Prognostic value of key variables from cardiopulmonary exercise testing in patients with COPD: 42-month follow-up

Running title: Prognostic value from CPET in COPD patients

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ABSTRACT

Aim: To identify better predictors of early death in patients with chronic obstructive pulmonary disease (COPD) using potential predictors derived from key measures obtained from cardiopulmonary exercise testing (CPET).

Methods: This is a prospective, cohort study with 42-month follow-up in 126 COPD patients. Every patient completed the clinical evaluation, followed by a pulmonary function test and CPET. CPET was performed on a cycle ergometer with electromagnetic braking and ventilatory expired analysis was measured breath-by-breath using a computer-based system. Peak oxygen consumption ($\dot{V}O_2$, $mlO_2.kg^{-1}.min^{-1}$), minute ventilation/carbon dioxide production and the, minute ventilation ($\dot{V}_E$, L/min), and the $\dot{V}_E$ /carbon dioxide production ($\dot{V}_E/\dot{V}CO_2$) slope were obtained from CPET.

Results: 48 (38%) patients died during the 42 month follow-up. Kaplan Meier analysis revealed a $\dot{V}_E/\dot{V}CO_2$ slope ≥30, peak $\dot{V}_E$ ≤25.7L/min and peak $\dot{V}O_2$ ≤13.8 $mlO_2.kg^{-1}.min^{1}$were strong predictors of mortality in COPD patients. Cox regression revealed that the

$\dot{V}O_2$ peak ≤13.8 $mlO_2.kg^{-1}.min^{-1}$ (CI 95% 0.08-0.93), $\dot{V}_E/\dot{V}CO_2$ slope ≥30 (CI 95% 0.070.94), $\dot{V}_E$ peak ≤25.7 L/min (CI 95% 0.01-0.15), Sex (CI 95% 0.04-0.55) and Age (CI 95% 1.03-1.2) were the main predictors of mortality risk.

Conclusion: Diminished exercise capacity and peak ventilation as well as ventilatory inefficiency are independent prognostic markers. Similar to patients with heart failure, CPET may be a valuable clinical assessment in the COPD population.

Keyword: COPD, CPET, oxygen uptake, mortality.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is characterized by persistent respiratory symptoms such as disabling dyspnea, airflow limitation, deconditioning and physical inactivity, and skeletal muscle dysfunction[1,2]. Skeletal muscle dysfunction is one of the extrapulmonary characteristics of the disease that is related to decreased exercise and functional capacity as well as significant morbidity and mortality [1,3].

Cardiopulmonary exercise testing (CPET), considered the gold standard for identifying exercise intolerance and systemic repercussions, has been a valuable assessment in patient populations with cardiorespiratory disease; the assessment of exercise capacity and using findings to guide therapeutic approaches are two primary benefits for CPET[4,5]. In addition, CPET is capable of generating objective, diagnostic and prognostic information about the cardiopulmonary functional status of patients [4,5]. In this sense, there is growing recognition that CPET based markers of exercise capacity and ventilatory inefficiency are associated to clinically relevant outcomes in COPD.

Neder et al.[6] investigated whether cardiocirculatory, ventilatory and pulmonary gas exchange variables measured during incremental CPET would add to standard lung function variables in estimating the risk of mortality in patients with COPD. The authors found that a widely used marker of ventilatory inefficiency [i.e., increased minute ventilation/carbon dioxide production ($\dot{V}_E/\dot{V}CO_2$)nadir)] was the only CPET variable to remain a predictor of mortality in conjunction with well-established clinical data. These results indicate that ventilatory inefficiency is a key physiological abnormality in COPD which is relevant to mortality prediction across the spectrum of disease severity[6].

In 150 patients with COPD and variable disease severity, Oga et al.[7] found that there were no deaths among individuals in the upper quartile of absolute peak oxygen consumption ($\dot{V}O_2$, i.e., >995 mL/min) during a five year follow-up. Conversely, more than half of the patients in the lower peak $\dot{V}$

O_2 (<654 mL/min) quartile died during the tracking period. These findings indicate peak $\dot{V}O_2$ was an independent predictor of death in this patient population[7].

