

# VE-VCO<sub>2</sub> Slope During Cardiopulmonary Exercise Test Predicts Acute Exacerbations of Chronic Obstructive Pulmonary Disease: A Retrospective Cohort Study

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**Background:** Cardiopulmonary Exercise Test (CPET) serves as an integrative assessment tool to evaluate cardiac function, respiratory responses, and neuromuscular capacity in patients with chronic obstructive pulmonary disease (COPD) during incremental cycling exercise. VE-VCO<sub>2</sub> slope during CPET was not fully understood in predicting acute exacerbations of COPD (AECOPD). This study aims to establish a predictive model for AECOPD based on the VE-VCO<sub>2</sub> slope.

**Methods:** In total, 79 patients with COPD were recruited between 2013 and 2019. All participants underwent baseline pulmonary function tests and CPET and were followed up for 5 years thereafter. Independent two-sample *t*-tests and Chi-square tests were used to compare AECOPD and Non-AECOPD groups. Univariate and multivariate Cox regression analyses were utilized to identify predictive factors for AECOPD. The diagnostic performance of these variables was evaluated by receiver operating characteristic (ROC) curve analysis. The optimal cutoff values calculated by Youden's index. Kaplan-Meier survival analysis between subgroups was based on the optimal cutoff values. Generating Forest plots to visualize Cox regression analysis results.

**Results:** The AECOPD group contains 62 participants and the Non-AECOPD group contains 17 participants. Groups comparisons revealed significant differences in VE-VCO<sub>2</sub> slope, age, BMI, FEV<sub>1</sub>%predicted, FEV<sub>1</sub>/FVC ratio, and EqCO<sub>2</sub>. Multivariate Cox regression analysis identified VE-VCO<sub>2</sub> slope (OR = 1.19, 95% CI: 1.09–1.29, *p* < 0.001), age (OR = 1.05, 95% CI: 1.02–1.09, *p* = 0.005), and FEV<sub>1</sub>%predicted (OR = 0.96, 95% CI : 0.94–0.99, *p* = 0.015) as significant predictors of AECOPD. The ROC curve analysis results about the above predictors found that the AUC of VE-VCO<sub>2</sub> slope is highest independently in 1 year, 3 years and 5 years, with the optimal cutoff values = 28.42 in 5 years (hazard ratio = 3.18, 95% CI: 1.639–6.2, *p* < 0.001).

**Conclusion:** The stratification of VE-VCO<sub>2</sub> slope  $\geq 28.42$  was an independent predictor of AECOPD. Our study established VE-VCO<sub>2</sub> slope as a novel stratified clinical biomarker for predicting AECOPD.

**Keywords:** COPD, exacerbation, CPET, VE-VCO<sub>2</sub> slope, ventilation-perfusion mismatch

## Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous respiratory disorder characterized by persistent and irreversible airflow limitation. It is important to clarify that the term “irreversible” refers to the progressive nature of the underlying structural damage (eg small airway remodeling and emphysema), which cannot be completely normalized by current pharmacotherapy.<sup>1</sup> Clinically, this does not imply a lack of therapeutic benefit. Inhaled bronchodilators remain the cornerstone of symptomatic management. They improve expiratory flow by reducing airway smooth muscle tone, decrease exercise-induced dynamic hyperinflation, increase exercise tolerance, and alleviate dyspnea. Furthermore, while bronchodilators alone may not slow the long-term decline in lung function, they significantly reduce the frequency of acute exacerbations. Importantly, inhaled corticosteroids (ICS), particularly when combined with long-acting

bronchodilators in patients with frequent exacerbations, have been shown to reduce exacerbation rates and may modestly attenuate the progression of airflow obstruction in specific phenotypes.<sup>2</sup> A 2019 systematic analysis conducted at global regional and national levels revealed that the prevalence of COPD among individuals aged 30–79 years reached 10.3%, with male sex, smoking history, and low body mass index ( $BMI < 18.5\text{kg/m}^2$ ) being identified as significant predisposing risk factors.<sup>3</sup> Most patients with COPD experience acute exacerbations during clinical progression, typically manifested as recurrent cough, dyspnea, rehospitalization, frequent outpatient visits requiring intensified antibiotic therapy. Frequent exacerbations significantly accelerate pulmonary function decline, and correlating strongly with elevated mortality.<sup>4</sup>

Frequent acute exacerbations in COPD patients not only impose substantial healthcare burdens but also significantly impair quality of life, correlating with adverse prognostic outcomes.<sup>5</sup> Increasing research studies focus on identifying clinical and biomarkers of disease severity to develop prevention strategies about AECOPD. A Chinese prospective cohort study utilizing CT imaging revealed airway mucus plugs strongly associate with exacerbation frequencies, and a significant proportion of COPD patients demonstrates that radiologically detectable mucus retention provides critical clinical implications for exacerbation surveillance.<sup>6</sup> Simplified nutritional assessments demonstrate malnutrition is a significant exacerbation risk factor.<sup>7</sup> Systematic reviews identify that age, sex, MRC Dyspnea Scale scores, CAT scores, platelet/leukocyte counts, blood eosinophil percentages and prior exacerbation history are the key determinants of exacerbations among patients with COPD.<sup>8</sup>

Cardiopulmonary Exercise Testing (CPET) provides a comprehensive assessment for COPD patients through neuromuscular strength, respiratory gas exchange, and cardiovascular hemodynamics.<sup>9</sup> Analysis between ventilation (VE) and carbon dioxide output (VCO<sub>2</sub>) during CPET reveals critical cardiopulmonary functional status and disease progression patterns.<sup>10</sup> In previous studies, the relationship between VE and VCO<sub>2</sub> has been extensively investigated, primarily through three approaches: the carbon dioxide ventilation equivalent (EqCO<sub>2</sub>), which refers to the ratio of VE to VCO<sub>2</sub> at a specific time point, the CO<sub>2</sub> ventilation efficiency nadir (EqCO<sub>2</sub> nadir) and the VE-VCO<sub>2</sub> slope. The VE-VCO<sub>2</sub> slope is a key index of ventilatory efficiency derived during CPET. It's calculated using linear regression analysis to quantify the relationship between minute ventilation (VE) and carbon dioxide output (VCO<sub>2</sub>) during incremental exercise (The data start from a work rate about 15 to 25 Watts until strictly only up to the Respiratory Compensation Point).<sup>10</sup> In heart failure research, VE-VCO<sub>2</sub> slope  $\geq 36$  independently predicts mortality, while VE-VCO<sub>2</sub> slope  $\geq 34$  significantly forecasts hospitalization risk.<sup>11</sup> Machine learning analyses of chronic heart failure cohorts identify VE-VCO<sub>2</sub> slope  $\geq 30$  is optimal threshold for adverse event prediction.<sup>12</sup> Comparative studies of exercise parameters by Alba demonstrated the VE-VCO<sub>2</sub> slope's superior prognostic power versus VE, OUES (Oxygen Uptake Efficiency Slope) and peak VO<sub>2</sub>.<sup>13</sup> Despite established cardiac applications, VE-VCO<sub>2</sub> slope's predictive value for AECOPD remains uninvestigated. Thus, this retrospective cohort study evaluates VE-VCO<sub>2</sub> slope's capacity to predict exacerbations in patients with COPD followed up by 5 years after finishing CPET.

