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Original Article

Expiratory Muscle Strength, Peak Oxygen Consumption and Hyperinflation Predicts Severe Exacerbation in Chronic Obstructive Pulmonary Disease Patients

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ABSTRACT

OBJECTIVE: To explore the predictive ability of physiological and clinical parameters, including respiratory muscle strength, peak oxygen consumption, exercise capacity assessed by the six-minute walk distance (6MWD), pulmonary function, and arterial blood gas for identifying patients with chronic obstructive pulmonary disease (COPD) who are at risk of frequent severe acute exacerbations.

MATERIAL AND METHODS: This retrospective, observational study analyzed data from 265 patients who were hospitalized for severe exacerbations between January 1st, 2018 to February 28th, 2024. Patients were classified as infrequent or frequent exacerbators based on the annual frequency of severe exacerbations. Binary logistic regression models were used to identify independent predictors, adjusting for clinically relevant covariates.

RESULTS: In adjusted multivariate analysis, maximal expiratory pressure [odds ratio (OR): 0.989; 95% confidence interval (CI): 0.980–0.998; $P = 0.014$], 6MWD (OR: 0.997; 95% CI: 0.994–1.000; $P = 0.028$), 6MWD% (OR: 0.985; 95% CI: 0.970–0.999; $P = 0.041$), peak oxygen consumption (OR: 0.874; 95% CI: 0.776–0.986; $P = 0.028$), residual volume (OR: 1.006; 95% CI: 1.001–1.011; $P = 0.017$), and functional residual capacity (OR: 1.008; 95% CI: 1.001–1.014; $P = 0.028$) emerged as significant predictors of frequent severe exacerbations.

CONCLUSION: Expiratory muscle weakness, reduced peak oxygen consumption, diminished exercise capacity, and pulmonary hyperinflation are independent predictors of frequent severe acute exacerbations in patients with COPD. Incorporating these parameters into routine assessments may enhance risk stratification and goal-directed therapies, and potentially reduce hospitalization rates.

KEYWORDS: Chronic obstructive pulmonary disease, flare-up, maximal respiratory pressures, oxygen consumption, walk test, functional residual capacity

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive lung condition marked by airflow limitation and respiratory symptoms such as dyspnea and cough.[1] Globally, COPD affected approximately 480 million people in 2020, with projections reaching 592 million by 2050.[2] In India, the overall prevalence is estimated at 7.4%,[3] with state-wise variations as 10% in Delhi,[4] 6.19% in Kerala.[5] Acute exacerbations of COPD (AECOPD), characterized by a sudden worsening of respiratory symptoms such as dyspnea, cough, and sputum production within a short period, typically less than two weeks, significantly contribute to hospitalizations and the healthcare burden. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) classifies exacerbations by severity; with severe events requiring emergency care or hospitalization.[6] In low- and middle-income countries, including India, 20.1% of patients with COPD experience a severe exacerbation annually, and the associated healthcare cost per severe exacerbation is substantial.[7]

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Exacerbation frequency varies widely among COPD patients, with more frequent exacerbations associated with more rapid decline in lung function and increased mortality. While multiple factors such as older age, smoking, low body mass index (BMI), cold temperatures, air pollution, poor quality of life, comorbidities, prior exacerbations, and elevated eosinophils have been previously linked to frequent and severe exacerbations,[8] the predictive role of physiological and clinical parameters remains inadequately explored. Therefore, a significant gap remains in studies that concurrently evaluate a comprehensive set of clinical and rehabilitative parameters, namely respiratory muscle strength, peak oxygen consumption (VO_2 peak), exercise capacity, arterial blood gas (ABG), and pulmonary function parameters beyond spirometry, in relation to severe acute exacerbation frequency, while adequately adjusting for multiple established clinical covariates in COPD patients. The objective of this research was to evaluate whether physiological and clinical parameters of COPD could serve as predictors of frequent severe acute exacerbations. We hypothesized that reduced respiratory muscle strength, reduced VO_2 peak, reduced exercise capacity, impaired pulmonary function, and abnormal ABG values would be significant predictors of frequent severe acute exacerbations in patients with COPD.

MATERIAL AND METHODS

Study Design and Subjects

The observational retrospective study was conducted at Metro Centre for Respiratory Diseases, Metro Hospitals & Heart Institute, Noida, India. The medical records and discharge summaries of all COPD patients admitted to hospital between January 1st, 2018 and February 28th, 2024 were reviewed, and 265 patients with a diagnosis of severe AECOPD were analyzed. Efforts were made to ensure data accuracy by cross-checking clinical variables against multiple sources in the medical records, where available, to minimize selection bias. We included patients aged 40–80 years who were clinically identified as having COPD, confirmed by post-bronchodilator spirometry showing forced expiratory volume in 1 second/forced volume capacity (FEV_1/FVC) <0.70 and grade II, III, or IV airflow limitation according to the GOLD criteria. COPD grades are classified as moderate (GOLD stage II): FEV_1 ≥50% predicted but <80% predicted; severe (GOLD stage III): FEV_1 ≥30% predicted but <50% predicted; and very severe (GOLD stage IV): FEV_1 <30% predicted. Severe AECOPD cases in which patients were hospitalized for aggravated respiratory status of less than two weeks' duration were included in this study. It included patients with comorbidities but excluded those with inflammatory diseases (such as rheumatoid arthritis, systemic lupus erythematosus, fibromyalgia, and inflammatory bowel disease), previously diagnosed asthma or asthma-COPD overlap syndrome, myopathy, and those hospitalized for unstable angina or acute myocardial infarction.

