"CLINICAL EFFECTIVENESS OF TRIPLE DRUG THERAPY COMBINATION CONTAINING LABA, LAMA AND ICS IN NON-SMOKING COPD PATIENTS- A PROSPECTIVE STUDY OVER A PERIOD OF 12 WEEKS"

Submitted by

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J. N. MEDICAL COLLEGE,

BELAGAVI- 590010. KARNATAKA

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BSpatil

Dr.Bhagyashri Patil MD
Professor and Head,
Department of Respiratory Medicine
J.N. Medical College,
Belagavi – 590 010. Karnataka.

Professor & HOD
Dept. of Pulmonary Medicine
J.N. Medical College, Belgaum

Date: 27/6/24
Place: Belagavi

Dr. (Mrs.) N S Mahantashetti MD (Paed.)
Principal
J.N. Medical College,
Nehru Nagar,
Belagavi – 590 010. Karnataka.

PRINCIPAL
J.N. Medical College,
BELAGAVI- 590 010

Date: 27/6/24
Place: Belagavi

KAHER * BELAGAVI * J.N. MEDICAL COLLEGE

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Nehru Nagar, Belagavi- 590 010, Karnataka, INDIA

0831 - 2471350 0831 - 2470759 www.jnmc.edu rincipal@jnmc.edu

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Dr. (Mrs.) N.S. Mahantashetti.
Chairperson-Antiplagiarism Committee &
Principal,
J. N. Medical College, Belagavi.

PRINCIPAL
J.N. Medical College,
BELAGAVI- 590 010

To,
Reg. No. BR0121002
Postgraduate Student,
2021-22 Batch,
Department of Pulmonary Medicine
J. N. Medical College, Belagavi.

K.L.E. ACADEMY OF HIGHER EDUCATION AND RESEARCH
(Deemed – to- be- University)
Accredited 'A+' Grade by NAAC in (3rd Cycle) Placed in Category 'A' by MHRD (GoI)
JNMC INSTITUTIONAL ETHICS COMMITTEE
JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)
Website: http//www.jnmc.edu
E-Mail : dome@jnmc.edu
Phone: (+ 91-(0)831 Office : 2472550
Principal: 2471701
Fax No. +91 (0)831 – 2470759

Ref No.MDC/JNMCIEC/ 32 **Date: 27/09/2022**

To,

Dr. [redacted]
PG Student in Respiratory Medicine,
J. N. Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"CLINICAL EFFECTIVENESS OF TRIPLE DRUG THERAPY COMBINATION CONTAINING LABA, LAMA AND ICS GIVEN FOR 12 WEEKS IN NON- SMOKING CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS, PROSPECTIVE OBSERVATIONAL STUDY OVER A PERIOD OF 1 YEAR"** is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee.

(Dr. Smita Sonoli)
Member Secretary
JNMC Institutional Ethics Committee
J.N.Medical College, Belagavi.

(Dr. Harsha Hegde)
Chairman,
JNMC Institutional Ethics Committee
J.N.Medical College, Belagavi

LIST OF ABBREVIATIONS

COPD	Chronic Obstructive Pulmonary Disease
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
FEF25-75	Forced expiratory flow 25-75%
PEFR	Peak Expiratory Flow Rate
BMI	Body Mass Index
HRQOL	Health related quality of life
SGRQ	St. George Respiratory Questionnaire
6MWT	6 Minute Walk Test
6MWD	6 Minute Walk Distance
GOLD	Global Initiative for Chronic Obstructive Pulmonary Disease
RV	Residual Volume
TLC	Total Lung Capacity
FRC	Functional Residual Capacity
DLCO	Diffusing Lung Capacity for Carbon monoxide
mMRC	Modified Medical Research Council dypnoea grading scale
BODE	BMI, Obstruction of airways, Dyspnoea scale, Exercise capacity
PFT	Pulmonary Function Test
SpO_2	Peripheral capillary oxygen saturation
PR	Pulse Rate
SBP	Systolic Blood pressure
DBP	Diastolic Blood pressure
RR	Respiratory Rate
RS	Respiratory System
NVBS	Normal Vesicular Breath Sound
T2DM	Type 2 Diabetes Mellitus
IHD	Ischemic Heart Disease
URTI	Upper Respiratory Tract Infection
BPM	Beats per minute
RIC	Respiratory Infections in Childhood
QOL	Quality of Life

SITT	Single Inhaler Triple Therapy
OPD	Out Patient Department
IND/GLY	Indacaterol/ Glycopyrronium;
BDP/FF/G	Beclomethasone-Dipropionate, Formoterol-Fumarate, Glycopyrronium
CAT	COPD Assessment test
PTB	Pulmonary Tuberculosis
TT	Triple Therapy
SABA	Short acting Beta- Agonist
SAMA	Short acting Muscarinic Antagonist
LABA	Long-acting Beta Agonist
LAMA	Long-acting Muscarinic Antagonist
ICS	Inhaled Corticosteroids
MDI	Metered Dose Inhaler
DPI	Dry-powder inhaler
LTOT	Long Term Oxygen Therapy
FF/UMEC/VI	Fluticasone Furoate/Umeclidinium/Vilanterol
GFF	Glycopyrrolate/Formoterol Fumarate
BGF	Budesonide/Glycopyrrolate/Formoterol Fumarate

ABSTRACT

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a significant global health issue, characterized by persistent respiratory symptoms, including dyspnoea, cough, sputum production, and recurrent lower respiratory tract infections. These symptoms degrade the quality of life and precipitate acute exacerbations leading to hospitalizations. A unique subgroup, nonsmoker-COPD (NS-COPD), is defined by the absence of tobacco smoke exposure but includes other environmental or internal illnesses contributing to COPD. This study aims to evaluate the clinical effectiveness of triple therapy (LABA, LAMA, ICS) in managing NS-COPD.

OBJECTIVE

To evaluate the clinical effectiveness of triple drug therapy combination containing LABA, LAMA and ICS in non-smoking COPD patients

METHODS

This 12-month prospective observational study was conducted at KLE'S Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi, from February 2023 to January 2024. The study included 95 non-smoking COPD patients aged over 40 years, diagnosed according to the latest GOLD COPD guidelines, with post-bronchodilator FEV1 < 80% predicted and FEV1/FVC ratio < 0.70. Patients underwent 12 weeks of triple drug therapy and were assessed for clinical

effectiveness as assessed by spirometry, 6-minute walk tests, CAT scores, BODE index, and SGRQ scores.

RESULTS

This study assessed the clinical effectiveness of triple drug therapy (LABA, LAMA, ICS) in non-smoking COPD patients by comparing various health parameters before and after the 12-week treatment period. Statistical analyses were conducted using paired t-tests for continuous variables and chi-square tests for categorical variables. The results demonstrated significant improvements across multiple measures. The mean FEV1 increased significantly from 62.3% ± 4.1 to 68.7% ± 3.9 predicted, indicating enhanced lung function ($p < 0.001$). Similarly, the mean distance covered in the 6-minute walk test improved from 320.5 ± 45.2 meters to 365.7 ± 43.8 meters, reflecting better exercise capacity ($p < 0.01$). The CAT score showed a significant reduction from 18.4 ± 3.6 to 13.2 ± 3.1, indicating reduced symptom burden ($p < 0.001$). Additionally, the BODE index, decreased from 5.2 ± 1.3 to 3.8 ± 1.1 ($p < 0.01$), suggesting overall improvement in disease severity. The SGRQ score, measuring health-related quality of life, also saw a significant reduction from 52.5 ± 6.7 to 44.2 ± 6.1 ($p < 0.001$). These findings underscore the efficacy of triple drug therapy in improving respiratory function, physical endurance, symptom relief, and quality of life in non-smoking COPD patients.

CONCLUSION

Triple drug therapy (LABA, LAMA, ICS) is clinically effective in managing non-smoking COPD patients. It significantly improves respiratory symptoms, enhances exercise capacity, and leads to better overall health outcomes. These findings

support the inclusion of triple therapy in treatment guidelines for NS-COPD, addressing a critical need for evidence-based management strategies in this specific patient population.

KEY WORDS:

Non-smoker COPD, Triple drug, BODE-index, SGRQ score, Quality of life

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) poses a significant worldwide health challenge, impacting millions of individuals globally. It is characterized by persistent respiratory symptoms, including dyspnoea, cough, production of sputum, and recurrent infections of the lower respiratory tract, alongside limitation of airflow. These symptoms degrade the patient's quality of life along with precipitating acute exacerbations, leading to hospitalizations and further deterioration of pulmonary function.

The projections indicate a worsening global burden of COPD, which is anticipated to be the fourth most common cause of mortality by 2040.[1] One of the foremost challenges in COPD management is the pervasive impact of dyspnoea on daily functioning. Activity-related dyspnoea is a common occurrence among COPD patients, leading to diminished physical activity and often culminating in a sedentary lifestyle. This perpetuates a cycle of deconditioning and declining lung function, emphasizing the need for tailored interventions to enhance functional capacity and improve quality of life.

A unique subgroup of COPD known as nonsmoker-COPD is characterized by the absence of exposure to tobacco smoke. This classification does not, however, exclude nonsmokers from being exposed to other environmental toxins or internal illnesses, which can also play a substantial role in the onset and progression of COPD. Out of all the environmental exposures, indoor air pollution from biomass fuels stands out as being especially important for nonsmokers with COPD. Comprehending the significance of environmental exposures is imperative in

clarifying the fundamental mechanisms and risk factors that contribute to COPD in nonsmokers.[2]

Papi et al studied the risk-benefit of dual bronchodilation (indacaterol, glycopyrronium; IND/GLY) against inhaled triple treatment (BDP/FF/G) in patients with COPD was compared. The randomized, double-blind experiment, which took place in 17 different countries, included 1,532 patients who had severe airflow limitation and symptomatic COPD. For 52 weeks, patients were given BDP/FF/G twice a day or IND/GLY once a day. Findings indicated that BDP/FF/G successfully lowers exacerbation rates in COPD patients without raising the risk of pneumonia. Specifically, compared to IND/GLY, BDP/FF/G considerably reduced the rates of moderate-to-severe exacerbations (0.50 vs. 0.59 per patient per year), with a rate ratio of 0.848 ($p=0.043$).[3]

In the TRINITY trial done by Vestbo et al. [4] a double-blind, randomized-control study, 2,691 individuals with a history of exacerbations and severe COPD examined the effectiveness of BDP/FF with tiotropium (open triple) and extra-fine (BDP/FF/GB) with tiotropium. Patients were assigned to 52 weeks of treatment with tiotropium, fixed triple, or open triple after a 2-week run-in with the drug. The fixed triple therapy improved pre-dose FEV1 more than tiotropium (0.57) and had lower exacerbation rates (0.46) (mean difference 0.061 L; $p<0.0001$). The research findings indicate that patients with symptomatic COPD may improve clinically from fixed triple treatment in comparison to tiotropium.

Few studies have documented the benefits of triple medication therapy, which consists of LABA, LAMA, and ICS, for individuals with COPD.[5–8]

When compared to their smoking counterparts, never-smokers with COPD have less chronicity of respiratory symptoms and limitations in airflow. However, despite this seemingly less severe presentation, the prognosis for never-smokers remains dismal, with an increased incidence of exacerbations. Despite this, there remains a significant gap in clinical data regarding the effectiveness of triple drug combinations containing long-acting β2-agonists (LABA), long-acting muscarinic antagonists (LAMA), and inhaled corticosteroids (ICS) in non-smoking COPD patients.[9]

This lack of comprehensive clinical evidence poses a challenge in developing optimal management strategies tailored to the needs of non-smoker COPD patients. By conducting clinical research to evaluate the safety and effectiveness of triple drug combinations in this specific population, we hope to close these information gaps. The results of this investigation will offer important new information on how well triple therapy works to control COPD symptoms and lower the chance of exacerbations in nonsmokers. This will therefore aid in the creation of evidence-based guidelines and suggestions for the treatment of COPD in people who do not smoke.[2,10–12]

Ultimately, this study will play a crucial role by bridging this knowledge gap, and will help to prioritize optimal management strategies and enhance outcomes for this often-overlooked population subset of COPD in non-smoking population.

OBJECTIVES

Primary Objective:

- To evaluate the clinical effectiveness of triple drug therapy combination containing LABA, LAMA and ICS in non-smoking COPD patients

REVIEW OF LITERATURE

DEFINITION OF COPD

The term "chronic obstructive pulmonary disease" refers to a variety of lung conditions that are characterized by persistent, frequently progressive airflow obstruction caused by abnormalities of the airways (bronchitis, bronchiolitis), alveoli (emphysema), and/or respiratory symptoms (dyspnoea, cough, sputum production, and/or exacerbations.[13]

BURDEN OF COPD

COPD stands as a formidable global health challenge, with its prevalence and impact on mortality continuing to rise. Current estimates suggest that over 210 million individuals worldwide are affected, making it one of the most prevalent diseases globally.[14]

Shockingly, COPD currently ranks as the fourth leading cause of death worldwide, but projections from the World Health Organization (WHO) indicate that by 2030, it will ascend to become the third leading cause of death.[15]

Global research projects, including the 12-site, 9,425-subject Burden of Obstructive Lung Disease (BOLD) study, have provided insight into the prevalence patterns of COPD in various geographic areas.[1]

For GOLD stage II or above, the study indicated an overall frequency of 10.1% for COPD, with a higher prevalence among men (11.8%) compared to women (8.5%).[16]

Although COPD incidence varies greatly between nations, trends suggest a greater incidence among older populations, particularly those aged 75 years and above. Similar incidence trends between men and women throughout time have been observed by studies done in the USA and Canada. However, regional variations

exist, as evidenced by findings from Australia where the incidence decreased among men but showed an increase among women.[1]

China and India bear a substantial burden of mortality in patients diagnosed as COPD, with mortality rates ranking among the highest globally. According to the WHO Global Infobase, the estimated age-standardized death rate per 100,000 individuals exceeds 64.7 in these countries. Extrapolating from this data, it is estimated that India alone accounts for approximately 5,56,000 annual COPD cases, representing 20% of global cases.[17]

The prevalence of the disease in India has been the subject of several studies over many years, shedding light on the burden of this disease across different regions and demographic groups.