## Materials and Method

### Study Participants

#### Inclusion and Exclusion Criteria

This is a retrospective study that enrolled COPD patients recruited from the outpatient clinic of the Beijing Friendship Hospital between 2013 and 2019. All participants before the training, all participants were provided with written and oral information about this program and signed an informed consent form. Our study complies with the Declaration of Helsinki. The Ethics Committee of Beijing Friendship Hospital approved the study protocol (No: 2024-P2-125-01, Date: 2024-04-19).

This retrospective cohort study analyzed COPD patients enrolled between 2013 and 2019, their age were between 40 and 85 years, including 68 males and 11 females, meeting the GOLD diagnostic confirmation (post-bronchodilator FEV<sub>1</sub>/FVC  $< 0.70$ ), clinically stable status (within 6 weeks prior to study participation).<sup>14</sup> Patients with cardiac morbidities (heart failure, arrhythmias, valvulopathies, or coronary artery disease), using  $\beta$ -blocker/outcome-interfering medication, hypoxemia requiring supplemental oxygen ( $SpO_2 < 90\%$  on room air) and physical limitations contra-indicating CPET (degenerative knee pathologies incompatible with cycle ergometry) were excluded.

## Pulmonary Function Tests

All patients underwent pulmonary function test by using the Master Screen Body plethysmograph (CareFusion Corp, San Diego, CA, USA). The evaluation protocol included: Spirometry: VC (Vital Capacity), FVC (Forced Vital Capacity), FEV1 (Forced Expiratory Volume in 1 second) and DLCO (diffusion Capacity), KCO (Transfer Factor:  $KCO = DLCO/VA$ : Carbon Monoxide Diffusing Capacity per Alveolar Volume). RV (Residual Volume), TLC (Total Lung Capacity) and RV/TLC ratio were detected by Body Plethysmography. All procedures strictly adhered to European Respiratory Society (ERS) technical standards.<sup>15</sup>

## Cardiopulmonary Exercise Test

The standards and implementation procedures of CPET were referenced from the guidelines of the American Thoracic Society/European Respiratory Society.<sup>16</sup> After excluding contraindications, all patients with COPD were required to rest on a cycle ergometer for 3 minutes after attaching electrocardiogram (ECG) electrodes, blood pressure cuffs, pulse oximetry sensors, and standard mouthpieces. Subsequently, they underwent 3 minutes of unloaded cycling exercise. Then, an incremental symptom-limited exercise test was conducted using an electronically braked cycle ergometer (model Via Sprint, CareFusion Corporation, Sieberg, Germany) at a speed of 40–70 revolutions per minute (rpm), usually approximately 60 rpm. Before CPET, patients with COPD needed to undergo static pulmonary function tests to obtain forced expiratory volume in one second (FEV1) data. Then combining with height, weight and the body mass index (BMI) values, the CPET device calculated the maximal oxygen uptake ( $VO_{2max}$ ) and target load. Generally, it took about 10 minutes for COPD patients to complete the entire incremental power cycling test. The incremental power per minute was calculated based on the maximum target power.<sup>9</sup> The criteria for completing the CPET test were achieving the maximum effort exercise goal or encountering circumstances that required termination, such as arrhythmia, dyspnea, chest pain. During the test, blood pressure was measured every 2 minutes, and continuous attention was paid to changes in blood oxygen saturation and electrocardiogram (ECG) signals.<sup>17</sup> The VE-VCO<sub>2</sub> slope (the slope of the relationship curve between VE and carbon dioxide production VCO<sub>2</sub> was calculated by linear regression of VE and VCO<sub>2</sub>, data start from a work rate about 15 to 25 Watts until strictly only up to the Respiratory Compensation Point). The one-minute heart rate recovery (HRR1) was defined as the peak heart rate during exercise minus the heart rate at 1 minute of recovery.

## Follow Up of AECOPD Patients

Seventy-nine research subjects underwent a 5 years' follow up after completing baseline tests and the collection of clinical indicators. The subjects were followed up at three months intervals. Clinical symptoms, comorbidities, smoking status and frequency of outpatient visits were recorded. Whether administering additional antibiotics and hospitalization to alleviate the condition was necessary to record. During the follow up, acute exacerbations of COPD (AECOPD) were defined as the emergence of frequent respiratory symptoms and the need for hospitalization and additional outpatient treatments.<sup>18</sup>

## Statistical Analyses

Statistical analyses were performed using SPSS (version 31.0) and R software (version 4.4.0). Continuous variables were summarized as mean  $\pm$  standard deviation and compared between the AECOPD and Non-AECOPD groups using independent samples *t*-tests, with Levene's test employed to assess homogeneity of variance. When variances were heterogeneous, the Mann–Whitney *U*-test was applied. Categorical variables were presented as frequencies and percentages and analyzed using the chi-square test or Fisher's exact test where appropriate. Univariate and multivariate Cox proportional hazards regression models were conducted to identify significant predictors of AECOPD. To identify factors associated with AECOPD, we first performed univariable regression analysis to screen potential predictors. All variables with a *p*-value  $< 0.05$  in the univariable analysis were then entered into the multivariable regression model to adjust for potential confounders. The multivariable analysis was performed to determine the independent predictors of AECOPD. The diagnostic performance of these predictors was evaluated through receiver operating characteristic

(ROC) curve analysis. Kaplan-Meier survival curves were generated using R packages survival and survminer, with differences assessed via the Log rank test. Forest plots were constructed to visualize hazard ratios and 95% confidence intervals from the Cox models. All statistical tests were two-sided, and a p-value < 0.05 was considered statistically significant.