Main Points

- The present retrospective trial highlights that expiratory muscle weakness, impaired peak oxygen uptake, impaired exercise tolerance, and pulmonary hyperinflation may independently predict severe exacerbations in chronic obstructive pulmonary disease patients.
- These markers enhance early identification of high-risk individuals and improve clinical risk stratification.
- Incorporating these predictors into routine assessments may help reduce exacerbation-related hospital admissions.

Patients were further categorized based on the frequency of severe COPD exacerbations. Severe AECOPD events were defined as exacerbations leading to hospitalization in intensive care units or medical wards. Group A, infrequent exacerbators included patients who were not rehospitalized for severe AECOPD within one year after the index event. Group B, frequent exacerbators, included patients who were rehospitalized for severe AECOPD one or more times within one year after an index event.[8] Cases with incomplete or missing data for key variables were excluded from the final analysis. Complete-case analysis was adopted to ensure the robustness of statistical comparisons.

Sample Size

A priori sample size of 102 participants was calculated using G*Power version 3.1.9.7, based on an expected odds ratio (OR) of 2.9 for maximal inspiratory muscle strength (PImax) reported in a previous study.[9] This calculation assumed a significance level (α) of 0.05 and a statistical power of 0.95, with an additional 20% to account for potential incomplete data. However, given the retrospective nature of the study and the availability of data from 265 eligible patients, the full dataset was utilized to enhance the statistical power, improve the precision of estimates, and minimize the risk of type II error.

Data Collection

The primary end points, PImax and maximum expiratory muscle strength (PEmax), were assessed at the time of hospital discharge, when patients were clinically stable, with the objective of evaluating their ability to predict frequent severe exacerbations of COPD. The secondary end points were exercise capacity [six-minute walk distance (6MWD), percent predicted 6MWD (6MWD%), six-minute walk work (6MWW), VO_2 peak], static lung volumes for pulmonary function [tidal volume (TV), inspiratory reserve volume (IRV), expiratory reserve volume (ERV), residual volume (RV), inspiratory capacity (IC), functional residual capacity (FRC), vital capacity (VC), total lung capacity (TLC), and dynamic lung volumes such as RV/TLC%, diffusing capacity of the lung for carbon monoxide (DLCO), FEV_1, FVC, FEV_1/FVC%, maximum inspiratory flow (MIF), maximal expiratory flow at 25%, 50% and 75% of FVC (MEF25%, MEF75%, MEF50%), peak inspiratory flow (PIF), peak expiratory flow (PEF)] measured were assessed at the time of hospital discharge, when patients were clinically stable and ABG [(pH, partial pressure of carbon dioxide ($PaCO_2$), partial pressure of oxygen (PaO_2), bicarbonate (HCO_3^-), oxygen saturation (SpO_2)] were obtained at hospital admission, during the acute exacerbation phase. The dependent outcome was frequent severe AECOPD episodes.

Respiratory muscle strength was assessed at the mouth using the MicroRPM manometer (Care Fusion, Hoechberg, Germany) to measure PImax and PEmax. According to Black and Hyatt's assessment,[10] the Muller maneuver is performed at RV for PImax, and the Valsalva maneuver is performed at TLC for PEmax. The best of at least three efforts is obtained following American Thoracic Society (ATS) guidelines.[10] Exercise capacity was measured via the 6MWT (Spiropalm, COSMED, Rome, Italy) with a pulse oximeter (Nonin Medical Inc., Plymouth, MN, USA), and mobile exercise testing (Vyntus™ WALK, Vyaire Medical, Hoechberg, Germany) was used to record the total distance walked according to ATS guidelines.[11] The 6MWW was calculated as 6MWD x body weight,[12] and VO_2 peak was estimated using the formula 4.948+0.023x6MWD.[13] Pulmonary function testing, including body plethysmography, was performed using the MasterScreen™ PFT (JAEGER, CareFusion, Hoechberg, Germany). ATS guidelines were followed to record lung volumes and capacities. ABG analysis was conducted using the modified Allen test.[14]

