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 (n=55) and heart failure with mid-range ejection fraction (HFmrEF) group (n=182). Of the 237 patients, 78 (22 in HFrEF group and 56 in HFmrEF group) 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 among the CR patients.

Results: Early CR significantly reduced cardiac death in patients with HFrEF (18.2% vs. 60.6%, P=0.02), and reduced re-hospitalization in patients with HFmrEF after AMI (3.6% vs. 21.4%, P=0.02). 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 (22.2% vs. 66.7%, P=0.035), with higher serum potassium (3.96mmol/l vs. 4.31mmol/l, P=0.043), and lower PETCO2 at ventilatory threshold (VT) (P=0.016). PETCO2 at VT was an independent risk factor for re-hospitalization. The incidence of re-hospitalization was significantly lower when the PETCO2 at VT was greater than 33.5mmHg (0(0.00% vs. 6(13.64%), P=0.03).

Conclusions: Early CR reduced the incidence of MACE in patients with heart failure after AMI following PCI. The PETCO2 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. It 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 secondary prevention through comprehensive cardiac rehabilitation (CR) were the most cost-effective intervention to ensure favourable outcomes, to improve exercise capacity and QoL, and to minimize re-hospitalizations in patients with CHF [5-7]. Furthermore, the use of web-based and mobile applications, telephonic interviews, and various wearable activity-tracking devices provides opportunities to regularly engage CR patients in secondary prevention at home, and has the potential to substantially increase accessibility, reduce costs, and improve prognosis [8]. 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 [9].Unfortunately, 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, AMI patients with CHF following PCI were identified in the Department of Cardiology at the First Hospital of Jilin University, a large comprehensive tertiary hospital with over 2,000 beds. 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 [10], 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 of 2 weeks of exercise including 3 supervised regular exercise sessions per week on a bicycle (Resistance System: Electromagnetically braked resistance, Power Requirements: Self-generated, Watt: 250 Watts, Heart Rate Monitor: Wireless and Contact Grips)[11] and 4 supervised electrical stimulation sessions per week for no regular exercise day [12]. 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 [11]. Electrical stimulation was performed 30min/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 25Hz frequency. The electrical current characteristics were set up as follows: "on–off" mode stimulus (3s stimulation, 6s rest), pulse width 300us, rise and fall time 1s. The intensity of the stimulation was adjusted to produce a visible muscle contraction but not too strong to make the patients uncomfortable [12]. 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. Individualized exercise prescription was created based on each patient's CRF from cardio-pulmonary exercise testing

(CPX) before discharge. The home exercise program included 3-4 sessions of walk or bicycle per week, in which the target training intensity was set at heart rate corresponding to ventilatory threshold (VT)[13]. 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 CPX 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 was used for the assessment of CRF, which is a widely accepted evaluation tool in both the United States (US) and Europe [14, 15]. The measurement of ventilatory gas exchange was used to predict prognosis of death and re-hospitalization [15-17]. 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:E100000011000001N:130619–05-1470,) after 2-week CR. The exercise load was determined by a cycle ergometer (egoselect 100 Typ: P mit BD, ergoline GmbH) work rate. The progressive load was 10 watts per minute during the graded exercise test, and the pedaling cadence kept 55-65 revolutions per minute (RPM) throughout the test. The exercise test was terminated if the patient developed any of the following subjective or objective conditions: abnormal hemodynamic or ECG 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 July2019, 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 ± 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.

Corrections were made to account for the multiple comparisons by cox multivariate regression analysis, in which test indices and variables showing a p-value< 0.05 in the univariate analysis were included, and were used to distinguish 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 AMI patients with CHF following PCI were identified, 21 patients who were lost to follow-up and 16 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 thrombus:1) who were not able to participate cardiopulmonary exercise testing (CPX) were excluded. 237 patients were included in the final analyses, 55 patients had HFrEF (n=22 in CR and n=33 in non-CR group) and 182 had HFmrEF (n=56 in CR and n=126 in non-CR group).