At this time, there is limited evidence evaluating changes in exercise capacity over time in patients with COPD, using CPET and measurement of peak $\dot{V}O_2$[8]; although the literature on CPET is robust, important knowledge gaps remain that, if evaluated, may further improve the clinical impact of CPET over time in this population[9].

The current study was undertaken to define optimal CPET threshold values to facilitate the management, risk stratification and cardiorespiratory rehabilitation strategies in patients with COPD. We hypothesize that CPET threshold values derived from this analysis c would be significant predictors of mortality over a period of 42 month follow-up in patients with mild-to-severe COPD.

METHODS

Design and Subjects

This is a prospective, cohort study with 42-month follow-up. The study population comprised 126 patients with a clinical and functional diagnosis of COPD according to the Global Initiative for Obstructive Lung Disease (GOLD) criteria, presenting with a forced expiratory volume in 1s/forced vital capacity ratio (FEV_1/FVC)<0.7 and postbronchodilator FEV_1 <60% predicted[10]. Patients gave a written informed consent and the study protocol was approved by the Institutional Medical Ethics Committee (CEP 0844/06)[11].

Before entering the study patients were required to be clinically stable for at least 3 months and receiving optimized medical management. No patient enrolled in the current study had used oral steroids in the preceding 6 months.

Exclusion criteria consisted of: 1) musculoskeletal disorders or neurological conditions affecting the ability to exercise; 2) deterioration of clinical status requiring hospitalization 3 months before the study;

3) diagnosis of malignant disease; 4) implantable pacemaker; 5) myocardial infarction (3 months before of study); 6) complex cardiac arrhythmias; 7) a diagnosis of anemia (hemoglobin <13 g%).

Experimental procedures

Every patient completed the comprehensive evaluation in two days consisting of the following: 1) **visit 1**: clinical evaluation by a physician and physical therapist, followed by a pulmonary function test (analyzed by a pulmonologist); and 2) **visit 2**: CPET.

All evaluations were performed at the same period of day; humidity and temperature were controlled, avoiding different physiological responses due to the influence of the circadian cycle. Patients were instructed not to consume any caffeine products, and they did not perform strenuous activities within 24 hours prior to the evaluations[12].

Measurements

Pulmonary Function

Spirometry was performed using the complete pulmonary function test (Medical Graphics Corporation, St Pauls Minnesota, USA) post-bronchodilator. The variables determined were: FEV_1 (L), FVC (L) and FEV_1/FVC (L)[10].

Cardiopulmonary exercise testing

Symptom-limited CPET was performed on a cycle ergometer using a computerbased exercise system (Oxycon Mobile Mijnhardt/Jäger, Würzburg, German). Breath-bybreath analysis ventilatory expired gas analysis was obtained throughout the test. Incremental adjustment of work rate was individually selected (usually 5–10 W/min)[13]. The load increment was individually selected based on the symptoms of dyspnea reported by the patient during physical activity and the experience of the research team. In patients with more severe symptoms such as dyspnea while walking on level ground, the load

increase was 5 W, while those who did not report fatigue for this activity, an increase of 10 W was selected, which is considered to test completion, ideally between 8 and 12 min[14].

The CO_2 and O_2 analyzers were calibrated before and immediately after each test using a calibration gas (CO_2 5%, O_2 12%, and N_2 balance) and a reference gas [room air after ambient temperature and pressure saturated to standard temperature and pressure, dry (STPD) correction]. A pneumotachograph was calibrated with a 3-L volume syringe by using different flow profiles.

The CPET protocol followed the following stages: 1) 5 minutes of rest; 2) 1 minute warm up at free-wheel with 60 rotations per minute (rpm); 3) incremental phase (5-10 W/min, ramp protocol); 4) 1 minute active cool-down at free-wheel; and 5) 5minute passive cool-down in the sitting position[9]. A twelve-lead electrocardiogram

(ECG) was continuously monitored throughout the test (WinCardio, Micromed, Brasilia, Brazil). The test was terminated when patients were pedaling at their maximum possible effort level (physical exhaustion) or presented with established termination such as angina, electrocardiographic evidence of ischemia, or malignant arrhythmias (ventricular tachyarrhythmia, bigeminism, arise branch block)[15]. The following data were recorded: $\dot{V}O_2$ (ml/min), $\dot{V}CO_2$ (ml/min), minute ventilation ($\dot{V}_E$, L/min), the oxygen uptake efficiency slope (OUES), and ventilatory efficiency (i.e., the $\dot{V}_E/\dot{V}CO_2$ slope).

