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Tidal volume expandability and ventilatory efficiency as predictors of mortality in Taiwanese male patients with chronic obstructive pulmonary disease: A 10-year follow-up study – Is $\dot{V}O_{2peak}$ or FEV_1% the gold standard?

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Abstract

Despite our knowledge of the risk factors for mortality associated with chronic obstructive pulmonary disease (COPD), the mortality rate for this condition continues to increase. This study aimed to investigate the predictive power of physiological variables on all-cause mortality in COPD patients compared to peak oxygen uptake ($\dot{V}O_{2peak}$) and forced expired volume in one second (FEV_1). We conducted a retrospective study of 182 COPD patients with complete lung function tests, cardiopulmonary exercise testing (CPET), and survival data. Cox regression analysis was used to estimate the hazard ratios for all-cause mortality. The median follow-up period was 6.8 (IQR 3.9-9.2) years. Out of the 182 patients in our study, sixty-two (34.1%) succumbed to various causes. Of these, 27.4% (n = 17) experienced acute exacerbations, 24.2% (n = 15) had advanced cancer, and 12.9% (n = 8) had cardiovascular disease as the primary cause of death. Another 25.8% (n = 16) passed away due to other underlying conditions, while 6.5% (n = 4) had an unknown cause of death. One patient's demise was attributed to a benign tumor, and another's to a connective tissue disease. The ratio of tidal volume to total lung capacity (V_{Tpeak}/TLC) and the ratio of minute ventilation and $\dot{V}O_2$ at nadir ($\dot{V}_E/\dot{V}O_{2nadir}$) (AUR 0.83, 95% CI 0.76-0.91) were superior predictors of all-cause mortality compared to $\dot{V}O_{2peak}$ and FEV_1%. A mortality prediction formula was derived using these variables. This study highlights the potential of V_{Tpeak}/TLC and $\dot{V}_E/\dot{V}O_{2nadir}$ as predictive markers for COPD all-cause mortality in COPD. CPET is an effective tool for evaluating COPD mortality; however, the predictive equation requires further validation.

Keywords

Survival, exercise testing, peak oxygen uptake, lung function test, prediction

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Key messages

The use of peak oxygen uptake ($\dot{V}O_{2peak}$) and forced expired volume in one second (FEV_1) as predictors of mortality in patients with COPD has been controversial in the literature. In this study, we discovered that tidal lung expandability (specifically, the ratio of tidal volume at peak exercise to total lung capacity) and ventilatory efficiency (represented by the ratio of minute ventilation to oxygen uptake at nadir during incremental symptom-limited exercise) offer superior predictive capabilities compared to $\dot{V}O_{2peak}$ and FEV_1. Our findings support the notion that these factors provide a more accurate prediction of all-cause mortality in patients with COPD. As a result of this research, we developed a predictive formula for all-cause mortality, which is presented in this report.

Introduction

Chronic obstructive pulmonary disease (COPD) is a prevalent chronic lung condition. In contrast to the declining mortality rates observed in many other chronic diseases, the mortality rate associated with COPD continues to rise.[1,2] Several predictive factors for COPD mortality have been identified, including anthropometric measures, primary and secondary lung pathophysiology, symptoms, and clinically significant outcomes.[3–25] These factors include lower body mass index (BMI),[5] emphysema,[15] poor lung function,[3,4,10,11,15,20,26] reduced inspiratory and upper and lower limb muscle strength,[20,27,28] hypoxemia/hypercapnia,[11] exertional oxyhemoglobin desaturation,[24] elevated dyspnea score,[17] exercise intolerance,[4,6,8,15,24,27,28] poor health status,[7] acute exacerbation frequency,[22] and comorbidities.[16] Importantly, these factors can contribute individually or in combination.[5,6,9,12–15,18,19,21–23,28,29]

Among these factors, BMI, forced expiratory volume in one second (FEV_1) % predicted (FEV_1%) and exercise intolerance, as measured by the six-minute walking distance (6MWD) and peak oxygen uptake ($\dot{V}O_{2peak}$), are widely recognized. The 6MWD is typically reported in meters[5,24,28] or as a percentage of predicted values, while $\dot{V}O_{2peak}$ is expressed in mL/min[27] or mL/min/kg[30] or as a percentage of predicted values ($\dot{V}O_{2peak}$%).[8,29] $\dot{V}O_{2peak}$ in mL/min/kg and $\dot{V}O_{2peak}$% are favored when using the BODE scoring system (B for body mass index, O for obstructive flow, D for dyspnea score, and E for exercise capacity).[28,29] However, it is important to note that $\dot{V}O_{2peak}$ % is influenced not only by lung pathophysiology in COPD[30–32] but also by skeletal muscle and circulatory functions,[33] individual patient effort,[30] and variations in the definitions of maximal exercise effort.[34] In addition, similarly variability has been shown in the relationship between FEV_1% with exercise intolerance[35–37] and its impact on survival.[3,10,27]

Furthermore, studies by Neder et al. and Ewert et al. have indicated that certain cardiopulmonary physiological variables are even more relevant to COPD survival.[8,26] Therefore, in this study, we focus on other exercise-related cardiopulmonary physiological variables, such as ventilation efficiency (e.g., ventilation-to-oxygen uptake ratio at nadir or anaerobic threshold, denoted as $\dot{V}_E/\dot{V}O_{2AT/nadir}$) and dynamic lung hyperinflation (e.g., tidal volume at peak exercise-to-total lung capacity ratio, denoted as V_{Tpeak}/TLC), which serves as a marker for reverse dynamic hyperinflation.[38,39] Our hypothesis was that these variables may have better predictive ability for COPD mortality than $\dot{V}O_{2peak}$ (mL/min) and FEV_1%.[27] To test this hypothesis, we investigated the role of exercise-related cardiopulmonary physiology in predicting COPD survival over a follow-up period of up to 10 years and compared these selected physiological variables with $\dot{V}O_{2peak}$% and FEV_1%.