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 27. Data are presented as mean ± standard deviation. Demographic details, clinical characteristics, comorbidities, medications, and smoking history were compared between the two groups of severe AECOPD patients, defined by exacerbation frequency; continuous variables were compared using the Mann–Whitney U test, and categorical variables were compared using the chi-square test. The chi-square test is used to compare categorical variables, which are presented as frequencies (n) and percentages (%). Univariate binary logistic regression analysis using the enter method was used to compute OR, 95% confidence intervals (CI), and *P* values. The OR, which represents the association between an exposure and an outcome, is computed to assess the predictive ability of each variable. A *P* value <0.25 in univariate analysis indicates a significant predictor of frequent severe AECOPD.[15] Significant predictors from the univariate analysis are included in multivariate logistic regression models (enter method), adjusted for clinically relevant covariates [BMI, gender, FEV_1, non-inflammatory musculoskeletal disorders (osteoarthritis, osteoporosis, osteopenia), use of bronchodilators, and corticosteroids (inhaled and/or systemic)]. The variables which showed significance in the univariate analysis and association with exacerbations previously are chosen as covariates.[16-22] A *P* value <0.05 in the multivariate analysis indicates a statistically significant predictor.[15] Multicollinearity analysis is conducted to identify any collinearity among each predictor variable and covariates. Variance inflation factors (VIFs) are computed, and a VIF <3 suggests the absence of multicollinearity.[15]

RESULTS

Baseline Characteristics of the Participants

Throughout the study, medical records of 304 subjects were reviewed. Of these, 289 patients (95%) hospitalized for severe AECOPD met the eligibility criteria and were included in the study. Two groups were formed from the patient population; group A infrequent exacerbations comprised 162 patients (56.1%), and group B frequent exacerbations comprised 127 patients (43.9%). However, 18 patients (11.1%) in group A and 6 (4.7%) in group B had incomplete data due to missing variables and were subsequently excluded from the final analysis. Consequently, 265 patients remained for the final analysis.

The baseline profiles of the patients, including demographic and clinical characteristics, are summarized in (Table 1). Data analysis demonstrated statistically significant differences in body weight and BMI between groups categorized by frequency of severe AECOPD ($P < 0.05$) (Table 1). No other baseline variables showed statistically significant differences between the groups. The comparative analysis of key physiological and clinical parameters, namely respiratory muscle strength, exercise capacity, pulmonary function tests, and ABG values, between the frequent and infrequent COPD exacerbator groups is presented in (Table 2). Statistically significant differences ($P < 0.05$) were observed in several variables, including PEmax, 6MWD, 6MWD%pred, 6MWW, VO_2 peak, FEV_1%, FEV_1/FVC%, PEF%pred, MIF (L/s), MEF75%pred, MEF50%pred, RV, TLC%pred, RV/TLC%, and FRC%pred. Overall, respiratory muscle strength parameters (PImax and PEmax), exercise capacity indicators (6MWD, 6MWD% predicted, 6MWW, and VO_2 peak), and pulmonary function parameters (FEV_1%, FEV_1/FVC% ratio, PEF%pred, MIF (L/s), MEF75%, MEF50%, TV%pred, TLC%pred, RV/TLC%, and DLCO) were notably better in the infrequent exacerbator group than in the frequent exacerbator group.

Univariate Binary Logistic Regression Analysis

In the present research, a binary logistic regression model identified predictors of frequent, severe AECOPD. Univariate analysis revealed predictive ability for several variables, including PImax (OR: 0.991; 95% CI: 0.980-1.003; $P = 0.162$), PEmax (OR: 0.989; 95% CI: 0.981-0.996; $P = 0.004$), 6MWD (OR: 0.997; 95% CI: 0.994-0.999; $P = 0.006$), 6MWD% (OR: 0.984; 95% CI: 0.971-0.997; $P = 0.014$), 6MWW (OR: 1.000; 95% CI: 1.000-1.000; $P < 0.001$), VO_2 peak (OR: 0.861; 95% CI: 0.773-0.959; $P = 0.006$), FEV_1/FVC % (OR: 0.971; 95% CI: 0.953-0.990; $P = 0.003$), PEF% predicted (OR: 0.988; 95% CI: 0.975-1.001; $P = 0.061$), maximal expiratory flow at 75% of FVC (MEF75% predicted) (OR: 0.990; 95% CI: 0.978-1.003; $P = 0.120$), RV (OR: 1.007; 95% CI: 1.002-1.011; $P = 0.002$), and FRC (OR: 1.008; 95% CI: 1.002-1.014; $P = 0.006$) as presented (Table 3).

Multivariate Binary Logistic Regression Analysis

A multicollinearity analysis was implemented to assess the relationship between each significant predictor variable and the clinical covariates. All variables had VIF <3, confirming the absence of significant multicollinearity and thereby reinforcing the strength of the regression analysis findings. Multivariate binary logistic regression models were constructed for each significant predictor identified in the univariate analysis and were adjusted for clinically relevant covariates, which were selected based on prior literature and univariate screening, including BMI, FEV_1, gender, use of bronchodilators and corticosteroids, and presence of musculoskeletal disorders. In the adjusted model, PEmax (OR: 0.989; 95% CI: 0.980–0.998; $P = 0.014$), 6MWD (OR: 0.997; 95% CI: 0.994–1.000;