Follow-up

Patients were followed for 42 months by telephone calls to their home or family physician after the first evaluation. The main outcomes assessed in this study was all-cause mortality.

Statistical analysis

The Shapiro-Wilk test was used to verify the data distribution. Descriptive data was shown as a mean, standard deviation, and frequency. The parametric Student's t-test was used to compare the groups (Nonsurvivors *vs* Survivors).

Receiver operating characteristic (ROC) curve analysis: Cut-off points discriminated the precision of CPET variables in determining mortality risk. The 95% confidence interval (CI) was used to determine the predictive ability of the clinical variables, with the lower limit being greater than 0.50. Subsequently, the cut-off points of the variables that obtained significant areas under the ROC curve were identified, with the respective values of sensitivity and specificity. ROC curve analyses selected the optimal threshold values (highest Youden's J index = Sensitivity + Specificity − 1)[16] for the CPET variables.

Kaplan-Meier analysis: We examined all death sat occurred during the 42-months follow-up. Mortality curves were analyzed according to the Kaplan-Meier method to explore the impact of the $\dot{V}_{E}/\dot{V}CO_2$ slope ≥30, $\dot{V}_{E}$ peak ≤25.7L/min and $\dot{V}O_2$ peak ≤13.8 $mlO_2.kg^{-1}.min^{-1}$. Differences between curves were evaluated using the log-rank test.

Cox proportional univariate and multivariate regression models (adjusted for $\dot{V}_{E}/\dot{V}CO_2$ slope ≥30, $\dot{V}_{E}$ peak ≤25.7L/min and $\dot{V}O_2$ peak ≤13.8 $mlO_2.kg^{-1}.min^{-1}$, age and sex) were performed, with associations expressed as risk ratios (HRs) and 95% CIs.

All tests were made in Statistical Package for the Social Sciences (SPSS) and p-values ≤ 0.05 were considered statistically significant.

RESULTS

Population characteristics

In the current study, of the cohort was predominantly elderly males (72%) and all patients were on optimal medical management. Within 42 months, 48 (38%) patients died and all patients presented with reduced maximal exercise capacity (peak VO_2 below the lower limit of normality) (**Table 1**).

Table 1 here

Survival analysis

When dividing our patients into survivors (n=78) and non-survivors (n=48) (**Table 2**), we found a predominance of women, worse lung function, inspiratory muscle weakness, and poorer CPET responses in non-survivors compared to survivors ($p<0.050$). **Table 2 here**

According to ROC analysis, cutoff values producing optimal sensitivity and specificity are: a $\dot{V}_E/\dot{V}CO_2$ slope ≥30 (sensitivity = 73 and specificity = 53), $\dot{V}_E$ peak ≤25.7L/min (sensitivity = 93 and specificity = 78) and peak $\dot{V}O_2$ ≤13.8 $mlO_2.kg^{-1}.min^{-1}$ (sensitivity = 70 and specificity = 68) (**Table 3 and Figure 1**).

Table 3 and Figure 1 here

When we evaluated the applicability of the cut-off points over a period of 42 months through Kaplan Meier's analysis, we found that patients who present during CPET a $\dot{V}_E/\dot{V}CO_2$ slope ≥30 (**Figure 2A**), $\dot{V}O_2$ peak ≤13.8 $mlO_2.kg^{-1}.min^{-1}$ (**Figure 2B**) and $\dot{V}_E$ peak ≤25.7L/min (**Figure 2C**) were strong predictors of mortality in COPD patients. The mortality curve differed significantly in the log-rank test ($p = 0.01$).

Figure 2 here

The Cox regression model revealed that a peak $\dot{V}O_2$ ≤13.8 $mlO_2.kg^{-1}.min^{-1}$ (CI 95% 0.08-0.93), $\dot{V}E/\dot{V}CO_2$ slope ≥30 (CI 95% 0.07-0.94), $\dot{V}_E$ peak ≤25.7 L/min (CI 95% 0.010.15), Sex (CI 95% 0.04-0.55) and Age (CI 95% 1.03-1.2) were the main predictors of mortality risk in our study (**Table 4**).

