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Research Protocol

Physiotherapy Section

Predicting the Gender-based Aerobic Capacity in Chronic Obstructive Pulmonary Disease Patients with superadded Infection: A Study Protocol

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ABSTRACT

Introduction: Chronic Obstructive Pulmonary Disease (COPD), a prevalent respiratory condition, can be prevented and treated. Among various triggers, infections are a leading cause of COPD exacerbations. Assessing aerobic capacity is essential in the management of COPD, as it serves as a fundamental indicator of both quality of life and mortality. However, determining this target value necessitates the estimation of a gender-based predictive aerobic capacity value for each individual.

Need of the study: The newly developed gender-based reference equation for aerobic capacity may have the potential to accurately calculate predicted values that assess the individual patient's aerobic capacity.

Aim: To develop a gender-based prediction equation to assess aerobic capacity in COPD patients with infection.

Materials and Methods: This cross-sectional study will recruit COPD patients with infections from the In-Patient Department (IPD) at a tertiary care super-specialty hospital (Maharishi Markandeshwar Institute of Medical Sciences and Research, Ambala, Haryana, India), using purposive sampling be conducted over a period of one year (from July 2024 to June 2025). The Forced Expiratory Volume in 1 second to Forced Vital Capacity (FEV1/FVC) ratio will be recorded using the post-bronchodilator PFT report, while aerobic capacity will be assessed through the Six-Minute Walk Test (6MWT) for 80 participants. Data will be analysed using IBM Statistical Package for the Social Sciences (SPSS) version 26.0. Depending on the data type, Chi-square, Spearman's, or Pearson's tests will be used to assess the relationship between FEV1/FVC and 6MWT. Multivariate linear regression with a step-wise approach will be employed to create a predictive equation for aerobic capacity. Subsequently, a standardised equation for aerobic capacity will be derived.

Keywords: Forced expiratory volume, Respiratory function tests, Six-minute walk test

INTRODUCTION

According to the Global Initiative for Chronic Obstructive Lung Disease guidelines, COPD is a heterogeneous respiratory condition characterised by persistent and often progressive airflow obstruction [1]. India bears a significant burden of COPD, with various risk factors and coexisting medical conditions [2]. Consequently, individuals with COPD experience chronic respiratory symptoms, including dyspnoea (shortness of breath), cough, sputum production and exacerbations. Exacerbations of COPD significantly impact morbidity, quality of life and healthcare costs. While most existing prediction models for COPD focus on mortality, few are specifically designed to predict exacerbations [3].

One of the primary factors contributing to exacerbations of COPD is infection, which is reported to be the most common cause among several potential triggers. Severity indices, such as the Body mass index, Obstruction, Dyspnoea and Exercise (BODE) Index and the Dyspnoea, Obstruction, Smoking and Exacerbations (DOSE) Index, have been evaluated for predicting future exacerbations [4]. This increase can be attributed to an ageing population, as COPD is more prevalent among individuals aged 50 years and older. Notably, the average age of COPD patients is 70 years. The elderly population continues to experience a significant incidence of COPD, further contributing to the upward trend.

Globally, the number of daily smokers was estimated to be exceptionally high, with approximately 1.14 billion individuals across 204 countries and territories. These smokers consumed a considerable quantity of tobacco, amounting to over 7.41 trillion cigarette units [5]. There are notable differences in the clinical manifestations of COPD between males and females. In particular, women tend to experience more pronounced symptoms, such as increased breathlessness, feelings of depression and a reduced quality of life related to their health [6]. The presence of concurrent chronic respiratory diseases can negatively impact the prognosis of COPD. Consequently, individuals with COPD often find themselves caught in a cycle of experiencing symptoms that can lead to a reduction in their overall physical activity levels. The interplay between genetic predisposition and exposure to environmental factors influences the risk factors for COPD. The primary risk factor for COPD is active smoking. While cigarette smoking is the most significant risk factor, it is important to note that not all smokers develop COPD during their lifetime, suggesting the involvement of genetic factors. However, factors such as gender, occupation, airway hyperresponsiveness, lung growth and development and infection also contribute significantly to the development of COPD [7]. Moreover, individuals who are 55 years old and do not have COPD have an estimated 24% risk of developing the condition over the next 40 years [8].

