PROTOCOL

Factors Affecting Survival in Severe and Very Severe COPD after Admission in ICUs of Tertiary Care Centers of India (FAST COPD): Study Protocol for a Multicentric Cohort Study

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide. However, there is a lack of comprehensive data from low- and middle-income countries (LMICs) regarding factors influencing COPD outcomes, particularly in regions where biomass exposure is prevalent.

Objective: The Factors Affecting Survival in Severe and Very Severe COPD Patients Admitted to Tertiary Centers of India (FAST) study aims to address this gap by evaluating factors impacting survival and exacerbation rates among COPD patients in LMICs like India, with a specific focus on biomass exposure, clinical phenotypes, and nutritional status in patients admitted to the Intensive Care Unit (ICU).

Methods: The FAST study is an observational cohort study conducted in university teaching hospitals across India. The study aims to enroll 1000 COPD patients admitted to the ICU meeting specific inclusion criteria, with follow-up assessments conducted every 6 months over a 2-year period. Data collection includes demographic information, clinical manifestations, laboratory investigations, pulmonary function tests, medications, nutritional status, mental health, and health-related quality of life. Adjudication of exacerbations and mortality will also be undertaken. The FAST study seeks to provide crucial insights into COPD outcomes in LMICs, informing more precise management strategies and mitigating the burden of COPD in these settings. By evaluating factors such as biomass exposure, clinical phenotypes, and nutritional status, the study aims to address key knowledge gaps in COPD research.

Keywords: Acute exacerbation, Intensive care unit, Malnutrition, Morbidity, Obesity, Phenotypes, Severe and very severe COPD, Survival.

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Highlights of the Study

- The study evaluates survival and exacerbation in severe chronic obstructive pulmonary disease (COPD) patients in ICUs in India, focusing on various clinical phenotypes based on risk factors as well as pathology, and nutritional status.
- It aims to enroll 1,000 patients for comprehensive data collection over 2 years, addressing a significant gap in COPD research in low- and middle-income countries (LMICs).
- Insights will guide a better understanding of outcomes and prognosis of different COPD phenotypes.

Introduction

The factors affecting survival in severe and very severe COPD patients admitted to Tertiary centers of India (FAST) is a multicentric study evaluating factors that affect survival in advanced COPD patients. Set in the backdrop of LMICs, the study encompasses patients having diverse etiologies for COPD, different ethnic backgrounds, and socio-economic status. The study aims to (1) evaluate the factors predicting survival and annual exacerbation

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rates in biomass COPD vs tobacco COPD, (2) distinct clinical phenotypes of COPD and their outcomes, and (3) study the effect of under and over-nutrition on the outcomes of COPD.

The goal of this study protocol is to detail the study rationale, methodology, and plan for statistical analysis.

Background

Literature and Studies

Chronic Obstructive Pulmonary Disease Burden Worldwide

Chronic obstructive pulmonary disease is one of the important non-communicable diseases that plague the world. Chronic obstructive pulmonary disease exacerbations are a major burden on patients, caregivers, and society as a whole. According to World Health Organization (WHO) estimates, worldwide, 65 million people have moderate to severe COPD.[1] In 2019, COPD was responsible for over 3.2 million deaths, accounting for 5% of the total worldwide mortality.[1] A recent systematic review reported a global prevalence of 10.3% (8.2–12.8%) in the age group of 30–70 years which translated to 391.9 million (312.6–487.9) people.[2] It is estimated to become the third leading cause of death worldwide by 2030 and the leading cause of death in 15 years; therefore, it is an important public health concern.[1,3] According to the Global Burden of Disease (GBD) data, COPD accounted for 5.8% (5.19–6.27%) of total deaths in 2019.[4] It disproportionately affected the elderly, accounting for 8.7% (7.78–9.48%) of total deaths in the age group of 70 years and above.[4] The morbidity from COPD is also significant worldwide. It accounted for 2.34% of total years lost to disease (YLD).[4] Elderly age groups (70 plus years of age) were more affected with 6.2% of total YLDs.[4] It accounted for 2.94% of total disability-affected life years (DALYs) lost.[4]

