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ORIGINAL RESEARCH

Equivalent of Carbon Dioxide at the Anaerobic Threshold Predicts Acute Exacerbations in Patients with Chronic Obstructive Pulmonary Disease: A Retrospective Cohort Study

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Purpose: To investigate the predictive value of the equivalent of carbon dioxide at the anaerobic threshold ($EqCO_2$@AT) for acute exacerbations (AE) in patients with chronic obstructive pulmonary disease (COPD).

Patients and Methods: This retrospective cohort study included 79 patients with COPD who underwent baseline pulmonary function testing and cardiopulmonary exercise testing (CPET). $EqCO_2$@AT = 30 was used only as an empirical threshold for descriptive stratification, rather than as an outcome-derived cutoff. Patients were also classified into non-AE and AE groups according to annualized exacerbation frequency. Baseline characteristics, pulmonary function, and CPET parameters were compared between groups. Logistic regression was used to evaluate the association between $EqCO_2$@AT and AE risk. Predictive performance was assessed using receiver operating characteristic curves, calibration analysis, decision curve analysis, Kaplan–Meier analysis, and a simplified nomogram.

Results: Of the 79 patients, 16 were classified into the low $EqCO_2$@AT group and 63 into the high $EqCO_2$@AT group. Patients with higher $EqCO_2$@AT were older, had lower BMI, greater smoking exposure, lower FEV_1% predicted and DLCO% predicted, reduced exercise capacity, and higher ventilatory inefficiency parameters. Compared with the non-AE group, the AE group had worse lung function, lower exercise capacity, and higher VE/VCO_2 slope and $EqCO_2$@AT. $EqCO_2$@AT was associated with AE risk in univariable analysis (OR 1.122, 95% CI 1.027–1.226, P = 0.011) and remained significant after adjustment for age, BMI, and FEV_1% predicted (OR 1.269, 95% CI 1.110–1.450, P < 0.001). The AUC of $EqCO_2$@AT alone was 0.739, whereas the combined model achieved an AUC of 0.850. Kaplan–Meier analysis showed significantly lower AE-free survival in the high $EqCO_2$@AT group (log-rank P = 0.002). The simplified nomogram provided an individualized visual tool for AE risk estimation.

Conclusion: Elevated $EqCO_2$@AT is associated with impaired ventilatory efficiency, reduced exercise capacity, and increased AE risk in COPD. A model incorporating $EqCO_2$@AT, age, BMI, and FEV_1% predicted showed good predictive performance and may support individualized AE risk stratification. These findings suggest that CPET-derived ventilatory efficiency parameters may provide clinically useful information beyond conventional pulmonary function assessment, although validation in larger multicenter prospective cohorts is still required.

Keywords: chronic obstructive pulmonary disease, acute exacerbation, anaerobic threshold, equivalent of carbon dioxide, cardiopulmonary exercise testing

Introduction

Chronic obstructive pulmonary disease (COPD) is a common chronic respiratory disorder characterized by persistent respiratory symptoms and airflow limitation, and remains a major cause of disability and mortality worldwide.[1] Acute exacerbations of COPD (AECOPD) are important events in disease progression because they may worsen symptoms,

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increase hospitalization risk, accelerate lung function decline, and raise mortality.[1,2] Current global COPD management strategies emphasize future exacerbation risk assessment based on prior exacerbation history, symptom burden, and pulmonary function indices.[1] However, these conventional measures mainly reflect disease severity at rest and may not fully capture abnormalities in ventilation, circulation, and metabolism during exercise. Therefore, dynamic cardiopulmonary parameters may provide additional value for refining risk stratification in stable COPD.

Cardiopulmonary exercise testing (CPET) enables integrated assessment of ventilation, gas exchange, circulatory reserve, and metabolic responses during incremental exercise, and is useful for clarifying mechanisms of exercise limitation and dyspnea.[3–6] The equivalent of carbon dioxide at the anaerobic threshold ($EqCO_2$@AT) reflects the ventilatory requirement for carbon dioxide elimination at a key metabolic transition point.[7,8] In COPD, increased dead-space ventilation, ventilation/perfusion mismatch, and wasted ventilation increase the ventilatory cost of carbon dioxide elimination, leading to impaired ventilatory efficiency and exertional dyspnea.[9,10] Although ventilatory inefficiency is associated with reduced exercise tolerance, evidence directly linking $EqCO_2$@AT to future exacerbation risk remains limited. This retrospective cohort study therefore aimed to evaluate the predictive value of $EqCO_2$@AT for AECOPD and its potential role in clinical risk stratification.

Materials and Methods

Study Design and Participants

This single-center retrospective cohort study enrolled patients with COPD who attended the Department of Respiratory Medicine, Beijing Friendship Hospital, Capital Medical University, between January 2020 and December 2025 and completed CPET during the stable phase. Baseline clinical data, pulmonary function, CPET parameters, and subsequent acute exacerbation events were retrospectively collected.

Eligible patients were aged ≥40 years, had COPD diagnosed according to GOLD criteria, defined as post-bronchodilator $FEV_1/FVC < 0.70$, had no acute exacerbation within 4 weeks before testing, and were able to complete CPET.[1] Patients were excluded if they had severe cardiovascular disease, other severe pulmonary diseases, skeletal muscle or neurologic disorders affecting exercise performance, incomplete baseline data, or missing follow-up information. Of 91 patients initially screened, 79 were included in the final analysis. The study was approved by the Ethics Committee of Beijing Friendship Hospital, Capital Medical University (Approval No. 2024-P2-125-01) and complied with the Declaration of Helsinki.