## Results

During a 5-year follow up period, 79 study subjects were prospectively followed until the occurrence of acute exacerbation, which served as the primary endpoint. Of these, 62 patients experienced acute exacerbations (AECOPD group), while 17 remained free of exacerbations (Non-AECOPD group). Baseline demographic characteristics, pulmonary function test results, and exercise cardiopulmonary function parameters are summarized in Table 1. The mean age of the total cohort was 67 years (SD = 8.2), with the AECOPD group being significantly older than the Non-AECOPD group ( $p < 0.001$ ). The body mass index (BMI) was significantly lower in the AECOPD group compared to the Non-

**Table 1** Study Population Characteristics

	<b>AECOPD (n = 62)</b>	<b>Non-AECOPD (n = 17)</b>	<b>Total (n = 79)</b>	<b>p-value</b>
Age, mean $\pm$ SD	68.2 $\pm$ 7.8	60.8 $\pm$ 6.8	66.6 $\pm$ 8.2	<0.001
Sex				
Male, % (n)	88.7(55)	76.5(13)	86.1(68)	0.238
Female, % (n)	11.3(7)	23.5(4)	86.1(68)	
BMI (kg/m <sup>2</sup> ) Mean $\pm$ SD	23.5 $\pm$ 3.2	25.8 $\pm$ 4.4	24.0 $\pm$ 3.6	0.02 <sup>#</sup>
Smoking (pack-years), mean $\pm$ SD	25.7 $\pm$ 21.8	14.1 $\pm$ 20.9	23.2 $\pm$ 22.0	0.054
Type of comorbidities				
CHD, % (n)	17.7(11)	11.8(2)	16.5(13)	0.723
DM, % (n)	14.5(9)	5.9(1)	12.7(10)	0.681
HBP, % (n)	32.3(20)	11.8(2)	27.8(22)	0.130
GOLD-classification (n)				
1, % (n)	1.6(1)	41.2(7)	10.1(8)	<0.001*
2, % (n)	64.5(40)	41.2(7)	59.5(47)	
3, % (n)	32.3(20)	17.6(3)	29.1(23)	
4, % (n)	1.6(1)	0	1.3(1)	
Pulmonary function				
VC (L), mean $\pm$ SD	2.64 $\pm$ 0.45	2.85 $\pm$ 0.77	2.68(0.54)	0.305
FVC (L), mean $\pm$ SD	2.70 $\pm$ 0.49	2.86 $\pm$ 0.73	2.74(0.55)	0.311
FEV1 (L), mean $\pm$ SD	1.48 $\pm$ 0.32	1.89 $\pm$ 0.76	1.57(0.47)	0.043 <sup>#</sup>
FEV1 (%pred), mean $\pm$ SD	53.59 $\pm$ 12.08	67.45 $\pm$ 17.34	56.57(14.44)	0.006*
FEV1/FVC (%), mean $\pm$ SD	0.55 $\pm$ 0.09	0.63 $\pm$ 0.13	0.57(0.10)	0.027 <sup>#</sup>
RV/TLC (%), mean $\pm$ SD	59.75 $\pm$ 5.96	64.70 $\pm$ 19.9	60.81(10.64)	0.089
DLCO, mean $\pm$ SD	64.63 $\pm$ 13.63	72.31 $\pm$ 16.19	66.28(14.46)	0.052

(Continued)

**Table 1** (Continued).

	AECOPD (n = 62)	Non-AECOPD (n = 17)	Total (n = 79)	p-value
KCO, mean $\pm$ SD	79.65 $\pm$ 15.49	89.15 $\pm$ 22.01	81.69(17.39)	0.045 <sup>#</sup>
Cardiopulmonary exercise test (CPET)				
Peak heart rate (beats/min), mean $\pm$ SD	126.68 $\pm$ 20.81	130.53 $\pm$ 15.29	127.51(19.72)	0.479
HRR1 (bpm), mean $\pm$ SD	19.37 $\pm$ 14.44	18.59 $\pm$ 3.97	19.20(12.90)	0.826
Peak VO <sub>2</sub> (mL/min), mean $\pm$ SD	1249.35 $\pm$ 286.89	1316.35 $\pm$ 332.64	1263.77(296.37)	0.412
PWORK (watt), mean $\pm$ SD	86.29 $\pm$ 22.14	99.29 $\pm$ 36.95	89.09(26.32)	0.182
VO <sub>2</sub> /W slope, mean $\pm$ SD	9.30 $\pm$ 1.65	9.38 $\pm$ 1.57	9.31(1.62)	0.861
VO <sub>2</sub> /HR (mL/beats), mean $\pm$ SD	9.95 $\pm$ 2.15	10.05 $\pm$ 2.09	9.97(2.13)	0.865
AT (mL/min), mean $\pm$ SD	899.23 $\pm$ 219.34	947.76 $\pm$ 176.42	909.67(210.74)	0.404
HR/VO <sub>2</sub> slope, mean $\pm$ SD	46.92 $\pm$ 12.27	52.26 $\pm$ 15.05	48.07(13.00)	0.134
Peak VCO <sub>2</sub> (mL/min), mean $\pm$ SD	1371.82 $\pm$ 355.03	1485.00 $\pm$ 405.91	1396.18(366.83)	0.262
PVE (L/min), mean $\pm$ SD	48.53 $\pm$ 14.02	44.53 $\pm$ 11.91	47.67(13.62)	0.286
VE-VCO <sub>2</sub> slope, mean $\pm$ SD	30.50 $\pm$ 4.70	26.21 $\pm$ 2.95	29.57(4.71)	<0.001*
EqCO <sub>2</sub> , mean $\pm$ SD	35.87 $\pm$ 5.59	31.42 $\pm$ 3.82	34.91(5.55)	0.003*

**Notes:** Results are expressed as the mean (standard deviation) or percentage, \*p-value < 0.01, <sup>#</sup>p-value < 0.05.

**Abbreviations:** AECOPD, Acute Exacerbations of COPD; BMI, body mass index; VC, vital capacity; FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1s; HRR1, heart rate recovery in 1min; Peak heart rate%, peak heart rate/maximum predicted heart rate; PWORK, peak work; VO<sub>2</sub>/W slope, VO<sub>2</sub> work rate slope (the difference between maximal oxygen uptake and resting oxygen uptake, divided by the maximum power); AT, Anaerobic threshold, oxygen uptake of Anaerobic threshold; VE-VCO<sub>2</sub> slope, slope of VE-VCO<sub>2</sub> (linear regression analysis of the relationship between minute ventilation VE and carbon dioxide output VCO<sub>2</sub> from a work rate about 15 to 25 Watts until strictly only up to the Respiratory Compensation Point), the efficiency of ventilation in relation to body's carbon dioxide production; EqCO<sub>2</sub>, carbon dioxide equivalence at the lactate threshold; PVE, peak ventilation.