Daily symptoms of COPD, including chronic and progressive dyspnoea, cough and sputum production, significantly contribute to the burden of the disease. These symptoms lead to limitations in physical activity and ultimately affect the ability of COPD patients to work and care for themselves. COPD patients often find themselves caught in a cycle of inactivity, which originates from the experience of breathlessness [9]. The exertional dyspnoea in COPD patients is usually multifactorial, involving factors such as peripheral muscle dysfunction, dynamic hyperinflation and increased fat mass. Respiratory muscle weakness is an additional

factor that contributes to the impaired lung mechanics observed in individuals with advanced-stage COPD and COPD-related weight loss.

A "flare-up" of COPD symptoms is termed an exacerbation. Exacerbations of COPD significantly affect the quality of life, lung function and socioeconomic costs for patients. Therefore, the prevention, early detection and timely treatment of exacerbations hold great significance in the management of this disease [10]. Various assessments, such as the 6MWT and the incremental shuttle walk test, are used to evaluate the exercise capacity of individuals with COPD [11]. Given these challenges, there is a need for a simple, widely applicable prediction model that can be used for all COPD patients, including those with mild disease and predict all types of exacerbations, including those not requiring hospitalisation [12]. Additionally, the model should be practical for everyday use, particularly in primary care settings where many patients with mild COPD are treated.

The goal is to develop and externally validate such a model [13]. Assessing exercise capacity is critical as it offers valuable information about the severity of the disease, lean muscle mass, nutritional status, the requirement for rehabilitation and mortality risk. These tests provide essential data that help healthcare professionals make informed decisions regarding treatment and management strategies for COPD patients.

Aim: To develop a gender-based prediction equation to assess aerobic capacity in COPD patients with infections.

Primary objective:

- To construct a prediction equation for assessing the aerobic capacity in male COPD patients with infections.
- To construct a prediction equation for assessing the aerobic capacity in female COPD patients with infections.

Secondary objective:

- To determine the association between the six-minute walk distance and the FEV1/FVC ratio in COPD patients with infections.

Null hypothesis: There is no significant correlation between the six-minute walk test and PFT in predicting gender-based aerobic capacity in COPD patients with infections.

Alternate hypothesis: There is a significant correlation between the six-minute walk test and PFT in predicting gender-based aerobic capacity in COPD patients with infections.

REVIEW OF LITERATURE

Similar studies on the physical assessment tools in COPD patients is displayed in [Table/Fig-1] [9,11,13-19].

MATERIALS AND METHODS

The proposed study has a cross-sectional study design. COPD patients with infections will be recruited from the IPD of a tertiary care hospital (Maharishi Markandeshwar Institute of Medical Sciences