Clinical Data Collection

Baseline data were obtained from the electronic medical record system, including age, sex, height, weight, BMI, smoking history, comorbidities, previous exacerbation history, and pulmonary function variables. Smoking exposure was expressed as pack-years. For descriptive comparisons, patients were stratified into a low $EqCO_2$@AT group (≤30) and a high $EqCO_2$@AT group (>30) according to baseline $EqCO_2$@AT.[7]

Pulmonary Function Testing

Pulmonary function testing was performed at baseline using a MasterScreen Body plethysmograph (CareFusion, San Diego, CA, USA) according to guideline-based procedures. The measured variables included vital capacity, forced vital capacity, forced expiratory volume in 1 second, FEV_1% predicted, residual volume/total lung capacity, DLCO% predicted, and DLCO/VA% predicted.

Cardiopulmonary Exercise Testing

Baseline CPET was performed using an electronically braked cycle ergometer (ViaSprint, CareFusion, Höchberg, Germany). After 3 minutes of rest and 3 minutes of unloaded pedaling, patients underwent symptom-limited incremental exercise with an individualized work-rate increase of 5–20 W/min while maintaining a cadence of approximately 60 rpm. Electrocardiography, blood pressure, pulse oxygen saturation, minute ventilation, oxygen uptake, and carbon dioxide output were monitored continuously.[5,6]

$EqCO_2$ was defined as VE/VCO_2, and $EqCO_2$@AT was defined as the VE/VCO_2 value at the anaerobic threshold.[8] AT was determined mainly by the V-slope method, with reference to the behavior of VE/VO_2 and VE/VCO_2.[5,8] Other recorded CPET parameters included Peak VO_2, peak work rate, $\Delta VO_2/\Delta$Work slope, oxygen pulse, VE/VCO_2 slope, Peak VCO_2, peak heart rate, heart rate recovery, and chronotropic index.

The main derived indices were calculated as follows: VE/VCO_2 slope was obtained from the linear relationship between VE and VCO_2 during incremental exercise; $\Delta VO_2/\Delta$Work slope was calculated as the change in VO_2 divided by the change in work rate; oxygen pulse was calculated as VO_2/heart rate; heart rate recovery was calculated as the difference between peak heart rate and early recovery heart rate; chronotropic index was calculated as (Peak HR − resting HR)/(age-predicted maximal HR − resting HR) × 100%; and BMI was calculated as weight divided by height squared.

Follow-Up and Outcome Definitions

The date of baseline CPET was defined as the start of observation. Because patients entered the cohort at different time points between January 2020 and December 2025, follow-up duration was not identical for all participants. Each patient was followed from baseline CPET until the first documented AE event, the last available follow-up visit, or the end of the study observation period, whichever came first. The maximum follow-up duration was 5 years.

AE was defined as an acute worsening of respiratory symptoms requiring additional antibiotics, systemic corticosteroids, or hospitalization.[1] Annualized exacerbation frequency was calculated as the total number of AE events divided by follow-up duration. Patients were categorized into a non-AE group (AE <1/year) and an AE group (AE ≥1/year).[1,11] For survival analysis, AE-free survival was defined as the time from baseline CPET to the first documented AE or censoring at the last follow-up visit.

$EqCO_2$@AT = 30 was used only as an empirical threshold for descriptive stratification based on the ERS statement on standardized CPET in chronic lung diseases and the distribution of this cohort; it was not used as the outcome-derived predictive cutoff.[7] The optimal cutoff for AE prediction was determined by ROC analysis and was used for Kaplan–Meier analysis. A combined model including age, BMI, FEV_1% predicted, and $EqCO_2$@AT was constructed and further evaluated using ROC, calibration, decision curve, and simplified nomogram analyses.

Data Completeness and CPET Interpretation

Data completeness was assessed before statistical analysis. Patients with incomplete baseline clinical data, pulmonary function results, CPET parameters, or missing follow-up information were excluded; therefore, no imputation was performed. CPET parameters, including AT determination, were interpreted according to standardized criteria by trained investigators. When uncertainty existed, results were reviewed by an experienced senior physician and resolved by consensus. Formal inter-observer variability analysis was not performed.

Statistical Analysis

All analyses were performed using R software, version 4.4.0. Continuous variables were tested for normality using the Shapiro–Wilk test. Normally distributed variables are presented as mean ± standard deviation and were compared using the independent-samples *t*-test. Non-normally distributed variables are presented as median and interquartile range and were compared using the Mann–Whitney *U*-test. Categorical variables are presented as number and percentage and were compared using the chi-square test or Fisher's exact test, as appropriate. A two-sided $P < 0.05$ was considered statistically significant.

Univariable and multivariable logistic regression analyses were performed to assess the association between $EqCO_2$@AT and AE risk, with odds ratios and 95% confidence intervals calculated. ROC curves were used to evaluate the predictive performance of $EqCO_2$@AT alone and the combined model. Calibration and decision curve analyses were used to assess model agreement and clinical utility. A simplified nomogram was constructed from the combined model to improve clinical interpretability. Kaplan–Meier analysis was performed using the ROC-derived cutoff, and group differences were compared with the Log rank test.

Results

A total of 79 patients with COPD were included. Using $EqCO_2$@AT = 30 as the descriptive threshold, 16 patients were classified into the low $EqCO_2$@AT group and 63 into the high $EqCO_2$@AT group (Figure 1). Compared with the low $EqCO_2$@AT group, the high $EqCO_2$@AT group was older (67.9 ± 7.6 vs 61.6 ± 8.6 years, P = 0.014), had lower BMI (23.5 ± 3.4 vs 26.0 ± 3.8 kg/m^2, P = 0.027), and had greater smoking exposure (26.3 ± 22.9 vs 10.9 ± 12.1 pack-years, P < 0.001). No significant between-group differences were observed in sex distribution, height, weight, GOLD stage, or major comorbidities, including hypertension, coronary artery disease, and diabetes (Table 1).