Through the use of high-quality physiological variables determined via stepwise Cox regression analysis, we aimed to provide valuable insights for making informed decisions related to patient care.[40]

Methods

Study design

A retrospective observational study was conducted on patients with COPD from 1995 to 2021, with each subject being followed up for 10 years, unless censored. All data were obtained from the hospital's electronic medical records. This study was approved by the Institutional Review Board of Chung Shan Medical University Hospital (CS2-21018) and complied with the Declaration of Helsinki. The requirement for informed consent was waived by the IRB.

Subjects

We included patients with COPD between the ages of 40-80 years who underwent their first cardiopulmonary exercise testing (CPET) between Jan 1, 1995, and July 31, 2021, and followed each subject for up to 10 years unless they were censored. For those lost to follow-up before 10 years, we checked the National Death Index for their death date for up to 10 years. The National Death Index in Taiwan provides individual mortality data, including the date and cause of death, upon formal application, with local IRB approval. COPD was diagnosed according to the Global Initiative for Chronic Lung Disease (GOLD) criteria as FEV_1/FVC <0.7 with a nonsignificant bronchodilator effect.[1] Eligible patients also had complete data on age, BMI,

oxygen-cost diagram score, smoking status, lung function, and symptom-limited cardiopulmonary exercise tests. Patients with lung diseases other than COPD or COPD mixed ventilatory defects (i.e., total lung capacity (TLC) <80% predicted) and those with contraindications for CPET were excluded. To minimize confounding factors for exercise tolerance, patients were also excluded if they had significant comorbidities, including electrolyte imbalance, uncontrolled hypertension, congestive heart failure, renal failure, chronic liver disease, diabetes mellitus, autoimmune disease, and cancer, or had participated in any physical training program during the study period. Patients with mild anemia (i.e., hemoglobin level >10 g/dL) were included to avoid rejecting too many participants from the study.

Measurements

An Oxygen-cost diagram (OCD) was used to scale daily functional activities and was assessed by the patients themselves. The OCD is a 100-mm long vertical line with everyday activities listed alongside the line.[41] The distance from the zero point was measured and scored in centimeters.

Complete pulmonary function tests (PFTs), including spirometry, lung volume, and diffusing capacity of the lung for carbon monoxide (D_LCO), were performed by trained technicians at the pulmonary function laboratory. All lung function data were expressed as % predicted, as reported in our previous studies, to maintain consistency.[42,43] At our institute, the currently employed predicted values are as follows: FEV_1 and FVC were adjusted for race using 90% of the prediction equations developed by Knudson et al.[44] Predicted TLC and D_LCO values were derived from the prediction equations by Goldman and Becklake[45] and Burrows et al.,[46] respectively, at 85%. Thus, we did not use Global Lung Function Initiative reference values.[47]

For cardiopulmonary exercise testing (CPET), the exercise protocol included a 3-min rest period, a 3-min period of unloaded cycling using a computer-controlled electronically braked cycle ergometer, and a ramp-pattern load exercise to the limit of the patient's tolerance. The work rate was selected at a slope of 5–20 watts per minute according to a predetermined fitness level based on our derived protocol formula.[48] Heart rate, oxyhemoglobin saturation, oxygen uptake ($\dot{V}O_2$ [ml/min]), CO_2 output ($\dot{V}CO_2$ [ml/min]), minute ventilation ($\dot{V}_E$), and blood pressure were measured. The exercise data were averaged and reported every 15 s. For details of calibrations of the pneumotachograph and the gas analyzers, please refer to references.[43,49,50] The onset of anaerobic metabolism during an incremental exercise test can result in the following observable changes: a rise in blood lactate (lactate threshold), a decrease in standard bicarbonate (lactic acidosis threshold), and a nonlinear increase in CO_2 output (V-slope gas exchange threshold).[50] The anaerobic threshold (AT), defined as the breakpoint of these three parameters, can be assessed noninvasively using dual methods or a single method, specifically the modified V-slope gas exchange and ventilatory equivalent for oxygen ($\dot{V}_E/\dot{V}O_{2AT}$) as appropriate.[46,51] During incremental exercise, $\dot{V}_E/\dot{V}O_2$ began to decrease from the beginning of the loaded exercise until reaching a nadir, after which it started to rise again. This nadir was specifically defined as $\dot{V}_E/\dot{V}O_{2AT}$ and also served as an indicator of ventilation efficiency. In cases where the breakpoint of $\dot{V}_E/\dot{V}O_2$ was uncertain, $\dot{V}_E/\dot{V}O_{2nadir}$ represented the lowest value of $\dot{V}_E/\dot{V}O_2$ observed during the loaded exercise.[52] For the sake of simplicity, we utilized $\dot{V}_E/\dot{V}O_{2AT/nadir}$ in this study. To define the maximum exercise, the following criteria were used[36,42–45]:1) heart rate (HR) reserve of 15% or 15 beats/min of predicted maximum heart rate or less, where the predicted maximum heart rate was calculated as 220 – age; or 2) respiratory exchange ratio ≥1.05. The $\dot{V}O_{2peak}$ achieved by the patients was the symptom-limited highest recorded point averaged over the last 15 s of the loaded exercise.

Outcomes

The primary outcome was all-cause mortality.