DISCUSSION

This study investigated whether metabolic and ventilatory variables measured during incremental CPET would be predictors of mortality risk in COPD patients followed for 42 months. We identified that widely used markers of ventilatory inefficiency and exercise capacity were the only CPET

variables to be independent predictors of mortality. There was a marked increase in the risk of mortality in patients with a $\dot{V}_E/\dot{V}CO_2$ slope ≥30, $\dot{V}_E$ peak ≤25.7 L/min and $\dot{V}O_2$ peak ≤13.8 $mlO_2.kg^{-1}.min^{1}$. Cox multivariate regression analysis found sex, age, a $\dot{V}_E/\dot{V}CO_2$ slope ≥30, $\dot{V}_E$ peak ≤25.7 L/min and $\dot{V}O_2$ peak ≤13.8 $mlO_2.kg^{-1}.min^{-1}$ remained significant in predicting mortality risk for COPD patients. The $\dot{V}_E$ peak response is directly related to the FEV_1 in COPD patients, factors such as dyspnea and increased leg discomfort negatively impact the $\dot{V}_E$ response during exercise[17]. This study addresses an evidence gap in relation to this variable, given its physiological importance as a predictor of events in this population. In this context, our results may hold clinical utility in refining the prognostic accuracy when a patient with COPD has a $\dot{V}_E$ peak ≤25.7 L/min. Moreover, clinical interventions, such as cardiorespiratory rehabilitation, are capable of improving the physiological response during exercise, including an increase in $\dot{V}_E$ peak, which, based on the current findings, may be an important marker of clinical improvement in patients with COPD.

In our study we found that a peak $\dot{V}O_2$ ≤13.8 $mlO_2.kg^{-1}.min^{-1}$, which have been considered as an independent predictor of mortality and it has been accepted as a primary marker of clinical status[18,19]. Yoshimura et al.[20] suggested that peak $\dot{V}O_2$ was a marker of mortality in COPD across the spectrum of disease severity, which is consistent with our findings. In 312 patients with COPD over a 5-10 year follow-up, Ewert et al.[21] found that $\dot{V}O_2$ peak, was a highly significant predictor of survival. The authors further suggest that prognostic assessment in COPD patients could be improved by adding peak $\dot{V}O_2$ and that prospective studies, such as the current study, are needed to confirm the findings regarding the prognostic relevance of exercise data[21].

In our study, an increased $\dot{V}_E/\dot{V}CO_2$ slope (i.e., ≥30), which is an indicator of ventilation/perfusion mismatch and overall worsening cardiopulmonary pathophysiology[22,23], was a predictor of mortality in the 42-month period in patients with COPD. There is evidence that the $\dot{V}_E/\dot{V}CO_2$ slope is relevant for a number of patient-related outcomes in COPD, as an increase in the $\dot{V}_E/\dot{V}CO_2$ slope reflects an

increased physiological dead space[24]. Torchio et al.[23] found that a $\dot{V}_E/\dot{V}CO_2$ slope ≥34 was related to a mortality risk of 5.5% and highlighted this variable for screening COPD patients who are candidates for pulmonary resection for potential ventilatory (Clinician's guide to cardiopulmonary exercise testing in adults: A scientific statement from the American heart association)failure. This evidence supports the use of the $\dot{V}_E/\dot{V}CO_2$ slope as a relevant parameter to define the preoperative risk before lung surgery. Our results lend further support to this CPET measure, which has been well investigated in the HF population, and may also be an important clinical marker in patients with COPD[25].

Limitation of the study

In our study, it was not possible to perform the assessment of complete pulmonary function in patients with COPD, which could lead to new potential variables. Also, we only assessed three CPET measures (i.e., $\dot{V}_E/\dot{V}CO_2$ slope, $\dot{V}_E$ peak and peak $\dot{V}O_2$). Evaluating the clinical utility of other CPET variables should be performed in future investigations.