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 (64.94±7.81 vs. 57.09±9.17, P=0.001) with fewer smokers (42.4% vs. 72.7% P=0.032) (Table 1). In HFmrEF group, there were more male patients in non-CR group (78.6% vs. 64.3%, P=0.046) otherwise there were no significant differences in baseline characteristics between CR and non-CR groups (Table 2).

Incidence of major cardiovascular events

In the HFrEF group, non-CR patients had higher MACE rate (60.6% vs. 18.2%, P=0.002) due to higher incidence of cardiac death (33.3% vs. 0.00%, P=0.002) as compared to CR patients (Table 1, Figure 1). In the HFmrEF group, non-CR patients had higher MACE rate (28.6% vs. 3.6%, P<0.001) due to higher incidence of heart failure (HF) re-hospitalization (14.3% vs. 1.8%, P=0.008) as compared to CR patients (Table 2, Figure 2).

In HFrEF group, patients who developed MACE had higher serum potassium level (4.40±0.54 mmol/l vs. 3.97±0.33 mmol/l, P = 0.001), lower end diastolic diameter of left ventricular (EDLV) (54.00±5.96 mm vs. 57.84±5.67 mm, P=0.018)and CR ratio (16.7% vs. 58.1%, 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, but not EDLV (OR=0.931，95%CI: 0.866-1.001，P=0.054). In HFmrEF group, patients who developed MACE tended to be female (P=0.013), older (65.84±10.41 vs. 57.69±11.64, P<0.001), with history of stroke (13.2%, vs. 3.5%, P=0.035), with lower hemoglobin (135.63±18.44 g/l vs. 143.76±17.38 g/l, P=0.012), higher serum potassium (4.12 mmol/l vs. 3.98 mmol/l, P = 0.009), and lower the CR ratio (5.3% vs. 37.5%, 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), and CR ratio (OR =0.115，95% CI: 0.028-0.482，P=0.003) were independent risk factors for MACE of HFmrEF patients, but not hemoglobin (OR =0.987，95% CI: 0.966-1.009，P=0.240)
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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 5).

Compared with non-MACE group, more patients in MACE group were diabetic (66.7% vs. 22.2%, P=0.035), had higher serum potassium (4.31mmol/l vs. 3.96mmol/l, P=0.043), higher incidence of heart failure re-hospitalization (P<0.001) and myocardial infarction (P=0.005), and lower $P_{ET}CO_2$ at VT (P=0.016) (Table 5).$P_{ET}CO_2$ 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 33.5mmHg (Figure 3). $P_{ET}CO_2$ at VT was an independent risk factor for re-hospitalization (OR=0.635, 95% CI: 0.463-0.871, P=0.005), but not serum potassium (OR=1.239, 95% CI: 0.246-6.249, P=0.795) and history of diabetes (OR=5.871, 95% CI: 0.778-44.282, P=0.086). The incidence of re-hospitalization was significantly lower when the $P_{ET}CO_2$ at VT was higher than 33.5mmHg (0(0.00% vs. 6(13.64%), P=0.03) (Figure 4).

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; $P_{ET}CO_2$ 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 [18, 19]. 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 [20]. Though two-week intervention in the CR-group seems quite short to make such a big effect on the outcome, possible reasons are: First, although the two-week early rehabilitation has little effect on cardiac function, the enhancement of lower limb muscle endurance could have improved the exercise intolerance of these patients, and it could make the patients interested in exercise rehabilitation and enhance their confidence in improving the QoL. Second, before discharge, individualized exercise prescription was made for CR patients according to VT level by CPX, so each patient knew how much exercise intensity and how long exercise time was safe and effective at home. Through tailored exercise experience, they could feel at ease rather than fear for exercise. As a result, they could continue their exercise after discharge. Third, every three months at follow-up, the CR patients would be reminded to