Statistical analyses

The raw data supporting the conclusions of this study have been uploaded to the supplementary file. For baseline characteristics, continuous variables were summarized as mean ± standard deviation or median (IQR), as appropriate, and categorical variables were presented as percentages. The quantitative variables were categorized as follows: BMI (kg/m^2) <18.5, 18.5-23.9, and ≥24. As the main objective of this study was to identify the physiological variables associated with all-cause mortality rather than to test the hypothesis of detecting an expected effect size in a clinical trial, our sample size consideration focused on ensuring stable and efficient regression coefficients. Thus, at least six to ten subjects per variable may achieve this goal.[53–55] However, we also conducted retrospective power estimations separately for Cox proportional hazards regression, based on the variables $\dot{V}_E/\dot{V}O_{2AT/nadir}$ and V_{Tpeak}/TLC in this study. For $\dot{V}_E/\dot{V}O_{2AT/nadir}$, with a hazard ratio (HR) of 1.07 and a standard deviation of 7.5, the sample size required was 144, and the estimated event probability

was 0.34. The calculated power for this analysis was 0.71. Concerning V_{Tpeak}/TLC, with an HR of 0.87 and a standard deviation of 5.8, the necessary sample size was 140, and the event probability was 0.34. The calculated power for this analysis was 0.98.

Univariate and subsequently multivariate analyses were conducted using stepwise Cox proportional hazard regression to assess both the unadjusted and adjusted hazard ratios (cHR and aHR) for mortality, along with 95% confidence intervals (95% CIs). The variables considered in this study encompassed a range of factors, such as age, smoking history, BMI, self-reported maximum daily physical activity, as well as cardiopulmonary functions. These cardiopulmonary functions were assessed through both lung function tests and cardiopulmonary exercise tests. We generated receiver operating characteristic (ROC) curves and calculated the area under the ROC (AUC) to compare the variables of interest, which were selected by stepwise Cox regression analysis, with $\dot{V}O_{2peak}$% and FEV_1%, as these two variables have traditionally been regarded as univariate risk factors for mortality in patients with COPD.[27] Mortality was predicted using logistic regression. All statistical analyses were performed using the SAS software version 9.4. Statistical significance was set at a two-sided p-value <.05.

Results

A total of 244 male subjects were screened, of whom 62 were excluded for the following reasons: not meeting the inclusion criteria (n = 26, Figure 1), exclusion criteria (n = 26), and declined to participate (n = 10). The remaining 182 subjects were analyzed after completing the PFT and CPET and were followed up for a median of 6.8 years (IQR: 3.9-9.2) (Table 1). A total of 120 subjects (65.9%) were aged over 65 years, and 138 subjects (75.8%) exhibited normal body habitus or were mildly overweight (i.e., BMI 24-27 kg/m^2). The average cigarette consumption was 46.5 pack-years (33.0–60.0), and the average OCD was 7.0 ± 1.2, indicating brisk walking on level ground or engaging in heavy shopping. The average TLC%, IC%, and FVC% were within normal ranges, while the average FEV_1/FVC ratio was decreased. Out of 179 subjects, 156 (87.2%) were classified as GOLD grades 2 and 3, with grades 1 and 4 being uncommon. The average RV/TLC was elevated, and there was mild impairment in D_LCO%. They had impaired exercise and cardiopulmonary performance, that is, reduced $Work_{peak}$%, $\dot{V}O_{2peak}$%, HR_{peak}%, and $\dot{V}_{Epeak}$%. They also had mildly inefficient ventilation ($\dot{V}_E/\dot{V}O_{2AT/nadir}$ of 37.1 ± 7.5), impaired lung expansion with dynamic lung hyperinflation (V_{Tpeak}/TLC of 0.22 ± 0.06), and reduced

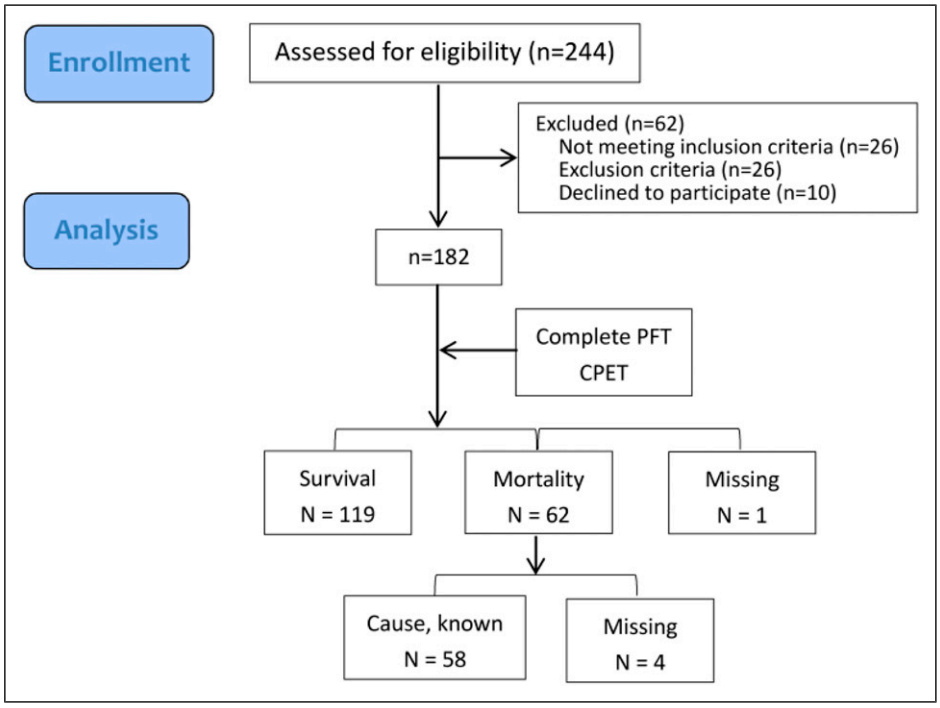

Figure 1. Flow chart of study inclusion. A total of 244 subjects with chronic obstructive pulmonary disease (COPD) were assessed for eligibility. For details regarding the inclusion and exclusion criteria of the participants, please refer to the text. Among them, 62 subjects were excluded for various reasons. The remaining 182 subjects completed the pulmonary function test (PFT) and cardiopulmonary exercise test (CPET). The PFT consisted of spirometry, lung volume measurement, and diffusing capacity of the lungs for carbon monoxide.

