total cholesterol

HDL-C: high-density lipoprotein cholesterol

non-HDL-C: non high-density lipoprotein cholesterol

FBG: fasting blood glucose

HGB: hemoglobin

EDLV: End diastolic diameter of left ventricle

EF: Ejection fraction

Declarations

Ethics approval and consent to participate

This work was approved by Medical Ethics Committee of The First Hospital of Jilin University (approval Number: 2016-281) and was exempted from the requirement for informed consent. All information used for data analysis in this study was anonymized.

Consent for publication

Not applicable.

Availability of data and materials

The data used to support the findings of this study are available from the corresponding author upon request.

Competing interests

The authors declare that they have no competing interests, and all authors should confirm its accuracy.

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Authors' contributions

P.C. and Y.Z. conceived and designed the study. H.C., Z.L., X.Z., R.L., W.S., L.W. and L.Z. performed the experiments and statistical analysis. H.C. wrote the paper. P.C. and Y.Z. reviewed and edited the manuscript. All authors read and approved the manuscript.

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Figures

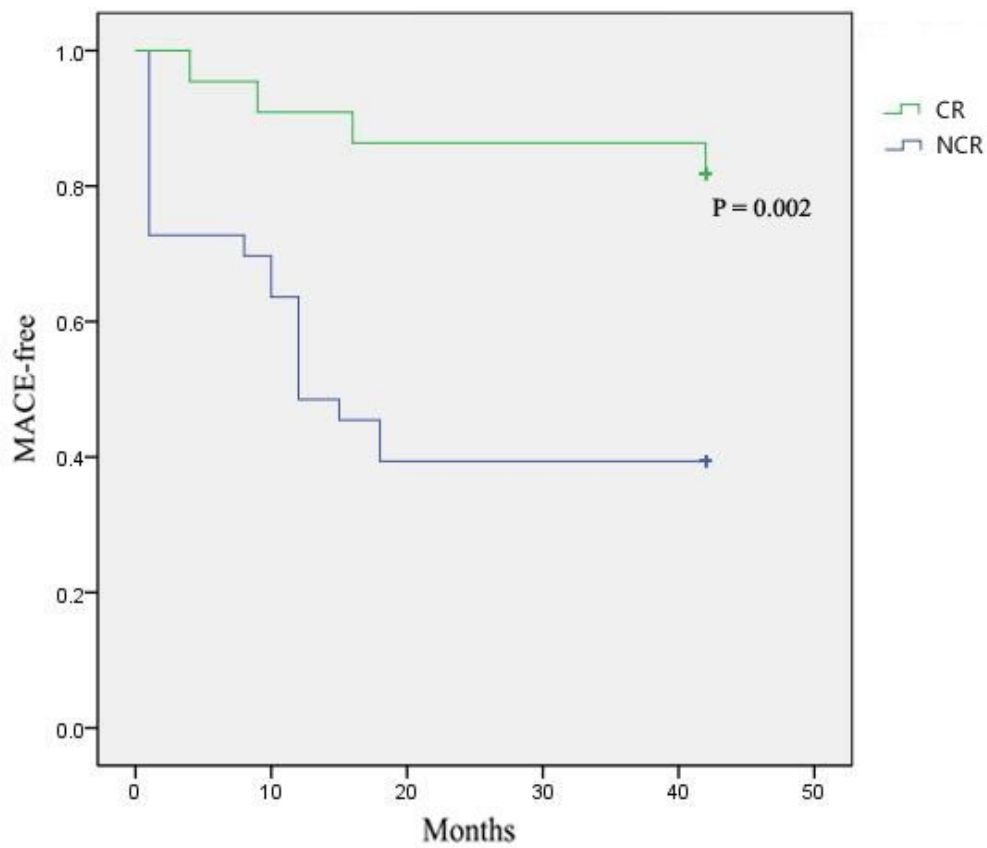


Figure 1

The Kaplan-Mayer curves of MACE-free survival in the HFrEF group. CR: cardiac rehabilitation, NCR: non cardiac rehabilitation, MACE: major cardiac events.