One of the landmark studies in recent years is the INSEARCH study, conducted from 2004 to 2006. This large-scale study involved over 85,000 men and 84,000 women from urban and rural areas across India. According to the study, the prevalence of chronic bronchitis in individuals over 35 was found to be 3.49% overall, with notable regional variances found in Thiruvananthapuram (10%) and Mumbai (1.1%). According to this survey, there are 14.84 million cases of chronic bronchitis in the country.[18]

Furthermore, the INSEARCH study identified several risk factors associated with COPD, including smoking and exposure to biomass fuels or firewood for cooking. Researchers discovered that smokers were three times more likely to acquire COPD than non-smokers, and that bidi smokers were more at risk (8.2%) than cigarette smokers (5.9%).[19]

Additionally, those who cooked with kerosene and/or biomass fuels had a higher prevalence of COPD (up to 5%) than people who used LPG.[20]

Overall, these studies underscore the significant burden of COPD in India, highlighting the need for targeted interventions to address risk factors and improve management strategies for this debilitating disease. Continued research and surveillance efforts are essential for better understanding and effectively combating COPD in the Indian population.

EPIDEMIOLOGY OF NON-SMOKER COPD

For more than 50 years, tobacco use has been recognized as a risk factor for COPD. Almost all of the understanding of the disease's clinical, physiological, pathological, and radiological characteristics, as well as the rates at which lung function declines and the effectiveness of different treatment options, is based on this population. It was found in 1990 that never-smokers belonged between 25 and 45 percent of people with COPD.[20]

Just 35% of COPD cases worldwide are caused by smoking, according to the Global Burden of Disease report of 2017, with the majority of these instances occurring in high-income countries.[21]

The remaining 65% of nonsmokers with COPD are primarily found in low- and middle-income nations worldwide.

COPD AETIOLOGY

COPD development and progression are influenced by various factors, including:

Table-1: Risk factors of COPD	
Host-based factors	**Environmental-factors**
1. Genetic factors	1. Smoking
2. Asthma/airway hyperreactivity	2. Occupational exposure

	3. Air pollution
	4. Childhood respiratory infections
	5. Low socioeconomic status

❖ **Host-based Factors:**

➢ Genetic Factors**:** Certain genetic predispositions can increase susceptibility to COPD, although environmental factors often play a significant role.

➢ Asthma/Airway Hyperreactivity**:** Individuals with a history of asthma or heightened airway reactivity may be at increased risk of developing COPD.

Other than smoking, it is the second most important risk factor for COPD, making for 15–17% of new cases in young adults.[22]

❖ **Environmental Exposures:**

➢ Smoking:

Cigarette smoking is the primary environmental risk factor contributing to mortality associated with chronic bronchitis and emphysema, the two main components of COPD. Longitudinal studies consistently demonstrate a dose-response relationship between cigarette smoking intensity and the accelerated decline in lung function, particularly measured by forced expiratory volume in one second (FEV1), over time. Individuals who smoke heavily or over a prolonged period tend to experience a more rapid decline in lung function compared to occasional or non-smokers. As individuals age and continue smoking, the risk of developing COPD rises significantly. Historically, there was a higher prevalence of smoking among males, resulting in a higher incidence of COPD in men. However, as smoking rates have become more balanced between genders, the disease burden has also shifted, with COPD

becoming increasingly prevalent among females. Despite this shift, COPD remains more prevalent in males overall due to historical smoking patterns.[23]

Pack years, a measure of cumulative cigarette-smoke exposure, is considered to be the best predictor of FEV1 decline. However, only a relatively small portion of the variability in FEV1 can be explained by pack years alone, suggesting that additional environmental and genetic factors play a role in the development of airflow obstruction. While the evidence linking cigar and pipe smoking to COPD is not as robust as that for cigarette smoking, these forms of tobacco use may also contribute to the development of the disease, albeit to a lesser extent. In summary, cigarette smoking represents the single most significant environmental risk factor for COPD, exerting its detrimental effects through a dose-response relationship with lung function decline. Despite efforts to reduce smoking rates, the burden of COPD remains substantial, underscoring the need for continued public health interventions aimed at smoking prevention and cessation.[24]

- Non-Smoking Factors: While smoking is the primary risk factor, non-smoking-related exposures such as biomass smoke from cooking and heating fuels, occupational pollutants, and environmental air pollution also contribute to COPD risk.

UNDERSTANDING NON- SMOKER COPD

Nonsmoker COPD represents a distinctive subset of COPD which is characterized by the absence of tobacco-smoke exposure. However, this designation does not preclude exposure to other environmental pollutants or endogenous ailments, which can significantly contribute to the development and progression of COPD among nonsmokers. Among the various environmental exposures, biomass fuel exposure

emerges as a particularly significant indoor air pollutant associated with nonsmoker COPD. Understanding the role of environmental exposures is essential for elucidating the underlying mechanisms and risk factors contributing to nonsmoker COPD.[2]

❖ **Prevalence and Risk Factors**

Population-based studies have revealed a low incidence and prevalence of nonsmoker COPD compared to smoker COPD. However, despite the absence of tobacco smoke exposure, nonsmoker COPD is significantly associated with other risk factors, including biomass exposure, treated pulmonary tuberculosis (PTB), and various environmental and occupational exposures.[10]

25–45% of COPD diagnoses are attributable to non-smoking, which is far more than doctors often anticipate.[21]

These risk factors may vary geographically, with differences observed between Western and non-Western populations.

According to Hnizdo et al [25] the work-related fraction of COPD development in never-smokers is estimated to be 31.1%, with the majority of vocations related to the handling, stocking, and transportation of materials used in building and processing.

In Western countries, nonsmoker COPD prevalence tends to be lower compared to non-Western regions, reflecting differences in environmental exposures, healthcare infrastructure, and socioeconomic factors. However, biomass fuel exposure and other environmental pollutants remain relevant risk factors for nonsmoker COPD, particularly among certain demographic groups or in communities with limited access to clean energy sources.[26] Numerous investigations have clarified that COPD-related consequences are caused by occupational exposure to dust, fumes, coal, or volatile chemicals.[10]

Hagstad, S. et al.[27] in his study found workplace exposure to gas, dust, or fumes is a significant risk factor for COPD prevalence and risk factors among never-smokers in two regions of Sweden.

In addition to cigarette smoking, there are several other environmental risk factors associated with the development of chronic obstructive pulmonary disease (COPD), particularly in non-smokers. While cigarette smoking remains the primary cause of COPD worldwide, non-smokers can also develop the disease due to various environmental exposures and genetic predispositions.[23]

- Occupational Exposure:

One significant environmental risk-factor for COPD in non smoking population is occupational exposure to harmful substances such as chemicals, dust and toxic fumes. Individuals who work in sectors including manufacturing, construction, mining, and agriculture may be exposed to airborne pollutants that over time can harm the lungs and cause the disease.

Exposure to these occupational hazards without adequate respiratory protection can increase significantly the risk of development of the disease.[28]

According to reports, the population-attributable risk of COPD exposure at work is between 12 and 55 percent.[29]

Some of the occupational exposures, identified so far have a significant risk factor for COPD include dust exposure from coal, hard rock, concrete, building, tunnelling, brick, iron and steel founding, crop and animal farming, gold mining, chemicals (textiles, plastics, rubber industry, leather-manufacturing), diesel-exhaust, and road dust (sweeping). These occupations often involve exposure to airborne pollutants that can lead to airway obstruction and increased respiratory symptoms over time.[30]

In a study by P.D. Blanc et al[31] exposure to the environment and at work has a substantial impact on the occurrence of COPD in nonsmokers. Specifically, for every 10 percent increase in exposure prevalence, the prevalence of COPD rises by 0.8 percent, indicating that occupational risks are a major contributing factor to the development of the disease in non-smokers. Additionally, it has been found that a 20 percent relative reduction in the disease burden may be reached with an 8.8% drop in occupational exposure prevalence, implying that lowering these exposures could significantly lower the incidence of COPD.

- Biomass fuel

Patients with COPD who do not smoke frequently had exposure to biomass fuel smoke in the past. Pollutants that cause lung damage and COPD are released when fuels like wood, crop residues, and animal dung, are commonly used for cooking and heating purposes in households without access to clean energy sources. Studying this exposure contributes to our understanding of the distinct traits and clinical manifestations of nonsmoker COPD.[32]

Biomass fuels for cooking has been regularly utilised by 2800 million people and more.[33]

Around 90% of rural and one-third of urban homes in countries like India use biomass fuels for cooking and heating. The percentage in rural areas varies widely between countries and regions, ranging from 30% to 75%. In fact, indoor air pollution from biomass fuel used for cooking kills about 1.5 million people worldwide each year from lung cancer, chronic respiratory conditions, and pneumonia.[34]

2.9% of fatalities globally and 3.7% of the burden of illness and mortality in emerging nations are attributable to biomass fuels.[35]

A cross-sectional investigation showed that exposure to biomass smoke was linked to minor airway constriction and increased air trapping[36] and was also seen in another study from India by Salvi et al.[37]

Indoor air pollution from biomass fuels used for cooking and heating is another important risk factor for COPD, particularly in low- and middle-income countries where access to clean energy sources may be limited.[38]

The use of biomass fuel is one of the most significant non-tobacco risk factors, affecting about 3 billion people globally. This number is found to be higher in developing nations, where it may impact over 80 percent of the population. Since the incidence of biomass fuel usage is higher in developing nations, the amount of COPD caused by exposure to biomass-smoke may have been overestimated. The rate of exposure is about 3 times higher than that of cigarette-smoking. When compared to patients with smoking-related COPD, these biomass smoke exposure-related COPD patients are more likely to be female, have higher lung function, but similar symptoms, exercise capacity, and life quality.[39]

Women particularly due to prolonged exposure to smoke from biomass combustion used for cooking purposes has emerged as a major risk-factor of the disease. Biomass fuels like wood, dung, and crop residues release harmful pollutants when burned indoors, leading to respiratory symptoms and reduced lung function over time. Furthermore, second-hand smoke, often referred to as passive-smoke exposure, has been connected to a decline in lung function; however, its exact significance in the development of severe airflow-limitation in COPD is still unknown and needs further research.[40]

There is a substantial correlation between the development of COPD and certain activities that include exposure to harmful gases at work, grain dust on farms[41] and fumes and dust in factories, have observed a strong-association with the development of COPD.[42]

- Air Pollution:

Prolonged exposure to indoor and outdoor air pollutants, including particulate matter, gases, and volatile compounds, is associated with an elevated risk of COPD.

Industrialization and urbanization have led to increased levels of air pollution in many areas, which has been associated with a higher prevalence of COPD, particularly in urban settings compared to rural areas. Women and children who spend significant time indoors near open fires or inefficient stoves are particularly vulnerable to the adverse effects of indoor air pollution. Outdoor air pollution, including particulate matter, nitrogen dioxide, sulphur dioxide, and ozone, is also associated with an increased risk of COPD exacerbations and progression in non-smokers. Exposure to traffic-related pollution, industrial emissions, and environmental tobacco smoke (second-hand smoke) can contribute to chronic airway inflammation and respiratory symptoms, even in individuals who do not smoke themselves.[43]

Only women showed a statistically significant correlation between traffic exposure and poor lung function, according to a cross-sectional cohort research.[44]

Schikowski et al. [45] in a 3-year follow up study examined relationship between the annual mean concentrations of PM and NOx and the prevalence of COPD; however no significant relationship was seen. Only in female patients NO2, NOx, PM10, and

traffic indicators indicate a significant correlation with COPD, according to a meta-analysis involving 6550 individuals.[46]

Doiron et al.[47] found that while PM2.5, PM10, and NO2 concentrations were significantly connected with the prevalence of COPD, but PMcoarse concentrations were not in a cross-sectional study involving 30,887 individuals exposed to air pollution between the ages of 40 and 69.

- Genetic factors

Deficiency of Alpha-1-antitrypsin, a hereditary condition defined by low levels of a protective protein in the blood, can predispose individuals to early-onset COPD, even in the absence of smoking or significant environmental exposures. While smoking cigarettes continues to be the world's top cause of COPD, non-smokers can also develop the disease due to occupational exposures, indoor and outdoor air pollution, and genetic predispositions. Recognizing and addressing these additional risk factors is crucial for preventing COPD and reducing its burden, particularly in populations where smoking rates are low or declining.[48]

- Childhood Respiratory Infections:

Early-life exposure to respiratory infections, particularly during critical developmental stages, may predispose individuals to COPD later in life.

In a study by Roberts M et al.[49] 43% of the COPD group consisted of individuals who had never smoked. This highlights that factors other than smoking, such as severe childhood asthma, can significantly contribute to the development of COPD.

- Socioeconomic Factors:

Low Socioeconomic Status: Individuals from socioeconomically disadvantaged backgrounds, characterized by inadequate access to healthcare, poor living

conditions, and limited resources, may face heightened COPD risk due to increased exposure to environmental pollutants and reduced access to preventive measures and healthcare services.

Understanding and addressing these multifactorial influences is crucial for effective COPD prevention, management, and public health interventions. Efforts to mitigate COPD risk should encompass comprehensive tobacco control measures, occupational safety regulations, pollution reduction strategies, early-life respiratory health interventions, and initiatives to alleviate socioeconomic disparities in healthcare access and environmental exposures.

❖ **Understanding the Complexity of Nonsmoker COPD**

1. Exploring Etiological Diversity

Nonsmoker COPD encompasses a spectrum of aetiologies beyond tobacco exposure. Environmental pollutants, such as biomass fuel smoke, diesel exhaust, and indoor air pollution, play a significant role in nonsmoker COPD development, particularly in regions where these exposures are prevalent. Additionally, occupational hazards, respiratory infections, genetic factors, and socioeconomic determinants contribute to the multifactorial nature of nonsmoker COPD. Understanding the diverse aetiologies is crucial for tailored management approaches.

2. Unravelling Pathophysiological Mechanisms

While the pathophysiological pathways underlying smoker COPD are well-studied, the mechanisms driving nonsmoker COPD are still being elucidated. Biomass smoke exposure, for example, can lead to airway inflammation, oxidative stress, and lung tissue remodelling, contributing to airflow limitation and respiratory symptoms. Research efforts are focused on unravelling the specific pathophysiological

mechanisms unique to nonsmoker COPD to identify novel therapeutic targets and interventions.[50]

❖ **Clinical Heterogeneity and Presentation**

1. Variability in Clinical Presentation

Nonsmoker COPD often presents with clinical features similar to smoker COPD, including cough, dyspnoea, and sputum production. However, certain characteristics may distinguish nonsmoker COPD cases, such as earlier onset of symptoms, lower burden of smoking-related comorbidities, and differential response to standard treatments. Recognizing these nuances is essential for accurate diagnosis and personalized management strategies.