Chronic obstructive pulmonary disease also has substantial direct and indirect economic costs. The annual direct costs involved due to exacerbations (hospitalizations and emergency department visits), home oxygenation, and medications ranged from $540 to $9,981, as estimated by J Foo in 12 countries in 2016.[5] The annual indirect cost ranged from $979 to $20,844.[5] An annual societal cost per patient (calculated from combined direct and indirect costs) ranged from $1,721 in Russia to $30,826 in the USA.[5] A systematic literature review in 2020 reported a direct mean cost per patient per year between €1047 and €38,820.[6] The direct cost increased with increasing severity of COPD.[6]

COPD Disease Burden in LMICs in General and in India in Particular

Most of the data on COPD are from high-income countries.[1] It is also known that 90% of deaths occur in LMICs.[1] Chronic obstructive pulmonary disease due to smoking is common in high-income countries (HICs), whereas in LMICs it is due to biomass fuel exposure and household air pollution.[1] Burning of solid fuels like cow dung, wood, and charcoal serves as an energy source for cooking and lighting for a third of the world's population which translates to roughly three billion people in LMICs.[3] Household air pollution is estimated to account for four million deaths annually.[3] It is estimated that cooking with solid fuels is equivalent to smoking two packs of cigarettes/day.[3] A recent systematic review also consistently found the prevalence of COPD to be higher in LMICs when compared with HICs among the studies included for analysis.[7] The study also found the prevalence of COPD to be one of the highest in Southeast Asian countries despite the well-known underdiagnosis, misdiagnosis, and under-reporting.[7] Around 10% of AECOPD patients who are admitted with hypercapnic acidosis die in the hospital. For patients in need of mechanical ventilation, the mortality rate can reach 40%, and over a 3-year period, the general mortality rate can reach 49%. Thus, there is a need for data from LMICs to understand more about the outcomes related to severe COPD needing hospitalizations, and mortality among various clinical phenotypes of COPD to initiate steps to mitigate the adverse outcomes of severe COPD especially in LMICs.

Among LMICs, India is considered a particularly important nation to study the emerging burden of non-communicable diseases (NCD). Due to its large population and deteriorating risk factor profile linked to recent economic expansion, India is expected to witness the highest number of deaths from NCDs compared with any other country in the coming decade. According to a recent GBD study, the prevalence of COPD has increased from 3.3% in 1990 to 4.2% in 2016.[8] Chronic obstructive pulmonary disease contributed to 8.7% of total deaths and 4.8% of total DALYs in India, thereby becoming the second leading cause of disease burden in India.[8] In accordance with the rest of the world, the age-specific prevalence of COPD was highest among the elderly (80 years and older).[8] When compared with similar regions globally, the age-standardized DALYs were 2.3 times higher in India.[8] The study also found that the dominant risk

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factor for DALYs was air pollution (indoor and outdoor) followed by smoking.[8] A small cross-sectional study in India showed that COPD management during exacerbation accounts for 83% of the direct medical cost incurred and the other 17% is for chronic medications. The mean total direct medical cost was Rs. 29,885 and the direct non-medical cost was Rs. 7,441.25 in 2018.[9]

Biomass and Tobacco COPD

Biomass COPD

Worldwide, 3 billion people use coal and biomass fuel for heating and cooking. Exposure to biomass smoke is linked to a number of chronic lung conditions, including COPD.[10] Many studies have shown the mechanism by which biomass causes COPD. On acute exposure, there is more neutrophilic inflammation of the lung while subacute exposure produces predominantly eosinophilic, macrophagic, and lymphocytic response, and on chronic exposure, there is deposition of fibroblast and type 1 collagen. Several studies show a dose-response association between exposure to biomass smoke and the degree of airflow obstruction.[10] There is evidence suggesting that there is increased exacerbation of COPD on chronic exposure to Biomass.[10] Despite the huge burden of respiratory diseases linked to biomass smoke, the exposure is largely under-recognized globally, particularly in high-income nations. Around 2 million women and children are estimated to lose their lives every year due to biomass exposure.[10]