Authors	Objective	Study population	Outcomes	Conclusions
Karcıoğlu O et al., (2022) [11]	To investigate the role of 4-meter gait speed (4mGS) in evaluating exercise capacity in COPD.	23 COPD patients	1. 4mGS measurement 2. 6MWT distance 3. CPET – Cardiopulmonary Exercise Test 4. mMRC score – Modified Medical Research Council Dyspnoea Scale 5. CAT score – COPD Assessment Test 6. BODE index – Body Mass Index, Obstruction, Dyspnoea and Exercise Capacity Index	Easy applicability and reproducibility, 4mGS seems to be a strong candidate for daily clinical use in monitoring the exercise capacity of COPD patients. Further studies in larger patient groups are needed to support these results.
Minakata Y et al., (2021) [14]	To determine Reference Equations for Assessing the Physical Activity of Japanese Patients with Chronic Obstructive Pulmonary Disease.	227 COPD patients	1. Postbronchodilator spirometry 2. Grip strength 3. Upper arm circumference 4. Triceps branch subcutaneous fat thickness 5. modified Medical Research Council (mMRC) dyspnoea score 6. Hospital Anxiety and Depression Scale (HADS) 7. Blood tests	Using the PA-related factors of the 6MWD, mMRC, HADS-A, FEV1 %pred and partly age or Brain Natriuretic Peptide (BNP), we were able to create reference equations of four indicators of PA in Japanese patients with COPD. The predictive values calculated with these equations might be useful for setting the target PA value in each patient.
Nakanishi M et al., (2019) [15]	The aim of this study was to produce a simple standard equation for the daily step count using some factors that influence PA in Japanese patients with COPD.	162 COPD patients	1. Triaxial accelerometer 2. Spirometry was performed in the post-bronchodilator condition 3. mMRC dyspnoea scale 4. Active style Pro HJA-750C (HJA-750C; OMRON)	A simple standard equation for the step count in Japanese patients with COPD was created using age, mMRC and IC. This equation could provide the predicted value of steps in individual patients, especially for patients with <6500 steps/day.
Su KC et al., (2019) [16]	To develop a logit model by using easily assessed variables, including the age, smoking status, PEFR and CAT score, to estimate the probability of COPD (PCOPD) and clinically significant COPD. Moreover, the robustness of the final model was examined through sensitivity analysis.	301 COPD patients	1. CAT score 2. PEFR measurement 3. PFT	This prediction model can help physicians effectively identify at-risk, undiagnosed COPD patients for further diagnostic evaluation and timely treatment when spirometry is unavailable.
Machado FVC et al., (2018) [9]	To verify the agreement of different reference equations in classifying patients with Chronic Obstructive Pulmonary Disease (COPD) as having reduced or preserved 6MWD.	159 patients with COPD	1. 6MWT, used to evaluate the functional exercise capacity 2. Modified Borg scale (0-10)	Even reference equations from the same country vary considerably in the classification of reduced or preserved 6MWD and it is recommended that the region-specific ones be used as they give with higher agreement for similar and comparable interpretation of the patients' functional exercise capacity.
Carvalho LCS et al., (2018) [17]	To assess the correlation between easily accessible variables, usually available in clinical practice, such as the CATs and pulmonary function parameters and maximum aerobic capacity and to determine models for peak VO_2 estimation in COPD patients.	249 COPD subjects	1. VO_2 peak 2. Lung function test (FEV1) 3. CAT score 4. CPET	COPD patients' maximum aerobic capacity has a significant correlation with easily accessible and widely used clinical variables, such as the CATs and FEV1, which can be used to estimate peak VO_2.

Chen W et al., (2016) [18]	The objective of this study was to create and externally validate a probabilistic model to predict the individualised rate of decline in FEV1 over 11 years and the corresponding GOLD severity grades in current smokers with mild-to-moderate COPD.	5594 COPD patients	Pulmonary Function Test (FEV1 value)	This framework will allow clinicians to risk-stratify patients with mild-to-moderate COPD in terms of their future lung-function decline and to identify patients with rapid disease progression, who can be targeted for close follow-up and intervention.
Andrianopoulos V et al., (2015) [13]	To investigate the impact of several 6MWD reference equations for adults in patients with Chronic Obstructive Pulmonary Disease (COPD) and factors accountable for different 6MWD% predicted values.	2757 patients with COPD	1. 6MWT distance 2. Transcutaneous oxyhaemoglobin saturation (SpO_2%) 3. Heart Rate (HR)	The choice of 6MWD reference equation should consider the consistency of 6-min walk test operating procedures and at least be specific for the country/region of origin.