Clinical application

The highlights of our study include the novelty of finding cutoff points that determine a marked increase in the risk of mortality in patients with COPD, including a $\dot{V}_E/\dot{V}CO_2$ slope ≥30, $\dot{V}_E$ peak ≤25.7 L/min and peak $\dot{V}O_2$ peak ≤13.8 $mlO_2.kg^{-1}.min^{1}$. Moreover, therapeutic approaches, such as cardiopulmonary rehabilitation, may consider focusing on improving these metabolic and ventilatory markers as an indicator of clinical improvement and prognosis in patients with COPD.

CONCLUSION

Depressed exercise ventilation and exercise capacity as well as ventilatory inefficiency are independent prognostic marker in COPD patients. As such, CPET may be considered as a standard clinical assessment in this patient population.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Author Contributions

All authors approved the final manuscript and contributed to the conception of the work, the acquisition and analysis of data and drafting and revising intellectual content.

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LEGEND FIGURES

Figure 1. Receiver operating curves in patients with COPD. The area under the curve (AUC) of $\dot{V}_{E/}\dot{V}CO_2$ slope, $\dot{V}_E$ peak (L/min) and $\dot{V}O_2$ peak (mL/min/kg).

Figure 2. Kaplan-Meier curve for mortality according to presence of $\dot{V}_{E/}\dot{V}CO_2$ slope ≥30, $\dot{V}_E$ peak ≤25.7L/min and $\dot{V}O_2$ peak ≤13.8 mL/min/kg over a period of 42 months.

Table 1. Clinical, pulmonary function, medications, mortality and CPET of COPD patients.

Variables	COPD (n=126)
Age (years)	65±8
Sex, n (%)	
Woman	35 (27)
Male	91 (73)
Height (kg)	65±11
Pulmonary function	
FVC, L	2.5±1.0
FEV_1, L	1.1±0.6
FEV_1/FVC, L	0.45±0.1
Medications, n (%)	
Anti-coagulants	14 (10)
Anti-Hypertensives	25 (18)
Beta-blockers	3 (2)
Inhaled Corticosteroid	136 (100)
Death, n (%)	
Yes	48 (38)
No	78 (62)
CPET	
$\dot{V}_E$ peak (L/min)	31±15
$\dot{V}O_2$ peak (mL/min/kg)	15±4
RER	1.06±0.1
$\dot{V}E/\dot{V}CO_2$ slope	31±6
OUES	1.5±0.75
SpO_2 rest (%)	93±2
HR peak (bpm)	120±20
SBP peak (mmHg)	171±31
DBP peak (mmHg)	92±11

Notes: COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume-one second; $\dot{V}O_2$: oxygen uptake; RER: respiratory exchange ratio; $\dot{V}_E$: Minute ventilation; $\dot{V}_E/\dot{V}CO_2$ slope: linear relation between minute ventilation and carbon dioxide production; OUES: Oxygen uptake efficiency slope; SBP: Systolic blood pressure; SBP: Diastolic blood pressure.

Table 2. Clinical, pulmonary function and medications CPET in COPD patients.

Variables	Nonsurvivors (n=48)	Survivors (n=78)	p
Age (years)	67±8	64±7	0.10
Sex, n (%)			<0.001
Woman	25 (52)	10 (13)	
Male	23 (48)	68 (87)	
Height (kg)	63±5	67±13	0.04
Pulmonary function			
FVC, L	1.7±0.5	3.0±0.8	<0.001
FEV_1, L	0.78±0.3	1.4±0.6	<0.001
FEV_1/FVC, L	0.45±0.13	0.46±0.13	0.60
CPET			
$\dot{V}_E$ peak (L/min)	21±7	38±15	<0.001
$\dot{V}O_2$ peak (L/min)	0.81±0.2	1.13±0.3	<0.001
$\dot{V}O_2$ peak (mL/min/kg)	12±3	16±4	<0.001
RER	1.02±0.1	1.08±0.1	0.003
$\dot{V}E/\dot{V}CO_2$ slope	32±6	29±7	0.02
OUES	1.4±0.6	1.5±0.7	0.18
SpO_2 rest (%)	92±2	93±2	0.03
SBP (mmHg) peak	160±22	178±34	0.02
DBP (mmHg) peak	86±9	96±12	0.03
HR (bpm) peak	110±17	126±19	0.96
HR (bpm) rec 1’	101±17	114±19	0.96

Notes: COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume-one second; $\dot{V}O_2$: oxygen uptake; RER: respiratory exchange ratio; $\dot{V}_E$: Minute ventilation; $\dot{V}E/\dot{V}CO_2$ slope: linear relation between minute ventilation and carbon dioxide production; OUES: Oxygen uptake efficiency slope; SBP: Systolic blood pressure; SBP: Diastolic blood pressure.