Table 1. Baseline characteristics of patients

Variables	Infrequent exacerbator group (n = 144)	Frequent exacerbator group (n = 121)	*P* value
Demographics			
Age (years)	66.31±7.07	67.09±7.41	0.340
Body weight (kg)	63.77±15.31	57.32±12.19	**<0.001***
Height (cm)	164.19±7.99	161.90±8.77	0.175
BMI (kg/m^2)	23.90±5.98	21.85±5.00	**0.003***
Gender, n (%)			
Male	115 (79.9%)	88 (72.7%)	0.172
Female	29 (20.1%)	33 (27.3%)	
Smoking status, n (%)			
Non-smoker	36 (25%)	31 (25.6%)	0.993
Active smoker	19 (13.2%)	16 (13.2%)	
Former smoker	89 (61.8%)	74 (61.2%)	
Symptoms, n (%)			
Dyspnea	143 (99.3%)	121 (100%)	0.358
Cough	111 (77.1%)	100 (82.6%)	0.263
Sputum	107 (74.3%)	97 (80.8%)	0.208
Medications, n (%)			
Use of bronchodilator	138 (95.8%)	120 (99.2%)	0.091
Use of corticosteroid	74 (51.4%)	51 (42.1%)	0.133
Use of combination drug	132 (91.7%)	109 (90.1%)	0.654
Comorbidities, n (%)			
Musculoskeletal disorder	63 (43.8%)	65 (53.7%)	0.106
Metabolic disorder	79 (54.9%)	73 (60.3%)	0.370
Pneumonia	26 (18.1%)	27 (22.3%)	0.388
Pulmonary tuberculosis	22 (15.3%)	22 (18.2%)	0.527
Sleep disorder	21 (14.6%)	22 (18.2%)	0.429
Psychological disorder	6 (4.2%)	5 (4.1%)	0.989
Inflammatory marker			
CRP (mg/dL)	73.04±84.76	78.27±96.29	0.878

*Significance considered at $P < 0.05$ (bold). Data presented in mean ± standard deviation
BMI: body mass index, CRP: C-reactive protein

P = 0.028), 6MWD% (OR: 0.985; 95% CI: 0.970–0.999; *P* = 0.041), VO_2 peak (OR: 0.874; 95% CI: 0.776–0.986; *P* = 0.028), RV (OR: 1.006; 95% CI: 1.001–1.011; *P* = 0.017), and FRC (OR: 1.008; 95% CI: 1.001–1.014; *P* = 0.028) emerged as significant independent predictors of frequent severe AECOPD, while 6MWW (OR: 1.000; 95% CI: 1.000–1.000; *P* = 0.026) showed statistical significance, however, the odds ratio of 1.000 indicates an absence of clinically meaningful association with exacerbations in both univariate and multivariate analyses as shown in (Table 4).

DISCUSSION

The primary findings of the univariate analysis revealed that: (i) respiratory muscle strength (inspiratory and expiratory muscle strength; PImax, PEmax), overall exercise capacity measures (6MWD, 6MWD%, VO_2 peak), and pulmonary function parameters (FEV_1/FVC%, PEF%pred, MEF75%pred, RV%pred, and FRC%pred) were significantly associated with frequent severe AECOPD; and (ii) in the multivariate analysis, expiratory muscle strength (PEmax), overall exercise capacity measures (6MWD, 6MWD%, VO_2 peak), and pulmonary hyperinflation (RV%pred and FRC%pred) remained significant independent predictors even after adjusting for various clinical covariates. The significance of this study is rooted in its emphasis on the interplay between clinical and physiological parameters as potential predictors of frequent severe exacerbations in COPD. This approach underscores the value of incorporating a comprehensive assessment of physiological dysfunction, moving beyond traditional risk factors. The integration of these diverse markers enhances our ability to stratify exacerbation risk based on key functional impairments.

Table 2. Comparison of clinical characteristics such as arterial blood gas, respiratory muscle strength, exercise capacity and pulmonary function parameters

Variables	Infrequent exacerbator group (n = 144)	Frequent exacerbator group (n = 121)	*P* value
Arterial blood gas			
pH	7.39±0.07	7.40±0.06	0.666
$PaCO_2$ (mmHg)	45.62±15.47	45.39±13.70	0.773
PaO_2 (mmHg)	84.75±36.68	84.58±32.07	0.914
HCO_3^- (mEq/L)	26.60±6.37	27.29±5.69	0.328
SpO_2 (%)	93.51±7.82	93.85±6.23	0.791
Respiratory muscle strength			
PImax (cm H_2O)	65.94±21.33	62.42±19.19	0.217
PEmax (cm H_2O)	110.06±34.70	98.26±29.60	**0.003***
Exercise capacity			
6MWD (meters)	291.79±128.00	253.64±84.95	**0.006***
6MWD% (% predicted)	58.09±20.68	52.27±16.27	**0.015***
6MWW (kg-meter)	18973.79±11816.80	14531.42±5877.23	**<0.001***
VO_2 peak (mL/kg/min)	11.65±2.94	10.78±1.95	**0.006***
Pulmonary function tests			
FVC (% predicted)	72.28±15.70	74.72±19.31	0.471
FEV_1 (% predicted)	43.29±16.11	39.79±16.97	**0.027***
FEV_1/FVC% (%)	47.62±13.08	42.60±13.15	**0.002***
PIF (L/s)	3.27±1.27	3.38±1.32	0.522
PEF (% predicted)	47.99±19.24	43.45±19.45	**0.016***
MIF (L/s)	1.20±3.76	1.04±3.86	**0.031***
MEF75% (% predicted)	22.65±19.71	18.61±21.78	**0.001***
MEF50% (% predicted)	15.24±14.76	15.09±29.70	**0.006***
MEF25% (% predicted)	13.97±10.62	13.97±15.79	0.269
TV (% predicted)	154.45±61.53	147.24±54.65	0.357
IRV (L)	0.77±0.37	1.14±3.50	0.552
ERV (% predicted)	91.76±39.35	92.44±35.12	0.799
IC (% predicted)	61.88±17.35	62.21±17.96	0.962
VCmax (% predicted)	70.64±14.46	73.12±20.47	0.675
RV (% predicted)	165.82±56.02	191.22±69.94	**<0.001***
TLC (% predicted)	149.77±31.56	112.37±25.07	**<0.001***
RV/TLC% (%)	66.72±21.79	66.39±9.73	**0.049***
FRC (% predicted)	142.46±42.70	158.60±47.56	**<0.001***
DLCO (% predicted)	51.92±17.71	50.26±19.06	0.215