Static pulmonary function showed that patients with higher $EqCO_2$@AT had lower FEV_1% predicted (54.82 ± 14.06% vs 63.56 ± 14.23%, P = 0.030), lower DLCO% predicted (64.59 ± 15.03% vs 72.96 ± 9.68%, P = 0.038), and higher RV/TLC (66.98 ± 18.28% vs 59.25 ± 7.02%, P = 0.009) than those with lower $EqCO_2$@AT. Other pulmonary function variables, including VC, FVC, FEV_1, FEV_1/FVC, and DLCO/VA% predicted, did not differ significantly between groups (Table 2).

On CPET, the high $EqCO_2$@AT group showed lower Peak VO_2 (1211.81 ± 283.14 vs 1468.38 ± 263.39 mL/min, P = 0.002), peak work rate (82.81 ± 22.40 vs 113.81 ± 26.62 W, P < 0.001), $\Delta VO_2/\Delta$Work slope (9.18 ± 1.76 vs 9.85 ± 0.70, P = 0.021), anaerobic threshold (880.27 ± 204.61 vs 1025.44 ± 199.94 mL/min, P = 0.016), VO_2/HR (9.71 ± 2.22 vs 10.99 ± 1.31 mL/beat, P = 0.005), and Peak VCO_2 (1332.03 ± 341.11 vs 1648.75 ± 365.31 mL/min, P = 0.005), but higher HR/VO_2 slope (48.87 ± 14.38 vs 44.90 ± 3.21, P = 0.049), VE/VCO_2 slope (30.74 ± 4.43 vs 24.98 ± 2.49, P < 0.001), and $EqCO_2$@AT (36.78 ± 4.53 vs 27.55 ± 1.72, P < 0.001) than the low $EqCO_2$@AT group. Peak HR, HRR, CI, and Peak VE were comparable between groups (Table 2).

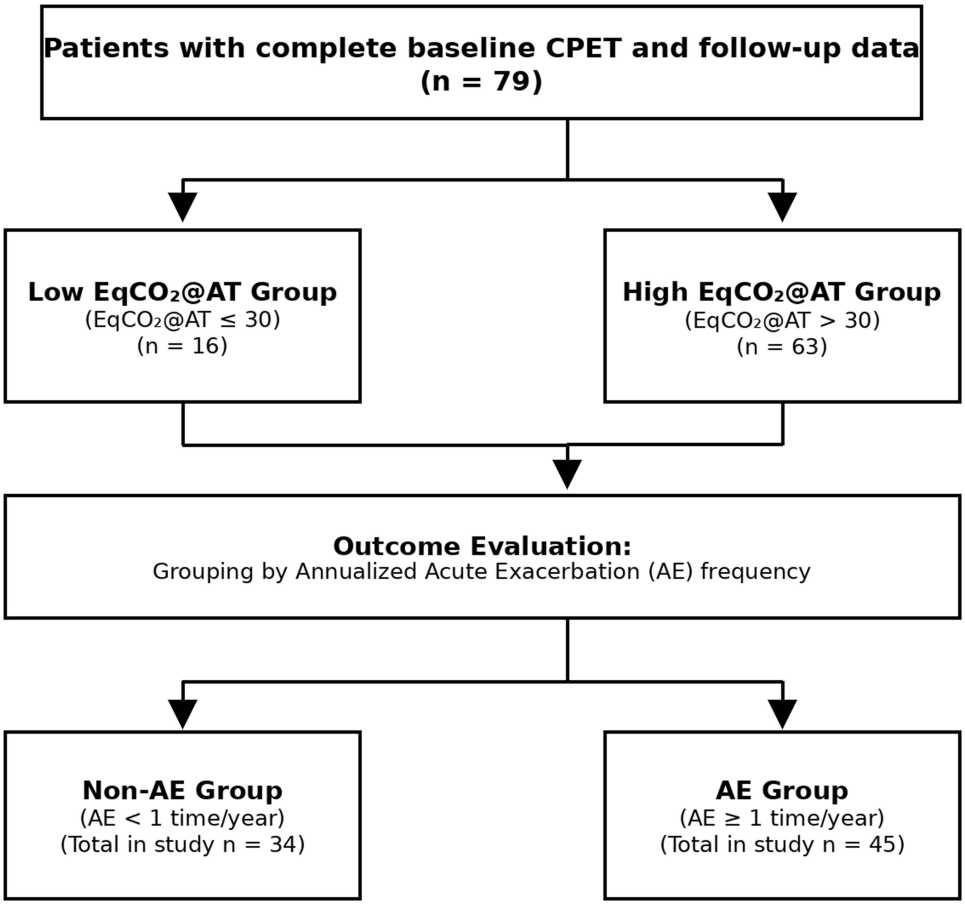

Figure 1 Flow chart showing patient inclusion and study grouping according to baseline $EqCO_2$@AT and annualized acute exacerbation frequency. Patients with complete baseline cardiopulmonary exercise testing (CPET) and follow-up data were included in the final analysis. $EqCO_2$@AT = 30 was used for descriptive stratification only.

Table 1 Baseline Clinical Characteristics Stratified by $EqCO_2$@AT

Variable	Low $EqCO_2$@AT (n=16)≤30	High $EqCO_2$@AT (n=63)>30	Total (n=79)	P value
Age, years	61.6 ± 8.6	67.9 ± 7.6	66.6 ± 8.2	0.014
Male/Female, n	12/4	56/7	68/11	0.219
Height, cm	168.0 ± 6.9	167.9 ± 6.8	167.9 ± 6.8	0.948
Weight, kg	73.5 ± 13.1	66.4 ± 11.3	67.8 ± 12.0	0.061
BMI, kg/m^2	26.0 ± 3.8	23.5 ± 3.4	24.0 ± 3.6	0.027
Smoking exposure, pack-years	10.9 ± 12.1	26.3 ± 22.9	23.2 ± 22.0	<0.001
GOLD stage, n (%)				0.105
Stage 1, n (%)	3 (18.8)	5 (7.9)	8 (10.1)	
Stage 2, n (%)	12 (75.0)	35 (55.6)	47 (59.5)	
Stage 3, n (%)	1 (6.2)	22 (34.9)	23 (29.1)	
Stage 4, n (%)	0 (0.0)	1 (1.6)	1 (1.3)	
Hypertension, n (%)	2 (12.5)	20 (31.7)	22 (27.8)	0.211
Coronary artery disease, n (%)	1 (6.2)	12 (19.0)	13 (16.5)	0.286
Diabetes, n (%)	0 (0.0)	10 (15.9)	10 (12.7)	0.200