2. Challenges in Diagnosis and Recognition

Diagnosing nonsmoker COPD presents challenges due to the absence of a smoking history and overlapping symptoms with other respiratory conditions. Clinicians must consider alternative risk factors, such as environmental exposures and occupational hazards, in nonsmoker individuals presenting with respiratory symptoms. Improved diagnostic tools, including advanced imaging modalities and biomarker assays, may enhance the accuracy of nonsmoker COPD diagnosis.[51]

Nonsmoker COPD represents a complex and heterogeneous disease entity with diverse aetiologies, clinical presentations, and prognostic implications. While the recognition of nonsmoker COPD has grown in recent years, there remains an urgent need for clearer guidance, increased awareness, and collaborative research efforts to address the unique challenges and unmet needs of this patient population. By advancing our understanding of nonsmoker COPD, tailoring diagnostic and

treatment approaches, and strengthening collaborative efforts, we can improve outcomes and enhance the quality of life for individuals affected by this under-recognized form of COPD.

PATHOGENESIS

1. Inflammation and extracellular matrix proteolysis:

The oxidants found in cigarette-smoke activate the macrophages along with alveolar epithelial cells, triggering an inflammatory reaction. This results in the production of proteinases and chemokines like MMPs, IL-8, and TNF-α, and recruits the neutrophils to the site of inflammation. CD8+ T cells release IP-10 (CXCL7), stimulating macrophages to produce MMP-12. MMPs and serine proteinases degrade the extracellular matrix, causing lung tissue destruction in COPD.[52]

Autoimmunity could accelerate the course of COPD. In lung tissue, advanced patients frequently have higher numbers of B cells and lymphoid follicles, a sign of immunological dysregulation. This exacerbates inflammation and adds to the pathophysiology of COPD. Chronic COPD inflammation is characterized by high levels of CRP, IL-6, and fibrinogen, and it can be both systemic and localized. Osteoporosis, muscular atrophy, and cardiovascular disease are comorbidities associated with systemic inflammation in people with COPD. Additionally, the oxidants in cigarette smoke outweigh the antioxidants in the lungs, damaging lipids, proteins, and DNA in the process, hence extending inflammation and limiting lung healing. Comorbidities and progress of COPD are driven by immunological dysregulation, oxidative stress, and inflammation.[53]

2. Cell death

Oxidants in cigarette smoke cause lung cell death by inhibiting mTOR, leading to inflammation. Normally, macrophages clear apoptotic cells and promote repair. Cigarette smoke disrupts this, impairing macrophage function and cell clearance, resulting in prolonged inflammation and lung tissue destruction. Accumulated apoptotic cells worsen inflammation and perpetuate oxidative stress, creating a cycle of damage and impaired repair in COPD.[53]

Dysregulated cell death in COPD damages the lungs and causes systemic inflammation, leading to comorbidities like cardiovascular disease and muscle dysfunction. Understanding these mechanisms can help develop therapies to preserve lung function, promote repair, and reduce inflammation, potentially slowing COPD progression and improving outcomes.[54]

3. Ineffective repair

Chronic inflammation in COPD perpetuates tissue damage and disrupts the balance between repair and degradation. Ageing further impairs repair by reducing the regenerative capacity of lung stem cells. This decline in repair mechanisms is worse in elderly individuals with COPD, leading to a progressive decline in lung function and respiratory symptoms. Targeting repair and regeneration pathways could help restore lung function and slow disease progression. Reducing exposure to environmental toxins, such as through smoking cessation & pollution control, is also essential for promoting effective lung repair. [55]

4. Systemic Inflammation in COPD:

In severe COPD or during exacerbations, systemic inflammation is evident from elevated cytokines, acute phase reactants, chemokines, and abnormal cell lines. The exact cause is unclear; it may stem from lung inflammation, develop independently, or be linked to comorbid conditions.[56]

Systemic inflammation in COPD can worsen the disease and exacerbate comorbidities. Serum C-reactive protein, leukocytes, and fibrinogen elevations raise the risk of diabetes, lung cancer, and cardiovascular disorders. Studies employing indicators such as CRP, fibrinogen, leukocytes, TNF-α, Interleukin-6, and CXCL8 reveal that 70% of people with COPD exhibit inflammation, with 16% enduring persistent inflammation, thereby linking to more frequent exacerbations, higher mortality, and faster lung function decline.[57]

Additionally, dysregulated signalling pathways in COPD disrupt normal repair processes. Inflammatory pathways, abnormal growth factors and cytokine production interfere with lung repair and remodelling, exacerbating tissue damage.[58]

PATHOLOGY

In those with COPD, exposure to cigarette smoke affects the alveoli, small airways (≤2 mm diameter), and large airways. Changes in the large airways are the main cause of cough and sputum, but small airways and alveoli also play an integral part in physiological changes. Although the link and relative contributions of small airway disease and emphysema to pathophysiology differ throughout individuals, most COPD patients exhibit both conditions.

- LARGE AIRWAYS:

In COPD, the large airways, including the trachea and bronchi, undergo significant pathological changes. Metaplasia of the goblet-cells transforms specialized airway epithelial cells into cells secreting mucus due to chronic irritation and inflammation, increasing mucus production and causing chronic cough and sputum. Stimuli for goblet-cell metaplasia include neutrophil elastase, bacterial lipopolysaccharides (LPS), pro-inflammatory cytokines like Interleukin-1β, TNF-α, and cigarette smoke-induced oxidative-stress.

Chronic cigarette-smoke exposure also causes squamous metaplasia, where columnar epithelial cells convert into squamous cells. Although protective, this disrupts mucociliary clearance, impairing mucus and debris removal. Squamous metaplasia also increases the risk of lung cancer, especially in smokers.[59]

- SMALL AIRWAYS:

The small airways, also known as bronchioles, play a crucial role in regulating airflow and gas exchange within the lungs. In COPD, these airways become narrowed and obstructed due to inflammation, fibrosis, and smooth muscle hypertrophy. Chronic exposure to cigarette smoke and other environmental pollutants triggers an inflammatory response in the small airways, leading to the recruitment of immune cells such as neutrophils and macrophages. One hallmark feature of the involvement of small-airway pathology in COPD is epithelial goblet cell metaplasia. Normally, these airways are lined with Clara cells that secrete surfactant, a substance that helps maintain the airway's patency and facilitates gas exchange. However, in COPD, the Clara cells undergo metaplasia and transform into mucus-secreting goblet cells. This excessive mucus production, coupled with inflammation and fibrosis, narrows the airway lumen, impairing airflow and ventilation.

A study by Knox Brown et al [60] demonstrates that small airway obstruction is a prevalent condition globally, often more common than chronic airflow obstruction. Despite significant geographical variations, the risk factors for small airway obstruction are consistent with those for chronic airflow obstruction. These include increasing age, low BMI, smoking (both active and passive), low educational attainment, prolonged exposure to dusty jobs, history of tuberculosis, and family

history of COPD. The findings highlight the importance of recognizing and addressing small airway obstruction in public health strategies.

Identifying small airway abnormalities is essential for understanding and managing chronic respiratory diseases. Early discussions by William Gairdner and recent studies indicate that small airway dysfunction can be a biomarker for chronic conditions like COPD and asthma. However, these airways are difficult to study due to their size and inaccessibility. Spirometric measurements like FEF25–75 and FEV3/FVC are practical but have limitations. A universally accepted gold standard for testing small airway abnormalities is needed to improve study comparisons across different populations.[61]

Furthermore, fibrotic changes in the airway wall, characterized by the deposition of collagen and other extracellular matrix proteins, contribute to airway remodelling. Smooth muscle hypertrophy, another feature of small airway pathology, further constricts the airways, exacerbating airflow limitation. As a result, individuals with COPD experience symptoms such as wheezing, dyspnoea (shortness of breath), and decreased exercise tolerance due to compromised lung function.

- LUNG PARENCHYMA:

The lung parenchyma, consisting of alveoli and small airways, is crucial for gas exchange. In COPD, it undergoes destructive changes due to chronic inflammation and oxidative stress. Emphysema, a key feature of COPD, involves the irreversible destruction of alveolar walls, leading to enlarged air spaces and reduced gas exchange surface area.

Emphysema is classified into centriacinar and panacinar types. Centriacinar emphysema, often caused by smoking, primarily affects the respiratory bronchioles

and upper lung lobes. Panacinar emphysema, associated with alpha-1 antitrypsin deficiency (AATD), involves uniform enlargement of alveolar spaces throughout the lung, typically affecting the lower lung zones. These pathological changes result in progressive lung function decline, impaired gas exchange, and characteristic COPD respiratory symptoms.[62]

PATHOPHYSIOLOGY

- AIRFLOW OBSTRUCTION:

Airflow limitation, a key feature of COPD, is assessed using spirometry, which measures FEV1 and FVC. A reduced FEV1/FVC ratio indicates obstruction. Unlike asthma, COPD shows persistent airflow limitation, with only modest bronchodilator improvement (around 15%). Early COPD presents a "scooped-out" flow-volume curve, with abnormalities appearing at lower lung volumes. As COPD progresses, the entire curve shows reduced expiratory flow, indicating advanced obstruction.

Airflow obstruction in COPD is due to airway inflammation, mucus hypersecretion, airway remodelling, and loss of lung elasticity from emphysema. These changes increase airway resistance and impair gas exchange, leading to COPD symptoms and progression.[63]

- HYPERINFLATION:

In advanced COPD, "air trapping" and progressive hyperinflation occur, significantly affecting respiratory physiology. Hyperinflation increases lung volume beyond normal, which helps preserve maximum expiratory airflow. The increased lung volume boosts elastic recoil pressure, reducing airway resistance during expiration. This allows for more efficient airflow despite the obstruction.

Hyperinflation damages respiratory mechanics in severe COPD by flattening the diaphragm, decreasing its mobility, and raising the effort required to breathe. This results in symptoms such as dyspnoea and exercise intolerance, as well as weaker inspiratory muscles and increased labour of breathing. Furthermore, because of the minimal shunting and ventilation-perfusion mismatch caused by COPD, gas exchange is disrupted, and the ensuing hypoxia is frequently managed with oxygen therapy.[64]

- GAS EXCHANGE

It is essential for oxygenating blood and removing carbon dioxide (CO2), is impaired in COPD due to several factors:

1. Ventilation-Perfusion Mismatch:

COPD causes regional differences in lung compliance and resistance, leading to variations in ventilation (air reaching the alveoli) and perfusion (blood flow through pulmonary capillaries). This mismatch reduces blood oxygenation, as some alveoli receive air but inadequate blood flow, while others receive blood but inadequate airflow.

2. Minimal Shunting:

In COPD, shunting (blood bypassing ventilated alveoli) is minimal. Hypoxia primarily results from ventilation-perfusion imbalance rather than significant shunting.

3. Oxygen Therapy:

Supplemental oxygen can manage COPD-related hypoxia by increasing alveolar oxygen concentration and compensating for impaired gas exchange. Careful monitoring is essential to avoid complications like hypercapnia (elevated CO2 levels) in patients with retained respiratory drive.

4. Addressing Complications:

Persistent hypoxemia or complications from oxygen therapy, such as hypercapnia, require investigation and management of other factors. These may include worsening lung function, COPD exacerbations, pulmonary hypertension, or heart disease.

Understanding these mechanisms is crucial for managing hypoxia and optimizing respiratory function in COPD patients.[64]

SYMPTOMS OF COPD

The clinical presentation of COPD is heterogeneous, encompassing a wide range of manifestations that evolve as the disease progresses. Understanding these symptoms is crucial for accurate diagnosis and effective management.

1. Dyspnoea (Shortness of Breath): Dyspnoea is a hallmark symptom of COPD and often the most distressing for patients. Initially, it may manifest only during exertion but gradually worsens over time. As the disease advances, patients may experience dyspnoea even at rest. Factors contributing to dyspnoea include airway obstruction, hyperinflation, and decreased respiratory muscle strength.

2. Chronic-Cough: The persistence of cough is another typical COPD symptom which begins as a response to airway irritation from cigarette-smoke or other environmental pollutants. Over time, the cough becomes chronic and may worsen during exacerbations. Coughing episodes significantly can impact a patient's life quality and may interfere with sleep and daily activities.

3. Sputum Production: COPD patients often produce sputum, especially in the morning. The sputum is typically mucoid or clear, but during exacerbations, it may

become thicker and purulent. Excessive sputum production is associated with airway inflammation and can contribute to respiratory symptoms and exacerbations.

4. Exacerbations: Exacerbations are acute episodes characterized by a sudden worsening of COPD symptoms, such as increased dyspnoea, cough, and sputum production. They are often triggered by respiratory infections or exposure to environmental pollutants. Exacerbations can have a significant impact on lung function, quality of life, and mortality risk.

5. Wheezing: Wheezing, a high-pitched whistling sound during breathing, may occur in COPD patients, particularly during exacerbations or in advanced stages of the disease. It results from airflow obstruction in the smaller airways and can contribute to dyspnoea and respiratory distress.

6. Chest Tightness: Some patients with COPD experience chest tightness or discomfort, which may worsen during exacerbations or periods of increased respiratory effort. Chest tightness can be distressing and may contribute to feelings of anxiety and panic in some individuals.

7. Fatigue: Fatigue is a common symptom in COPD patients and can significantly impact daily functioning and quality of life. It may result from increased work of breathing, sleep disturbances due to nocturnal symptoms, or systemic inflammation associated with the disease.

8. Weight Loss: Unintentional weight loss is often observed in advanced COPD and is associated with muscle wasting and cachexia. Weight loss can further exacerbate weakness and fatigue, leading to functional impairment and decreased tolerance for physical activity.

By recognizing and addressing these symptoms, healthcare providers can better manage COPD patients' care, improve their quality of life, and reduce the risk of disease progression and complications.

A study of 727 COPD patients by Miravitlles et al, over 60% reported experiencing symptoms at any time of day, with higher incidences early in the morning (81.4%) and daytime (82.7%) than at night (63.0%). Over half of the patients (56.7%) experienced symptoms constantly for the entire day. Regardless of the severity of the condition, symptoms were linked to worsening of dyspnoea, health status, sleep quality, and higher levels of worry and depression. There was also a link amid symptoms and reduced physical-activity across all times of day.[65]

PHYSICAL FINDINGS IN COPD [66]

A physical examination is essential for evaluating COPD because it sheds light on the severity and course of the illness. Important conclusions consist of:

1. Lack of wheeze: As COPD advances, extended expiration becomes regular, albeit early stages may not exhibit any anomalies.