Data presented in mean ± standard deviation. *Significance considered at $P < 0.05$

PImax: maximum inspiratory pressure, PEmax: maximum expiratory pressure, 6MWD: six-minute walk distance, 6MWD%: percent predicted six-minute walk distance, 6MWW: six-minute walk work, VO_2 peak: peak oxygen uptake, FVC: forced vital capacity, FEV_1: forced expiratory volume in 1 second, PIF: peak inspiratory flow, PEF: peak expiratory flow, MIF: maximal inspiratory flow, MEF75%, MEF50%, MEF25%: maximum expiratory flow at 75%, 50%, 25% of FVC, respectively, TV: tidal volume, IRV: inspiratory reserve volume, ERV: expiratory reserve volume, IC: inspiratory capacity, VCmax: maximum vital capacity, RV: residual volume, TLC: total lung capacity, FRC: functional residual capacity, RV/TLC%: residual volume/total lung capacity ratio, DLCO: diffusing capacity of the lungs for carbon monoxide

In present study, although both inspiratory and expiratory muscle weakness were significantly associated with frequent severe exacerbations in the univariate analyses, only expiratory muscle weakness retained significance as an independent predictor of frequent severe exacerbations in COPD after adjustment for clinical covariates. Thus, our study suggests that greater expiratory muscle strength is associated with lower odds of frequent, severe exacerbations in COPD. Though a prior study,[23] linked % predicted PImax with risk of exacerbation using a time-course Cox proportional hazards model, their work did not focus specifically on the frequency of severe exacerbations. In contrast, our findings offer a distinct and clinically meaningful perspective by identifying PEmax as a stronger and more practical predictor of frequent, severe, exacerbation-related hospitalizations. This

Table 3. Univariate binary logistic regression analyses

Variables	OR	95% CI	*P* value
Predictor variables			
Arterial blood gas analyses			
pH	2.151	0.069-6.868	0.662
$PaCO_2$ (mmHg)	0.999	0.983–1.016	0.896
PaO_2 (mmHg)	1.000	0.993–1.007	0.968
HCO_3^- (mEq/L)	1.019	0.979–1.061	0.355
SpO_2 (%)	1.007	0.973–1.042	0.699
Respiratory muscle strength			
PImax (cm H_2O)	0.991	0.980–1.003	**0.162***
PEmax (cm H_2O)	0.989	0.981–0.996	**0.004***
Exercise capacity			
6MWD (meters)	0.997	0.994–0.999	**0.006***
6MWD (% predicted)	0.984	0.971–0.997	**0.014***
6MWW (kg meters)	1.000	1.000–1.000	**<0.001***
VO_2 peak (mL/kg/min)	0.861	0.773–0.959	**0.006***
Pulmonary function tests			
FVC (L)	1.008	0.994–1.022	0.259
FEV_1/FVC (%)	0.971	0.953–0.990	**0.003***
PIF (L/s)	1.066	0.884–1.285	0.506
PEF (% predicted)	0.988	0.975–1.001	**0.061***
MIF (L/s)	0.989	0.925–1.057	0.736
MEF75 (% predicted)	0.990	0.978–1.003	**0.120***
MEF50 (% predicted)	1.000	0.989–1.010	0.955
MEF25 (% predicted)	1.000	0.982–1.018	0.999
TV (% predicted)	0.998	0.994–1.002	0.317
IRV (L)	1.353	0.760–2.409	0.305
ERV (% predicted)	1.000	0.994–1.007	0.884
IC (% predicted)	1.001	0.987–1.015	0.879
VCmax (% predicted)	1.008	0.994–1.022	0.252
RV (% predicted)	1.007	1.002–1.011	**0.002***
TLC (% predicted)	0.999	0.996–1.001	0.308
RV/TLC (%)	0.999	0.985–1.013	0.879
FRC (% predicted)	1.008	1.002–1.014	**0.006***
DLCO (% predicted)	0.995	0.982–1.008	0.464
Covariates			
Age (years)	1.015	0.982–1.050	0.378
BMI (kg/m^2)	0.933	0.889–0.978	**0.004***
CRP (mg/dL)	1.001	0.998–1.003	0.637
FEV_1 (%)	0.987	0.972–1.002	**0.088***
Gender			
Female (ref)			
Male	0.672	0.380–1.190	**0.173***
Smoking status			
Non–smoker (ref)			
Active smoker	0.978	0.431–2.221	0.957
Former smoker	0.966	0.546–1.709	0.904
Medications (ref: no use)			
Use of Bronchodilator	5.217	0.619–43.952	**0.129***
Use of Corticosteroid	0.689	0.424–1.121	**0.134***
Use of Combination drug	0.826	0.357–1.912	0.655
Comorbidities (ref: absent)			
Musculoskeletal disorder	1.492	0.918–2.426	**0.106***
Metabolic disorder	1.251	0.766–2.043	0.370
Pneumonia disorder	1.304	0.713–2.382	0.389
Pulmonary tuberculosis disorder	1.232	0.645–2.355	0.527
Sleep disorder	1.302	0.677–2.503	0.429
Psychological disorder	0.991	0.295–3.332	0.989