Notes: $EqCO_2$@AT = 30 was used as an empirical threshold for descriptive stratification only, based on the ERS statement on standardized CPET in chronic lung diseases and the distribution characteristics of this cohort.[7]
Abbreviations: $EqCO_2$@AT, equivalent of carbon dioxide at the anaerobic threshold; BMI, body mass index; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Table 2 Pulmonary Function and CPET Parameters Stratified by $EqCO_2$@AT

Variable	Low $EqCO_2$@AT (n=16)	High $EqCO_2$@AT (n=63)	Total (n=79)	P value
Static pulmonary function				
VC, L	2.89 ± 0.46	2.63 ± 0.55	2.68 ± 0.54	0.092
FVC, L	2.86 ± 0.45	2.71 ± 0.57	2.74 ± 0.55	0.313
FEV_1, L	1.75 ± 0.58	1.52 ± 0.44	1.57 ± 0.47	0.095
FEV_1% predicted, %	63.56 ± 14.23	54.82 ± 14.06	56.59 ± 14.44	0.030
FEV_1/FVC, %	59.58 ± 10.43	56.22 ± 10.03	56.90 ± 10.14	0.239
RV/TLC, %	59.25 ± 7.02	66.98 ± 18.28	60.81 ± 10.64	0.009
DLCO% predicted, %	72.96 ± 9.68	64.59 ± 15.03	66.28 ± 14.46	0.038
DLCO/VA% predicted, %	85.99 ± 7.90	80.63 ± 18.97	81.72 ± 17.40	0.274
CPET parameters				
Peak VO_2, mL/min	1468.38 ± 263.39	1211.81 ± 283.14	1263.77 ± 296.37	0.002
Peak work rate, W	113.81 ± 26.62	82.81 ± 22.40	89.09 ± 26.31	<0.001
$\Delta VO_2/\Delta$Work slope	9.85 ± 0.70	9.18 ± 1.76	9.31 ± 1.62	0.021

(*Continued*)

Table 2 (Continued).

Variable	Low $EqCO_2$@AT (n=16)	High $EqCO_2$@AT (n=63)	Total (n=79)	P value
AT, mL/min	1025.44 ± 199.94	880.27 ± 204.61	909.67 ± 210.74	0.016
Peak HR, beats/min	133.81 ± 19.83	125.90 ± 19.53	127.51 ± 19.72	0.167
VO_2/HR, mL/beat	10.99 ± 1.31	9.71 ± 2.22	9.97 ± 2.13	0.005
HR/VO_2 slope	44.90 ± 3.21	48.87 ± 14.38	48.07 ± 13.00	0.049
HRR, beats/min	25.38 ± 21.52	17.63 ± 9.21	19.20 ± 12.90	0.178
CI, %	86.63 ± 24.99	65.80 ± 21.98	67.29 ± 22.54	0.283
Peak VE, L/min	47.00 ± 11.73	47.84 ± 14.14	47.67 ± 13.62	0.808
Peak VCO_2, mL/min	1648.75 ± 365.31	1332.03 ± 341.11	1396.18 ± 366.83	0.005
VE/VCO_2 slope	24.98 ± 2.49	30.74 ± 4.43	29.57 ± 4.71	<0.001
$EqCO_2$@AT	27.55 ± 1.72	36.78 ± 4.53	34.91 ± 5.55	<0.001

Abbreviations: $EqCO_2$@AT, equivalent of carbon dioxide at the anaerobic threshold; CPET, cardiopulmonary exercise testing; VC, vital capacity; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; RV, residual volume; TLC, total lung capacity; DLCO, diffusing capacity of the lung for carbon monoxide; VA, alveolar volume; VO_2, oxygen uptake; $\Delta VO_2/\Delta$Work slope, oxygen uptake/work rate slope; AT, anaerobic threshold; HR, heart rate; VO_2/HR, oxygen pulse; HRR, heart rate recovery; CI, chronotropic index; VE, minute ventilation; VCO_2, carbon dioxide output.

According to annualized exacerbation frequency, 34 patients were classified into the non-AE group and 45 into the AE group. The AE group had lower FEV_1% predicted than the non-AE group (52.27 ± 12.53% vs 59.38 ± 15.03%, P = 0.032), while other static pulmonary function variables were similar. CPET showed that the AE group had lower Peak VO_2 (1170.65 ± 310.59 vs 1323.92 ± 273.46 mL/min, P = 0.024), Peak HR (121.84 ± 21.06 vs 131.17 ± 18.10 beats/min, P = 0.039), VO_2/HR (9.65 ± 2.31 vs 10.17 ± 2.00 mL/beat, P = 0.029), and CI (49.24 ± 19.02 vs 71.53 ± 21.37%, P = 0.010), but higher VE/VCO_2 slope (31.97 ± 4.96 vs 28.03 ± 3.87, P < 0.001) and $EqCO_2$@AT (36.49 ± 5.75 vs 30.89 ± 5.24, P < 0.001) than the non-AE group (Table 3 and Figure 2). Peak work rate, $\Delta VO_2/\Delta$Work slope, AT, HR/VO_2 slope, HRR, Peak VE, and Peak VCO_2 did not differ significantly between groups.