Tobacco COPD

Worldwide, smoking tobacco is a well-known risk factor for COPD.[11] Because of its inherent toxicity and irritability, tobacco smoke leads to an imbalance in the enzymes that break down proteins and antioxidants and an improper repair mechanism. Additionally, smokers experience an increase in inflammatory cells, specifically neutrophils, macrophages, and T lymphocytes, primarily $CD8^+$ T cells, which are cytotoxic.[11] As a result, following prolonged exposure to tobacco smoke, the lung becomes inflamed and thick in mucus, which makes it a prime location for bacterial and viral colonization. There is a dose–response association between exposure to tobacco smoke and the expiratory volume in one second (FEV1) reduction in COPD patients.[11] Morbidity and death from COPD can be predicted by the starting age of smoking, total number of pack years, and current smoking status. It is not surprising that active smoking exacerbates bacteria-induced airway inflammation in an additive way, increasing the frequency of exacerbations in patients with COPD.[11,12] The most effective and, frequently, the only method to slow the course of COPD is to stop smoking. Cessation of smoking slows down the decline in FEV1, even parallels that with the non-smokers, decreasing the progression of COPD.[11,12]

Clinical Phenotypes of COPD

A "phenotype" encompasses the discernible attributes of an organism arising from the interplay between its genetic makeup and environmental factors. Chronic obstructive pulmonary disease extends beyond the conventional classifications of emphysema and bronchitis, presenting a diverse spectrum of interconnected conditions delineated into many distinct phenotypes.[13–15] The nuanced clinical phenotyping of COPD serves as a valuable tool for healthcare practitioners, aiding in the identification of individuals who stand to gain therapeutic advantages from specific pharmacological interventions. The following phenotypes have been well recognized: (1) asthma-COPD overlap phenotype, (2) frequent exacerbator phenotype, (3) upper lobe predominant emphysema phenotype, (4) rapid decliner phenotype, (5) comorbid COPD phenotype, (6) physical frailty phenotype, and (7) emotional frailty phenotype.

Asthma-COPD Overlap Phenotype

The asthma-COPD overlap phenotype represents a confluence of COPD and asthma, traditionally considered separate entities with distinct pathophysiological bases. Determining whether chronic respiratory symptoms and airflow limitation stem from asthma, smoking-related COPD, or a combination of both can pose a diagnostic challenge, particularly in elderly individuals and smokers.[16] The hallmark of the asthma-COPD overlap phenotype lies in the presence of heightened airflow variability in individuals experiencing partially reversible airway obstruction. Identifying patients manifesting this overlapping phenotype holds clinical significance, aiding clinicians in making informed decisions regarding the appropriate course of medication.[17]

Frequent Exacerbator Phenotype

The occurrence of two or more exacerbations per year is a generally recognized criterion for the frequent exacerbator phenotype.[17] Frequent exacerbations have a significant negative impact, including an up to three-fold increase in mortality, a chance of developing depressive symptoms, a decline in lung function, a reduction in quality of life, and a decrease in physical activity.[18]

Upper Lobe Predominant Emphysema Phenotype

This is a genetically predisposed anatomic phenotype that is distinct because it may benefit significantly from surgical lung volume reduction (LVR).[16]

Rapid Decliner Phenotype

Patients who are relatively younger, without significant cardiovascular problems, who appear to experience a rapid loss in lung function, have poor nutrition and general health and have a high mortality rate, fall into the category of rapid decliner phenotype.[19] Aggressive disease management, including lung transplants, can potentially save lives and decrease mortality in these patients.

Comorbid Phenotype

Older adults with moderate respiratory disease and a significant comorbidity burden are referred to as having the comorbid phenotype. "Systemic COPD" characterized by a high body mass index and very high rates of diabetes, congestive heart failure, and ischemic heart disease falls under the Comorbid phenotype.[16]

Physical Frailty Phenotype

Characterized by loss of physiologic and cognitive reserve that has prognostic importance. Physical frailty phenotype is defined by "meeting 3 or more of 5 criteria (weakness, slowness, low level of physical activity, self-reported exhaustion, and unintentional weight loss) and the frailty deficit index (measured by cumulative deficits identified in a comprehensive geriatric assessment)."