*Statistically significant considered at $P < 0.25$ (bold)

OR: odds ratio, CI: confidence interval, pH: potential of hydrogen, $PaCO_2$: partial pressure of carbon dioxide, PaO_2: partial pressure of oxygen, HCO_3^-: bicarbonate, SpO_2: peripheral capillary oxygen saturation, PImax: maximal inspiratory pressure, PEmax: maximal expiratory pressure, 6MWD: six-minute walk distance, 6MWW: six-minute walk work, VO_2 peak: peak oxygen uptake, FVC: forced vital capacity, FEV_1: forced expiratory volume in 1 second, PIF: peak inspiratory flow, PEF: peak expiratory flow, MIF: maximal inspiratory flow, MEF75%, 50%, 25%: maximal expiratory flow at 75%, 50%, and 25% of FVC respectively, TV: tidal volume, IRV: inspiratory reserve volume, ERV: expiratory reserve volume, IC: inspiratory capacity, VCmax: maximal voluntary capacity, RV: residual volume, TLC: total lung capacity, RV/TLC%: percentage of residual volume to total lung capacity ratio, FRC: functional residual capacity, DLCO: diffusing capacity of the lung for carbon monoxide, BMI: body mass index, CRP: C-reactive protein

discrepancy may stem from differences in demographics, environment, study region, statistical methods, and the severity or frequency of exacerbations considered. Our study included older, hospitalized patients with advanced COPD and multiple comorbidities, who were mostly former smokers, unlike the study,[23] which involved a population with a milder disease stage and a mix of moderate and severe exacerbations.

The pathophysiological basis for our findings is well-supported. Expiratory muscles are essential for effective coughing and secretion clearance but are highly susceptible to dysfunction due to chronic mechanical loading, increased airway resistance, and reduced lung elastic recoil.[24] These factors lead to progressive muscle fatigue, reduced PEmax, impaired secretion clearance, and heightened airway inflammation, all of which increase the likelihood of severe exacerbations.[25] These effects are further exacerbated in older patients due to age-related declines in muscle strength, lung compliance, and chest wall mobility.[26] Although PImax did not emerge as a strong predictor in multivariate analysis, it was associated with the frequency of severe exacerbations in univariate analysis. Hence, in clinical practice, this suggests that greater expiratory muscle strength, particularly PEmax, may contribute to reducing the frequency of severe exacerbations and may be considered in rehabilitative strategies for COPD patients. Our findings support the clinical value of incorporating respiratory muscle assessment into COPD risk stratification and highlight the potential benefits of targeted expiratory muscle training to reduce the frequency of severe exacerbations and hospitalizations.[27]

Table 4. Multivariate binary logistic regression analyses (adjusted model)