exercise according to the individualized exercise prescription. However, the non-CR patients were only reminded to exercise moderately. Taken together, the greater role of early rehabilitation is to provide physical fitness reserve and mental self-confidence for the continuous implementation of long-term exercise rehabilitation at home. Typically, an outpatient CR for secondary prevention includes 3-4 weekly supervised exercise and educational sessions for 12 weeks. Despite the health benefits associated with these interventions, few cardiovascular patients could complete such programs. Similar to our study, recent research found that early hospital practice guidance, tailored physical activity intervention and follow-up (1, 2, 3, and4 months after hospital discharge) at home can effectively improve physical performance, QoL, and frailty status in elderly acute coronary syndrome patients [21, 22]. Taken together, an important role is played by early CR that helps patients to make home-based tailored exercise a habit and maintain their improvement. This can help to overcome the main limitations of typical outpatient CR, such as the high number of sessions, high costs, low compliance and lack of long-term maintenance of an active lifestyle.

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 [23]. Exercise can provide numerous benefits for CHF patients including decreased long-term morbidity and mortality [24], improved cardiac remodeling [25], increased neurovascular functional competency [26], reduced re-hospitalization and improved of cardiorespiratory capacity and QoL [1, 27]. The benefits of electrical stimulation included improving blood supply and muscle strength, as well as exercise tolerance in severe CHF patients [28, 29], so it could be offered as an alternative to bicycle training as part of a home-based rehabilitation program [12]. 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 cardiorenal syndrome in chronic heart failure rats [30]. 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 zucker diabetic fatty (ZDF) rats [31].

CRF is now being considered as an essential variable and should be assessed in health screenings [32]. 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 [32].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 [33].The characteristic of CPX data in patients with CHF are: decreased VO_2 at VT < 40% of the predicted VO_2max, O_2 pulse < 85% of the age-predicted value and as a plateau, increased VE/VCO_2, wide breathing reserve and usually normal O_2 saturation [33, 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 [13].For patients under medical treatment, a peak VO_2<10.0 ml/kg/min and a VE/VCO_2 slope ≧45 exist at the same time would indicate a very poor prognosis over the following 4-year[13].Similarly our results indicated that CR patients with VE/VCO_2 slope<36 had a good cardiovascular prognosis. 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].

It should be noted that, in order to achieve the prediction accuracy of peak VO_2 value on CHF, maximal exercise (at least RER>1.05) should be achieved during the test[33]. 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 VT <10.5 ml/kg/min indicated a poor long term prognosis [40]. The $P_{ET}CO_2$ both at rest and in exercise have been found to be positively correlated with the prognosis of systolic heart failure [41]. Abnormalities in the $P_{ET}CO_2$ in patients with HCM have been thought to enhance pulmonary pressures [41, 42].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.

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 acute ST segment elevation myocardial infarction (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 [43]. The difference in $P_{ET}CO_2$ might be attributed 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 [44]. 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[45].

The limitations of this study include: (1) The patients in the non-CR group were not assessed for CRF using CPX before discharge. So, it is not clear which parameters of cardiopulmonary fitness (cardiac outcome or pulmonary reserve or peripheral skeletal muscle function) can be improved by early rehabilitation in two weeks. (2) The number of re-hospitalized patients who participated in early CR was low. Therefore, the influence of CRF parameters on prognosis prediction and the accuracy of cut-off value needs further research. (3) Lack of home exercise data in CR group and non-CR group, so further research is needed to explore the influence of early CR on home-based healthy lifestyle development and the influence of home exercise amount on long-term prognosis.

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 HFrEF but also with HFmrEF 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

STEMI：acute ST segment elevation myocardial infarction

ZDF：zucker diabetic fatty

MACE: major adverse cardiovascular events

CPX: cardio-pulmonary exercise testing

CRF: cardio-respiratory fitness

QoL: quality of life

VO_2: oxygen consumption

VCO_2: carbon dioxide production

VE: minute ventilation

$P_{ET}CO_2$: partial pressure of end-tidal carbon dioxide

RER: respiratory exchange ratio

ROC: receiver operating characteristic

WBC: white blood cell

Cr: creatinine

AST: glutamic pyruvic ransaminase

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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Tables

Table 1. Baseline characteristics and MACE (4 years) of CR patients and NCR patients with HFrEF