Table 1. Demographic characteristics, lung function, and exercise data in 182 subjects with chronic obstructive pulmonary disease.

Variables	*N* (%)	Mean ± SD
Age, years	182 (100)	67.8 ± 8.5
<65	62 (34.1%)	
≥65	120 (65.9%)	
Body mass index, kg/m^2	182 (100)	23.6 ± 3.8
<18.5	12 (6.6)	
18.5-23.9	89 (48.9)	
≥24	81 (44.5)	
Smoking, pack-year	166	46.5 (33.0–60.0)[a]
Oxygen-cost diagram, cm	143	7.0 ± 1.2
Lung function		
TLC %predicted	175	108.4 ± 22.3
FRC %predicted	175	127.2 ± 33.4
RV %predicted	175	144.3 ± 54.0
RV/TLC, %	175	52.6 ± 11.6
D_LCO %predicted	171	78.8 ± 24.6
FVC %Predicted	179	84.5 ± 21.0
FEV_1 %predicted	179	57.5 ± 17.6
GOLD stage I/II/III/IV, *n*	18/106/45/5	
FEV_1/FVC, %	179	53.1 ± 11.6
IC %Predicted	176	82.5 ± 22.9
IC/TLC, %	138	30.4 ± 8.3
During exercise		
Loaded work duration, min	173	8.2 ± 2.3
$\dot{V}O_{2peak}$ %predicted	173	67.9 ± 19.0
$Work_{peak}$ %predicted	180	73.3 ± 27.1
HR_{peak} %predicted	178	81.4 ± 11.5
$\dot{V}_{Epeak}$ %predicted	179	57.3 ± 16.2
$\dot{V}_{Epeak}$/MVV, %	159	84.8 ± 28.7
V_{Tpeak}/TLC, %	140	21.8 ± 5.8
$\dot{V}_E/\dot{V}O_{2@AT/nadir}$	144	37.1 ± 7.5
S_PO_{2peak}, %	169	92.8 ± 4.6

[a]median (IQR). Abbreviations: TLC, total lung capacity; FRC, functional residual capacity; RV, residual volume; D_LCO, diffusing capacity of lung for carbon monoxide; FVC, forced vital capacity; FEV_1, forced expired volume in one second; GOLD; the global initiatives for obstructive lung disease; IC, inspiratory capacity; $\dot{V}_{Epeak}$, minute ventilation at peak exercise; $\dot{V}O_2$, oxygen uptake; @AT/nadir, at anaerobic threshold or the nadir value; MVV, maximum voluntary ventilation; S_PO_2, oxyhemoglobin saturation by pulse oximetry; V_T, tidal volume; HR, heart rate.

oxyhemoglobin saturation (92.8 ± 4.6%) at peak exercise. Sixty-two (34.1%) of the 182 participants died during the 6.8-year follow-up, with the top three causes of death being lower respiratory tract diseases including infections (27.4%), malignant neoplasms (24.2%), and cardiovascular diseases (12.9%), including cerebral vascular disease (Table 2).

In the univariate analysis of the causes of death, the crude hazard ratio (cHR) for advanced age was 1.06 (1.03-1.10), and for the OCD score, it was 0.76 (0.61-0.94). However, categorical BMI and pack-years of cigarette consumption did not prove to be predictive factors (see Table 3). In terms of lung function, the cHR for RV/TLC was 1.03 (1.00-1.05), while FEV_1/FVC and D_LCO% had cHRs of 0.96 (0.94-0.99) and 0.99 (0.98-0.99), respectively. FEV_1%, IC%, and IC/TLC did not show predictive value for all-cause mortality. Concerning cardiopulmonary exercise testing, the cHR for $Work_{peak}$%, $\dot{V}O_{2peak}$%, HR_{peak}%, $\dot{V}_{Epeak}$%, $\dot{V}_{Epeak}$/MVV, and V_{Tpeak}/TLC were 0.98 (0.97-0.99), 0.98 (0.97-0.99), 0.98 (0.95-0.998), 0.97 (0.95-0.98), 0.99 (0.98-1.00), and 0.87 (0.82-0.92), respectively. In addition, the cHR for $\dot{V}_E/\dot{V}O_{2AT/nadir}$ was 1.07 (1.03-1.11), whereas S_PO_{2peak} was not found to be predictive. In the stepwise Cox proportional hazards model analysis, conducted with the aim of automating variable selection, streamlining model construction, and enhancing interpretability by identifying the most influential factors, only $\dot{V}_E/\dot{V}O_{2AT/nadir}$ and V_{Tpeak}/TLC emerged as substantial predictors of all-cause mortality. This outcome was observed after eliminating all other variables initially included in the crude HR model, which can be found in Table 3 and Figure 2 for reference.