Emotional Frailty Phenotype

The traits of emotional frailty in COPD patients like anxiety, depression, and fear of breathlessness are known to increase morbidity, mortality, hospitalizations, length of stay, and readmissions.[16]

There are many more COPD phenotypes being recognized. The phenotype identification will aid the physicians in better management and improved outcomes for patients with COPD.

Obesity and Malnourishment in COPD

Malnutrition is among the most common extrapulmonary manifestations of COPD.[20] Characterized by cachexia is lean body mass and weight loss is most commonly observed in advanced COPD patients.[21] Independent of its effects on FEV1, malnutrition, and weight loss are associated with poor prognosis. Nutritional status can be assessed by various means body mass index (BMI), fat-free muscle (FFM) mass, handgrip strength using a handheld dynamometer, cross-sectional area of rectus femoris muscle, and pennation angle using ultrasound. The BMI risk threshold is 21, and the fat-free mass index (FMI) risk threshold is 17 for males and 14 for women, respectively (FFMI).[21]

Malnutrition/Cachexia/Undernutrition

Patients with severe COPD are typically lean and frequently in a condition known as pulmonary cachexia, which is significant undernutrition.[22] Low body weight and low fat-free mass have been identified as negative prognostic variables in patients with COPD.[23,24] The prevalence of undernutrition is almost 25–40% as per few studies.[22,25] Moreover, acute exacerbations are more common in COPD patients with a BMI of less than 20 kg/m^2 than in those with a BMI of 20 kg/m^2 or more.[22] In patients with severe disease who are lean and have a FEV1% of less than 50%, the survival time is reported to be around 2–4 years.[22] Acute exacerbations of COPD in patients who were hospitalized showed a positive relationship between body weight and FEV1% and a negative correlation between BMI and length of stay.[26] Causes of undernutrition in COPD include energy deficiency resulting from reduced nutritional intake brought on by appetite loss linked to depression or dyspnea while eating.[27] Secondly, greater energy expenditure brought on by increased work of breathing may also contribute to undernutrition. Also, patients with COPD have higher resting energy expenditures (REEs), and this has also been shown in lean COPD patients.[22] Effects of humoral variables such as inflammatory cytokines, adipokines, and hormones on nutrition have been identified as the third main cause of undernutrition in COPD patients.[22]

Obesity

Data indicate that obese individuals with a diagnosis of COPD have a lower health-related quality of life (HRQoL) and more physical restrictions as a result of their respiratory symptoms.[28] Obesity is linked to elements that can exacerbate the dyspnea and wheezing symptoms that are caused by airflow obstruction, including decreased thoracic compliance, higher airway resistance, and increased work of breathing.[29] Overweight or obese patients with severe COPD who maintained or lost weight over 5 years had much better survival than those who gained weight during that time.[30] Though weight loss is considered to be a poor prognostic sign in COPD, it leads to better survival and improvement in symptoms of Obese COPD patients.[31]

Survival in COPD Patients

When compared with age and sex-matched controls, the 15-year survival in COPD patients is 7.3 vs 40%.[32] Survival also varies with the stage of COPD. For COPD stages I to IV, the 5-year survival rate is 24, 11, 5.3, and 0%, respectively.[32] Also, COPD patients suffer from significant comorbidities when compared with a matched cohort of the general population like cardiovascular diseases, osteoporosis, lung cancer, anxiety, and depression which decreases survival.[33,34] The hazards of death remained three-fold higher even after adjusting for comorbidities.[35] Thus, survival rates are poor for severe and very severe COPD patients.

Known Factors Affecting Survival

Known factors affecting survival in hospitalized COPD patients are older age, the severity of COPD (lower FEV1), extremes of BMI, presence of cardiovascular diseases, malignancy, diabetes, current smoking status, longer disease duration, higher frequency of exacerbations, presence of anxiety, and depression.[32,36–38] Patients with low albumin levels, low arterial partial pressure of oxygen, and high arterial partial pressure of carbon dioxide also have lower survival rates.[39] Patients with higher Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages, and higher scores on indices like the [body mass index (B), degree of airflow obstruction (O), degree of functional dyspnea (D), and exercise capacity (E)- (BODE)], age, dyspnea and airflow obstruction (ADO), baseline dyspnea index (BDI), and Charlson comorbidities index (CCI) also have lower survival rates.[37,40,41]