AECOPD group ( $p = 0.02$ ). There was a significant difference in the distribution of GOLD stages between the two groups, with higher proportions of patients classified as GOLD stage 2 and 3 in the AECOPD group. Pulmonary function analysis revealed that both FEV<sub>1</sub>% predicted (FEV<sub>1</sub>%pred) and FEV<sub>1</sub>/FVC ratio were significantly lower in the AECOPD group ( $p = 0.006$ ,  $p = 0.027$ ). Furthermore, cardiopulmonary exercise testing (CPET) outcomes showed that the VE-VCO<sub>2</sub> slope was significantly elevated in the AECOPD group ( $p < 0.001$ ), as was the ventilatory equivalent for carbon dioxide (EqCO<sub>2</sub>) ( $p = 0.003$ ).

As shown in [Table 1](#), significant differences were observed between the AECOPD and Non-AECOPD groups in age, body mass index (BMI), forced expiratory volume in one second as a percentage of predicted value (FEV<sub>1</sub>%pred), FEV<sub>1</sub>/FVC ratio, VE-VCO<sub>2</sub> slope, and carbon dioxide ventilatory equivalent measured at the Anaerobic Threshold (AT) (EqCO<sub>2</sub>). Univariate and multivariate Cox proportional hazards regression analyses were therefore performed to evaluate the predictive value of these variables for AECOPD. After adjusting for age, BMI, FEV<sub>1</sub>%pred, FEV<sub>1</sub>/FVC and EqCO<sub>2</sub>, VE-VCO<sub>2</sub> slope (data start from a work rate about 15 to 25 Watts until strictly only up to the Respiratory Compensation Point) remained a significant predictor of AECOPD ([Table 2](#)). Additionally, age and FEV<sub>1</sub>%pred also demonstrated significant predictive capacity. The results of the multivariate analysis are presented in the forest plot ([Figure 1](#)). For every one-unit increase in VE-VCO<sub>2</sub> slope, the risk of AECOPD increased by 19% (hazards ratio = 1.19, 95% CI: 1.09–1.29,  $p < 0.001$ ). Similarly, each one-year increase in age was associated with a 5% higher risk of AECOPD (HR = 1.05, 95% CI: 1.02–1.09,  $p = 0.005$ ).

Our findings identify the VE-VCO<sub>2</sub> slope, age, and FEV<sub>1</sub>%pred as risk factors for AECOPD. Subsequently, we employed ROC curve analysis to assess the predictive performance of these three factors for AECOPD at one, three, and

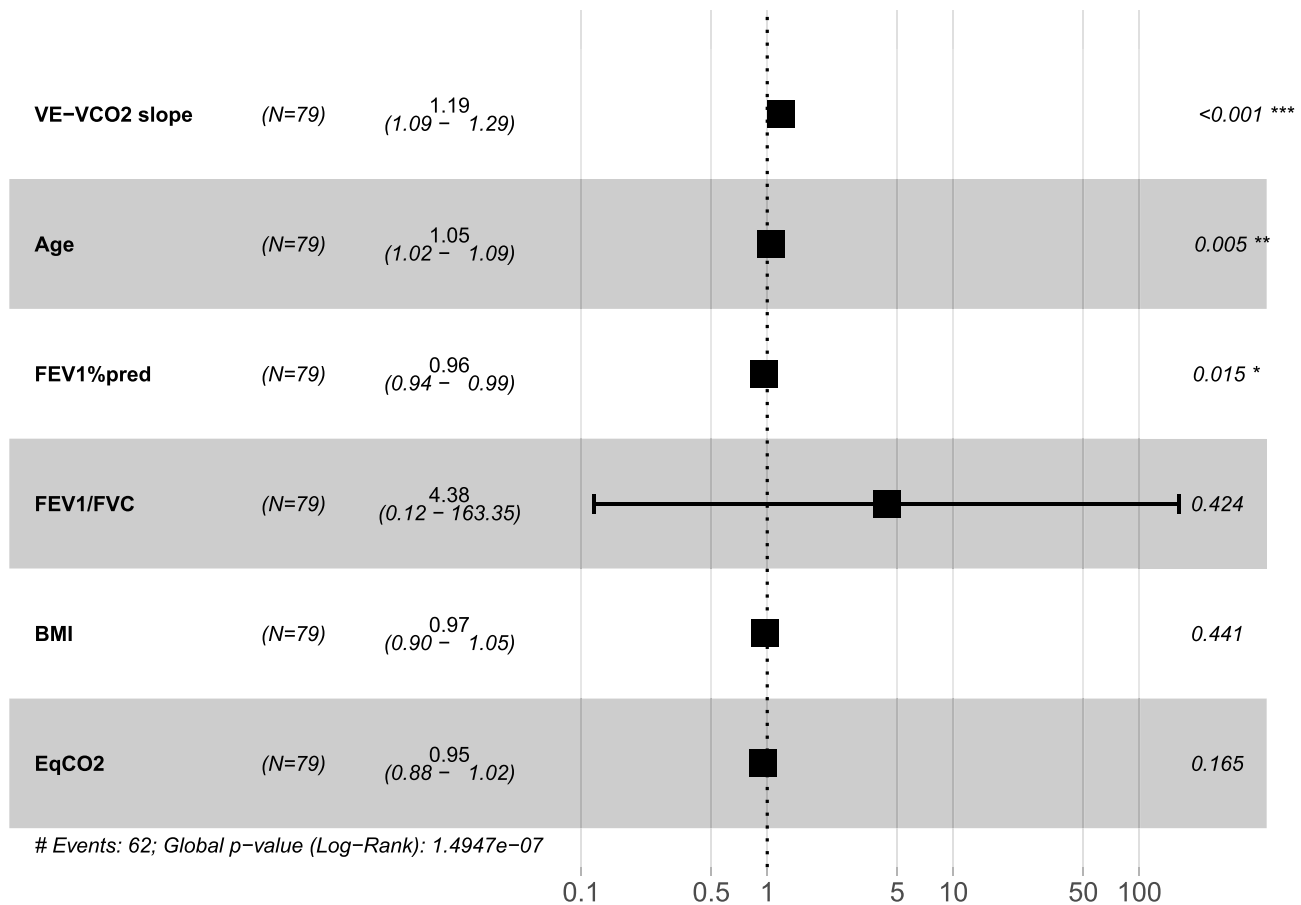
**Table 2** Univariate and Multivariate Proportional Hazards Analyses

Variables	Univariable Analysis			Multivariable Analysis		
	Odds Ratio, OR	95% CI	p-value	Odds Ratio, OR	95% CI	p-value
Age	1.06	1.024–1.093	<0.001*	1.05	1.02–1.09	0.005*
BMI	0.91	0.852–0.975	0.007*	0.97	0.90–1.05	0.441
FEV1 (%pred)	0.97	0.954–0.990	0.002*	0.96	0.94–0.99	0.015*
VE-VCO2 slope	1.16	1.094–1.228	<0.001*	1.19	1.09–1.29	<0.001*
EqCO2	1.076	1.028–1.126	0.002*	0.95	0.88–1.02	0.165
FEV1/FVC	0.098	0.010–0.932	0.043	4.38	0.12–163.35	0.424

**Notes:** \*p-values < 0.05 were considered statistically significant; BMI and EqCO2 were significant in univariable analysis but did not retain significance after multivariable adjustment.