The mortality prediction model was formulated as follows:

$$P = 1 \Big/ \left(1 + e^{\left(-0.056 + 22.6 V_{Tpeak}/TLC - 0.103 \dot{V}_E/\dot{V}O_{2AT/nadir}\right)}\right) \quad (1)$$

The AUC of V_{Tpeak}/TLC was significantly larger than the AUCs of $\dot{V}O_{2peak}$% and FEV_1% (Table 4, $p = .03$ and $<.001$, respectively). In contrast, the AUC of $\dot{V}_E/\dot{V}O_{2AT/nadir}$ was similar to those of $\dot{V}O_{2peak}$% and FEV_1%.

Discussion

The results of this study indicated that cardiopulmonary exercise testing (CPET) was a valuable tool for predicting mortality in male patients with COPD in Taiwan over a 6.8-year period. Tidal lung expandability, quantified by V_{Tpeak}/TLC, was identified as a significant predictor of survival. In contrast, ventilatory inefficiency, measured by $\dot{V}_E/\dot{V}O_{2AT/nadir}$, was a noteworthy adverse predictor. When considered together, these two factors collectively offered the most robust predictive value for COPD mortality in this study, surpassing the predictive utility of both $\dot{V}O_{2peak}$% and FEV_1%.

Most of the participants in this study had a normal body habitus and were heavy smokers, yet they maintained the ability to engage in brisk walking and heavy shopping in their daily lives. Most were diagnosed with COPD at GOLD stages 2 and 3, and they demonstrated normal FVC and TLC but exhibited signs of air trapping. In addition, they exhibited mild impairments in diffusing capacity of

Table 2. Causes of death in 62 of 182 (34.1%) patients with chronic obstructive pulmonary disease (COPD) during the 6.8-year follow-up.

Cause of death	*N* = 62	%
Lower airway disease including infections and AECOPD	17	27.4
Malignant neoplasms	15	24.2
Cardiovascular disease including cerebral vascular disease	8	12.9
Benign tumor	1	1.6
Skeletal muscle and connective tissue disease	1	1.6
Others, not specified*	16	25.8
Unknown*	4	6.5

Abbreviations: AECOPD, acute exacerbation of COPD. Survival = 119 (65.4%); missing = 1 (0.5%); * causes of death were not specified or mentioned in medical records.

Table 3. Stepwise Cox proportional hazard model analysis for risk of all-cause mortality.

	cHR (95% C.I.)	*p* value	aHR (95% C.I.)	*p* value
Age, years	1.06 (1.03-1.10)	<0.001		
BMI, kg/m^2				
18.5-23.9	Reference			
<18.5	1.88 (0.83-4.25)	0.13		
≥24	0.68 (0.40-1.16)	0.16		
Smoke, pack-year	1.00 (0.99-1.01)	0.50		
OCD, cm	0.76 (0.61-0.94)	0.01		
TLC% predicted	1.01 (1.00-1.02)	0.07		
FRC% predicted	1.00 (1.00-1.01)	0.22		
RV% predicted	1.00 (1.00-1.01)	0.07		
RV/TLC, %	1.03 (1.00-1.05)	0.02		
IC% Predicted	1.00 (0.99-1.01)	0.86		
IC/TLC, %	0.98 (0.94-1.02)	0.28		
D_LCO% predicted	0.99 (0.98-0.999)	0.04		
FVC% Predicted	1.00 (0.99-1.01)	0.79		
FEV_1% predicted	0.99 (0.97-1.00)	0.08		
FEV_1/FVC	0.96 (0.94-0.99)	0.001		
$Work_{peak}$% predicted	0.98 (0.97-0.99)	<.0001		
$\dot{V}O_{2peak}$% predicted	0.98 (0.97-0.99)	<0.001		
HR_{peak}% predicted	0.98 (0.95-0.998)	0.03		
V_{Epeak}%	0.97 (0.95-0.98)	<.0001		
V_{Epeak}/MVV, %	0.99 (0.98-1.00)	0.008		
S_PO_{2peak}	0.97 (0.91-1.03)	0.26		
$V_E/\dot{V}O_{2AT/nadir}$	1.07 (1.03-1.11)	<0.001	1.11 (1.05-1.18)	<0.001
V_{Tpeak}/TLC, %	0.87 (0.82-0.92)	<.0001	0.86 (0.80-0.93)	<0.001

Abbreviations: aHR, adjusted hazard ratio; AT/nadir, anaerobic threshold or nadir; BMI, body mass index; cHR, crude hazard ratio; D_LCO, diffusing capacity of lungs for carbon monoxide; FEV_1, forced expired volume in one second; FRC, functional residual capacity; FVC, forced vital capacity; HR, heart rate; IC, inspiratory capacity; MVV, maximum voluntary ventilation; OCD, oxygen-cost diagram; RV, residual volume; S_PO_2, oxyhemoglobin saturation by pulse oximetry; TLC, total lung capacity; $\dot{V}_{Epeak}$, minute ventilation at peak exercise; $\dot{V}O_2$, oxygen uptake; V_T, tidal volume.