Unknown Factors Affecting Survival Needing Further Evaluation

Despite the current extensive literature about COPD, there are a few significant knowledge gaps. Firstly, we found several studies that have evaluated COPD patients in the Western world but most of them have captured data on patients who developed COPD after tobacco exposure and air pollution.[42–46] Torres-Duque et al. in their review have elucidated the different pathophysiology of biomass COPD vs tobacco COPD.[47] A systematic review and meta-analysis revealed 13 cross-sectional studies and 9 case-control studies on biomass COPD but most of the studies had a low sample size.[48] Thus, there is limited data on biomass COPD from LMICs. Secondly, there is emerging evidence of changes in the lung microbiome seen in COPD patients.[49] We do not know its effect on survival, although small studies have some association with change in genus affecting mortality.[49] Thirdly, data are scarce on malnourished vs normally nourished patients and obese and non-obese patients. Finally, it is now proven that COPD is a heterogeneous disease with clinically different phenotypes. Although GOLD classification recognizes three exacerbation phenotypes (A, B, and E) for the purpose of management, more than 50 different clinical phenotypes have been identified by various studies. However, many of these studies have been done in Europe with very little data from the Asian sub-continent. Hence, there is a need to identify clinically relevant phenotypes in LMICs which will help clinicians better categorize different phenotypes and effectively manage COPD exacerbations.

Rationale for this Study

The FAST is a prospective study that will enroll approximately 1,000 patients with severe and very severe COPD both due to biomass and

tobacco exposure and study factors that influence their survival. It is the first of its kind in South Asia to study these patients (to the best of our knowledge) with a special focus on nutritional status and infections. With the enrollment of a mixed population of urban and rural patients in India, the study will fill the knowledge gaps on disease characteristics and progression in biomass vs tobacco COPD, malnourished vs obese patients, and the effect of infectious and non-infectious exacerbations in these patients especially in LMICs. The present project also aims to identify different acute exacerbation phenotypes of COPD over a period of 2 years of follow-up. With accurate identification of these factors, clinicians can take steps to manage these patients with greater precision and help bring down the disease burden in LMICs.

Study Objectives

Primary Aims

Primary aim 1: To study the differences in survival and annual exacerbation rates between biomass COPD and tobacco COPD patients with severe and very severe COPD.

Hypothesis 1: There is a significant difference in the survival and annual acute exacerbation rates between biomass COPD and tobacco COPD patients with severe and very severe COPD.

Objective 1: To evaluate the factors predicting survival and annual exacerbation rates in biomass COPD vs tobacco COPD patients with severe and very severe COPD.

Secondary Aims

Secondary aim 1: To identify the distinct clinical phenotypes of COPD and their differences in survival and annual exacerbation rates.

Hypothesis 1: COPD is a heterogeneous disease with multiple phenotypes.

Objective 1: To identify different clinical exacerbation phenotypes in severe and very severe COPD and map their characteristics and disease progression over 2 years.

Secondary aim 2: To study the effect of under- and over-nutrition on the outcomes of COPD.

Hypothesis 2: Obese COPD subjects and malnourished COPD subjects have poorer outcomes than non-obese and normally nourished COPD subjects.

Objective 2: To evaluate the annual exacerbation rates and factors predicting survival in obese COPD vs non-obese COPD and malnourished vs normally nourished COPD patients with severe and very severe COPD.

Study Design

This is an observational cohort study.

Primary Exposures

The severity of COPD–severe and very severe categories as per GOLD definition.