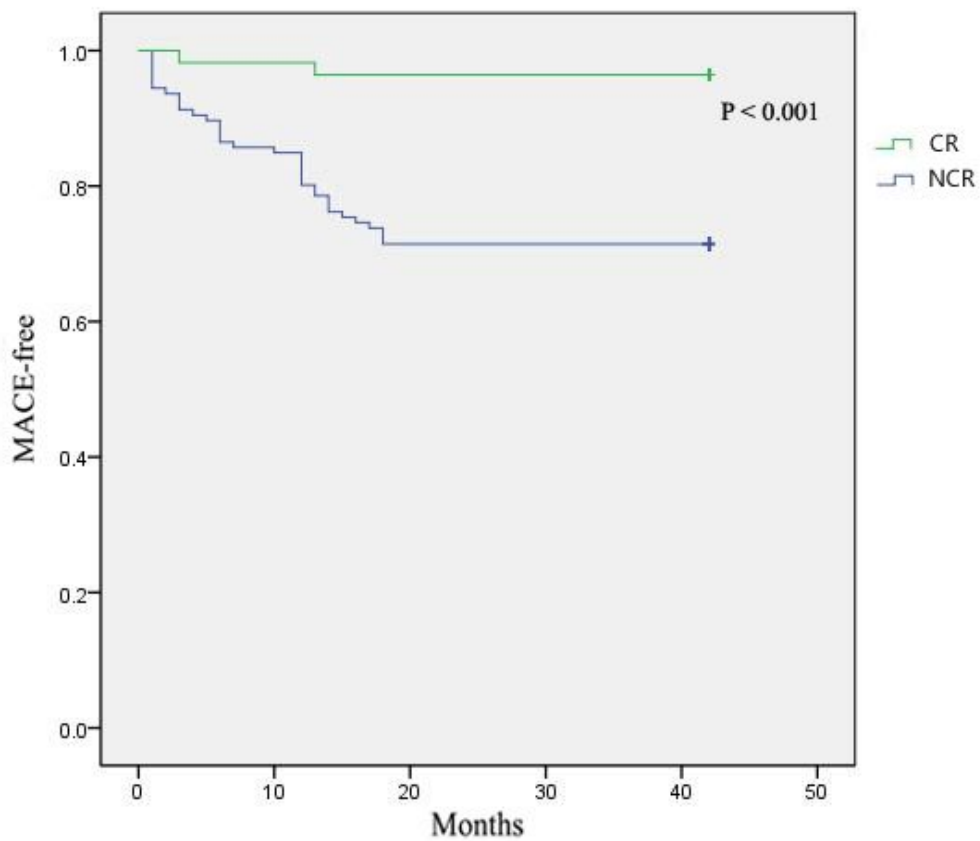


Figure 2

The Kaplan-Mayer curves of MACE-free survival in the HFmrEF group. CR: cardiac rehabilitation, NCR: non cardiac rehabilitation, MACE: major cardiac events.