	HFrEF group（n=55）		
	CR （n=22）	NCR （n=33）	P
Sex, male (%)	17(77.3%)	26(78.8%)	1.000
Age (years)	57.09±9.17	64.94±7.81	0.001
History of hypertension, n(%)	13(59.1%)	15(45.5%)	0.412
History of diabetes, n(%)	6(27.3%)	12(36.4%)	0.565
Smoking history, n(%)	16(72.7%)	14(42.4%)	0.032
History of stroke, n (%)	2(9.1%)	2(6.1%)	1.000
WBC (10^9/L), median (IQR)	9.13±3.22	10.36±3.73	0.212
Platelet (10^9/L) , median (IQR)	217.45±67.00	197.42±75.13	0.317
HGB (g/l)	139±22.31	133.39±20.31	0.339
Blood potassium (mmol/l)	4.06±0.40	4.22±0.53	0.229
Urea nitrogen (mmol/l) , median (IQR)	6.19±1.57	5.76±2.30	0.451
Creatinine (umol/L), median (IQR)	76.70 (64.25,92.85)	80.00 (63.65,95.35)	0.904
AST (U/L), median (IQR)	108.3 (22.05,353.72)	120.4 (27.75,420.25)	0.327
ALT (U/L), median (IQR)	44.05 (25.33,76.45)	51.4 (20.7,93.8)	0.624
HDL-C(mmol/l)	1.09±0.23	1.16±0.33	0.380
non-HDL-C (mmol/l)	3.58±0.95	3.46±1.28	0.707
TC (mmol/L), median (IQR)	1.46(1.07,2.03)	1.31(0.93,2.18)	0.525
FBS(mmol/L), median (IQR)	6.14 (5.51,7.39)	7.08 (5.84,11.04)	0.071
EDLV(mm)	58.09±5.52	54.88±6.13	0.053
EF(%), median (IQR)	34(31,37)	35(30,38)	0.938
Target lesion location			
LAD, n (%)	10(45.5%)	17(51.5%)	0.790
LCX, n (%)	2(9.1%)	3(9.1%)	1.000
RCA, n (%)	10(45.5%)	13(39.4%)	0.782
KILLIP class			

I, n (%)	0(0.0%)	0(0.0%)	-
II, n (%)	7(31.8%)	12(36.4%)	0.780
III, n (%)	12(54.5%)	10(30.3%)	0.100
IV, n (%)	3(13.6%)	11(33.3%)	0.130
Cardiogenic death, n (%)	0(0.0%)	11(33.3%)	0.002
Rehospitalization, n (%)	4(18.2%)	9(27.3%)	0.528
Myocardial infarction, n(%)	1(4.5%)	6(18.2%)	0.223
Heart failure, n (%)	3(13.6%)	3(9.1%)	0.674
Stroke, n(%)	0(0.0%)	0(0.0%)	-
MACE, n (%)	4(18.2%)	20(60.6%)	0.002

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.

Table 2. Baseline characteristics and MACE (4 years) of CR patients and NCR patients with HFmrEF.