Clinical Phenotypes

Number of exacerbations per year, the requirement of non-invasive or invasive mechanical ventilation during exacerbations, presence/absence of right heart failure, presence/absence of pulmonary hypertension and any other extrapulmonary organ involvement,

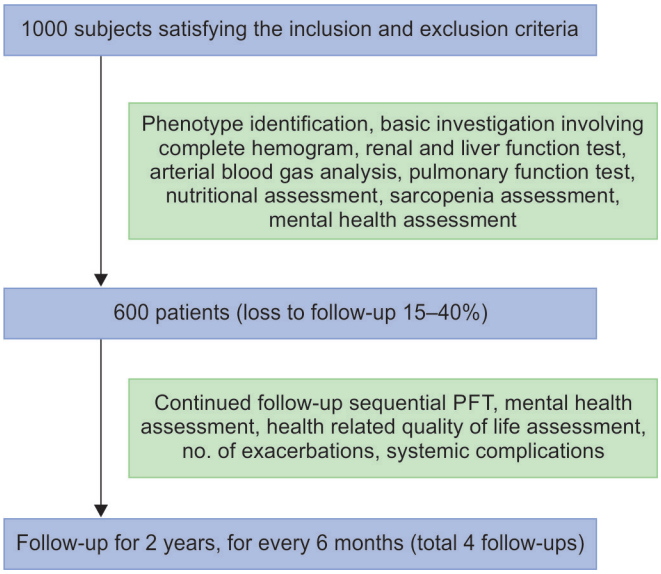

Fig.1: Flowchart of the study design

Table 1: The planned tests to be carried out during the follow-up for every six months

Schedule and planned tests to be carried out during the follow-up for every six months				
Tests and follow-up	*Visit 1*	*Visit 2*	*Visit 3*	*Visit 4*
1. PFT	√	√	√	√
2. ECHO	√	√	√	√
3. Lung scan	√	√	√	√
4. Hand grip	√	√	√	√
5. Muscle mass	√	√	√	√
6. Rectus femoris cross sectional area	√	√	√	√
7. HAM-A, HAM-D	√	√	√	√
8. SLI	√	√	√	√
9. SGRQ-C	√	√	√	√

ECHO, echocardiogram; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; PFT, pulmonary function test; SGRQ-C, St George's Respiratory Questionnaire-COPD; SLI, standard of living index

biomass/tobacco COPD, obese/non- obese COPD, malnourished or normally nourished COPD.

How the primary exposures would be assessed and severity quantified–the tobacco smoking exposure will be quantified by pack-years and the biomass exposure will be quantified by biomass index; the severity of COPD will be assessed by pulmonary function test (PFT) and graded as per the GOLD definition. Obesity will be defined as BMI >30 kg/m^2 and subclassified as Class I: BMI of 30 to <35 kg/m^2, Class II: BMI of 35 to <40 kg/m^2, Class III: BMI of 40 kg/m^2 or higher. Malnutrition will be defined as a BMI less than 18 kg/m^2 (Fig. 1 and Table 1).

Outcomes to be Assessed

- Primary outcome: The 2-year survival rates of tobacco vs biomass COPD, obese vs non-obese COPD, frequent vs infrequent exacerbations, malnourished vs normally nourished COPD.

- Secondary outcomes: In-hospital mortality, need for mechanical ventilation, length of hospital stay, health-related quality of life (assessed by SGRQ-C), BODE, and ADO indices.

The Key Covariates

- Microbiological covariates—The type of bacterial or viral infection, multi-drug resistant or pan-drug-resistant (multi-drug resistance is defined as "acquired non-susceptibility to at least one agent in three or more antimicrobial categories," and extensive drug resistance is defined as "acquired non-susceptibility to at least one agent in all but two or fewer antimicrobial categories"), secondary hospital-acquired pneumonia if any (as defined by American thoracic guidelines).
- Mental health—related factors are depression and anxiety
- Socioeconomic status (poverty)
- Occupation
- Presence of frailty—Frailty will be defined as "fulfilling three out of the five phenotypic criteria that indicate compromised energetics: weakness, slowness, low level of physical activity, self-reported exhaustion, and unintentional weight loss." It will be assessed by a Simple FRAIL questionnaire.

Study setting: The study will be conducted in university teaching hospitals in India which serve as the tertiary referral centers for the surrounding population.

Sampling strategy: Consecutive sampling of all subjects satisfying inclusion and exclusion criteria.

Study subjects: Subjects will be recruited from tertiary care university teaching hospitals each serving a large population. The following will be the inclusion and exclusion criteria.