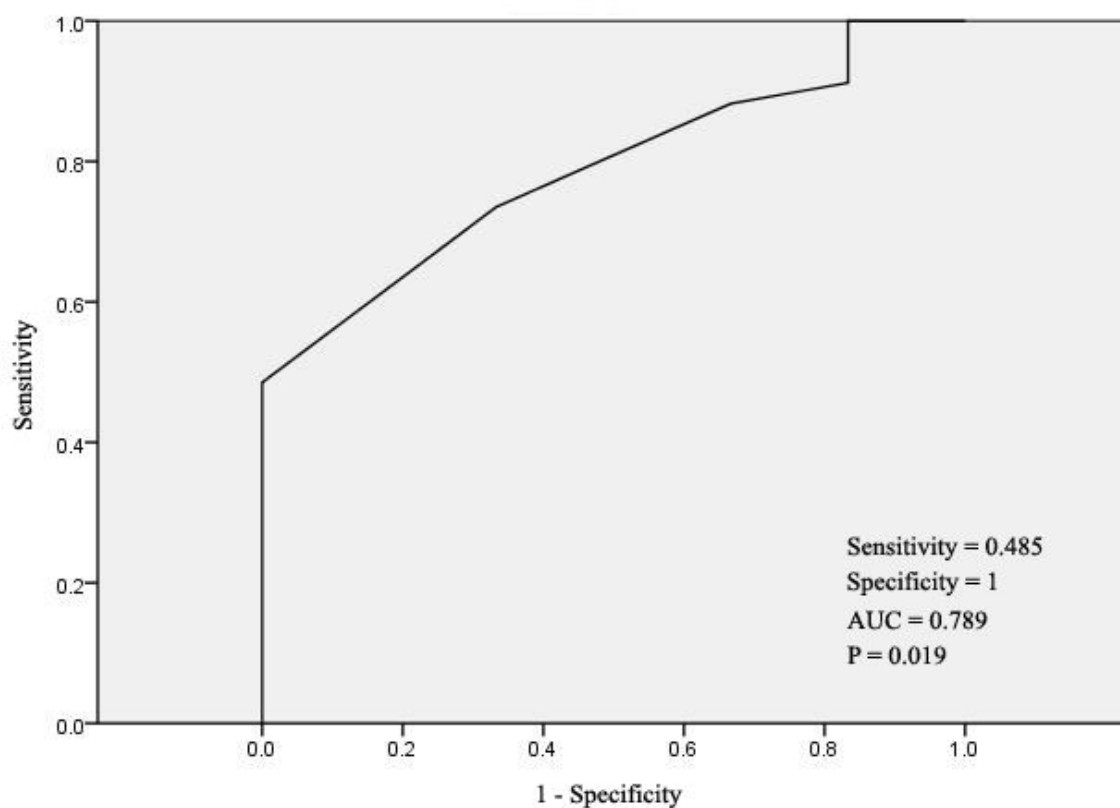


Figure 3

The ROC curve of PETCO₂ at VT. PETCO₂ at VT: Partial pressure of end-tidal carbon dioxide at anaerobic threshold.

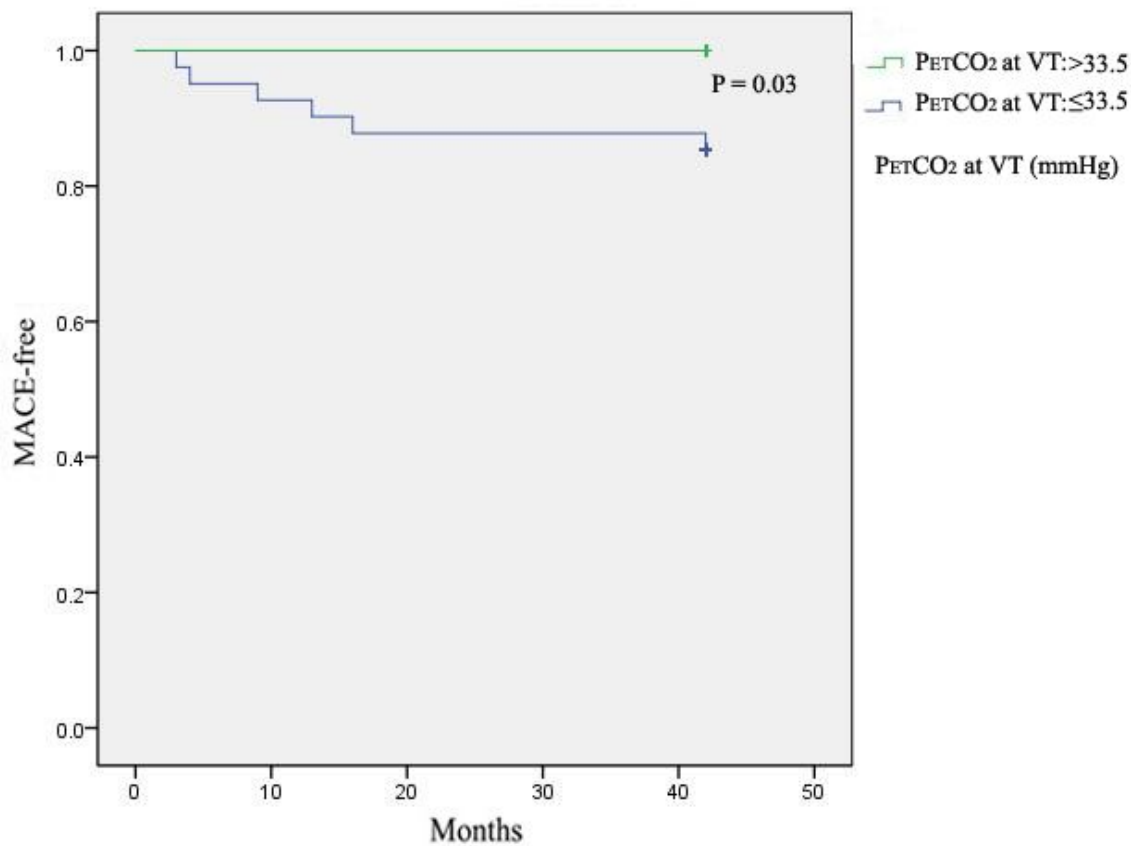


Figure 4

The Kaplan-Mayer curves of MACE-free survival in patients with rehabilitation. PETCO₂ at VT: Partial pressure of end-tidal carbon dioxide at anaerobic threshold; MACE: major cardiac events.