	HFmrEF group（n=182）		
	CR （n=56）	NCR （n=126）	P
Sex, male (%)	36(64.3%)	99(78.6%)	0.046
Age (years)	58.84±10.37	59.63±12.47	0.677
History of hypertension, n(%)	29(51.8%)	60(47.6%)	0.633
History of diabetes, n(%)	14(25%)	36(28.6%)	0.720
Smoking history, n(%)	28(50%)	79(62.7%)	0.142
History of stroke, n (%)	1(1.8%)	9(7.1%)	0.285
WBC (10^9/L), median (IQR)	9.88 (7.70,12.89)	9.84 (7.83,12.44)	0.913
Platelet (10^9/L) , median (IQR)	228.5 (186,271.75)	216.5 (180.5,245.25)	0.128
HGB (g/l)	141.68±17.316	142.24±18.165	0.846
Blood potassium (mmol/l)	3.92(3.66,4.14)	4.03(3.77,4.28)	0.123
Urea nitrogen (mmol/l) , median (IQR)	5.27(4.20,6.27)	5.57(4.80,6.91)	0.136
Creatinine (umol/L), median (IQR)	63.80 (56.53,82.80)	70.65 (57.50,81.55)	0.541
AST (U/L), median (IQR)	71.65 (34.43,198.98)	94.60 (41.73,224.08)	0.151
ALT (U/L), median (IQR)	45.15 (24.20,67.63)	44.70 (28.68,69.00)	0.536
HDL-C(mmol/l)	1.19(1.00,1.38)	1.21(1.00,1.52)	0.306
non-HDL-C (mmol/l)	3.60±0.93	3.48±1.07	0.467
TC (mmol/L), median (IQR)	1.33(1.00,2.02)	1.40(1.02,2.07)	0.832
FBS(mmol/L), median (IQR)	6.60(4.93,8.37)	6.59(5.37,9.50)	0.350
EDLV(mm)	52.04±5.30	51.19±5.02	0.304
EF(%), median (IQR)	46(42,48)	46(44,49)	0.050
Target lesion location			
LAD, n (%)	41(73.2%)	88(69.8%)	0.730
LCX, n (%)	2(3.6%)	6(4.8%)	1.000
RCA, n (%)	13(23.2%)	32(25.4%)	0.853
KILLIP class			

I, n (%)	0(0.0%)	0(0.0%)	-
II, n (%)	31(55.4%)	73(57.9%)	0.750
III, n (%)	13(23.2%)	28(22.2%)	1.000
IV, n (%)	12(21.4%)	25(19.8%)	0.840
Cardiogenic death, n (%)	0(0.0%)	9(7.1%)	0.059
Rehospitalization, n (%)	2(3.6%)	27(21.4%)	0.002
Myocardial infarction, n(%)	1(1.8%)	7(5.6%)	0.438
Heart failure, n (%)	1(1.8%)	18(14.3%)	0.008
Stroke, n(%)	0(0.0%)	2(1.6%)	1.000
MACE, n (%)	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.

Table 3. Baseline characteristics of HFrEF patients

	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. Baseline characteristics of HFmrEF patients

	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. Baseline characteristics of 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
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
E-VE(L/min), median (IQR)	28.95(25.45,34.00)	30.95(22.88,35.42)	0.913
△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
△CO2(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
△$P_{ET}CO_2$(mm Hg), median (IQR)	4(3,5)	3(1.25,4.25)	0.107

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, △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, △VCO_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, △$P_{ET}CO_2$: Margin of Partial pressure of end-tidal carbon dioxide, MACE: major cardiac events, IQR: Interquartile range.