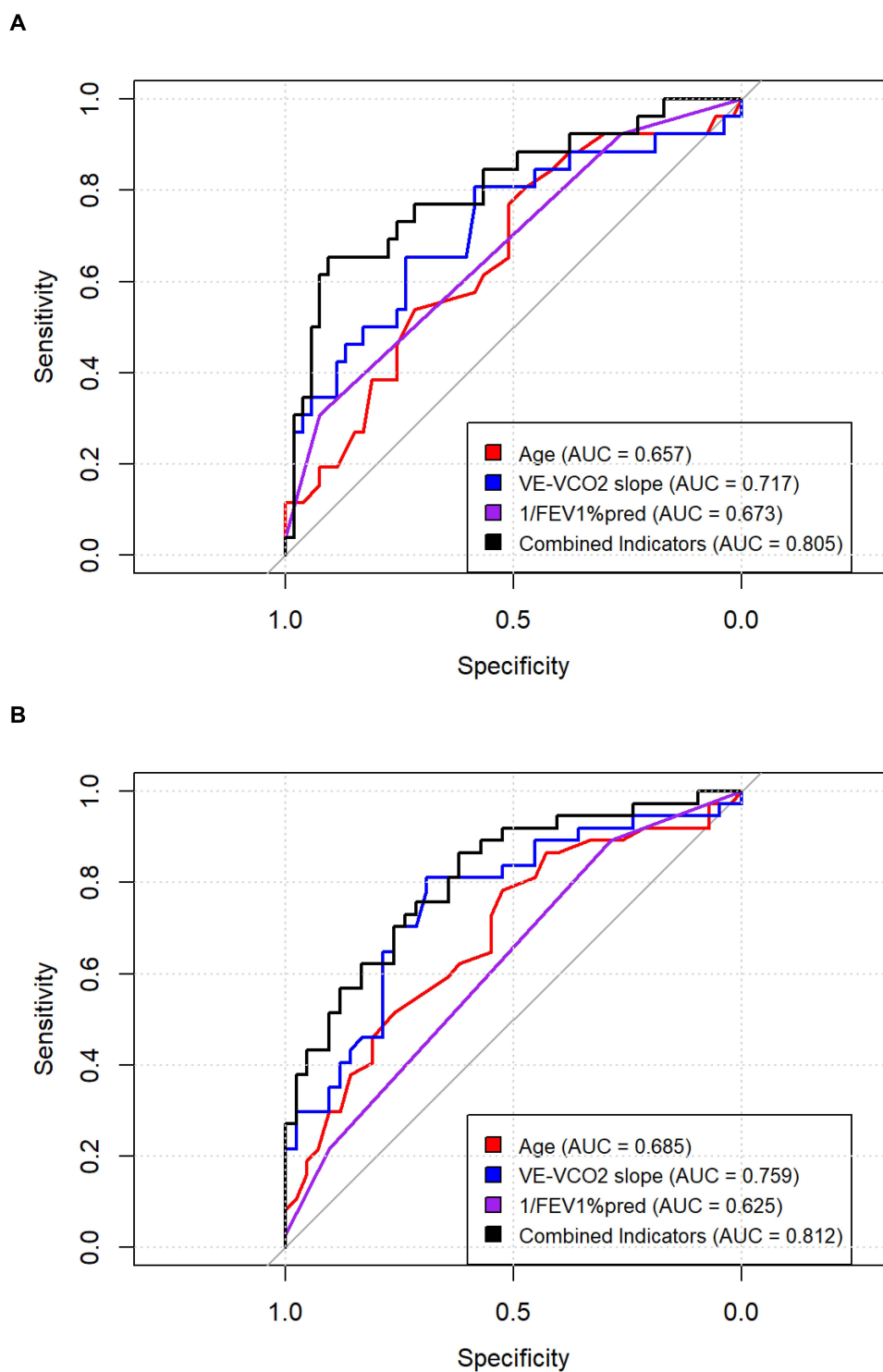
**Abbreviations:** BMI, body mass index; FEV1%pred, Forced Expiratory Volume in 1 second, percent predicted; FEV1/FVC, Forced Expiratory Volume in 1 second to Forced Vital Capacity ratio; VE-VCO2 slope, slope of VE-VCO2 (linear regression analysis of the relationship between minute ventilation VE and carbon dioxide output VCO2 during incremental exercise), the efficiency of ventilation in relation to body's carbon dioxide production; EqCO2, carbon dioxide equivalence at the lactate threshold.

five years. Given that a lower FEV1%pred value corresponds to better predictive ability, we used its reciprocal for comparison with the other two indicators (Figures 2A, B and 3). The results were as follows: (1) At one year: age (AUC = 0.657), VE-VCO2 slope (AUC = 0.717) and 1/FEV1%pred (AUC = 0.673); (2) At three years: age (AUC = 0.685),



**Figure 1** Forest Plot of Cox Regression Model.

**Notes:** Forest plot of COX regression in AECOPD with VE-VCO2 slope, age and FEV1%pred. \*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001.