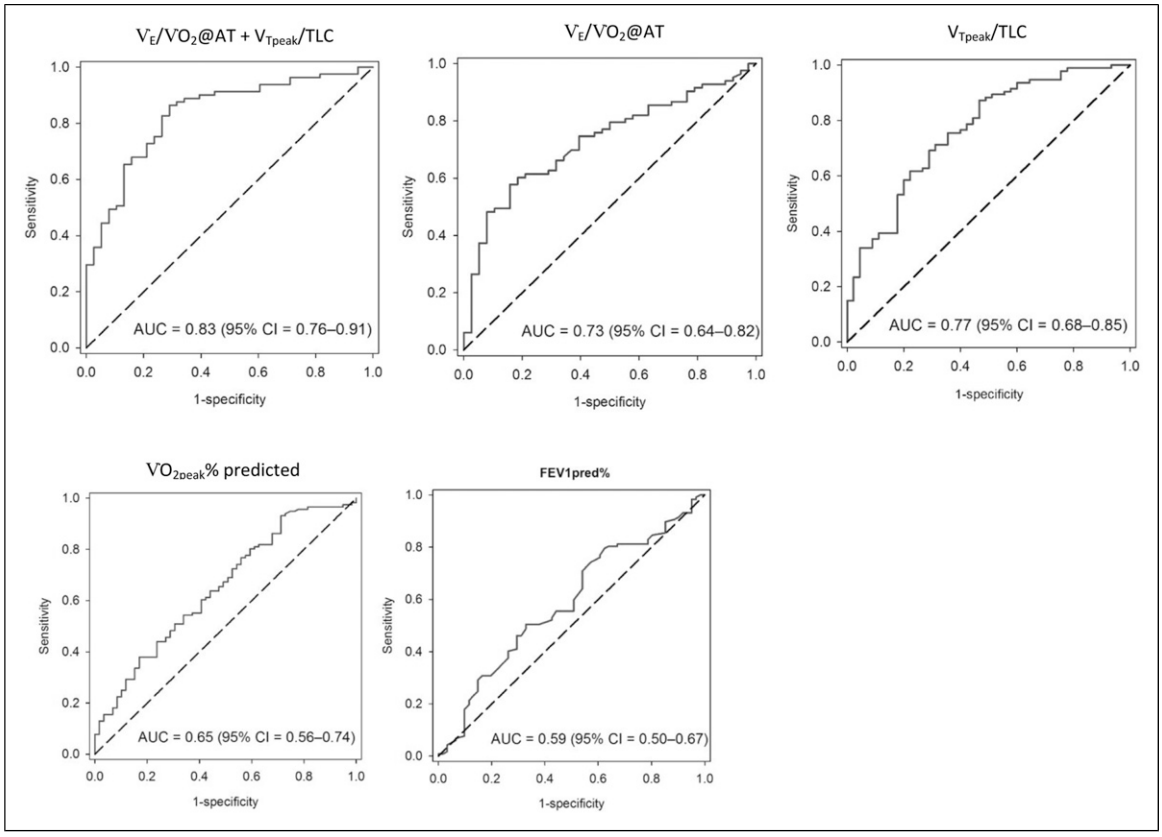

Figure 2. The area under the receiving operating characteristic (ROC) curve for survival analysis indicated that the ratios of tidal volume at peak exercise to total lung capacity (V_{Tpeak}/TLC) and minute ventilation to $\dot{V}O_2$ at nadir ($\dot{V}_E/\dot{V}O_{2nadir}$) (AUR 0.83, 95% CI 0.76-0.91) were superior predictors of all-cause mortality when compared to $\dot{V}O_{2peak}$ and FEV_1%.

the lungs for carbon monoxide (D_LCO) and cardiorespiratory exercise performance. Notably, while most of the COPD participants had minimal or no comorbidities at the beginning of the study, approximately 1/4 and 1/6 of the causes of death during the 6.8 years of follow-up were attributed to malignant neoplasms and cardiovascular diseases, respectively.

$\dot{V}_E/\dot{V}O_{2AT/nadir}$ and V_{Tpeak}/TLC versus $\dot{V}O_{2peak}$% and FE V_1%

The parameters $\dot{V}_E/\dot{V}O_{2AT/nadir}$ and $\dot{V}_E/\dot{V}CO_2$ at nadir are commonly used to determine the anaerobic threshold (AT) and respiratory compensatory points.[56,57] It is important to note that $\dot{V}_E/\dot{V}O_{2AT/nadir}$ and $\dot{V}_E/\dot{V}CO_{2AT/nadir}$ are closely related in assessing ventilatory efficiency.[56] Elevated values of $\dot{V}_E/\dot{V}O_{2AT/nadir}$ may suggest an increased dead space fraction and hyperventilation, a pattern analogous to that indicated by $\dot{V}_E/\dot{V}CO_{2AT/nadir}$. It is worth mentioning that although the $\dot{V}_E/\dot{V}CO_2$ slope has been used in patients with COPD,[6,8] $\dot{V}_E/\dot{V}CO_{2AT/nadir}$ is generally favored over $\dot{V}_E/\dot{V}CO_2$ slope.[26,56] In the present study, we opted to use $\dot{V}_E/\dot{V}O_{2AT/nadir}$ for simplicity and did not include $\dot{V}_E/\dot{V}CO_{2AT/nadir}$, which is a recognized limitation. Nevertheless, our results revealed that the predictive performance, as quantified by the area under the curve (AUC), of $\dot{V}_E/\dot{V}O_{2AT/nadir}$ was comparable to that of $\dot{V}O_{2peak}$% or FEV_1% in predicting all-cause mortality (see Table 4).

Furthermore, it is noteworthy that the addition of V_{Tpeak}/TLC to $\dot{V}_E/\dot{V}O_{2AT/nadir}$ significantly improved the predictive accuracy (see Figure 2). These findings are consistent with those of Neder et al., who reported that $\dot{V}_E/\dot{V}CO_{2nadir}$ (instead of $\dot{V}_E/\dot{V}O_{2AT/nadir}$ in this study) was associated with resting IC/TLC ≤0.34 (instead of V_{Tpeak}/TLC in this study), for all-cause mortality.[26] $\dot{V}_E/\dot{V}CO_{2nadir}$ and $\dot{V}_E/\dot{V}O_{2AT/nadir}$ both hold similar significance in terms of assessing ventilatory efficiency, while IC/TLC and V_{Tpeak}/TLC also represent similar concepts related to dynamic lung expandability.