Figures

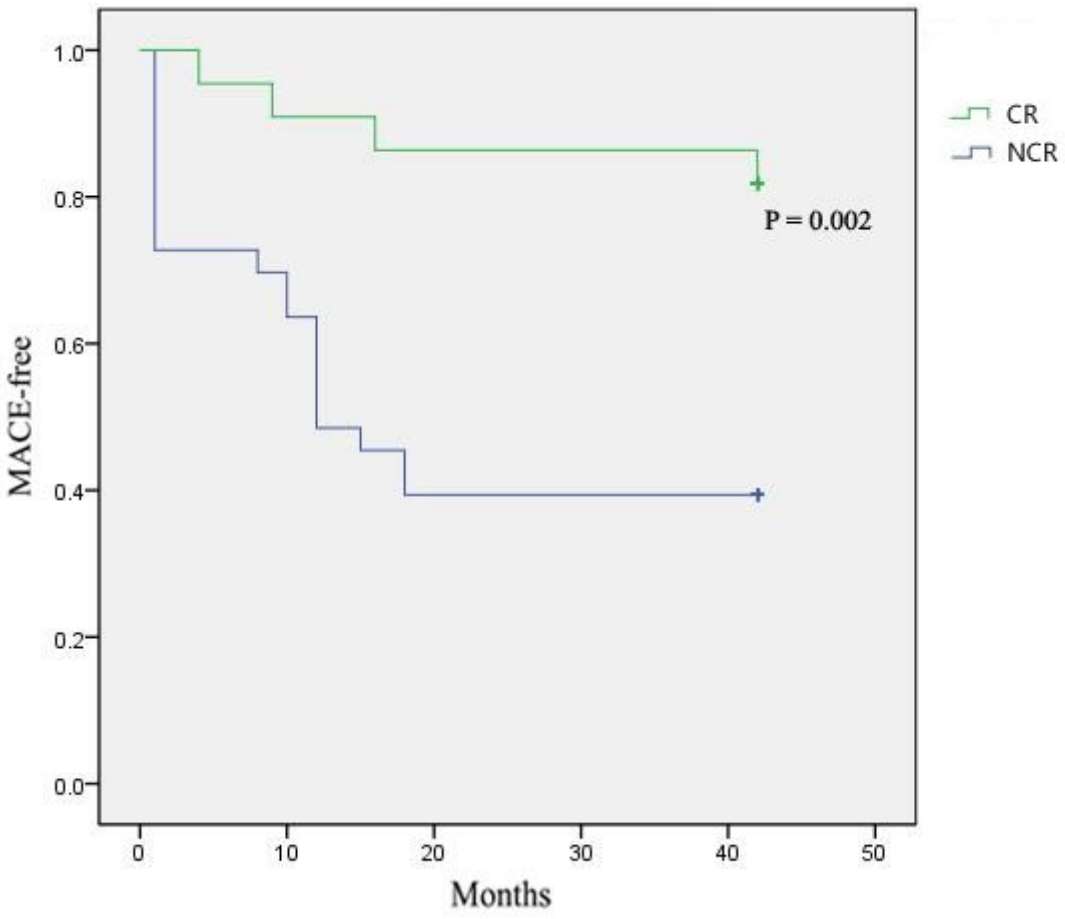

Figure 1

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

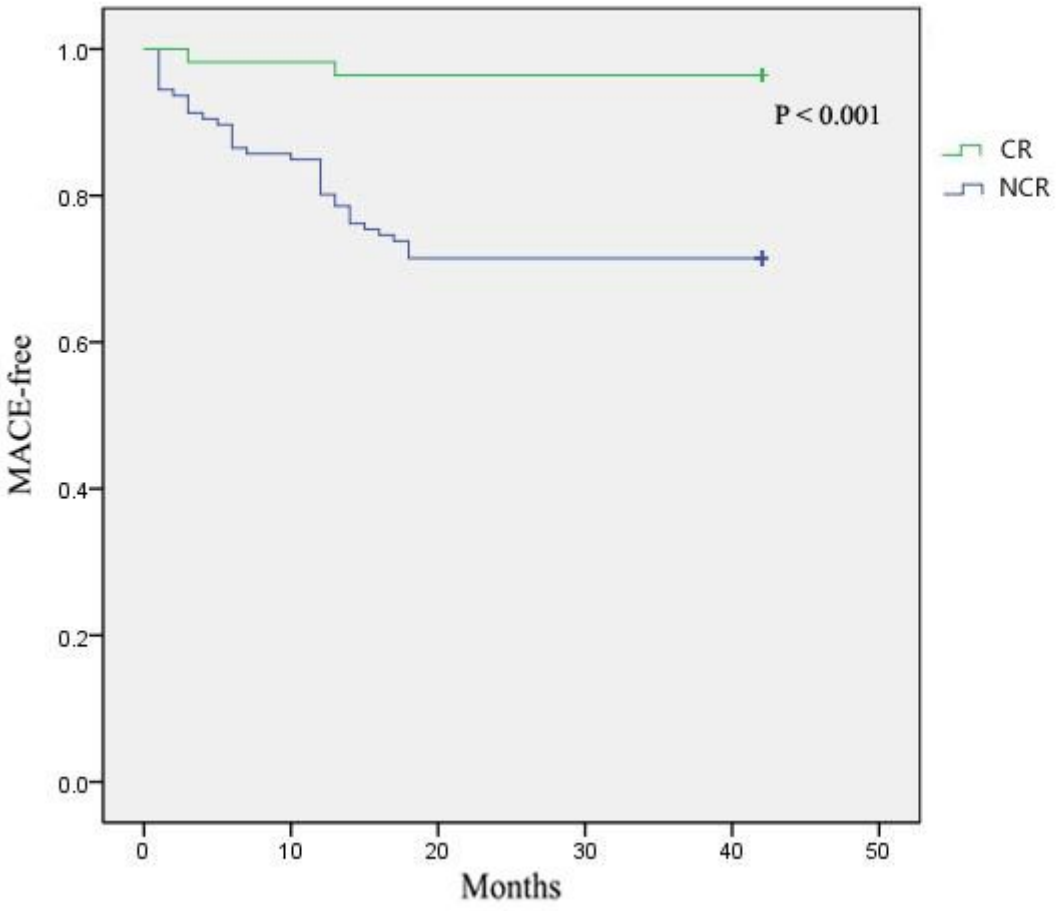