Inclusion Criteria

- The COPD subjects with either a history of smoking of >10 pack years or biomass exposure of >60 BMI.
- There should be objective evidence of COPD diagnosis by means as suggested by GOLD criteria with a ratio of FEV1/FVC of less than 70%.
- Acute exacerbation of COPD requiring hospital admission for >48 hours.
- The COPD patients with severe and very severe disease as per GOLD stages III and IV.

Exclusion Criteria

- Absence of an adequate sputum specimen as determined by gram stain.
- Patients with chronic pulmonary disorders other than COPD.
- Unwilling to provide informed consent.
- Lack of cooperation for nutritional or mental health assessment.

Data Collection

Ethics committee approval was obtained from both sites before the commencement of the study (Approval number: JSSMC/IEC/13042022/07NCT/2021-22 dated 25-04-2022 and EC REG: ECR/134/Inst/KA/2013/RR-19 dated 18-06-2022). All participants are provided with study-related information and written informed consent is obtained prior to the study. The following information is being collected from participants including age, sex, height, weight, underlying co-morbid diseases, clinical manifestations, and laboratory investigations like complete hemogram, liver function tests, renal functions tests, admission arterial blood gas analysis, and radiological findings. Medications taken for COPD are noted. Pulmonary function test results are used to confirm the COPD at admission or within 3 months of discharge. Following a baseline data collection, subjects are followed-up physically (if funding is available) at a total of 4 visits every 6 months. All follow-ups will be via telephone only at an interval of 6 months. Additional information like the 6-minute walk test, BODE and ADO indices, hand grip strength, and frailty scoring will be collected on all follow-ups. In addition to the study visits, COPD patients are telephoned every 6 months between visits in order to assess exacerbation rates. Subjects are requested to visit the hospital in case of exacerbations. Echocardiography is done to note the cardiovascular status of the patient and the presence of corpulmonale if any.

The COPD patients will be sub-grouped into groups based on the blood and sputum investigations, i.e., bacterial or viral. Nutritional status will be assessed using BMI. Sarcopenia will be assessed using cross-sectional area and pennation angle of the rectus femoris muscle using bedside ultrasound whenever available. Health-related quality of life is assessed using the SGRQ-C questionnaire. Depression and anxiety are measured by HAM-A and HAM-D questionnaires. Socioeconomic status is recorded using the standard of living index (SLI). Patients will be followed-up for 2 years and during these years, the number of exacerbations, development of systemic complications, and organ involvement-pulmonary and extrapulmonary, nutritional status, mental health, and health-related quality of life will be recorded.

Data are collected independently by two investigators using standardized protocol and data collection forms from the patients/patient's attenders after taking consent, through daily hospital ICU visits. Data entry is being done by the three investigators on Google Sheets. The utilization of web-based data collection, entry, and processing enables the development of real-time status reports and data queries for investigators to monitor research data as well as real-time data modifications at the time of data input. Access to data will be limited to the principal investigator and three investigators involved in the study, thus maintaining the privacy of the patient's information. The patient's name and IP number were given a separate code hence nowhere disclosing the patient's personal information and protecting the privacy of patients. The study personnel who processed the samples were unaware of the clinical status and information of the patients.

Data Analysis

Data Expression

The Shapiro–Wilk test will be used to assess normality in the distribution of continuous data. Continuous data that adhere to a Gaussian distribution will be presented as means ± standard deviation. In contrast, continuous data not following a Gaussian distribution will be shown as the median (interquartile range 25–75%). For categorical data, data presentation will involve the number of cases along with their respective percentages.

Statistical Analysis

Nominal variable distributions will be analyzed using the Chi-square test. For assessing factors potentially related to in-hospital mortality, continuous variables between groups will be compared using the unpaired *t*-test. Previous research has identified factors like age, disease duration, smoking intensity (pack-years), hospital stay length, FEV1, FEV1/FVC ratio, arterial oxygen tension [Partial pressure of oxygen (PaO_2), Partial pressure of carbon dioxide

($PaCO_2$)], BMI, BODE index, serum albumin levels, and Charlson's comorbidity index as influential on survival. These factors, along with newly identified independent variables, will undergo multivariate logistic regression and Cox's proportional hazards analysis. The Pearson correlation coefficient will help evaluate the relationship between new independent variables impacting survival and the time since the first hospitalization. The Kaplan–Meier method will be employed for the survival analysis of all participants.