Table 3 Pulmonary Function and CPET Parameters in the Non-AE and AE Groups

Variable	Non-AE (n=34)	AE (n=45)	Total (n=79)	P value
Static pulmonary function				
FVC, L	2.75 ± 0.63	2.72 ± 0.42	2.74 ± 0.55	0.786
VC, L	2.69 ± 0.59	2.68 ± 0.46	2.68 ± 0.54	0.960
FEV_1% predicted, %	59.38 ± 15.03	52.27 ± 12.53	56.59 ± 14.44	0.032
FEV_1/FVC, %	58.0 ± 11.0	55.0 ± 8.0	57.0 ± 10.0	0.250
RV/TLC, %	61.01 ± 12.91	60.52 ± 5.77	60.81 ± 10.64	0.843
PEF% predicted, %	66.95 ± 34.86	56.46 ± 21.82	58.79 ± 23.03	0.604
DLCO/VA% predicted, %	82.22 ± 18.21	80.93 ± 16.32	81.72 ± 17.40	0.750

(*Continued*)

Table 3 (Continued).

Variable	Non-AE (n=34)	AE (n=45)	Total (n=79)	P value
CPET parameters				
Peak VO_2, mL/min	1323.92 ± 273.46	1170.65 ± 310.59	1263.77 ± 296.37	0.024
Peak work rate, W	92.40 ± 26.15	83.97 ± 26.16	89.09 ± 26.31	0.166
$\Delta VO_2/\Delta$Work slope	9.09 ± 1.65	9.67 ± 1.55	9.31 ± 1.62	0.120
AT, mL/min	930.69 ± 181.43	877.13 ± 249.20	909.67 ± 210.74	0.273
Peak HR, beats/min	131.17 ± 18.10	121.84 ± 21.06	127.51 ± 19.72	0.039
VO_2/HR, mL/beat	10.17 ± 2.00	9.65 ± 2.31	9.97 ± 2.13	0.029
HR/VO_2 slope	50.25 ± 15.64	44.68 ± 6.07	48.07 ± 13.00	0.062
HRR, beats/min	19.98 ± 7.41	18.00 ± 18.55	19.20 ± 12.90	0.509
CI, %	71.53 ± 21.37	49.24 ± 19.02	67.29 ± 22.54	0.010
Peak VE, L/min	47.19 ± 12.57	48.42 ± 15.29	47.67 ± 13.62	0.697
Peak VCO_2, mL/min	1458.81 ± 339.52	1299.19 ± 391.49	1396.18 ± 366.83	0.058
VE/VCO_2 slope	28.03 ± 3.87	31.97 ± 4.96	29.57 ± 4.71	<0.001
$EqCO_2$@AT	30.89 ± 5.24	36.49 ± 5.75	34.91 ± 5.55	<0.001

Abbreviations: AE, acute exacerbation; CPET, cardiopulmonary exercise testing; FVC, forced vital capacity; VC, vital capacity; FEV_1, forced expiratory volume in 1 second; RV, residual volume; TLC, total lung capacity; PEF, peak expiratory flow; DLCO, diffusing capacity of the lung for carbon monoxide; VA, alveolar volume; VO_2, oxygen uptake; $\Delta VO_2/\Delta$Work slope, oxygen uptake/work rate slope; AT, anaerobic threshold; HR, heart rate; VO_2/HR, oxygen pulse; HRR, heart rate recovery; CI, chronotropic index; VE, minute ventilation; VCO_2, carbon dioxide output; $EqCO_2$@AT, equivalent of carbon dioxide at the anaerobic threshold.

Correlation analysis showed that $EqCO_2$@AT was negatively correlated with FEV_1% predicted (r = −0.257, P = 0.023), peak work rate (r = −0.364, P = 0.00098), anaerobic threshold (r = −0.350, P = 0.00158), Peak VCO_2 (r = −0.280, P = 0.0124), and Peak VO_2 (r = −0.280, P = 0.0125), and positively correlated with VE/VCO_2 slope (r = 0.701, P < 0.001)

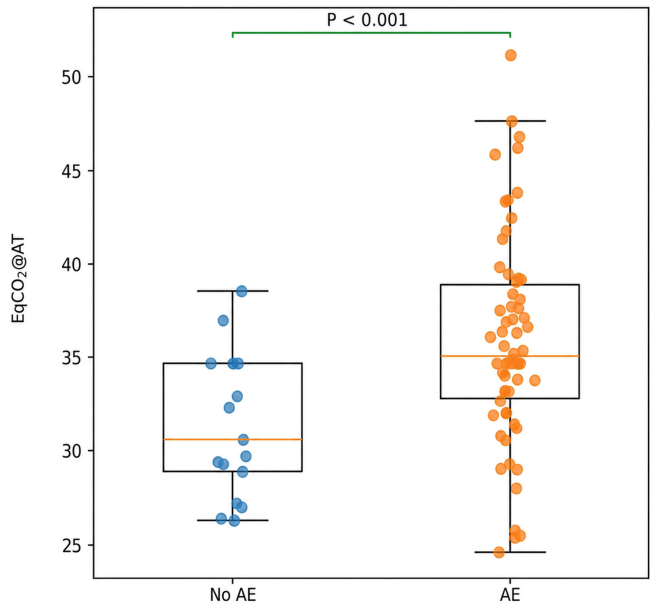

Figure 2 Comparison of $EqCO_2$@AT between the non-AE and AE groups. The AE group showed significantly higher $EqCO_2$@AT values than the non-AE group. AE, acute exacerbation; $EqCO_2$@AT, equivalent of carbon dioxide at the anaerobic threshold.

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(Supplementary Figure S1). These findings suggest that elevated $EqCO_2$@AT was associated with lower FEV_1% predicted, impaired ventilatory efficiency, and reduced exercise capacity.