2. Signs of Hyperinflation: Patients with hyperinflation frequently assume a "tripod" posture and have a barrel-shaped chest, diminished breath sounds, muted heart sounds, and enhanced resonance to percussion.

3. Pursed-Lip Breathing: This method helps people with severe COPD breathe better and lessen hyperinflation.

4. Systemic Manifestations: Right ventricular hypertrophy and an enhanced pulmonic component of the second heart sound are signs of cor pulmonale, which can be brought on by severe COPD.

5. Specialized Subtypes:

"*Pink Puffers*": linked to weight loss, muscle atrophy, and emphysema.

"*Blue Bloaters*" are linked to cyanosis, cor pulmonale, ventilation-perfusion mismatch, and chronic bronchitis.

6. Clubbing: Although uncommon in COPD, its existence indicates comorbidities or cancer.

Acknowledging these findings facilitates healthcare providers' ability to monitor the evolution of COPD, diagnose its severity, and successfully customize treatment plans.

DIAGNOSIS

1. Testing and diagnosis of pulmonary function

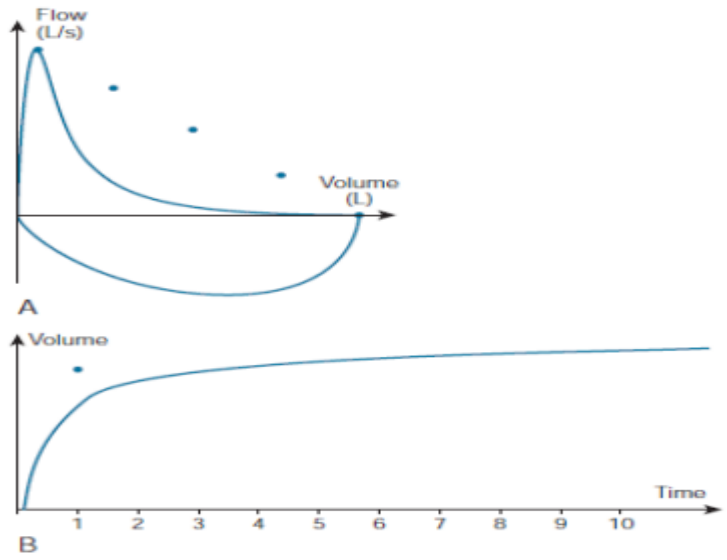
Spirometry plays a vital role in the staging and monitoring of COPD and is the cornerstone for identifying it. By assessing lung function parameters, spirometry helps differentiate COPD from other respiratory conditions that share similar clinical presentations. Despite its pivotal role, spirometry remains underutilized in clinical practice, leading to both underdiagnosis and overdiagnosis of COPD.

Spirometry involves several key components:

1. Forced Vital Capacity (FVC): This measures the maximum volume of air forcefully exhaled after a deep inhalation. It provides an indication of the lung's total capacity.

2. Forced Expiratory Volume in 1 second (FEV1): This measures the volume of air forcefully exhaled in the first second of the FVC manoeuvre. It reflects the efficiency of airflow through the airways.

3. FEV1/FVC Ratio: This ratio compares the FEV1 to the FVC and helps assess airflow obstruction. In COPD, airflow limitation results in a reduced FEV1/FVC ratio.



In the above figure, **Fig A** - shows concave flow volume loop; **Fig B** - shows prolonged Expiration Grading of severity with spirometry.

The GOLD guidelines recommend an FEV1/FVC ratio of <0.70 for diagnosing COPD, but this may misclassify individuals, especially the elderly. An alternative is the Lower Limit of Normal (LLN), which considers individual characteristics.

Spirometry is non-invasive, available in doctors' offices, and helps diagnose COPD, assess severity, guide treatment, and monitor progression. Other tests like lung volume measurements and diffusion capacity provide additional insights. Despite some limitations, spirometry remains essential for diagnosing and managing COPD.

- **<u>COPD Severity Grading Using FEV1 Predicted Percentage</u>**

The severity of COPD is commonly graded using the percent predicted forced expiratory volume in 1 second (FEV1). Both the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and the American Thoracic Society/European Respiratory Society (ATS/ERS) recommend using post-bronchodilator FEV1 values for greater reproducibility. This ensures accurate and stable lung function measurements for treatment decisions.[67]

Table-2: The classification of COPD severity according to FEV1 percent predicted		
GOLD Grade	**Severity of disease**	**FEV1 % (Predicted Range)**
1	Mild	≥80%
2	Moderate	50% ≤ FEV1 < 80%
3	Severe	30% ≤ FEV1 < 50%
4	Very Severe	<30%

2. Lung volumes

Plethysmography is a typical method used in a normal pulmonary function lab to quantify lung capacities such as Total Lung Capacity (TLC) and Residual Volume (RV). TLC tends to be higher in COPD, particularly emphysema, because of lung hyperinflation brought on by a reduction in lung elasticity. RV/TLC ratio rises when both RV and Functional Residual Capacity (FRC) rise, with RV increasing faster than TLC. These changes reflect COPD's pathological alterations, leading to characteristic lung hyperinflation.

3. Diffusion Capacity

DLCO, or diffusing capacity for carbon monoxide, measures how well the lungs transfer gas from inhaled air to the bloodstream. Reduced DLCO suggests issues like emphysema or pulmonary fibrosis, impairing gas exchange. When spirometry appears normal but DLCO is low, it may signal CPFE syndrome, combining fibrosis and emphysema. DLCO assessment is vital for diagnosing lung conditions accurately and planning suitable treatment.

4. Exercise testing

Exercise testing, particularly the 6-minute walk test (6MWT), assesses functional capacity and oxygenation in COPD patients. The 6MWT, which measures the distance a patient can walk in 6 minutes, is simple and accessible. It aids decisions on supplemental oxygen therapy and plays a key role in pre-transplant evaluations, predicting post-transplant prognosis and mortality risk as part of the BODE index.

5. Imaging

Chest radiography is often the initial imaging modality used in patients with suspected COPD. Flattening of the diaphragm and radiolucency, which indicates hyperinflation and air trapping, are common findings on chest X-rays that are suggestive of COPD. However, chest-CT remains the gold standard for the detection and quantification of COPD related lung changes providing detailed visualization of pulmonary structures and abnormalities, making it indispensable for preoperative assessment in lung volume reduction surgeries. Expiratory CT scans can reveal bronchial thickening and small airway disease, showing air trapping, which is characteristic of COPD. These scans are also vital for ruling out other respiratory conditions that may resemble COPD.[68]

ASSESSMENT OF SYMPTOMS

The evaluation of a patient's symptoms aids in both making an accurate diagnosis and selecting a course of treatment.

❖ COPD Assessment Test (CAT)

The COPD Assessment Test (CAT) is a simple and effective tool for evaluating the health status of COPD patients. With eight questions covering various symptoms and their impact on daily life, patients rate their experiences on a scale of 0 to 5. Its ease of use allows for quick completion, providing healthcare providers with

valuable information on symptom severity and overall health status. The CAT score aids in disease assessment and monitoring. Regular CAT score assessment helps track changes in health status and treatment effectiveness, enabling timely adjustments for improved outcomes.[69]

❖ Modified MRC dyspnoea scale (mMRC)

While the Modified British Medical Research Council (mMRC) Questionnaire has long been used to assess breathlessness in COPD, its focus on this single symptom may not capture the full complexity of the disease. Recent understanding emphasizes the need for more comprehensive symptom assessment tools considering COPD's systemic impact. Alongside dyspnoea, symptoms like cough, sputum production, fatigue, and reduced physical activity significantly affect patients' lives. Comprehensive tools like the CAT-scoring offers a broader assessment, aiding in understanding the overall burden of COPD and tailoring treatment plans. This holistic approach improves COPD management and patient outcomes.[70]

Table-3: Grade Classification for the Modified Medical Research Council (mMRC) Dyspnoea Scale

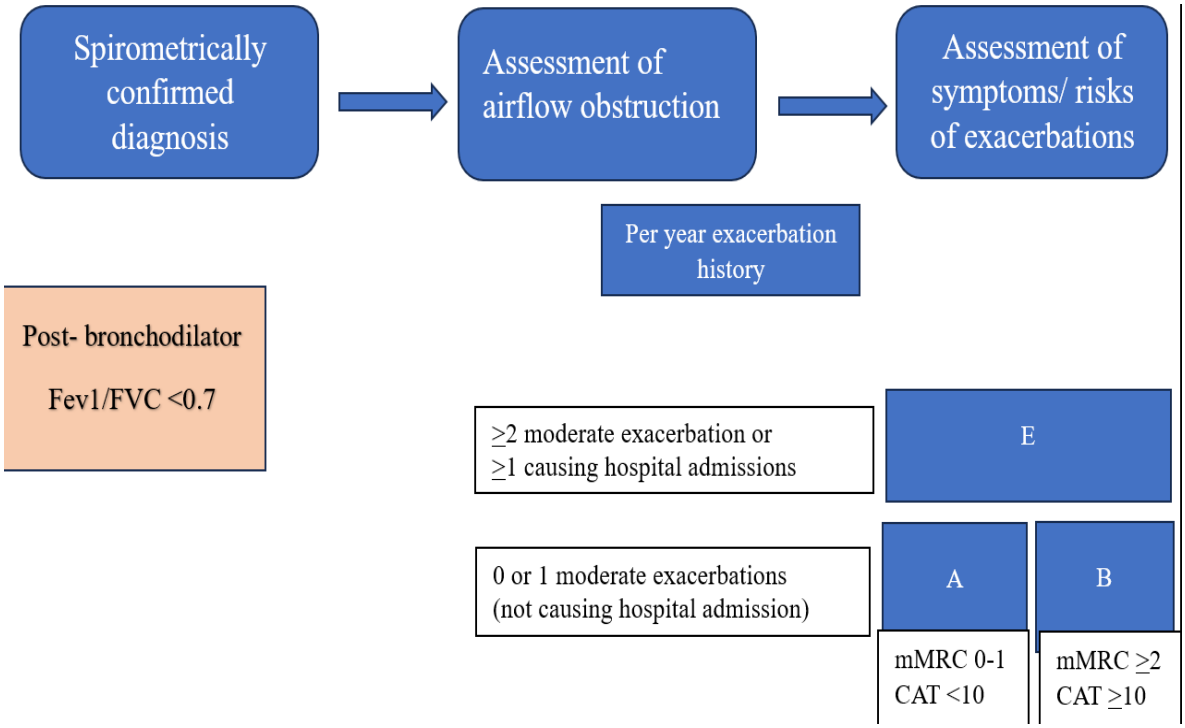
Grade	Degree of dyspnoea associated with the activities
0	No breathlessness except with strenuous exercise
1	Breathlessness when hurrying on the level or walking up a slight hill
2	Walks slower than peers on level ground due to breathlessness or stops frequently to catch their breath when moving at their own pace
3	Stops for breath after walking about 100 metres or after a few minutes

	on level ground
4	Breathless while getting dressed or undressed, or too breathless to leave the house

❖ Presence of comorbidities

In older people, COPD plays a significant role in a multimorbid condition. Cardiovascular disorders, skeletal muscle dysfunction, anxiety, depression, the metabolic syndrome, osteoporosis, and lung cancer are among the other prevalent comorbid conditions. Lung cancer risk is one of the conditions that COPD may increase. These patients exhibit comorbidities with varying degrees of airflow restriction, which can affect hospitalizations and mortality on their own. In addition to COPD medication, this needs special attention.[71]

The ABCD combination assessment tool was further evolved by GOLD in the 2023 GOLD report, which acknowledged the significance of exacerbations clinically, regardless of the patient's degree of symptoms. This concept is presented below. To emphasize the clinical significance of exacerbations, the C and D groups were combined into one single-group called "E," while other A and B groups stayed the same.[72]



❖ St. George Respiratory Questionnaire (SGRQ)

The St. George Respiratory Questionnaire (SGRQ) is a comprehensive tool used to assess health impairment in asthma and COPD patients consisting of two parts:

1. Part-1 (Questions from 1-8): Generates the symptom-score, based on a patient's recall of symptoms over varying periods. A validated 3-month recall version is available.
2. Part-2 (Questions from 9-16): Provides Activity and Impact scores, reflecting the patient's current state. The Activity score measures difficulty in daily activities, while the Impact-score assesses psycho-social effects.

Impact-score correlates strongly with respiratory symptoms, exercise performance, and mood disturbances. The questionnaire is designed for supervised self-administration, with scores ranging from zero (lowest) to 100 (highest).[73]

COPD patients have SGRQ scores >25. Scores < 25 are usually found in healthy people.[74]

❖ BODE Index

BODE index, a composite index measures BMI, FEV_1, breathlessness and exercise capacity. It's a simple multimodality approach to know the severity of disease.[74]

Components of BODE Index are:

a. Body Mass Index

One of the most frequent conditions found in individuals with severe COPD is nutritional insufficiency. The percentage of COPD patients who lose weight when they visit the outpatient department (OPD) starts at 20% and rises to 35% when they are hospitalized.[75] Low BMI has also been noted to be a potential risk factor for COPD mortality. A lower BMI was linked to a higher mortality risk.[76]

b. Airway obstruction:

Spirometry is an objective technique used to measure obstruction of the airways. A FEV1/FVC ratio of less than 0.7 indicates blockage. Predicted FEV1% values are used for grading. In accordance with the GOLD 2024 guidelines

c. mMRC grading:

Breathlessness is the most common incapacitating symptom of COPD. This is the primary cause for which a patient may seek medical care.[77]

Using the MMRC grading makes it easy to assess one's degree of dyspnoea and impairment during an activity. Although this is a useful scale, as dyspnoea is not the primary symptom of COPD, it is now seen as an antiquated way to measure symptoms and HRQOL. There is just a weak relationship between dyspnoea and

FEV1. It is one of the components of the BODE Index because it more accurately predicts dyspnoea.[78]

d. Six-Minute Walk Distance (6MWD):

The Six-Minute Walk Test (6MWT) is a rapid and accurate method of evaluating level of illness severity and ability to tolerate exercise in patients. Its consistency, dependability, and simplicity helped it become widely accepted.[79]

It is found decreased in feminine sex, shorter height, low motivation, cognitive impairment, and musculoskeletal or cardiopulmonary disorders. It aids in rating the severity of the disease and in survival prediction.[80] This test's primary drawback is that it measures the overall functioning of all muscles rather than just the tiredness of a particular muscle group or set of muscles. Patients with milder diseases might not show signs of diminished exercise capacity.