For distinguishing potential subgroups with unique phenotypes, cluster analysis will be performed. The receiver operating characteristic (ROC) curve analysis will determine which variables can differentiate patients within each cluster, with an area under the curve (AUC) >0.500 indicating significant discriminatory power. Youden's index will pinpoint cut-offs for enhanced specificity and sensitivity.

Kohen's kappa will evaluate the inter-observer and intra-observer variability among field workers at the study's outset, with a kappa value >0.7 deemed acceptable.

Study power: Assuming average ICU mortality of 15 and 11% in severe and very severe COPD, alpha of 0.05, beta 0.2%, and power of 80%, a sample size of 580 is required to assess the survivors in COPD. Due to logistical issues and expected loss to follow-up (10–15%), we will require more patients in this study for adequate power. Keeping in mind possible logistical issues like lack of consent, incomplete data due to lack of cooperation/difficulty in completing assessments like PFT, answering questionnaires, etc., we plan to screen and enroll 1000 patients during the study.

Discussion

The present study has great complexity, with interviews, measurements, and examinations, and the requirement of access to secondary health data. The patient's right to autonomy will be respected by obtaining consent from the patient if fit or from surrogates. Other rights such as preferring to not answer certain questions during the interviews, refusing to be submitted to examinations, asking for the substitution of the interviewer, or stopping participating in the research at any moment will be respected. However, minimum criteria for participation in the cohort will be established and these include answering specific blocks of the questionnaire, following protocolized care in ICU, blood and sputum sample collection, and ultrasound assessment. At every step, many factors influence the analysis of clinical samples, so we need to follow the standard procedure while collecting the sample, transportation, and processing of the clinical samples. If a person refuses to perform any of these, he/she will be informed that he/she cannot participate in the study, but routine care will not be affected. Preservation of confidentiality and secrecy will be ensured by electronic collection of data and it will be anonymized. Data will be stored in the Department of Respiratory Medicine, JSS. Data will be processed without personal identifiers. We are expecting a loss of subjects during follow-up. We are planning to minimize loss to follow-up to not more than 10% by appropriate counseling and support during follow-up. We expect the following types of bias; recall bias in history taking when asked for certain medical history. For example, smoking in pack-years, duration, and frequency of exacerbation of COPD over the past year. Hawthorne effect may alter nutritional status and smoking status over follow-up, which may lead to selective survival bias. With clear protocols and pre-specified criteria for inclusion and exclusion, and recruiting consecutive patients we plan to minimize selection bias. We are planning to minimize systematic bias by training the field workers and by using validated tools and standardized equipment to measure the clinical factors affecting survival (for example, the use of standardized questionnaires, ultrasound, and PFT equipment). To decrease interobserver bias during blood sample testing, it will be done in a single National Accreditation Board for Testing and Calibration Laboratories (NABL) accredited laboratory only. Inter-observer and intra-observer variability of laboratory workers, ECHO technicians, and sonographers assessing sarcopenia will be assessed by Kohen's kappa before the start of the study. An index of >0.7 will be considered acceptable to minimize inter-observer and intra-observer bias.

Data Availability Statement

All data generated or analyzed during this study are included in this article.

Ethical Approval

Institutional Review Board Statement: No animals were used for studies that were based on this research. This study was approved by the Institutional Ethics Committee of JSS Medical College, Mysuru (Approval number: JSSMC/IEC/13042022/07NCT/2021-22 dated 25-04-2022) and of Mysore Medical College and Research Institute (EC REG: ECR/134/Inst/KA/2013/RR-19 dated 18-06-2022).

Authors' Contributions

All authors of the paper have contributed to the design of the work, acquisition, analysis, and interpretation of the data. SA, SD, DSN, JBS, and PAM developed the research protocol. SA, SD, DSNS, MVG, IUH, JBS, DJC, SM, MKU, MS, and PAM were involved in the development of the intervention and design of the study. All authors have been involved in drafting the work or revising it critically for important intellectual content. All authors have read and approved the final manuscript for publication.

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