Predictor variables	OR	95% CI	*P* value
Model 1			
PImax (cm H_2O)	0.993	0.980–1.006	0.304
BMI (kg/m²)	0.923	0.876–0.972	**0.002***
FEV_1 (%)	0.990	0.974–1.006	0.203
Gender	0.501	0.263–0.952	**0.035***
Use of bronchodilator	7.791	0.843–71.972	0.070
Use of corticosteroid	0.537	0.314–0.918	**0.023***
Musculoskeletal disorder	1.247	0.748–2.082	0.397
Model 2			
PEmax (cm H_2O)	0.989	0.980–0.998	**0.014***
BMI (kg/m²)	0.929	0.882–0.979	**0.006***
FEV_1 (%)	0.988	0.972–1.004	0.143
Gender	0.572	0.297–1.101	0.095
Use of bronchodilator	8.206	0.889–75.717	0.063
Use of corticosteroid	0.494	0.287–0.851	**0.011***
Musculoskeletal disorder	1.229	0.733–1.061	0.434
Model 3			
6MWD (m)	0.997	0.994–1.000	**0.028***
BMI (kg/m²)	0.920	0.872–0.969	**0.002***
FEV_1 (%)	0.991	0.975–1.007	0.279
Gender	0.594	0.307–1.152	0.124
Use of bronchodilator	6.655	0.731–60.558	0.093
Use of corticosteroid	0.600	0.355–1.017	0.058
Musculoskeletal disorder	1.338	0.796–2.250	0.272
Model 4			
6MWD% (%)	0.985	0.970–0.999	**0.041***
BMI (kg/m²)	0.993	0.977–1.009	**<0.001***
FEV_1 (%)	0.914	0.867–0.963	0.371
Gender	0.561	0.291–1.081	0.084
Use of bronchodilator	6.936	0.756–63.628	0.087
Use of corticosteroid	0.619	0.365–1.050	0.075
Musculoskeletal disorder	1.296	0.771–2.177	0.328
Model 5			
6MWW (kg-m)	1.000	1.000–1.000	**0.026***
BMI (kg/m²)	0.946	0.895–0.999	**0.046***
FEV_1 (%)	0.991	0.975–1.007	0.271
Gender	0.660	0.333–1.306	0.233
Use of bronchodilator	6.818	0.746–62.307	0.089
Use of corticosteroid	0.604	0.356–1.024	0.061
Musculoskeletal disorder	1.298	0.744–2.178	0.323
Model 6			
VO_2 peak (mL/kg/min)	0.874	0.776–0.986	**0.028***
BMI (kg/m²)	0.920	0.872–0.969	**0.002***
FEV_1 (%)	0.991	0.975–1.007	0.279
Gender	0.594	0.307–1.152	0.124
Use of bronchodilator	6.655	0.731–60.558	0.093
Use of corticosteroid	0.600	0.355–1.017	0.058
Musculoskeletal disorder	1.338	0.796–2.250	0.272

Table 4. Multivariate binary logistic regression analyses (adjusted model)

Predictor variables	OR	95% CI	*P* value
Model 7			
FEV_1/FVC (%)	0.970	0.940–1.000	0.053
BMI (kg/m²)	0.931	0.883–0.982	**0.008***
FEV_1 (%)	1.006	0.983–1.030	0.612
Gender	0.452	0.236–0.866	**0.017***
Use of bronchodilator	7.344	0.787–68.485	0.080
Use of corticosteroid	0.586	0.347–0.990	**0.046***
Musculoskeletal disorder	1.177	0.701–1.975	0.537
Model 8			
PEF (% predicted)	0.997	0.976–1.019	0.782
BMI (kg/m²)	0.921	0.874–0.970	**0.002***
FEV_1 (%)	0.991	0.967–1.017	0.498
Gender	0.489	0.256–0.935	**0.030***
Use of bronchodilator	7.780	0.846–71.581	0.070
Use of corticosteroid	0.573	0.341–0.965	**0.036***
Musculoskeletal disorder	1.238	0.742–2.065	0.413
Model 9			
MEF75% (% predicted)	0.998	0.979–1.018	0.862
BMI (kg/m²)	0.919	0.872–0.968	**0.001***
FEV_1 (%)	0.990	0.966–1.014	0.401
Gender	0.454	0.237–0.868	**0.001***
Use of bronchodilator	8.239	0.886–76.615	0.064
Use of corticosteroid	0.558	0.330–0.941	**0.029***
Musculoskeletal disorder	1.260	0.753–2.109	0.379
Model 10			
RV (% predicted)	1.006	1.001–1.011	**0.017***
BMI (kg/m²)	0.920	0.874–0.970	**0.002***
FEV_1 (%)	0.998	0.981–1.016	0.836
Gender	0.494	0.259–0.944	**0.033***
Use of bronchodilator	9.760	0.992–95.982	0.051
Use of corticosteroid	0.613	0.362–1.039	0.069
Musculoskeletal disorder	1.143	0.680–1.922	0.615
Model 11			
FRC (% predicted)	1.008	1.001–1.014	**0.028***
BMI (kg/m²)	0.920	0.873–0.969	**0.002***
FEV_1 (%)	0.997	0.980–1.014	0.725
Gender	0.474	0.248–0.905	**0.024***
Use of bronchodilator	10.359	1.058–101.408	**0.045***
Use of corticosteroid	0.598	0.354–1.011	0.055
Musculoskeletal disorder	1.143	0.680–1.921	0.614

*Statistically significant considered at $P < 0.05$ (bold)

OR: adjusted odds ratio, CI: confidence interval, PImax: maximal inspiratory pressure, PEmax: maximal expiratory pressure, 6MWD: six-minute walk distance, 6MWD%: six-minute walk distance percent predicted, 6MWW: six-minute walk work, VO_2 peak: peak oxygen uptake, FEV_1/FVC%: ratio of forced expiratory volume in 1 second to forced vital capacity in percent, FEV_1: forced expiratory volume in 1 second, PEF: peak expiratory flow, MEF75%: maximal expiratory flow at 75% of FVC, RV: residual volume, FRC: functional residual capacity, BMI: body mass index