Another study by Casanova et al. reported that resting IC/TLC was related to COPD survival.[4] In addition, the oxygen

uptake efficiency slope (OUES), derived from the formula $\dot{V}O_2$ = a log $\dot{V}_E$ + b, where 'a' represents OUES, has been used as a variable for evaluating cardiovascular and skeletal muscle functions.[58] The OUES has shown promise in distinguishing between mild and severe COPD[59] and between COPD and chronic heart failure.[60] Although we did not include OUES in our study, it is worth noting that both the formula used to derive it and $\dot{V}_E/\dot{V}O_{2AT/nadir}$ incorporate the same variables, suggesting a possible shared significance, which warrants further investigation. However, $\dot{V}_E/\dot{V}O_{2AT/nadir}$ is a more accessible parameter than OUES.

In this study, IC/TLC was measured at 0.30 ± 0.08 and V_{Tpeak}/TLC at 0.22 ± 0.06 (Table 1), and a strong correlation was established between these two parameters (r^2 = 0.25, $p < .0001$). V_{Tpeak}/TLC is a recently developed marker for inverse dynamic lung hyperinflation in patients with COPD,[38,39] and it is a primary lung function marker that is hierarchically related to exertional dyspnea and exercise intolerance.[32] Notably, impaired V_{Tpeak}/TLC alone was a stronger predictor of all-cause mortality in our patients with COPD than $\dot{V}O_{2peak}$% or FEV_1% (Table 4).

Although $\dot{V}O_{2peak}$ expressed as a percentage or in mL/min/kg is an important factor when selecting candidates for heart or lung transplantation[30] and in predicting COPD mortality,[8] it can be influenced by the muscular, cardiovascular, and respiratory systems.[33] Thus, $\dot{V}O_{2peak}$% is a more general but a less respiratory-specific factor for survival than $\dot{V}_E/\dot{V}O_{2AT/nadir}$ and V_{Tpeak}/TLC in patients with COPD. We found that lung expandability and ventilatory efficiency were better predictors of all-cause mortality than $\dot{V}O_{2peak}$%, as also shown by Neder et al.[26] However, this finding is in contrast with the results reported by Ewert et al., who suggested that $\dot{V}O_{2peak}$% was a superior predictor compared to $\dot{V}_E/\dot{V}CO_{2nadir}$ and the modified BODE, ADO, and DOSE multidimensional indices for assessing survival.[8] Of note, both $\dot{V}_E/\dot{V}O_{2AT/nadir}$ and V_{Tpeak}/TLC are more respiratory-specific factors for survival and exhibit greater stability after reaching the AT or during the latter stages of incremental exercise. In contrast, $\dot{V}O_{2peak}$% is a more generalized factor associated with survival, but it is less stable as it can be influenced by various post-AT factors, including the level of exertion and physiological limitations. To the best of our knowledge, this is the first study to investigate the predictive significance of $\dot{V}_E/\dot{V}O_{2AT/nadir}$ and V_{Tpeak}/TLC in relation to COPD mortality. Previous studies[25,50] did not select $\dot{V}O_{2peak}$% or mL/min/kg as a significant predictor, consistent with the current study. Although $\dot{V}O_{2peak}$ in mL/min alone has been shown to be related to COPD mortality,[18,27] it is not recommended due to its strong dependency on anthropometric data.[56] Therefore, it would be more appropriate to express $\dot{V}O_{2peak}$ as %predicted or mL/min/kg, as suggested in previous studies.[8]

Table 4. Comparisons of the area under the receiver operating characteristics curves (AUC) for V_{Tpeak}/TLC% and $\dot{V}_E/\dot{V}O_{2AT/nadir}$ with those for FEV_1% predicted and $\dot{V}O_{2peak}$% predicted.

Comparison	*p* value
V_{Tpeak}/TLC% versus FEV_1% predicted	<0.001
$\dot{V}O_{2peak}$% predicted	0.03
$\dot{V}_E/\dot{V}O_{2AT/nadir}$ versus FEV_1% predicted	0.10
$\dot{V}O_{2peak}$% predicted	0.12

Abbreviations: AT, anaerobic threshold; FEV_1, forced expired volume in one second; TLC, total lung capacity; $\dot{V}_E$, minute ventilation; $\dot{V}O_2$, oxygen uptake.

Although previous studies have shown a negative correlation between COPD mortality and parameters such as FEV_1%, IC%, IC/TLC and D_LCO%,[3,4,10,11,15,20,26] we did not find that FEV_1%, IC% and IC/TLC were predictive of mortality. Instead, we identified FEV_1/FVC and RV/TLC as significant predictors. It is worth noting that FEV_1/FVC, RV/TLC, IC/TLC, and FRC/TLC are closely inter-related.[42] The discrepancies between the previous studies and the present study may stem from the fact that we only included a limited range of COPD severity.

BMI and SpO_2%$_{peak}$

A low BMI (≤21 kg/m^2) has been associated with an increased risk of mortality in patients with COPD, while a high BMI (>21 kg/m^2) has been associated with improved survival.[5] In addition, computed tomography measurements of the mid-thigh muscle cross-sectional area and FEV_1% have been associated with survival, indicating the importance of fat-free muscle mass.[50,51] However, in the current study, BMI was not found to be a significant contributor to mortality, possibly due to the small number of cases with BMI <18.5 kg/m^2 or the use of BMI categories.

Exertional oxyhemoglobin desaturation is also a known predictive factor for COPD mortality[24,25]; however, we did not find that S_PO_{2peak} was a significant predictor. This discrepancy may be due to mild oxyhemoglobin desaturation that occurred at peak exercise in the present study.