Figure 2

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

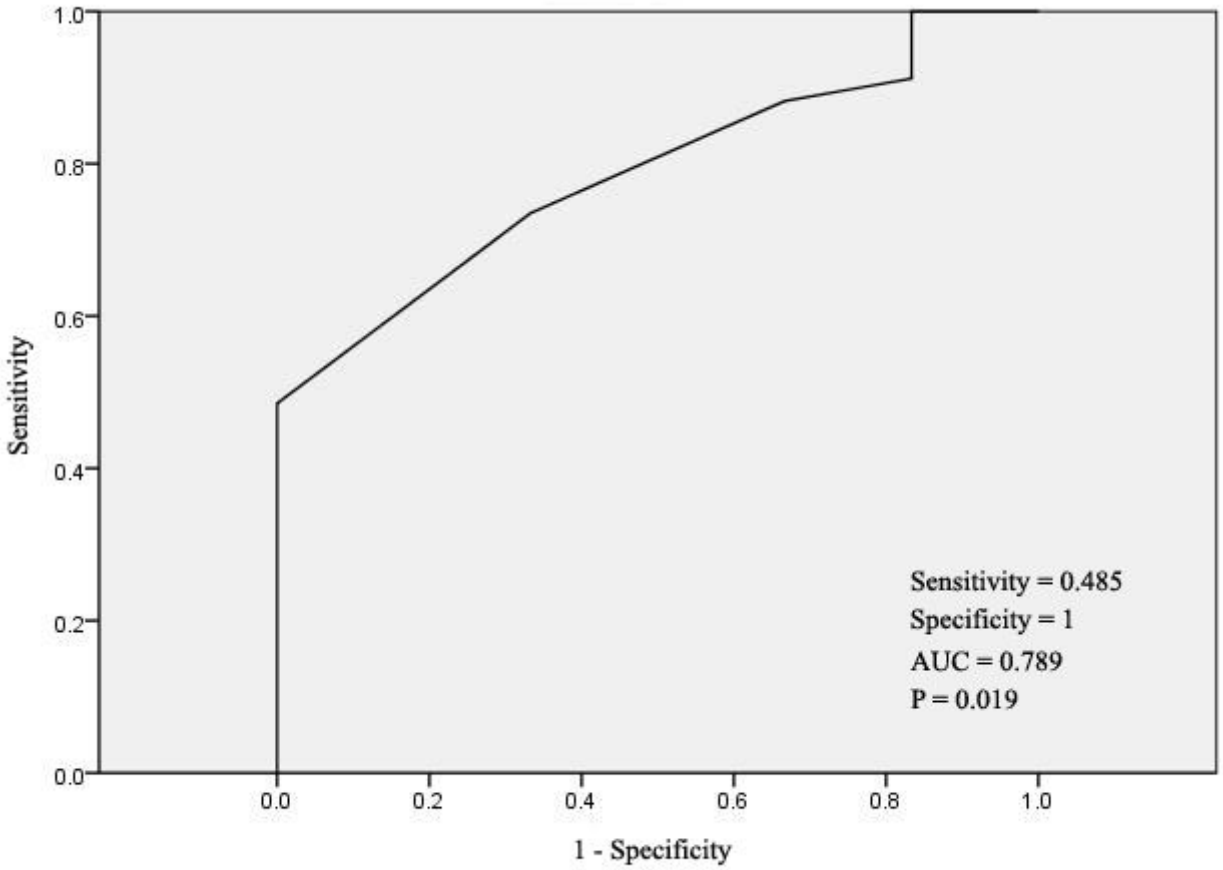

Figure 3