ROC analysis showed that the AUC of $EqCO_2$@AT alone for predicting AE was 0.739, whereas the combined model incorporating age, BMI, FEV_1% predicted, and $EqCO_2$@AT achieved a higher AUC of 0.850 (Figure 3). Calibration analysis showed good agreement between predicted and observed probabilities (Figure 4). Decision curve analysis further indicated that the combined model provided greater net benefit than $EqCO_2$@AT alone and the treat-all or treat-none strategies across a broad range of threshold probabilities (Figure 5).

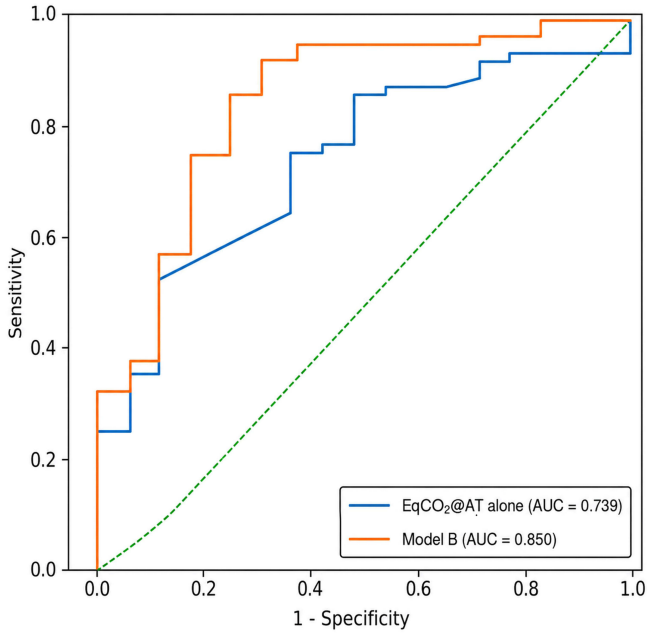

Figure 3 Receiver operating characteristic (ROC) curves of $EqCO_2$@AT alone and Model B for predicting AE. Model B included age, body mass index (BMI), FEV_1% predicted, and $EqCO_2$@AT. The area under the curve (AUC) was 0.739 for $EqCO_2$@AT alone and 0.850 for Model B.

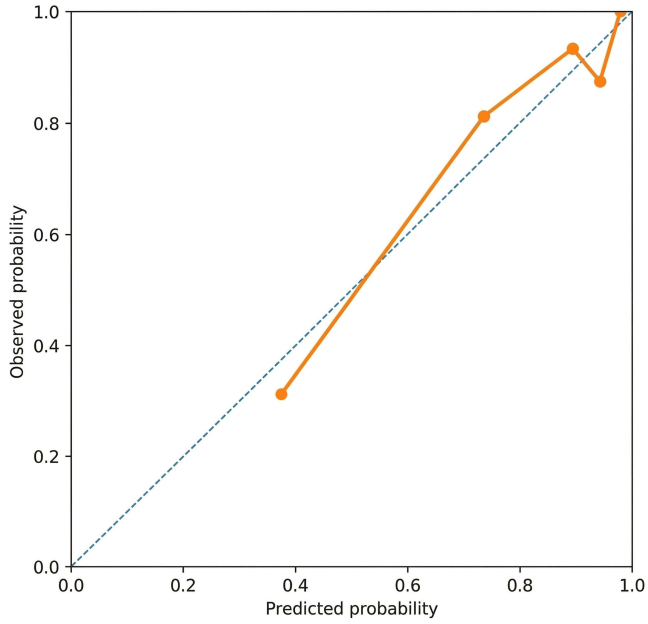

Figure 4 Calibration curve of Model B for predicting AE risk. The diagonal line represents ideal agreement between predicted and observed probabilities, and the model curve represents the observed calibration performance of Model B.

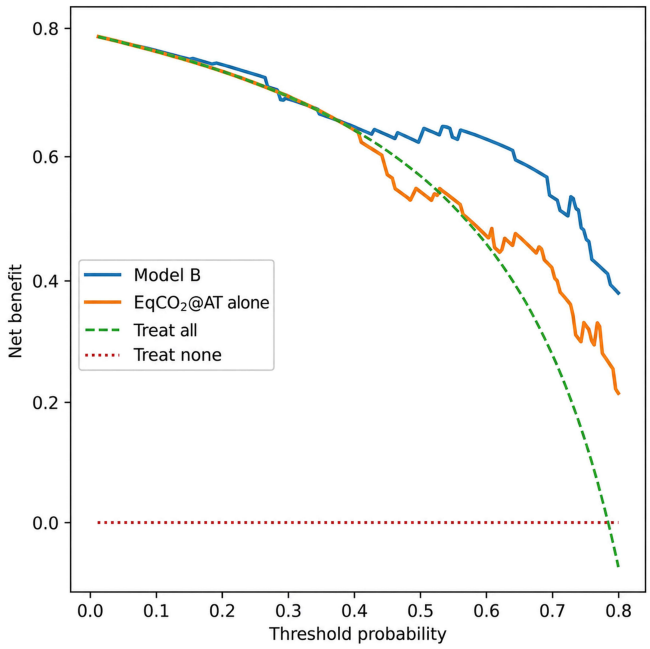

Figure 5 Decision curve analysis comparing Model B with $EqCO_2$@AT alone for predicting AE. Model B provided greater net benefit than $EqCO_2$@AT alone and than the treat-all or treat-none strategies across a broad range of threshold probabilities.

In univariable logistic regression, $EqCO_2$@AT was associated with increased AE risk (OR 1.122, 95% CI 1.027–1.226, P = 0.011), while higher FEV_1% predicted was associated with lower AE risk (OR 0.960, 95% CI 0.933–0.987, P = 0.005). Age and BMI were not significantly associated with AE risk in univariable analysis. In multivariable analysis adjusted for age, BMI, and FEV_1% predicted, $EqCO_2$@AT remained independently associated with AE risk (OR 1.269, 95% CI 1.110–1.450, P < 0.001). BMI was positively associated with AE risk (OR 1.608, 95% CI 1.254–2.061, P < 0.001), whereas FEV_1% predicted remained protective (OR 0.919, 95% CI 0.879–0.961, P < 0.001); age was not significant (OR 1.005, 95% CI 0.933–1.082, P = 0.895) (Table 4).