[Table/Fig-1]: Physical Activity assessment tools for COPD patients [9,11,13-19].

and Research, Ambala, Haryana, India) using purposive sampling. The FEV1/FVC ratio will be recorded using the post-bronchodilator PFT report, while aerobic capacity will be assessed through the 6MWT. The investigation will be conducted during the period from July 2024 to June 2025. Informed consent will be obtained and duly signed by COPD patients with infections before their recruitment into the present study.

The study protocol adheres to the principles outlined in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. The research protocol has received approval from the Institutional Research Advisory Committee (RAC) and ethical clearance has been obtained from the Institutional Ethical Committee (MMDU/IEC/2700) on 2 December 2023. The study has been registered on clinicaltrials.gov with the registration number Indian Council of Medical Research (ICMR)/2024/05/066979. The research will be conducted in accordance with the 2013 revision of the Helsinki Declaration and the 2017 National Ethical Guidelines for Biomedical Research Involving Human Participants [19].

The study aims to include COPD patients aged 30-80 years with exacerbations, specifically those with a post-bronchodilator spirometry FEV1/FVC ratio of <0.7, who are admitted to the Respiratory IPD and have stable vital signs for the duration of one year.

Inclusion criteria: Relevant information on COPD patients aged 30-80 years, of both genders, specifically those with a post-bronchodilator spirometry FEV1/FVC ratio of <0.7, who are admitted to the Respiratory IPD, will be extracted from the hospital records as documented in their files.

Exclusion criteria: The COPD patients who are haemodynamically unstable (experiencing hypoxia or hypercapnia), those with a history of exposure to smoke, individuals with clinically significant bronchial asthma and those receiving oxygen therapy will be excluded from the study.

Sample size calculation: The sample size was determined using the following calculation formula:

$$n=\{(Z\alpha+Z\beta)/C\}^2+3$$

Where $Z\alpha$ is the standard normal deviate for α, $Z\beta$ is the standard normal deviate for β and C was calculated as:

$$C=0.5\times\ln\{(1+r)/(1-r)\}$$

The correlation coefficient value (r=0.47) was obtained from a previous study [20]. Using the sample size calculation formula mentioned above, the minimum required sample size was determined to be n=30. Taking into account the patient footfall and the minimum sample size, a total of 80 patients will be recruited for the study. The data will be analysed using the SPSS version 26.0 software.

Primary Outcome

Six-Minute Walk Test (6MWT): The six-minute walk test is a widely analysed cardiopulmonary functional evaluation that allows for a comprehensive assessment of the multiple systems involved in physical activity. This test measures an individual's cardiopulmonary endurance and functional capacity by asking them to walk as far as they can within a six-minute time frame. The distance covered during the test provides valuable insights into their cardiovascular and respiratory fitness levels [21].

Pulmonary Function Test (PFT): Spirometry is a diagnostic test employed to evaluate an individual's respiratory function, specifically their ability to inhale and exhale air over time. One of the key outcomes derived from spirometry is the measurement of FEV1. The measurement of FEV1 is valuable for assessing and classifying the severity of obstructive lung diseases, including conditions such as asthma and COPD.

Secondary Outcome

mMRC: The mMRC (modified Medical Research Council) dyspnoea scale assesses breathlessness, particularly in patients with COPD. It evaluates the severity of dyspnoea based on daily activities. The scale ranges from 0 (breathless only with strenuous exercise) to 4 (too breathless to leave the house or even dress). The higher the grade, the more severe the breathlessness [15].

STATISTICAL ANALYSIS

Data will be analysed using IBM SPSS version 26.0. Demographics and outcomes will be checked for normality using the Shapiro-Wilk test. Depending on the data type, Chi-square, Spearman's, or Pearson's tests will be used to assess the associations or correlations between the FEV1/FVC ratio and the 6MWT. Multivariate linear regression with a step-wise approach will be used to create a predictive equation for aerobic capacity. Subsequently, a standardised equation for aerobic capacity will be derived.

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