After measuring all the indices, BODE index will be scored as:

Table-4: BODE scoring system

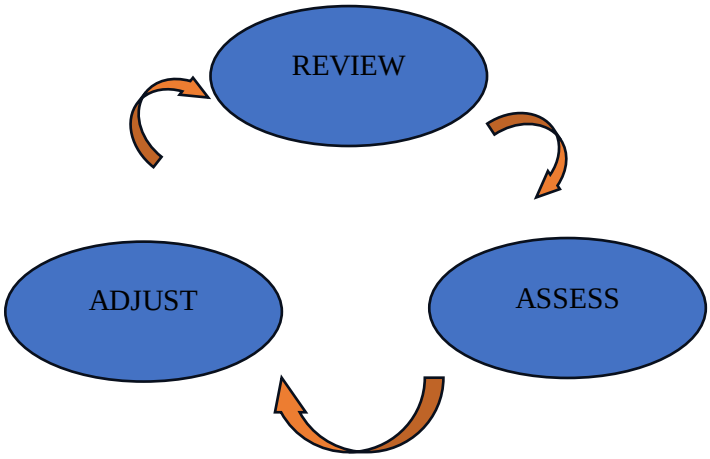
BODE COMPONENTS	0	1	2	3
Predicted FEV_1 %	≥65	50-64	36-49	≤35
6MWD (mts)	≥350	250-349	150-294	≤149
Dyspnoea scale	0-1	2	3	4
BMI	>21	≤21	-	-

When the predictive validity of the aforementioned variables was evaluated in a 2004 study with 207 COPD patients, Celli et al.[81] reported that these variables were predictive of mortality in COPD.

Claudia et al.[82] studied 625 patients with COPD in a six-month follow-up for two years, and the BODE index scores, which varied from 0 to 10, were split into four quartiles and compared to the death rate. When compared to other quartiles, they found that the 4th quartile, which had 7–10 BODE scores, produced higher mortality. Thus, it has been demonstrated that composite indices outpredict mortality more accurately than their separate components.[83]

MANAGEMENT STRATEGIES IN COPD

The COPD Management Cycle, a continuous process involving three main steps: Review, Assess, and Adjust.



1. **Review**:

- Symptoms: Evaluate the patient's symptoms, focusing on dyspnoea and the frequency and severity of exacerbations.

2. **Assess**:

- Inhaler Technique and Adherence: Ensure the patient is using their inhaler correctly and consistently.
- Non-pharmacological Approaches: Consider additional interventions such as pulmonary rehabilitation and self-management education to support overall health and COPD management.

3. **Adjust**:

- Escalate: If symptoms are not well-controlled, consider increasing the intensity of treatment.
- Switch Inhaler Device or Molecules: Change the inhaler device or medication molecules if the current treatment is ineffective or unsuitable.
- De-escalate: If the patient's condition is stable, consider reducing treatment intensity to avoid overtreatment and minimize side effects.

This cycle is designed to be repeated regularly to ensure optimal management of COPD, adapting the treatment plan based on the current status and needs of a patient.

TREATMENT OF STABLE COPD

Managing stable COPD involves a multifaceted approach aimed at alleviating symptoms, reducing exacerbation frequency, and improving overall quality of life. While no treatment can alter the natural course of COPD, several interventions have demonstrated efficacy in symptom control and exacerbation prevention.

❖ **Identify and reduce risk factor exposure**

➢ Smoking Cessation:

The cornerstone of COPD management is smoking cessation. About 40% of persons with COPD still smoke, and this practice has a negative effect on the prognosis and course of the disease. A large fraction of people with COPD continue to smoke despite knowing they have the disease.[84] Stopping to smoke reduces daily symptoms[85] and lowers the frequency of exacerbations.[86]

Pharmacotherapy, including nicotine replacement therapy (NRT), bupropion, and varenicline, combined with counselling, significantly increases cessation rates and improves outcomes.

➢ Air pollution in households and outdoors

Reducing exposure to indoor and outdoor air pollution requires a combination of public policy, local and federal resources, cultural changes, and patient-specific preventive strategies. Decreasing exposure to biomass-fuel smoke is an essential objective in the global effort to lower the prevalence of COPD. It is conceivable and advisable to recommend actions such as effective ventilation, non-polluting cooking stoves, and similar measures.[87],12

❖ **Vaccination**[88]

Individuals who have COPD should get all advised immunizations

Table-5: Vaccination Recommendations for COPD Patients

Vaccination	**Recommendation**
Influenza	Recommended annually for individuals with COPD

SARS-CoV-2 (COVID-19)	Advised by WHO and CDC for individuals with COPD
20-valent pneumococcal conjugate (PCV20)	CDC suggests one dose for people with COPD
15-valent pneumococcal conjugate (PCV15)	Recommended one dose followed by a 23-valent pneumococcal polysaccharide (PPSV23) for individuals with COPD
Pneumococcal	Proven to reduce the risk of community-acquired pneumonia and exacerbations in COPD patients
Respiratory-syncytial virus (RSV)	CDC recommends for those more than 60 years and/or with existing chronic heart or lung conditions
Tdap (dTaP/dTPa)	CDC advises for protection against pertussis for COPD patients not vaccinated in adolescence
Zoster	Suggested for preventing shingles in COPD patients over 50 years

❖ **Pharmacotherapy**

Pharmacological interventions are central to COPD management and include various classes of medications aimed at improving symptoms and reducing exacerbation risk.

❋ **Bronchodilators:**

There are two types of beta2-agonists: short-acting (SABA) and long-acting (LABA). The main effect of SABAs is to relax airway smooth muscle by stimulating beta2-adrenergic receptors, which increases cyclic AMP and produces functional antagonism to bronchoconstriction. The effect of SABAs usually wears off within 4 to 6 hours.[89,90]

LABAs exhibit a 12-hour or longer duration of effect, and they do not prevent further benefit from additional SABA therapy as needed.[91]

The twice-daily LABAs salmeterol and formoterol significantly reduce hospitalization rates, exacerbation rates, dyspnoea, lung volumes, and FEV1. They have little impact on mortality or the rate at which lung function declines, though. One daily LABA is called indacaterol.[92]

In those who are vulnerable, stimulation of beta2-adrenergic receptors can cause resting sinus tachycardia and may also cause cardiac rhythm abnormalities. Concerning elderly individuals receiving greater dosages of beta2-agonists, is exacerbated somatic tremor. While hypokalemia can happen when thiazide diuretics are used in conjunction with therapy, and people with chronic heart failure may need more oxygen while they are at rest [93], both of these circumstances can lead to tachyphylaxis[94]

❋ **Anticholinergics:**

The bronchoconstrictor effect of acetylcholine on M-3 receptors in airway smooth muscle is inhibited by antimuscarinic drugs. Ipratropium and oxitropium are examples of short-acting antimuscarinics (SAMAs) that inhibit M-2 receptors, perhaps leading to bronchoconstriction. Long-acting antimuscarinics (LAMAs) such as tiotropium and aclidinium provide extended bronchodilation by binding longer to M3 receptors and quickly dissociating from M2 receptors. A thorough analysis of RCTs revealed that ipratropium, a short-acting muscarinic antagonist, by itself offered very slight benefits over short-acting beta2-agonists in terms of lung function, health status, and the requirement for oral steroids.[95]

LAMA therapies enhance both the patient's health and symptoms, such as sputum and cough. Exacerbation rates are more affected by LAMA treatment (tiotropium) than by LABA treatment, according to clinical studies [96],100 and lessen hospitalizations

Anticholinergic medicines that are inhaled have little systemic effects due to their low absorption. The primary adverse effect is dry mouth, and they are normally harmless. Ipratropium is associated with a modest increase in cardiovascular events and a harsh taste, according to some individuals. Tiotropium does not raise the risk of cardiovascular disease. Other LAMAs have comparable and mild adverse effects, despite the paucity of available evidence. If the solution gets in the eyes while wearing a facemask, it might cause acute glaucoma.[98]

❋ **Inhaled Corticosteroids (ICS):**

Regular treatment with inhaled corticosteroids (ICS) increases the risk of pneumonia, particularly in those with severe disease. Combining ICS with a LABA is more effective than using the components individually, improving lung function, health status, and reducing exacerbations in moderate to severe COPD. Triple therapy (LABA+LAMA+ICS) is superior to LABA+ICS, LABA+LAMA, or LAMA monotherapy for improving lung function, symptoms, health status, and reducing exacerbations. In COPD patients with asthma features, treatment should include an ICS. Blood eosinophil count <2% independently increases pneumonia risk. Single inhaler therapy may be more convenient and effective than multiple inhalers.

- Treating with only ICS:

Individuals treated with fluticasone propionate alone in the TORCH study showed a tendency toward increased mortality than individuals treated with placebo or salmeterol + fluticasone propionate combination[99] but not so observed in the SUMMIT experiment.[100]

In patients with intermediate COPD, fluticasone furoate, either by itself or in combination with vilanterol, was linked to a 9 mL/year slower average decrease in FEV1 in contrast to vilanterol or a placebo alone.[100]

- Combination therapy with ICS:

An ICS + LABA combo is superior to either medication alone in improving lung function, health status, and lowering exacerbations in patients with moderate to severe COPD with exacerbations.

In a primary healthcare environment in the United Kingdom, an RCT compared standard care with the combination of LABA and ICS. The primary result showed a significant improvement in the CAT score and an 8.4% decrease in the number of moderate-to-severe exacerbations.[101]

In a study by Alberto Papi et al [3] done in 1532 patients across 17 countries triple therapy BDP/FF/G significantly reduced the rate of moderate-to-severe COPD exacerbations compared to dual bronchodilator therapy IND/GLY, with similar rates of adverse events and no increased risk of pneumonia.

In the TRINITY trial, patients with symptomatic COPD, a FEV1 of less than 50%, and a history of exacerbations responded better clinically to extrafine fixed triple therapy than to tiotropium.[4] In comparison to the fluticasone furoate-vilanterol group (1.07 per year) and the umeclidinium-vilanterol group (1.21 per year), the triple-therapy group saw a lower rate of moderate or severe COPD exacerbations (0.91 per year) in a study by Lipson DA et al. In terms of lowering hospital stays and moderate-to-severe exacerbations, triple therapy proved more successful.[5]

When compared to LAMA alone, inhaled therapy with LABA + LAMA plus ICS has been demonstrated to enhance lung function, patient-reported-outcomes, and decrease exacerbations

- **Oral Steroids:**

Short courses of oral steroids may be prescribed during exacerbations to hasten recovery and improve lung function. However, chronic use is discouraged due to the risk of adverse effects such as osteoporosis, diabetes, and infections.[102]

❋ **Methylxanthines:**

The effects of xanthine derivatives are controversial, possibly acting as non-selective phosphodiesterase inhibitors with disputed non-bronchodilator actions. Data on their duration of action in COPD are lacking. Theophylline, the most used methylxanthine, is metabolized by cytochrome P450, with clearance declining with age. It may improve inspiratory muscle function, but its exact mechanism is unclear. Theophylline shows modest bronchodilator effects and improves FEV1 and breathlessness when added to salmeterol. Studies on its impact on exacerbation rates are contradictory. Adverse effects are dose-related and include arrhythmias, convulsions, headaches, insomnia, nausea, and significant drug interactions.[103]

❋ **Phosphodiesterase-4 (PDE4) inhibitor- Roflumilast:**

This selective phosphodiesterase-4 (PDE-4) inhibitor can reduce exacerbation frequency in severe COPD by inhibiting inflammatory pathways. In individuals with chronic bronchitis and a history of recurrent exacerbations, it is recommended as an adjuvant treatment.[104]

❋ **Mucolytics:**

Regular treatment with mucolytics such as carbocysteine and N-acetylcysteine (NAC) may lessen exacerbations and marginally improve health status in COPD patients who are not on ICS. Regardless of ICS treatment, erdosteine dramatically lowers minor exacerbations.[105]

❋ **Antibiotics:**

Daily azithromycin administration has been found to reduce exacerbation frequency, possibly due to its antimicrobial and anti-inflammatory properties. Macrolide

antibiotics are preferred due to their immunomodulatory effects and reduced risk of bacterial resistance.

In a study by Seemungal et al when given for a year to individuals who are prone to exacerbations, compared with usual therapy, the risk of exacerbations was reduced by either Erythromycin (250 mg twice daily) or Azithromycin (250 mg/day or 500 mg three times per week).[106,107] In patients with chronic bronchitis and recurrent exacerbations, every eight weeks, moxifloxacin (400 mg/day for five days) showed total exacerbation rate was not improved by pulse therapy.[108]

- **Supplemental Oxygen:**

Oxygen therapy is indicated in COPD patients with resting hypoxemia (oxygen saturation ≤88% or <90% in the presence of pulmonary hypertension or right heart failure) to reduce mortality and improve outcomes. Long-term oxygen therapy (LTOT) has been shown to decrease mortality in this population and should be prescribed judiciously based on arterial blood gas analysis.

- **Fundamental Ideas for Selecting the Right Inhalation Device:** [109]

1. Verify that the medication is in the device.
2. Take into account patient preferences and contentment with available technology.
3. Reduce the variety of devices each patient has.
4. Refrain from switching devices without a valid clinical reason and appropriate aftercare.
5. Make decisions jointly with the patient, the prescriber.
6. Evaluate the patient's strength, dexterity, and mental capacity.
7. Verify the patient's capacity to use the proper inhaling method.

8. Select the type of device (e.g., dry powder, metered-dose, gentle mist) according to its inhaling capability.
9. Think about additional aspects including cost, size, and portability.
10. Smart inhalers can aid in problems related to technique and adherence.
11. Only recommend equipment that the doctor and the care staff are familiar with.

❖ **Non-Pharmacological Interventions**

In addition to pharmacotherapy, several non-pharmacological interventions play a crucial role in COPD management.

❋ **Patient Education and Self-Management**[110]

Patient education and self-management strategies are essential components of COPD management.

- Education: Patients should receive education on COPD, including its pathophysiology, management strategies, and the importance of adherence to treatment and smoking cessation. Healthcare providers should empower patients to actively participate in their care by providing them with knowledge and skills to self-manage their condition effectively.
- Self-Management: Encouraging patients to monitor symptoms, recognize exacerbations, and adhere to treatment plans can empower them to better manage their condition and reduce healthcare utilization. Action plans outlining steps to take during exacerbations should be provided to patients to facilitate timely intervention and prevent complications.