Table 3. Cut-off values, sensitivity and specificity of V̇ E/V̇ CO_2 slope, V̇ E peak (L/min) and V̇ O_2 peak (mL/min/kg) in CPET for mortality in COPD patients.

				COPD (N=126)			
Variables	***Cut-off***	***Sensitivity***	***Specificity***	***AUC [CI 95%]***	Youden Index	Positive likelihood	Negative likelihood
$\dot{V}_E/\dot{V}CO_2$ slope	≥30	0.73	0.53	0.63 [0.51-0.72]	0.26	1.36	0.60
$\dot{V}_E$ peak (L/min)	≤25.7	0.93	0.78	0.88 [0.80-0.93]	0.71	2.25	0.14
$\dot{V}O_2$ peak (mL/min/kg)	≤13.8	0.70	0.68	0.74 [0.64-0.81]	0.38	2.27	0.42

COPD: chronic obstructive pulmonary disease; V̇ O2: oxygen uptake; V̇ E: Minute ventilation; V̇ E/V̇ CO2 slope: linear relation between minute ventilation and carbon dioxide production.

Table 4. Risk factors for mortality in 126 patients with COPD.

Covariates	**Coefficient**	**Standard Error**	**Hazard Ratio (CI 95%)**	**I**
V̇ E/V̇ CO2 slope (0: <30, 1: ≥30)	-1.3	0.64	0.26 (0.07-0.94)	0
V̇ E peak (0: >25.7, 1: ≤25.7L/min)	-3.1	0.66	0.43 (0.01-0.15)	0
V̇ O2 peak (0: >13.8, 1:≤13.8 mL/min/kg)	-1.2	0.61	0.28 (0.08-0.93)	0
Age (0: <65 years, 1: >65 years)	0.11	0.04	1.12 (1.03-1.22)	0
Sex (0: M, 1: F)	-1.9	0.67	0.14 (0.04-0.55)	0

Notes: $\dot{V}O_2$: oxygen uptake; $\dot{V}_E$: Minute ventilation; $\dot{V}E/\dot{V}CO_2$ slope: linear relation between minute ventilation and carbon dioxide production.