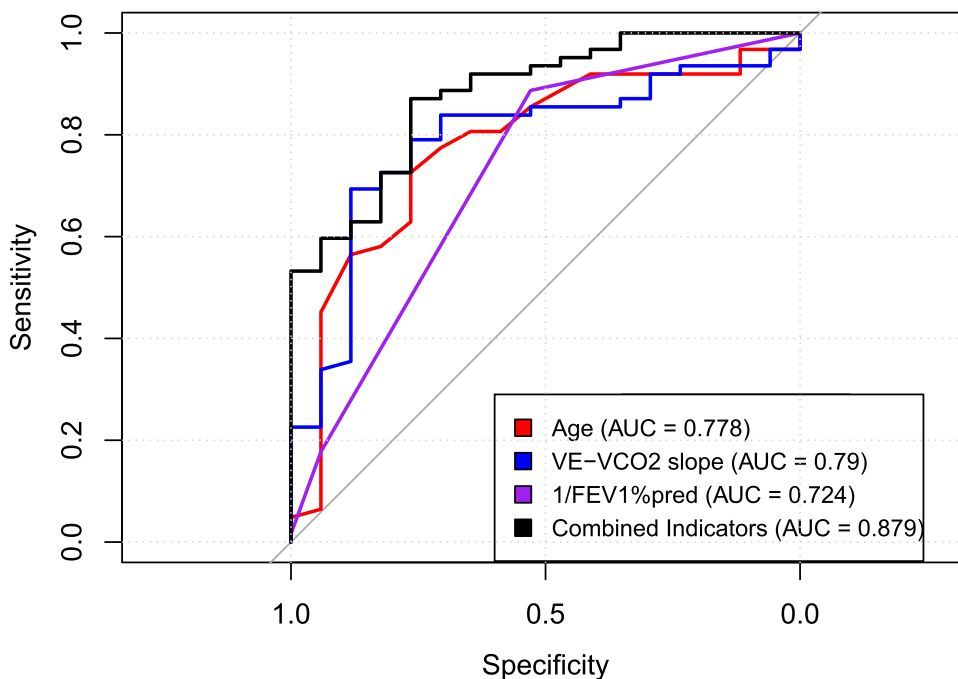


**Figure 2** (A) Timepoint: 12 months. (B) Timepoint: 36 months.

**Notes:** Receiver Operating Characteristic Curve Comparison at time point of 12 Months. Receiver Operating Characteristic Curve Comparison at time point of 36 Months.

VE-VCO2 slope (AUC = 0.759) and 1/FEV1%pred (AUC = 0.625); (3) At five years: age (AUC = 0.778), VE-VCO2 slope (AUC = 0.790) and 1/FEV1%pred (AUC = 0.724).

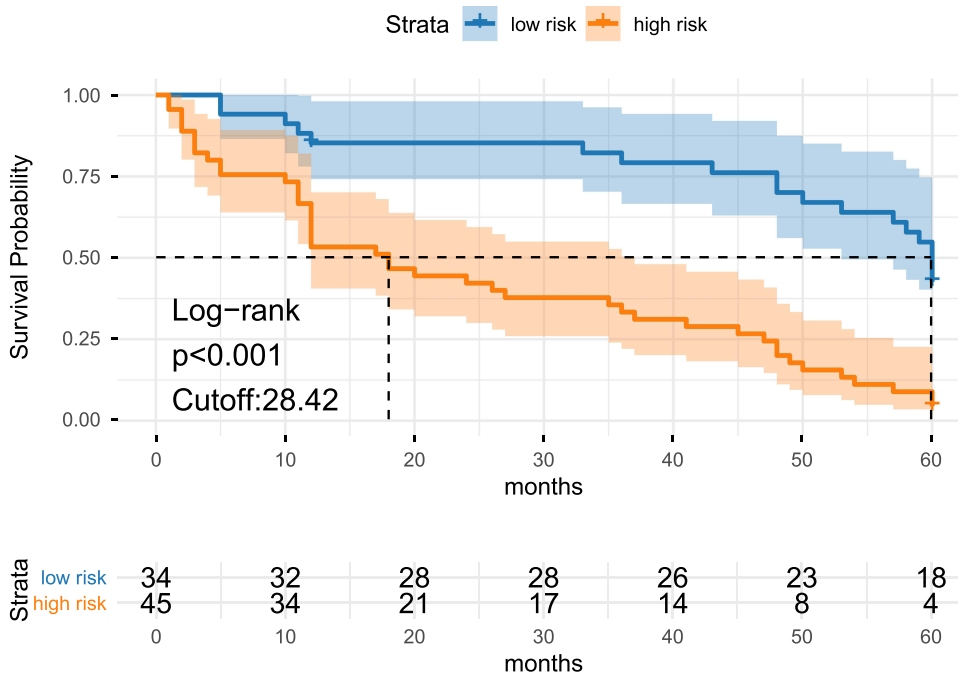
We used the DeLong test (see [Supplementary Table 1](#)) to compare the AUC values among the three individual indicators and a combined indicator. No statistically significant differences were observed. Nevertheless, in terms of



**Figure 3** Receiver Operating Characteristic Curve Comparison at time point of 60 Months.

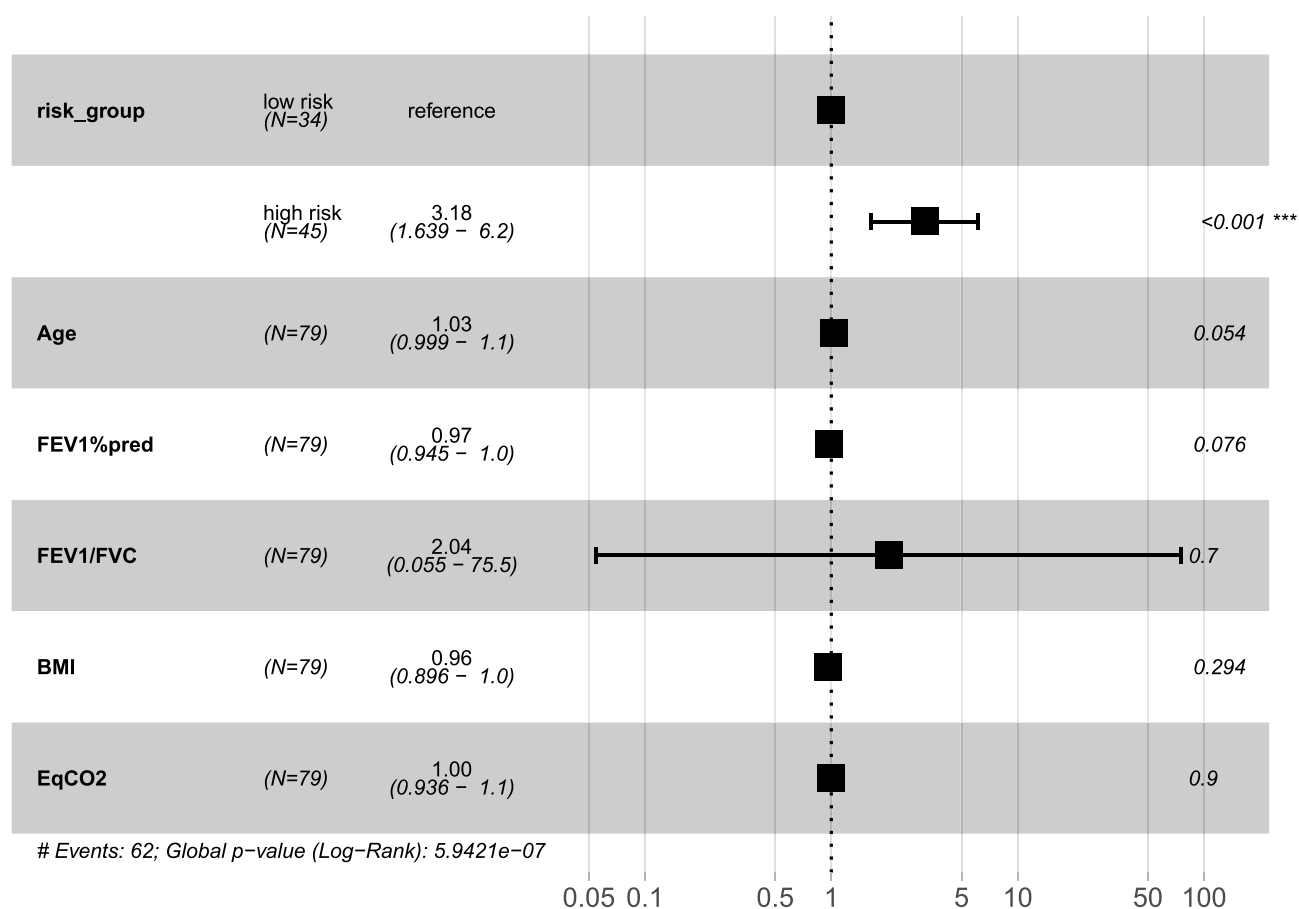
AUC magnitude, the VE-VCO2 slope demonstrated superior predictive performance compared to the other two indicators across all time points, although the combined model did not yield a significant improvement.