❋ **Pulmonary Rehabilitation:**

Comprehensive programs involving exercise training, education, and behavioral interventions can improve exercise capacity, symptoms, and quality of life in COPD

patients. Pulmonary rehabilitation is recommended for all symptomatic COPD patients, irrespective of disease severity.[111]

❋ **Lung Volume Reduction Surgery (LVRS):**

For select patients with severe emphysema and significant hyperinflation, surgical procedures like LVRS may improve lung function and exercise tolerance. LVRS involves removing damaged lung tissue to improve lung mechanics and gas exchange.

❋ **Regular Follow-Up**

Regular follow-up visits with healthcare providers are essential to assess treatment efficacy, monitor disease progression, and adjust therapy as needed. Objective measures such as spirometry and symptom assessment tools should be utilized during follow-up evaluations to track disease status and guide treatment decisions. Shared decision-making between patients and healthcare providers is crucial in optimizing COPD management and improving patient outcomes.

TREATMENT STRATEGIES FOR NON-SMOKERS WITH COPD

Chronic obstructive pulmonary disease (COPD) can also affect individuals who have never smoked or have minimal exposure to cigarette smoke. While smoking cessation remains a crucial component of COPD management for all patients, non-smokers may require tailored treatment approaches. Here are some strategies for managing COPD in non-smokers:

1. Environmental Modification [12]

- Avoidance of Indoor and Outdoor Pollutants: Non-smoking COPD patients should minimize exposure to indoor air pollutants such as biomass fuel smoke,

dust, and chemical fumes. Outdoor air pollution, including traffic-related emissions and industrial pollutants, should also be avoided whenever possible.

- Occupational Hazards: Exposure to chemicals, dust, and fumes at work may accelerate the onset and progression of COPD. Non-smoking individuals with COPD should identify and minimize exposure to workplace hazards through proper ventilation, personal protective equipment, and workplace modifications.

2. Pharmacotherapy

- Bronchodilators: Non-smoking COPD patients may benefit from bronchodilator therapy, including short-acting and long-acting anticholinergics and beta-agonists. These medications help alleviate symptoms of airflow limitation and improve exercise tolerance.
- Inhaled Corticosteroids (ICS): Inhaled corticosteroids, often combined with long-acting bronchodilators, may be prescribed for non-smoking COPD patients with frequent exacerbations and evidence of airway inflammation. However, the use of ICS should be carefully monitored due to the risk of side effects, particularly pneumonia and osteoporosis.
- Mucolytics: Mucolytic agents such as N-acetylcysteine (NAC) may be considered in non-smoking COPD patients with chronic bronchitis to reduce sputum viscosity and improve cough clearance. However, their efficacy in non-smokers is less well-established compared to smokers with COPD.[112]

The IMPACT trial demonstrated that triple therapy with fluticasone furoate/ umeclidinium/ vilanterol (FF/UMEC/VI) significantly reduces moderate/severe exacerbation rates and improves lung function and health status in COPD patients compared to dual therapies (FF/VI or UMEC/VI), regardless of smoking status. But

the advantages were greater among ex-smokers, perhaps because they had less corticosteroid resistance than smokers now. The trial also noted a higher incidence of pneumonia in former smokers receiving inhaled corticosteroid-containing therapy, highlighting the need for careful patient management based on smoking history.[6]
In comparison to TIO and SFC alone, the "triple" therapy combination of SFC and TIO improved bronchodilation in 41 patients with moderate to severe COPD in a randomized, double-blind, three-way crossover design by D. Singh et al. The benefits of this triple therapy were seen in a number of important physiological measures, such as lung volumes and airway conductance. Additionally, triple therapy provided patient-related benefits by improving the Transition Dyspnoea Index (TDI) and reducing the use of rescue medication.[113]

In comparison to umeclidinium/vilanterol (UMEC/VI), Lipson et al [114] in his study on 10,355 participants showed that fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) triple therapy significantly reduced 42% in all-cause mortality (ACM) and a 25% lower chance of moderate-to-severe exacerbations among COPD patients who are susceptible to exacerbations in the future, as shown by the IMPACT trial. The chance of mortality has significantly decreased, according to recorded deaths, particularly from respiratory and cardiovascular conditions. This demonstrates that FF/UMEC/VI a triple therapy is beneficial in reducing the death rate of COPD patients.
In contrast to glycopyrrolate/formoterol fumarate (GFF), triple therapy with budesonide/glycopyrrolate/formoterol fumarate (BGF 320) significantly reduced all-cause mortality in COPD patients, according to the 52-week ETHOS trial, a randomized, double-blind, parallel-group trial that was conducted across 26 countries and included 8509 recruit participants (hazard ratio: 0.51, P = 0.0035). In

comparison to budesonide/formoterol fumarate (BFF), BGF 320 did not significantly lower mortality. When compared to dual therapy, the lower dose of BGF 160 did not significantly reduced mortality. Over a one-year period, triple therapy resulted in 46% fewer fatalities and 24% fewer moderate-to-severe exacerbations than LAMA-LABA.[115]

In pooled analyses of the TRILOGY[7], TRINITY[4], and TRIBUTE [3]studies, the triple therapy significantly delayed the time to clinically important deterioration in patients with symptomatic COPD and FEV1 <50%, compared to dual therapies.

The TRILOGY study assessed the efficacy of triple therapy with beclomethasone dipropionate, formoterol fumarate, and glycopyrronium bromide (BDP/FF/GB) in COPD patients compared to beclomethasone dipropionate and formoterol fumarate (BDP/FF). Conducted across 159 sites in 14 countries, the study involved 1368 patients with severe COPD. According to results at week-26, BDP/FF/GB considerably raised pre-dose FEV1 by 0.081 L and 2-hour post-dose FEV1 by 0.117 L compared to BDP/FF.The study supports the clinical benefits of stepping up to triple therapy for improved lung function and reduced exacerbations in COPD patients.[7]

The TRINITY study found that triple therapy with beclomethasone dipropionate, formoterol fumarate, and glycopyrronium bromide (BDP/FF/GB) significantly reduced moderate-to-severe COPD exacerbation rates compared to tiotropium given alone (0.46-vs.-0.57; p= 0.0025) and improved pre-dose FEV1 (0.061 L; p<0.0001). This double-blind, randomized trial involved 2691 patients with severe COPD. Adverse events were similar across treatment groups. The study concluded that fixed

triple therapy offers clinical benefits over tiotropium for patients with symptomatic COPD and a history of exacerbations.[4]

The TRIBUTE trial examined the safety and effectiveness of two bronchodilator combinations in individuals with symptomatic COPD: indacaterol plus glycopyrronium (IND/GLY) and (BDP/FF/G). The double-blind, randomized-trial, which was carried out across 187 sites in 17 countries, involved 1,532 patients with severe COPD and a history of exacerbations. Over the course of 52 weeks, the rates of moderate-to-severe COPD exacerbations were found to be significantly lower when compared to dual therapy with indacaterol and glycopyrronium (IND/GLY) (0.50 vs. 0.59 per patient per year; p=0.043).[3]

While dual bronchodilator therapy benefits many COPD patients, triple therapy (TT) shows modest overall benefits but is recommended for those with severe symptoms, frequent exacerbations, poor quality of life, and high eosinophil counts. GOLD guidelines suggest TT for patients not adequately controlled by LABA/LAMA or ICS/LABA therapies. Some real-world studies indicate that TT is often used even without prior exacerbations, with dyspnoea being a key factor for therapy change.[9,116]

A study in Spain showed that de-escalation from TT is more common in severe cases within the first year, with 50% stepping down within five years. This de-escalation can result from either lack of efficacy or disease stability with triple therapy. According to recent research, stopping ICS from TT in patients with stable COPD does not raise the chance of an exacerbation, especially in non-exacerbators with low eosinophil counts.[117]

A phase 3 randomized controlled trial compared the efficacy of triple therapy with budesonide/glycopyrrolate/formoterol fumarate metered-dose inhaler (BGF MDI) to dual therapies in 1,902 symptomatic COPD patients across two hundred fifteen sites in various countries. During a 24-week period, BGF MDI markedly enhanced lung function (FEV1 AUC 0–4) compared to budesonide/formoterol fumarate MDI (BFF MDI) and budesonide/formoterol fumarate dry-powder inhaler (BUD/FORM DPI), and pre-dose trough FEV1 compared to glycopyrrolate/formoterol fumarate MDI (GFF MDI). BGF (triple drug) MDI was well-tolerated and more effective, making it a preferable option for treating symptomatic COPD patients, regardless of their exacerbation history.[8]

For severe uncontrolled asthma, SITT has been recently approved, providing an additional treatment option. GINA-guidelines recommend TT in severe asthma before stepping up to oral-corticosteroids or biologics, acknowledging that asthma severity can vary, necessitating changes in treatment intensity. Step-down from TT is suggested for minimal effective treatment but can be challenging if patients are reluctant to change a successful therapy.

3. Pulmonary Rehabilitation [111]

- Exercise Training: Non-smoking COPD patients can benefit from pulmonary rehabilitation programs that include structured exercise training tailored to their individual needs and functional limitations. Exercise helps improve muscle strength, endurance, and overall exercise capacity, leading to enhanced quality of life.
- Education and Behavioural Support: Pulmonary rehabilitation also provides education on COPD management, breathing techniques, energy conservation

strategies, and coping skills to empower non-smoking patients to better manage their condition and improve self-efficacy.

4. Symptom Management and Supportive Care

- Oxygen Therapy: Non-smoking COPD patients with hypoxemia may gain from further oxygen therapy in order to raise general well-being, lessen symptoms, and increase oxygenation. It should be prescribed based on arterial blood gas measurements and titrated to maintain target oxygen saturation levels.
- Nutritional Support: Malnutrition and weight loss are common in advanced COPD and can exacerbate symptoms and impair functional status. Non-smoking COPD patients should receive nutritional assessment and support to ensure adequate intake of calories, protein, and micronutrients.

5. Regular Monitoring and Follow-Up

- Disease Monitoring: Non-smoking COPD patients should undergo regular monitoring of symptoms, lung function, and disease progression to assess efficacy of treatment and therapy adjustment as needed. Objective measures such as spirometry, symptom assessment tools, and exacerbation history should guide treatment decisions.
- Psychosocial Support: Living with COPD can have a significant impact on mental health and quality of life. Non-smoking patients should have access to psychosocial support services, including counselling, support groups, and interventions to address anxiety, depression, and social isolation.[118]

6. Individualized Approach

- Tailored Treatment Plans: Treatment strategies for non-smokers with COPD should be individualized based on disease severity, symptoms, comorbidities, and patient preferences. Shared decision-making between patients and healthcare

providers is essential to develop personalized treatment plans that optimize outcomes and improve quality of life.

MATERIALS AND METHODS

A 12-month observational study was conducted in KLE'S Dr Prabhakar Kore Hospital and Medical Research Centre, Belagavi.

- **Study design**

The study design was a prospective observational study

- **Study period and duration**

It was done in patients coming on OPD basis or admitted COPD patients from February 2023- January 2024

- **Study place**

This study was a Prospective observational study carried out in the Department of Respiratory Medicine, at KLE'S Dr Prabhakar Kore Hospital and Medical Research Centre, Belagavi.

- **Sample size**

The expected sample size was determined using the mean change in FEV1 at 52 weeks amongst COPD patients on Triple therapy at 94 ± 4 from the study by David A. Lipson et al.[5] Considering SD of 4, at 5% alpha error, 95% Confidence level and precision at 1% sample size of 62 was obtained. Considering 10% non-response rate 62 + 6 = 68 subjects were to be included in the study.

$$\text{Sample size} = \frac{Z_{1-\alpha/2}{}^2 SD^2}{d^2}$$

$Z_{1-\alpha/2}$ = Is standard normal variate as mentioned in previous section.
SD = Standard deviation of variable. Value of standard deviation can be taken from previously done study or through pilot study.
d = Absolute error or precision as mentioned in previous section

After the allotted time, 95 participants were examined in total.

- **Study protocol:**

Cases at KLE'S Dr Prabhakar Kore Hospital and Medical Research Centre, Belagavi will be screened and those who fulfil the inclusion and exclusion criteria were recruited for the study. With the approval of the ethical committee written informed consent was taken from all the participants enrolled for the study

- **Outcomes**

Evaluating the clinical effectiveness of triple drug therapy combination containing LABA, LAMA and ICS in non-smoking COPD patients is the primary outcome of the study

- **Inclusion Criteria:**

  - Non- smoking COPD patients
  - Age> 40 years
  - Clinically confirmed cases of COPD according to latest GOLD COPD guidelines
  - Post-bronchodilator FEV1< 80% predicted
  - Post-bronchodilator FEV1/FVC ratio< 0.70
  - CAT score≥ 10

- **Exclusion Criteria:**

  - Current diagnosis of Bronchial Asthma or other clinically significant respiratory disorders

- COPD due to smoking
- Respiratory tract infection that had not resolved for ≥ 7 days prior to screening.
- Active PTB

♦ **Method of collection of data**

- The study was a prospective observational study which was conducted over a period of one year. Every participant who had been given a COPD diagnosis and who met the criteria set forth by the most recent guidelines from the Global Initiative for COPD was evaluated in-depth using a proforma.

- COPD diagnosis was confirmed as per the latest GOLD guidelines.

- A thorough history of symptoms, addictions, occupation, exposures, past illness along with relevant family history was taken.
- Thorough general and physical examination of the patient was recorded.
- All the patients with non-smoking aetiology for COPD were evaluated with X-ray chest, Lung function test, absolute eosinophil counts, 6-minute walk test, filling of SGR- Questionnaire, COPD Assessment test and anthropometry evaluation following which CAT score, BODE index, SGRQ ratio were calculated at enrolment.
- Patients were given 12 weeks of triple drug therapy with MDI/DPI as a single inhaler device.
- Patients were told to report in case of any signs of aggravation of symptoms like breathlessness, cough, expectoration etc. or any other adverse effect faced due to the drug.
- After 12 weeks, the study participants underwent a comprehensive examination. with repeat Lung function test, 6-minute walk test, Chest X-ray, filling of SGR-

Questionnaire, COPD Assessment test and anthropometry evaluation following which CAT score, BODE index, SGRQ ratio were calculated and clinical effectiveness of the triple drug therapy were assessed based on the comparison of parameters involving various scores and grading.