A simplified nomogram based on the combined model was constructed to improve clinical interpretability (Figure 6). BMI contributed the largest point score, followed by FEV_1% predicted and $EqCO_2$@AT, while age contributed minimally. The nomogram visually integrates clinical, pulmonary function, and CPET-derived variables for individualized AE risk estimation.

Using the ROC-derived optimal cutoff of $EqCO_2$@AT = 34.88, Kaplan–Meier analysis showed significantly lower AE-free survival in the high $EqCO_2$@AT group than in the low $EqCO_2$@AT group (log-rank P = 0.002; Figure 7).

Table 4 Logistic Regression Analysis of $EqCO_2$@AT and Acute Exacerbation Risk

Variable	Univariable OR (95% CI)	P value	Multivariable OR (95% CI)	P value
$EqCO_2$@AT	1.122 (1.027–1.226)	0.011	1.269 (1.110–1.450)	<0.001
Age	1.013 (0.952–1.078)	0.679	1.005 (0.933–1.082)	0.895
BMI	1.105 (0.961–1.271)	0.161	1.608 (1.254–2.061)	<0.001
FEV_1% predicted	0.960 (0.933–0.987)	0.005	0.919 (0.879–0.961)	<0.001

Abbreviations: $EqCO_2$@AT, equivalent of carbon dioxide at the anaerobic threshold; OR, odds ratio; CI, confidence interval; BMI, body mass index; FEV_1, forced expiratory volume in 1 second.

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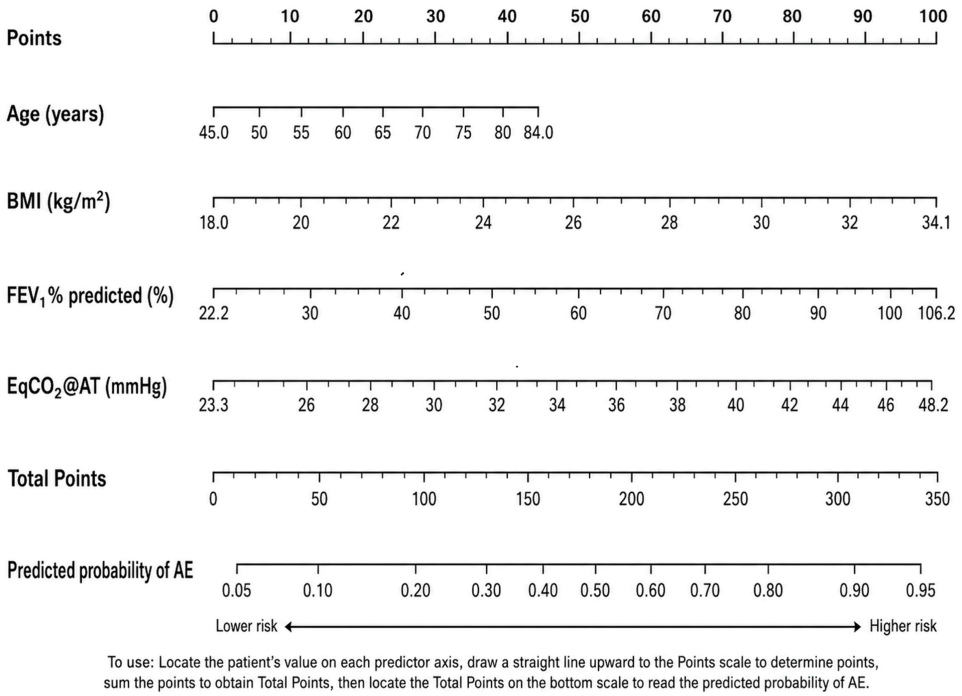

Figure 6 Simplified nomogram based on Model B for individualized AE risk estimation. The nomogram integrates age, BMI, FEV_1% predicted, and $EqCO_2$@AT. Each predictor corresponds to a point score, and the total points can be mapped to the predicted probability of AE. AE, acute exacerbation; BMI, body mass index; FEV_1, forced expiratory volume in 1 second; $EqCO_2$@AT, equivalent of carbon dioxide at the anaerobic threshold.

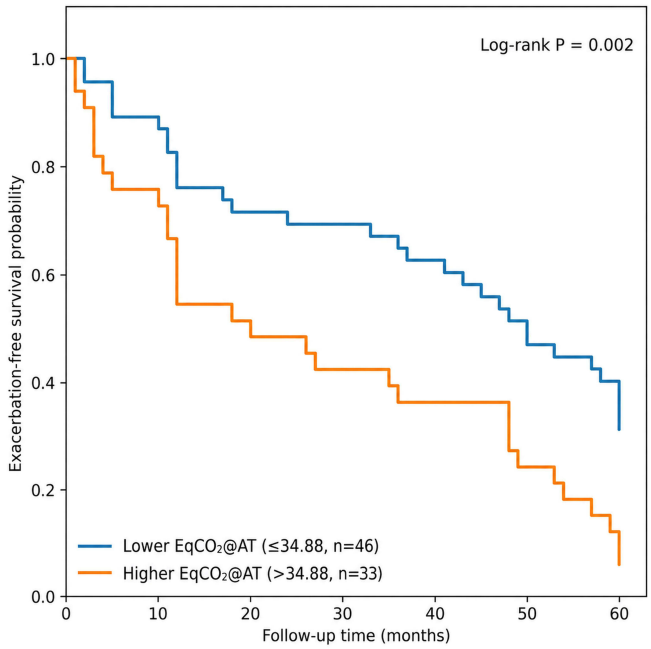

Figure 7 Kaplan–Meier curve of AE-free survival stratified by the ROC-derived optimal cutoff of $EqCO_2$@AT. AE-free survival was significantly lower in the high $EqCO_2$@AT group than in the low $EqCO_2$@AT group (log-rank P = 0.002).