Causes of death

At the beginning of the study, the participants had no comorbidities or minimal comorbidities. However, during the 6.8-year follow-up period, lower respiratory tract diseases including infections, malignant neoplasms, and cardiovascular diseases including cerebral vascular disease were the top three causes of death. This finding is in line with previous

studies in which AECOPD,[22,50] cancers, and cardiovascular disease[61] were identified as the primary causes of death in patients with COPD, accounting for approximately 2/3 of cases. These findings are important, and clinicians should be aware that patients with COPD may develop cancer and cardiovascular diseases over time, even if they do not initially present with these conditions. The mortality rate in this study was 34.1% over a 6.8-year follow-up period. This may be interpreted as a mortality rate of approximately 5% per year, which is consistent with previous reports from Europe and Canada, and suggests that mortality does not notably vary by geographical location.[8,26]

One of the strengths of this study is the large sample size and the long follow-up period. In addition, a comprehensive set of CPET and lung function variables was analyzed using Cox regression and stepwise selection, providing a more robust analysis compared to previous studies. For example, one previous study initially only used a limited set of CPET variables, such as $\dot{V}_E$, $\dot{V}O_{2peak}$, and $\dot{V}_E/\dot{V}CO_2$ slope in their Cox regression analysis, and subsequently sex and age variables were introduced arbitrarily.[6] The authors of that study suggested that future investigations should include other CPET variables. Another study by Ewert et al. in the same year also used multivariate Cox regression with stepwise selection and selected age, dyspnea, and $\dot{V}O_{2peak}$/kg among other variables.[8] In contrast, we included a wider range of CPET and lung function variables, allowing for a more thorough analysis. In addition, we used the same statistical techniques as those used in the previous studies and analyzed 22 variables. V_{Tpeak}/TLC and $\dot{V}_E/\dot{V}O_{2AT/nadir}$ were selected as predictors of COPD all-cause mortality, with an AUC of 0.83 (95% CI 0.76-0.91). The statistical techniques used in the current study are supported by previous studies.[53–55] V_{Tpeak}/TLC is a novel and convenient marker for inverse dynamic lung hyperinflation,[38,39] and it is highly related to exertional dyspnea.[32] Furthermore, V_{Tpeak}/TLC and $\dot{V}_E/\dot{V}O_{2AT/nadir}$ were strongly associated with COPD mortality in this study. To the best of our knowledge, this is the first study to report a prediction equation using V_{Tpeak}/TLC and $\dot{V}_E/\dot{V}O_{2AT/nadir}$ to estimate the probability of mortality in patients with COPD.

The current study has several limitations. First, female subjects were not enrolled, and data on emphysema score,[15] acute exacerbation,[62] dyspnea score,[17] inspiratory, upper and lower limb muscle strength[20,25,26] and health status[7] were not obtained before entry. Therefore, the study results cannot exclude the potential contribution of these variables to COPD mortality. However, the study focused on the contributions of physiological factors to clinically important outcomes according to the American Thoracic Society/European Respiratory Society Statement: Research Questions in COPD.[40] Second, the respiratory causes of death were not provided in the current study, although the risk factors were similar to those reported in previous studies of all-cause mortality.[26] Third, since this was a retrospective study, we were unable to identify the specific causes of death in 16 patients, or the confirmed causes of death in another five patients. Finally, as mentioned above, we did not use $\dot{V}_E/\dot{V}CO_{2AT/nadir}$ in this study.

Conclusion

The study showed that V_{Tpeak}/TLC and $\dot{V}_E/\dot{V}O_{2AT/nadir}$ were better predictors of all-cause mortality in patients with COPD than $\dot{V}O_{2peak}$ and FEV_1%, indicating the usefulness of CPET in assessing mortality risk. However, a mortality prediction formula using these variables needs to be validated in future studies.

Author contributions

MLC initiated and designed the study, analyzed and interpreted the data, wrote the manuscript, and approved the version to be published. YHW analyzed and interpreted the data, wrote the manuscript, and approved the version to be published.

Authors' note

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Ethical statement

Ethical approval

The requirement for signed informed consent was waived by the Institutional Review Board of the institution. The local Institutional Review Board approved this study. The name of the ethics committee is Chung Shan Medical University Hospital (CS2-21018). Registered at this site: Chung Shan Medical University Hospital, Taichung, Taiwan. Registration number: CSH-2021-C −041.

Review board

The Institutional Review Board of Chung Shan Medical University Hospital.

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Appendix

Abbreviations

6MWD	Six-minute walking distance in meters
aHR	Adjusted hazard ratio
AT	Anaerobic threshold
AUC	Area under curve
AECOPD	Chronic obstructive pulmonary disease with acute exacerbation
BMI	Body mass index
BODE	BMI, obstruction of airway, dyspnea score, exercise capacity
cHR	Crude hazard ratio
D_LCO	Diffusing capacity for carbon monoxide
FEV_1/FVC	Forced expired volume in one second (FEV_1)/forced vital capacity
FRC	Functional residual capacity
GOLD	The Global Initiative for Chronic Lung Disease
HR	Heart rate
IC	Inspiratory capacity
OCD	Oxygen-cost diagram
PFTs	Pulmonary function tests
ROC	Receiving operating characteristic curve
RV	Residual volume
TLC	Total lung capacity
$\dot{V}_E$	Minute ventilation
$\dot{V}_E/\dot{V}$	Ventilatory equivalent for oxygen uptake
$\dot{V}_E/\dot{V}CO_2$	Ventilatory equivalent for CO2 output
V_T	Tidal volume.