- **Investigations**
  - Chest X-ray
  - Spirometry

- **Ethical Clearance**

Before the study began, ethical approval was received by the KLE Academy of Higher Education and Research, Belagavi, Ethical and Research Committee.

- **Informed Consent**

All of the patients who met the requirements were told about the study's procedures and their involvement before they were enrolled. Patients were taken into consideration for the study after obtaining written informed consent.

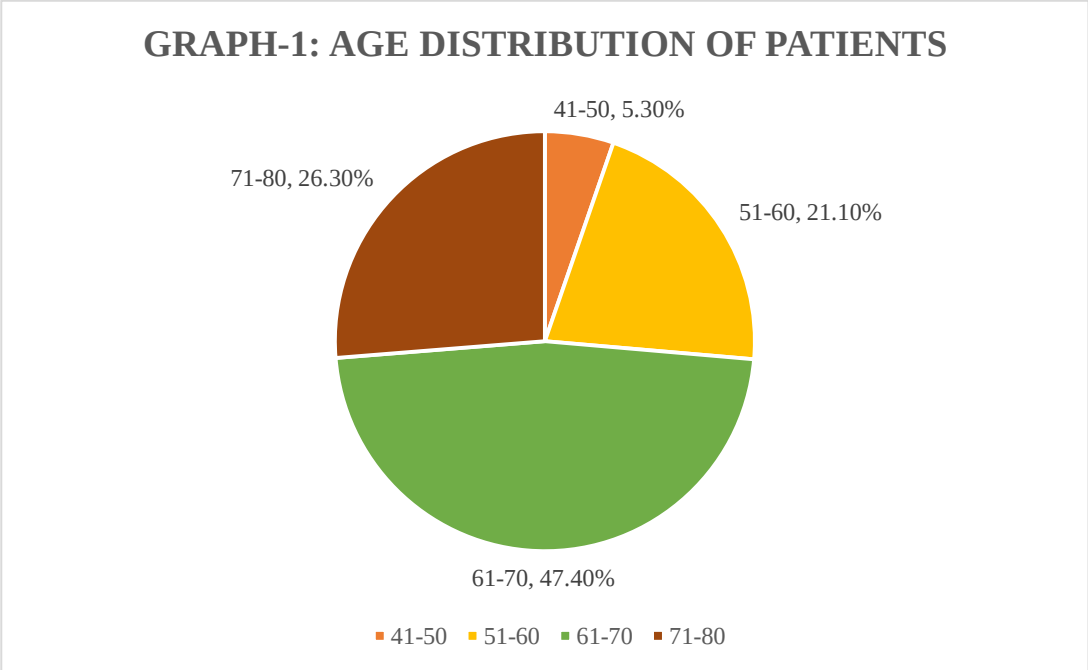
- **Statistical analysis**

Data was entered into MS Excel spreadsheet and analysed using SPSS v21. Categorical data was represented as frequencies and percentages. Continuous data was presented as mean and standard deviation. Paired t test was used as test of significance for continuous data. Chi square test was used as test of significance for categorical data. P value less than 0.05 was considered as statistically significant. Bar charts and pie charts were used for pictorial representation of data.

RESULTS

Table-6: Age distribution of patients

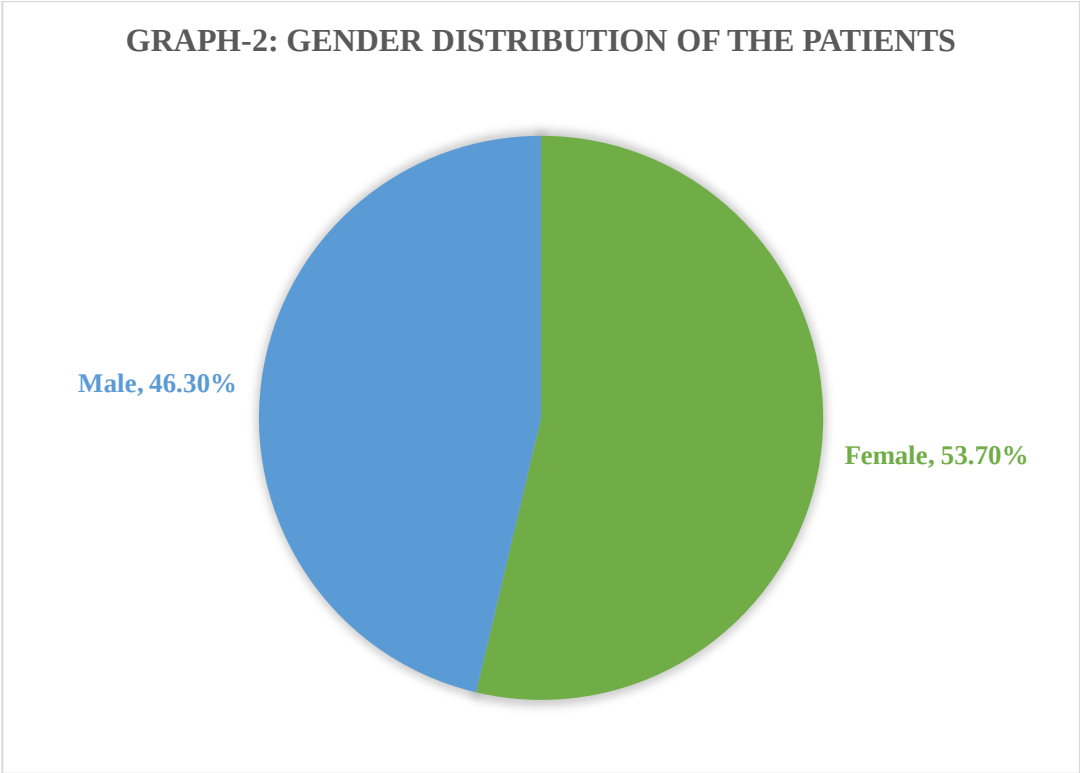
	Frequency	Percent
41-50	5	5.3
51-60	20	21.1
61-70	45	47.4
71-80	25	26.3
Total	95	100.0



- This graph shows the age distribution of the sample population.
- The majority of the participants are in the age group 61-70 (47.4%), followed by 71-80 (26.3%). The smallest groups are 41-50 (5.3%) and 51-60 (21.1%).

Table-7: Gender distribution of the patients

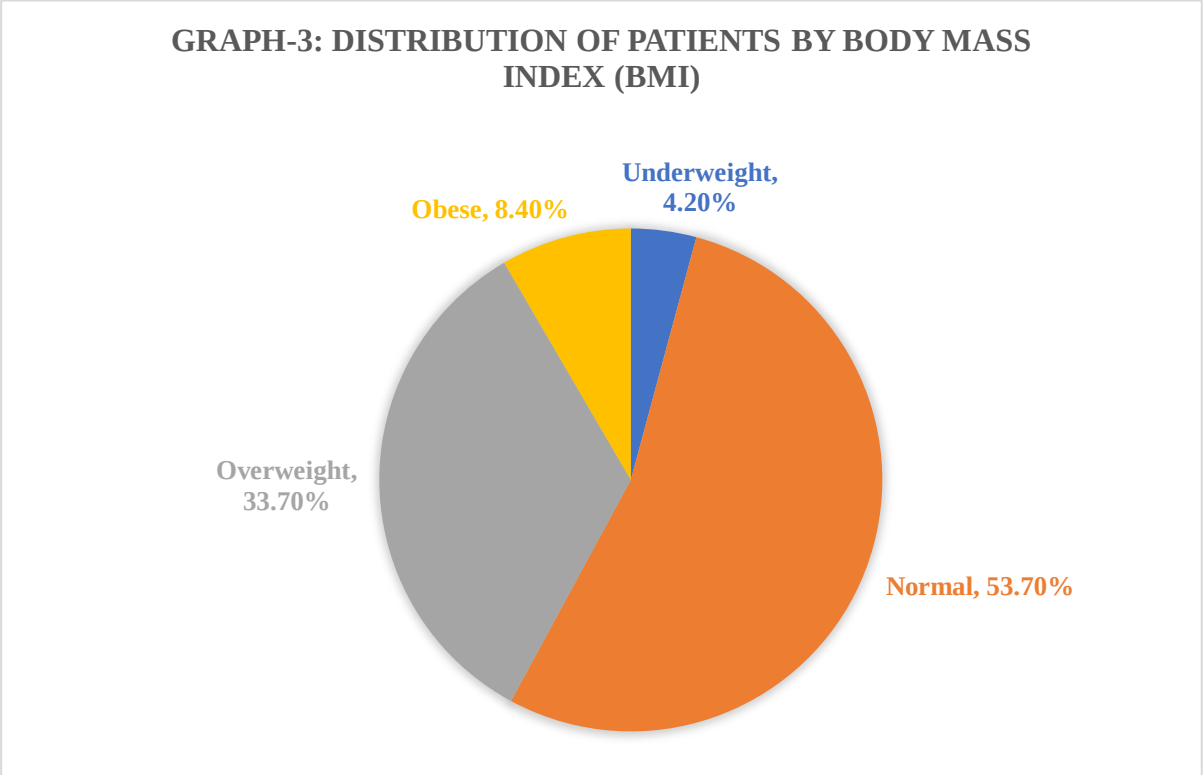
	Frequency	Percent
Female	1	53.7
Male	44	46.3
Total	95	100.0



- This graph presents the gender breakdown of the participants.
- The sample has slightly more females (53.7%) compared to males (46.3%).

Table-8: Distribution of patients by body mass index (BMI)

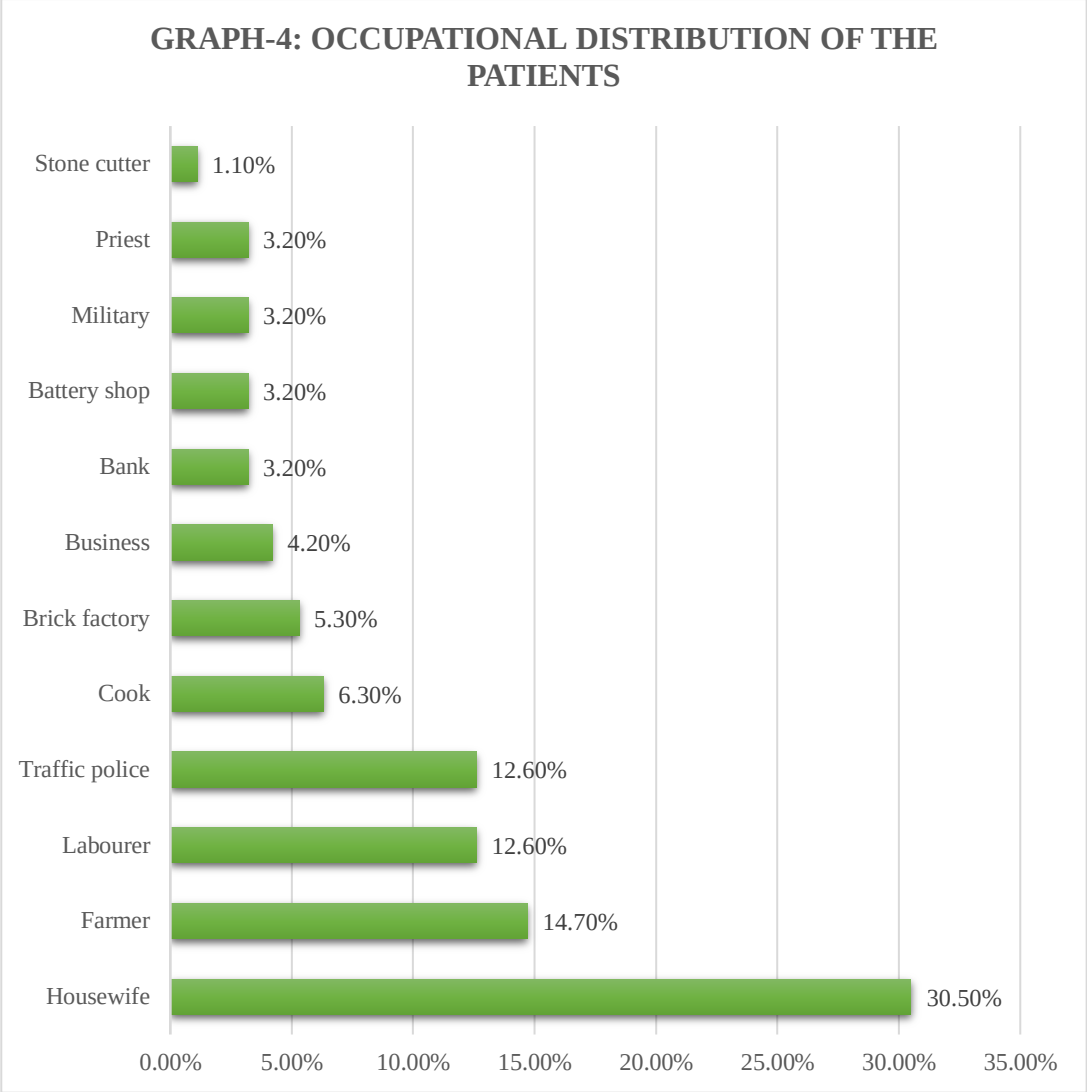
	Frequency	Percent
Underweight	4	4.2
Normal	51	53.7
Overweight	32	33.7
Obese	8	8.4
Total	95	100.0



- This graph categorizes participants based on their BMI.
- Most participants have a normal BMI (53.7%), followed by overweight (33.7%), obese (8.4%), and underweight (4.2%).