Integration of our analytical results identified the VE-VCO2 slope as the strongest prognostic determinant, with ROC analysis at the 5-year follow-up revealing superior discriminative capacity (AUC = 0.790). Using the optimal cutoff value ( $\geq 28.42$ ), patients were categorized into high-risk ( $\geq 28.42$ ) and low-risk groups for Kaplan–Meier survival analysis (Figure 4). The high-risk group showed a median time to acute exacerbation of 18 months, compared with 60 months in



**Figure 4** Survival Analysis Based on VE-VCO2 slope Risk Stratification.

**Note:** Kaplan-Meier curve of the time of AECOPD according to the two different VE-VCO2 slope groups.



**Figure 5** Forest plot of Multivariable Cox Regression Analysis for VE-VCO<sub>2</sub> slope Risk Stratification.

**Notes:** Forest plot of COX regression in AECOPD with VE-VCO<sub>2</sub>slope  $\geq 28.42$ . \*\*\*p < 0.001.

the low-risk group (Log rank test: p < 0.001). Following risk stratification, a multivariable Cox proportional hazards regression model, adjusted for other covariates, confirmed that an elevated VE-VCO<sub>2</sub> slope (high-risk group) remained an independent predictor of AECOPD (hazards ratio = 3.18, 95% CI 1.64–6.20, p < 0.001), as shown in [Figure 5](#).

## Discussion

The present study demonstrated a significant association between the VE-VCO<sub>2</sub> slope and acute exacerbation events in patients with COPD during a 5-year longitudinal observation. Furthermore, this parameter exhibited discriminative capacity for predicting AECOPD in the early and intermediate phases of follow up. CPET serves as a critical evaluative tool to assess aerobic and anaerobic metabolic capacities through measurements of oxygen consumption (VO<sub>2</sub>) and carbon dioxide production (VCO<sub>2</sub>).<sup>19</sup> COPD patients with concomitant emphysema exhibited an elevated residual volume to total lung capacity ratio (RV/TLC), indicative of air trapping.<sup>20</sup> Ventilation-perfusion (V/Q) mismatch represents the principal pathophysiological mechanism underlying exertional dyspnea in COPD populations. Notably, a subset of COPD patients manifests minimal dyspneic symptoms during rest or low-intensity activities, a phenomenon that limits the diagnostic utility of conventional 6-minute walk tests (6MWT). The subjective nature of 6MWT and variable patient effort levels compromise its reliability in assessing true ambulatory capacity, particularly regarding standardized walking performance evaluations.<sup>21</sup> Conversely, CPET protocols unmask accentuated dyspnea severity in COPD cohorts. This exacerbation correlates mechanistically with augmented dead space ventilation, necessitating compensatory hyperventilation to maintain eucapnia during CO<sub>2</sub> elimination. Consequently, the elevated VE-VCO<sub>2</sub> slope serves as an indicator of impaired ventilatory efficiency.<sup>22</sup> And the higher VE-VCO<sub>2</sub> slope values demonstrating significant correlation with exertional dyspnea intensity.<sup>23</sup> Patients stratified as GOLD Grade I typically preserve exercise

capacity parameters comparable to healthy controls. However, the co-occurrence of diffusion impairment within this subgroup portends adverse prognostic implications and exhibits frequent association with diminished body mass index (BMI) metrics.<sup>24</sup>

However, in our text, we realize variables like BMI and EqCO<sub>2</sub>, where the univariable analysis was significant ( $p < 0.05$ ) but the multivariable was not. This suggests that the effect of BMI on AECOPD was confounded by other variables in the model (eg. age and FEV1%pred). And, the EqCO<sub>2</sub> was confounded by the VE-VCO<sub>2</sub> slope variables in the model. Thus, we did not pay attention to these two variables, highlighting the importance of age, FEV1%pred and VE-VCO<sub>2</sub> slope in the pathophysiology of COPD. In our preliminary multivariate Cox regression analysis prior to risk stratification of the VE-VCO<sub>2</sub> slope, both age and FEV1% pred were identified as significant predictors of AECOPD. This aligns with established epidemiological observations, as COPD prevalence escalates with aging.<sup>25</sup> And lower FEV1%pred correlates with higher Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades, reflecting greater disease severity. Consistent with prior studies, declining FEV1%pred predicts high susceptibility to acute exacerbations during disease progression.<sup>26</sup> Following risk stratification of the VE-VCO<sub>2</sub> slope, subsequent multivariate Cox regression analysis revealed that elevated VE-VCO<sub>2</sub> slope in the high-risk cohort remained an independent predictor of AECOPD. Consequently, our investigation focused on analyzing the VE-VCO<sub>2</sub> slope after establishing baseline assessments for age and FEV1%pred. While the prognostic significance of VE-VCO<sub>2</sub> slope in heart failure has been well established and widely utilized, with extensive validation of the VE-VCO<sub>2</sub> slope as a robust predictor of adverse outcomes in population, however, its role in predicting acute exacerbations in COPD remains underexplored.<sup>27</sup> Although CPET is increasingly recognized for guiding pulmonary rehabilitation in COPD, the predictive utility of VE-VCO<sub>2</sub> slope for AECOPD has not been systematically investigated. Our study pioneers the development of a VE-VCO<sub>2</sub> slope-based predictive model for AECOPD, addressing this critical gap in COPD risk stratification.