Discussion

In this retrospective cohort study, elevated $EqCO_2$@AT was associated with impaired ventilatory efficiency, reduced exercise capacity, and increased acute exacerbation (AE) risk in patients with COPD. This association remained

significant after adjustment for age, BMI, and FEV_1% predicted, suggesting that $EqCO_2$@AT may provide prognostic information beyond conventional clinical and spirometric indices. The combined model incorporating $EqCO_2$@AT, age, BMI, and FEV_1% predicted showed better discrimination than $EqCO_2$@AT alone, and the simplified nomogram provided an intuitive format for individualized AE risk estimation.

The physiological relevance of $EqCO_2$@AT is consistent with the known mechanisms of ventilatory inefficiency in COPD. $EqCO_2$@AT reflects the ventilatory requirement for carbon dioxide elimination at the anaerobic threshold, a key metabolic transition during exercise. In COPD, increased dead-space ventilation, ventilation/perfusion mismatch, abnormal gas exchange, and dynamic hyperinflation may increase the ventilatory cost of exercise, contributing to exertional dyspnea and exercise intolerance.[4–6,9,10,12] Compared with resting spirometry, exercise-derived indices may better capture integrated abnormalities in ventilation, gas exchange, circulation, and metabolic reserve.[4–6] Therefore, $EqCO_2$@AT may serve as a dynamic marker of ventilatory burden and reduced physiological reserve.

The association between $EqCO_2$@AT and AE risk may be explained by several mechanisms. Higher $EqCO_2$@AT indicates poorer ventilatory compensation during exercise, which may reflect limited reserve when patients encounter infection, inflammation, or other stressors. Ventilation/perfusion mismatch and impaired gas exchange may also indicate broader pulmonary parenchymal, pulmonary vascular, or cardiopulmonary dysfunction, thereby increasing vulnerability to exacerbations.[13–16] In addition, ventilatory inefficiency often coexists with exertional symptoms, reduced physical activity, and deconditioning, all of which are associated with adverse COPD outcomes.[6,14,17]

The clinical value of the combined model lies in integrating CPET-derived ventilatory efficiency with conventional clinical and pulmonary function variables. GOLD-based assessment mainly relies on prior exacerbation history, symptom burden, and lung function.[1] Our findings suggest that $EqCO_2$@AT may refine risk stratification by adding dynamic functional information. The simplified nomogram translates the multivariable model into a clinically interpretable format. However, because it was derived from a single-center retrospective cohort, it should be regarded as an exploratory risk-visualization tool rather than a validated decision instrument.

BMI also contributed substantially to the multivariable model. The relationship between BMI and COPD outcomes is complex and may depend on disease stage, body composition, nutritional status, and systemic metabolic phenotype. Previous studies have emphasized the prognostic significance of underweight status, BMI decline, and low fat-free mass index in COPD.[18–21] In the present cohort, higher BMI was associated with increased AE risk after adjustment. This finding should be interpreted cautiously. Higher BMI may increase ventilatory mechanical load, reduce chest wall compliance, increase work of breathing, and contribute to obesity-related inflammation or metabolic dysfunction. Conversely, low BMI or cachexia may reflect muscle wasting and systemic catabolism. Future studies should incorporate body composition, fat-free mass index, inflammatory biomarkers, and physical activity data to clarify BMI-related risk mechanisms.

From a clinical perspective, $EqCO_2$@AT is derived from routine CPET and may help evaluate ventilatory burden and gas-exchange stress during exercise. These findings provide hypothesis-generating evidence that CPET-derived ventilatory efficiency parameters may be useful for exacerbation risk assessment, pulmonary rehabilitation planning, and individualized follow-up.[22] Nevertheless, prospective validation is required before clinical implementation.

This study has several limitations. First, it was a single-center retrospective study with a relatively small sample size, so selection bias, residual confounding, and limited statistical power cannot be excluded. Second, although patients with incomplete baseline data or missing follow-up information were excluded, follow-up intervals, treatment adjustments, pulmonary rehabilitation exposure, and AE ascertainment could not be fully standardized. Third, inflammatory biomarkers, imaging variables, body composition measurements, and objective physical activity data were unavailable, limiting mechanistic interpretation. Fourth, the combined model and simplified nomogram have not been externally validated. Finally, annualized exacerbation frequency may not fully reflect exacerbation severity, phenotype, or temporal clustering. Larger multicenter prospective studies are needed to validate $EqCO_2$@AT-based models and assess their value in COPD management.

In conclusion, elevated $EqCO_2$@AT was associated with poorer lung function, lower exercise tolerance, and higher AE risk in patients with COPD. A combined model incorporating $EqCO_2$@AT, age, BMI, and FEV_1% predicted showed good performance for individualized AE risk stratification and was translated into a simplified nomogram. $EqCO_2$@AT

may provide dynamic information beyond static pulmonary function alone, but larger prospective multicenter studies are needed before incorporation into standardized COPD management algorithms.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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). This study was conducted in accordance with the Declaration of Helsinki. All participants were provided with written and oral information about the study and signed informed consent forms.

Author Contributions

Y.L. and X.L. conceived and designed the study. Y.L., F.L., X.H., S.L., M.Q., J.Z., R.Z., S.N., and B.X. contributed to patient recruitment, data collection, and data curation. Y.L., X.L., F.Y., and G.Y. performed data analysis, interpreted the results, and revised the manuscript. F.Y. and G.Y. supervised the study and provided critical intellectual input. All authors contributed to the work, participated in drafting or revising the manuscript, approved the final version, agreed on the target journal, and accept accountability for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to declare.

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