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

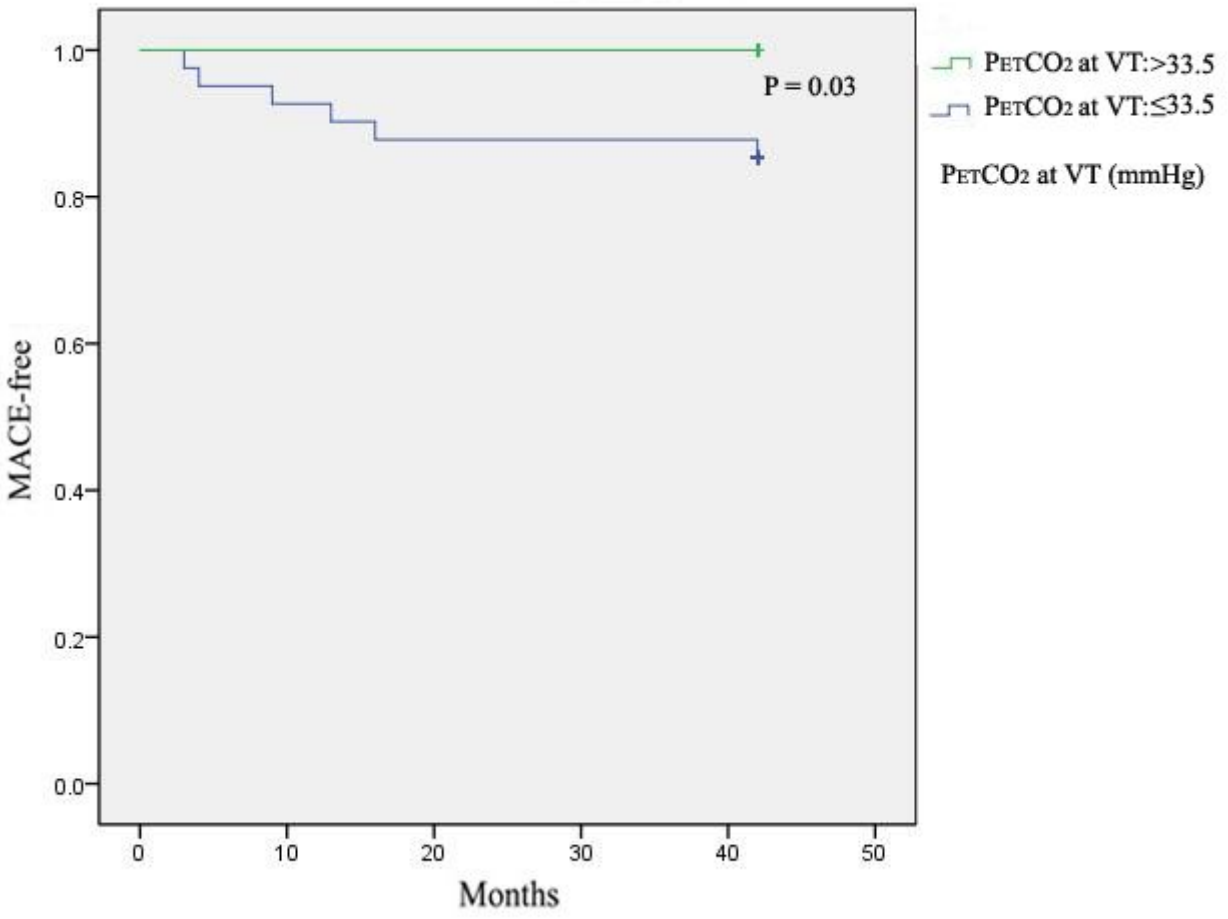

Figure 4

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.