Frequent acute exacerbations significantly impair quality of life in COPD patients. Established predictors of exacerbation risk include elevated neutrophil counts, eosinophil percentages in routine blood tests,<sup>28</sup> reduced FEV1%pred and prior exacerbation history.<sup>29</sup> Our retrospective cohort study demonstrated that VE-VCO<sub>2</sub> slope remained a significant prognostic indicator for COPD exacerbations over a 5-year horizon after adjusting for confounding variables. Notably, this predictive capacity exhibited comparable robustness during both 1-year and 3-year intervals. Despite limited recognition of the VE-VCO<sub>2</sub> slope in acute exacerbation of COPD (AECOPD) research, a prior investigation identified computed tomography (CT)-quantified emphysema severity as an independent determinant of abnormally elevated VE-VCO<sub>2</sub> slope in COPD populations,<sup>30</sup> suggesting imaging biomarkers may preliminarily estimate this parameter. Our findings extend these observations by providing novel physiological validation: the VE-VCO<sub>2</sub> slope accurately captures exercise-induced ventilation-perfusion (V/Q) mismatches, establishing mechanistic linkages between dynamic cardiopulmonary stress testing and clinical exacerbation susceptibility in natural disease progression. Also, it is essential to recognize that this parameter reflects global cardiopulmonary efficiency rather than a lung-specific phenomenon. In patients with COPD, elevated VE-VCO<sub>2</sub> slope may also arise from concurrent circulatory limitations, including reduced cardiac output response, chronotropic incompetence, or latent pulmonary vascular dysfunction. These factors are prevalent in COPD.

Our study has several limitations that should be acknowledged. First, the study population consisted predominantly of male participants. Consequently, the prognostic value of the VE-VCO<sub>2</sub> slope for predicting acute exacerbations may be more applicable to men and requires further validation in female COPD populations. Second, as a retrospective cohort study, inherent issues such as missing data limited our ability to comprehensively correlate the VE-VCO<sub>2</sub> slope with other clinical parameters. The underlying clinical and pathophysiological mechanisms of the VE-VCO<sub>2</sub> slope warrant deeper investigation in future studies. Third, our single-center, retrospective design limits generalizability to other populations and clinical settings. The modest sample size, particularly the limited number of patients in Non-AECOPD, may affect the precision and stability of our multivariable models, and our findings should be considered hypothesis-generating pending validation in larger cohorts. Fourth, although patients with overt cardiac disease were excluded, we cannot completely rule out the presence of subclinical heart failure with preserved ejection fraction (HFpEF), which is common in COPD and known to elevate the VE-VCO<sub>2</sub> slope.<sup>31</sup> The absence of systematic natriuretic peptide measurements and comprehensive echocardiographic diastolic function assessment limits our ability to

differentiate pulmonary from cardiac determinants of ventilatory efficiency. Future studies integrating cardiopulmonary exercise testing with simultaneous echocardiography and cardiac biomarkers are needed to refine the mechanistic interpretation of VE-VCO<sub>2</sub> slope in this population. Moreover, the VE-VCO<sub>2</sub> slope is not a directly measured parameter; it is derived from CPET data using statistical processing (from low level exercise to RCP). This highlights the need to develop predictive models that can more intuitively assess factors associated with COPD exacerbations. Additionally, as a continuous variable, the dichotomization of the VE-VCO<sub>2</sub> slope for risk stratification may lead to uneven distribution between groups, potentially limiting the generalizability of our cutoff value to external cohorts. Further expansion of the sample size is necessary to identify an optimal VE-VCO<sub>2</sub> threshold for clinical application. It should also be noted that this dynamic prospective cohort was originally recruited from Beijing Friendship Hospital between 2013 and 2019, with a planned 5-year follow-up. Now, a decade after initiation, we conducted additional follow-up before manuscript completion. However, a number of patients were lost to follow-up, and among those who could be reached, significant recall bias was observed. Reassessment of baseline clinical characteristics at enrollment was not feasible. Therefore, our analysis relied on retrospective review of prior follow-up records and baseline data, with re-evaluation of CPET-derived metrics for predicting acute exacerbations and associated pathophysiological correlates. Moving forward, we plan to establish a new prospective COPD cohort. Building on CPET assessments, we will incorporate additional clinical evaluations such as thoracic CT imaging, nutritional status assessment, and cognitive function screening. With appropriate ethical approval, a biorepository will be established to bank biological samples alongside comprehensive clinical data. Crucially, to minimize loss to follow-up, we will implement a structured follow-up clinic system, aiming to build a long term, stable COPD research cohort with complete and high-quality longitudinal data. Finally, while the VE-VCO<sub>2</sub> slope demonstrated robust predictive value for AECOPD in our cohort, we acknowledge that its multifactorial determinants preclude attribution to any single physiological domain. Future studies integrating detailed cardiac and pulmonary vascular phenotyping are needed to disentangle the relative contributions of lung mechanics, gas exchange, and circulatory function to ventilatory efficiency and its prognostic significance in COPD.

## Conclusions

Our study identifies the VE-VCO<sub>2</sub> slope after CPET as a significant predictor of AECOPD. This is the first report demonstrating its ability to predict the 5-year risk of acute exacerbations of COPD. These findings position the VE-VCO<sub>2</sub> slope as a valuable risk stratification tool for identifying high risk patients with COPD group who are prone to rehospitalization and require intensified outpatient management. Moreover, it holds important implications for early and middle stage for identification of high-risk individuals. Based on these results, we emphasize the necessity of implementing early interventions in COPD populations, including smoking cessation, adherence to pharmacotherapy, and initiation of respiratory muscle training, along with a structured pulmonary rehabilitation program that incorporates anaerobic exercise combined with appropriate aerobic activity.

## Abbreviations

CPET, Cardiopulmonary Exercise Test; COPD, Chronic Obstructive Pulmonary Disease; AECOPD, Acute exacerbations of Chronic Obstructive Pulmonary Disease; 6MWT, 6-min walk test; AT, Anaerobic threshold; VCO<sub>2</sub>, Carbon dioxide production; VO<sub>2</sub>, Oxygen uptake; VE, Ventilation; EqCO<sub>2</sub>, ventilatory equivalents for CO<sub>2</sub> at defined time points; EqCO<sub>2</sub> nadir, lowest observed value; SpO<sub>2</sub>, Oxygen saturation via pulse oximetry; FEV<sub>1</sub>, Forced expiratory volume in 1 s; HRR, Heart rate recovery; CI, Confidence interval.

## Ethics Approval and Informed Consent

The Ethics Committee of Beijing Friendship Hospital approved the study protocol (No: 2024-P2-125-01, Date: 2024-04-19). All participants were provided with written and oral information about this program and signed an informed consent form.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors have no conflicts of interest to declare.

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