Figure 1

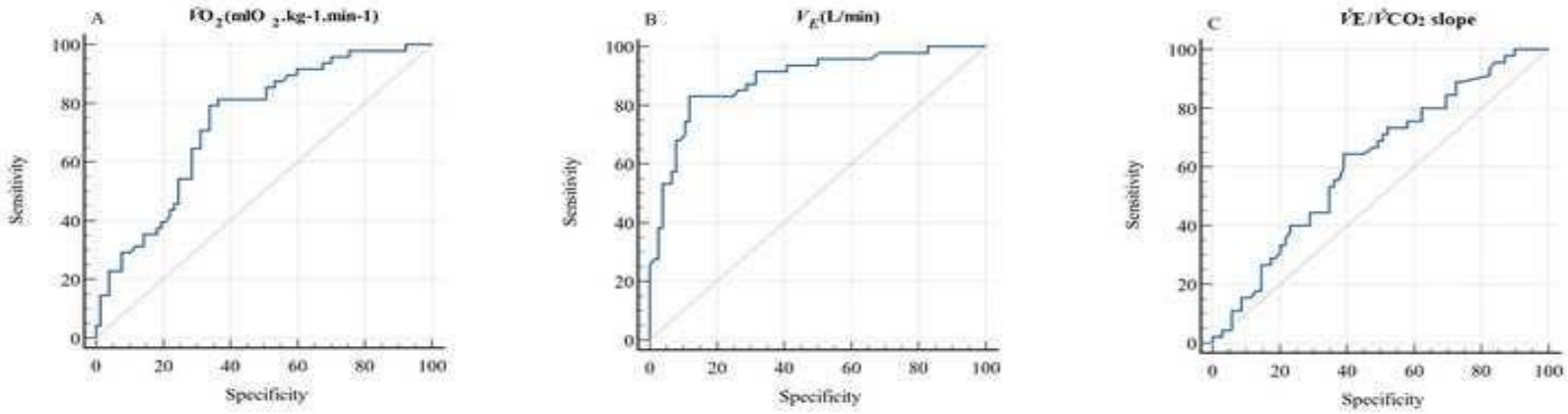
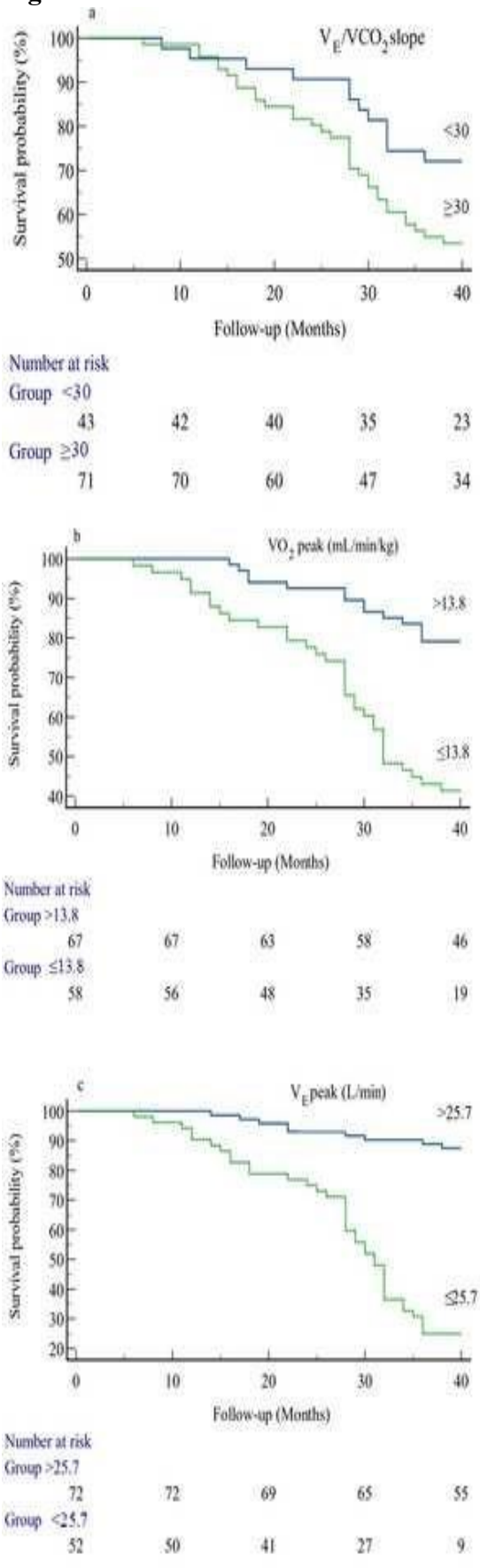

A
$\dot{V}O_2$(mlO_2.kg-1.min-1)
B
V_E(L/min)
C
$\dot{V}E/\dot{V}CO_2$ slope
Sensitivity
Specificity
0
20
40
60
80
100

Figure 2


a
V_E/VCO_2 slope
Survival probability (%)
100
90
80
70
60
50
<30
≥30
0
10
20
30
40
Follow-up (Months)
Number at risk
Group <30
43 42 40 35 23
Group ≥30
71 70 60 47 34
b
VO_2 peak (mL/min/kg)
Survival probability (%)
100
90
80
70
60
50
40
>13.8
≤13.8
0
10
20
30
40
Follow-up (Months)
Number at risk
Group >13.8
67 67 63 58 46
Group ≤13.8
58 56 48 35 19
c
V_E peak (L/min)
Survival probability (%)
100
90
80
70
60
50
40
30
20
>25.7
≤25.7
0
10
20
30
40
Follow-up (Months)
Number at risk
Group >25.7
72 72 69 65 55
Group <25.7
52 50 41 27 9