This study highlights peak VO_2 and exercise capacity as prognostic indicators of frequent severe exacerbations in COPD. We found that 6MWD, 6MWD%, and VO_2 peak were significant independent predictors of exacerbation risk, whereas 6MWW showed no association. Higher 6MWD values were linked to lower odds of exacerbations, consistent with previous research showing that reduced 6MWD predicts an increased risk of hospitalization and mortality.[28,29] Our study further confirms that even a single severe exacerbation can cause lasting reductions in 6MWD. To the best of our knowledge, this is the first study to explore the predictive value of variables derived from the six-minute walk test, such as 6MWW and VO_2 peak. VO_2 peak was a meaningful predictor of exacerbation risk than 6MWW; higher VO_2 peak was associated with lower exacerbation risk, underscoring the importance of oxygen uptake efficiency in assessing patients with COPD. Since actual VO_2 peak is determined by direct measurement, this study suggests that indirectly estimated VO_2 peak may also serve as a practical surrogate, given its demonstrated predictive value, facilitating its application in clinical rehabilitation and professional practice.

In the present study, FEV_1/FVC%, PEF%pred, MEF75%, RV%pred, and FRC%pred were significantly associated with frequent severe exacerbations in the univariate analysis. However, markers of air trapping, elevated RV%pred and FRC%pred -remained as significant independent predictors of frequent severe exacerbations in COPD after adjustment for clinical covariates. Previous studies have proposed FEV_1/FVC% and PEF as clinical markers, but their clinical utility has been limited by the lack of reported OR.[30,31] A study[32] addressed this, showing that FEV_1/FVC% (OR: 0.994) and PEF (OR: 0.891) were associated with exacerbation risk in univariate analysis, although PEF lost significance in multivariate analysis. Similarly, our study is consistent with previous findings,[32] showing that FEV_1/FVC% (OR: 0.97) and PEF (OR: 0.98) were significant only in univariate models.

Together, these findings emphasize the limited predictive power of spirometric indices and reinforce the need for alternative markers, such as pulmonary hyperinflation. Hyperinflation was defined as RV >120% predicted and/or FRC >120% predicted, according to established guidelines.[33-35] Notably, RV%pred and FRC%pred remained significant predictors in our study despite bronchodilator and corticosteroid treatment, reinforcing the independent role of hyperinflation. Our findings align with prior research showing that a 10% increase in RV/TLC% is associated with a 36% rise in exacerbation risk, particularly in the absence of triple inhaler therapy.[33] While earlier studies mainly used Cox proportional hazards models, static hyperinflation, measured by IC/TLC% and RV/TLC%, has consistently predicted mortality, exercise capacity, and quality of life.[34,35] By quantifying these associations using logistic regression, our study provides further evidence that lung-volume measures reflecting hyperinflation are more robust and consistent predictors of frequent severe exacerbations in COPD.

Study Limitations

This research employed robust statistical methods, including both univariate and multivariate analyses. Furthermore, the study confirmed the absence of multicollinearity among predictors and covariates, thereby strengthening the statistical validity and robustness of the model. These findings support the development of multifactorial predictive models that include not only clinical variables but also physiological indicators, facilitating more targeted and individualized management strategies. This study has several limitations. First, a retrospective study design may introduce inherent bias in data collection and analysis. Second, it was a single-center study. Third, no specific cut-off values for predictors were established, limiting clinical applicability.

CONCLUSION

The findings of the present study extend the concept that susceptibility to extrapulmonary manifestations is related to frequent severe AECOPD. Our results indicate that lower PEmax, reduced VO_2 peak, diminished exercise capacity (6MWD, 6MWD%), and greater pulmonary hyperinflation (RV and FRC) are independent predictors of frequent severe AECOPD. However, variables such as PImax, FEV_1/FVC%, PEF%pred, and MEF75%pred were predictive only in univariate analyses. These findings suggest that incorporating them into routine assessment may prompt recognition of high-risk patients and the stratification of individuals with elevated risk of frequent severe exacerbations, potentially leading to reduced hospitalization rates. Future multicenter, prospective, and longitudinal studies are recommended to confirm these findings, to better understand causal relationships, extrapulmonary influences, and to improve risk stratification in COPD.

Ethics

Ethics Committee Approval: 1) Metro Ethical Review Board, Metro Hospitals and Heart Institute, Noida, India (ECR/335/Inst/UP/2013/RR-20); approval number: 93/MERB/2024; date of approval: 23rd January, 2025. 2) Institutional Ethics Committee, Jamia Millia Islamia EC/NEW/INST/2022/DL/0170); approval number: 3/10/523/JMI/IEC/2024; date of approval: 12th March, 2025.

Informed Consent: The study involved a retrospective analysis of existing medical records; therefore, the requirement for informed consent was waived. Patient confidentiality was strictly maintained, and all data were anonymized prior to analysis.

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Footnotes

The patient's data was anonymized and study was listed under Clinical Trial Registry-India (CTRI), CTRI/2025/01/079833.

Authorship Contributions

Concept: M.M.T., A.M., O.A., D.T., Design: M.M.T., A.M., O.A., D.T., Data Collection or Processing: M.M.T., A.M., O.A., D.T., Analysis or Interpretation: M.M.T., A.M., Literature Search: M.M.T., A.M., Writing: M.M.T., A.M., O.A., D.T.

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