Table-9: Occupational distribution of the patients

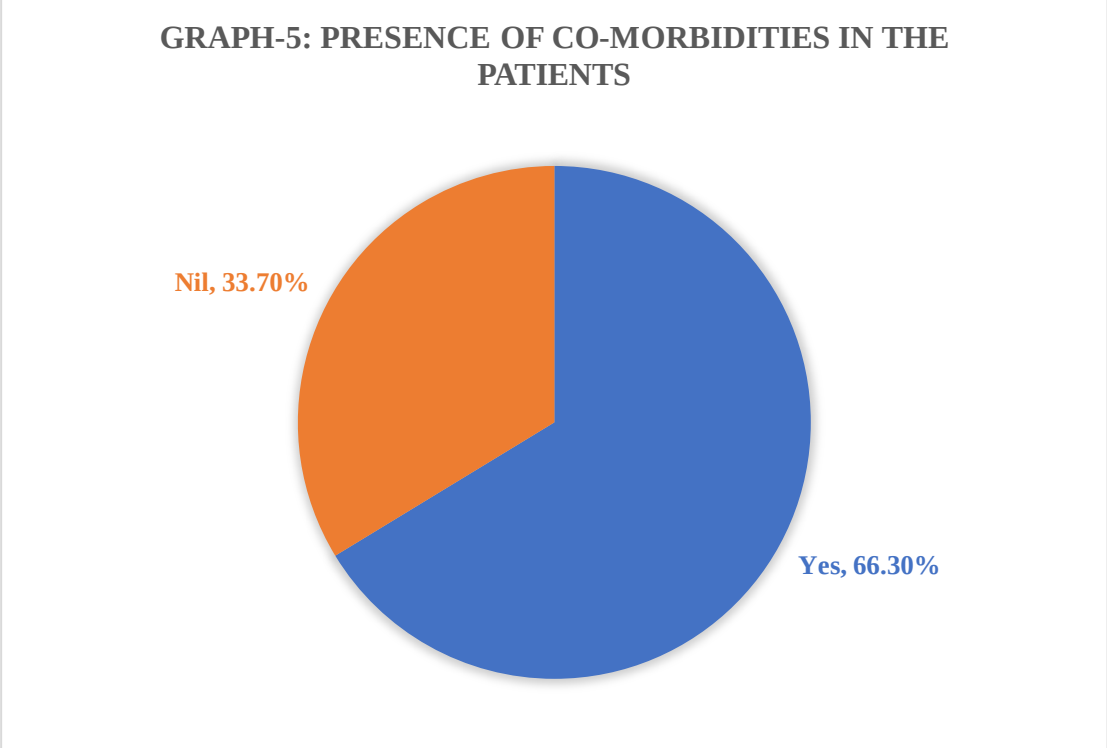
	Frequency	Percent
Housewife	29	30.5
Farmer	14	14.7
Labourer	12	12.6
Traffic police	12	12.6
Cook	6	6.3
Brick factory	5	5.3
Business	4	4.2
Bank	3	3.2
Battery shop	3	3.2
Military	3	3.2
Priest	3	3.2
Stone cutter	1	1.1
Total	95	100.0



- This graph shows the various occupations of the participants.
- The most common occupation among the individuals is being a housewife, accounting for 30.5% of the total sample. Farmers and labourers each make up a significant portion, at 14.7% and 12.6% respectively, along with traffic police. The least represented occupation is stone cutting, with only one individual, constituting 1.1% of the sample. The total sample size is 95 individuals, making up 100% of the data set.

Table-10: Presence of co-morbidities in the patients

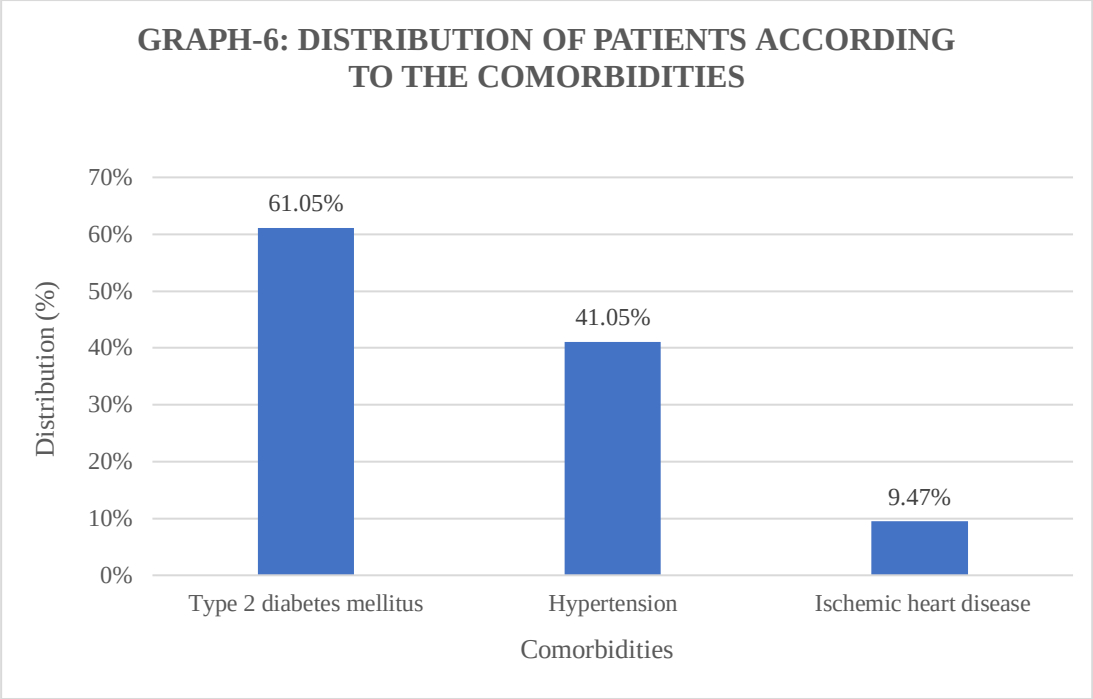
	Frequency	Percent
Yes	63	66.3
Nil	32	33.7
Total	95	100.0



- This graph shows the presence of comorbidities in the sample.
- A significant portion (66.3%) of participants have comorbidities, while 33.7% do not.

Table-11: Distribution of patients according to the comorbidities and its association with GOLD grading

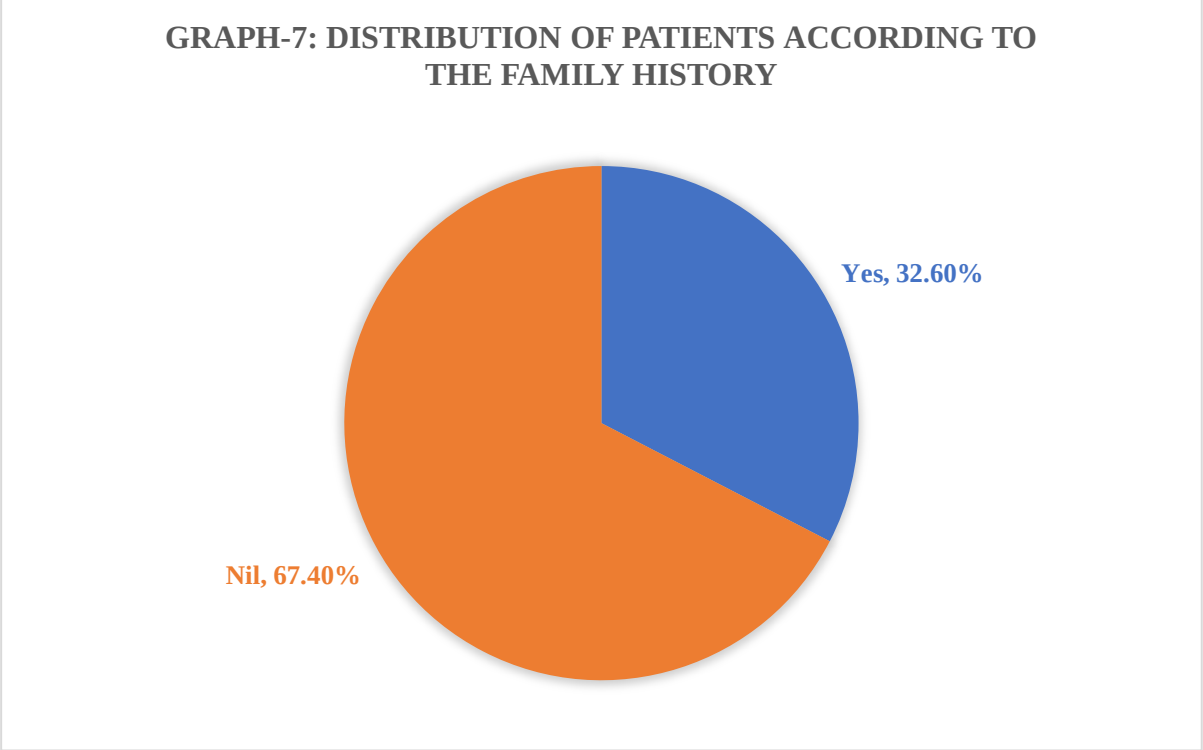
Comorbidities	GOLD grading								Total		p value
	1		2		3		4		No.	%	
	No	%	No	%	No	%	No	%			
TDM	2	3.45	45	77.59	9	15.52	2	3.45	58	61.05	0.919
Hypertension	2	5.13	29	74.36	7	17.95	1	2.56	39	41.05	0.890
IHD	1	11.11	5	55.56	3	33.33	0	0.00	9	9.47	0.168



- The graph shows the distribution of co-morbidities in the study population, having T2DM, hypertension and IHD noted in 61.05%, 41.05% and 9.45% respectively.

Table-12: Distribution of patients according to the family history

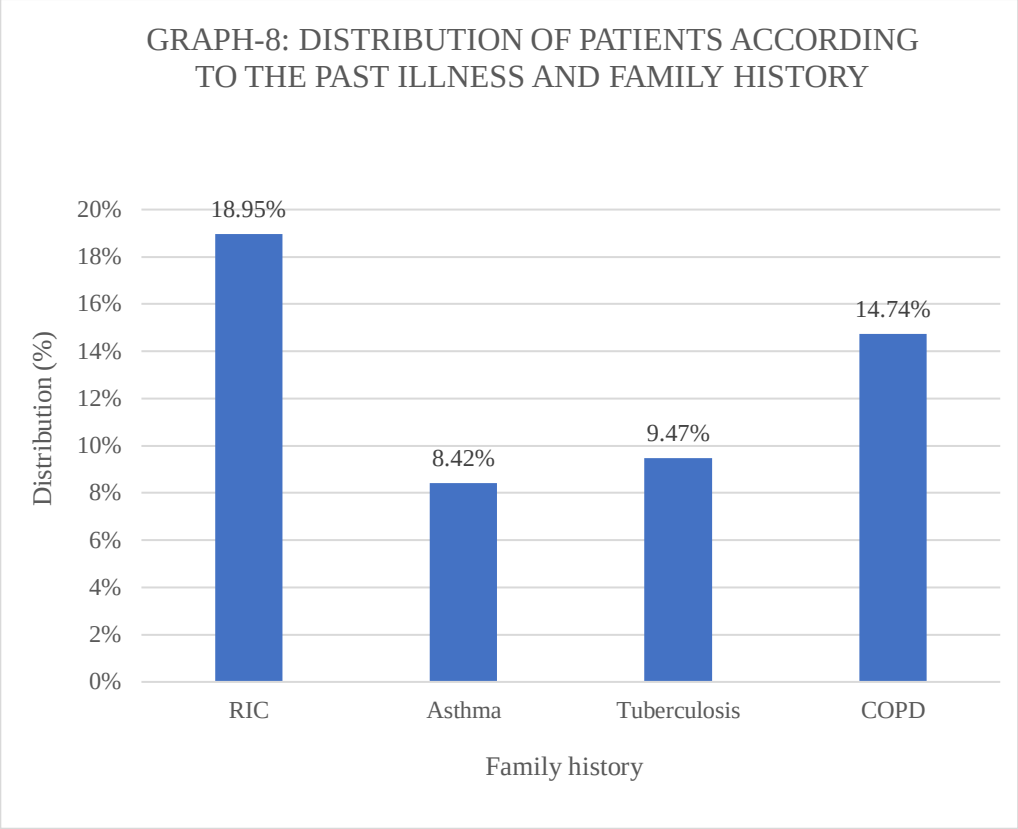
	Frequency	Percent
Yes	31	32.6
Nil	64	67.4
Total	95	100.0



- This graph shows whether participants have a family history of illness.
- About one-third (32.6%) have a family history of illness, while 67.4% do not.

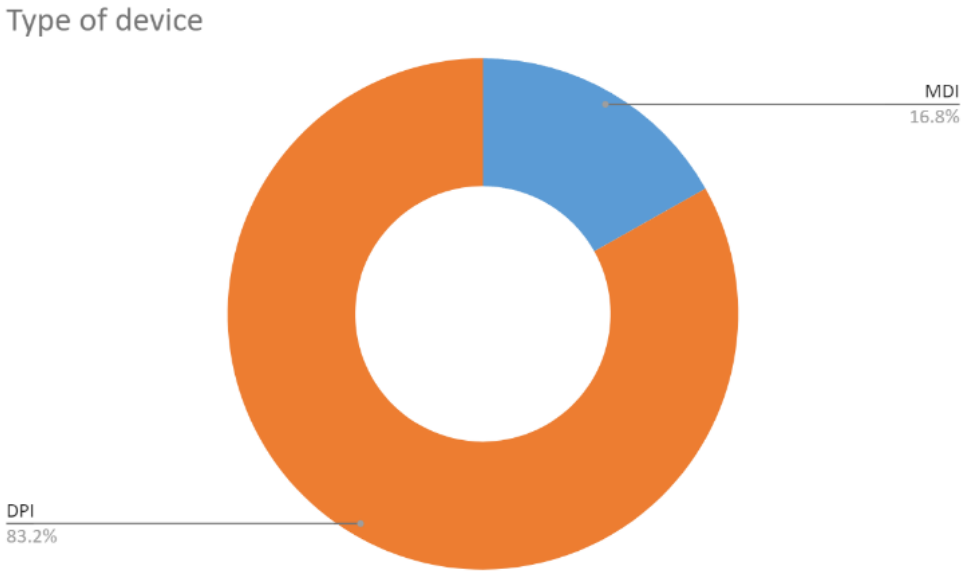
Table-13: Distribution of patients according to the past illness* and family history, and its association with GOLD grading

History of past illness	GOLD grading								Total	
	1		2		3		4		No.	%
	No	%	No	%	No	%	No	%		
*RIC	0	0.00	17	94.44	1	5.56	0	0.00	18	18.95
Asthma	0	0.00	7	87.50	1	12.50	0	0.00	8	8.42
PTB	1	11.11	8	88.89	0	0.00	0	0.00	9	9.47
COPD	0	0.00	9	64.29	4	28.57	1	7.14	14	14.74
Total	**3**	3.16	**72**	75.79	**17**	17.89	**3**	3.16	**95**	**100.00**



- In the present study history of RIC was noted in 18.95% of the patients and family history of asthma, tuberculosis and COPD was noted in 8.42%, 9.47% and 14.74% of the patients respectively.

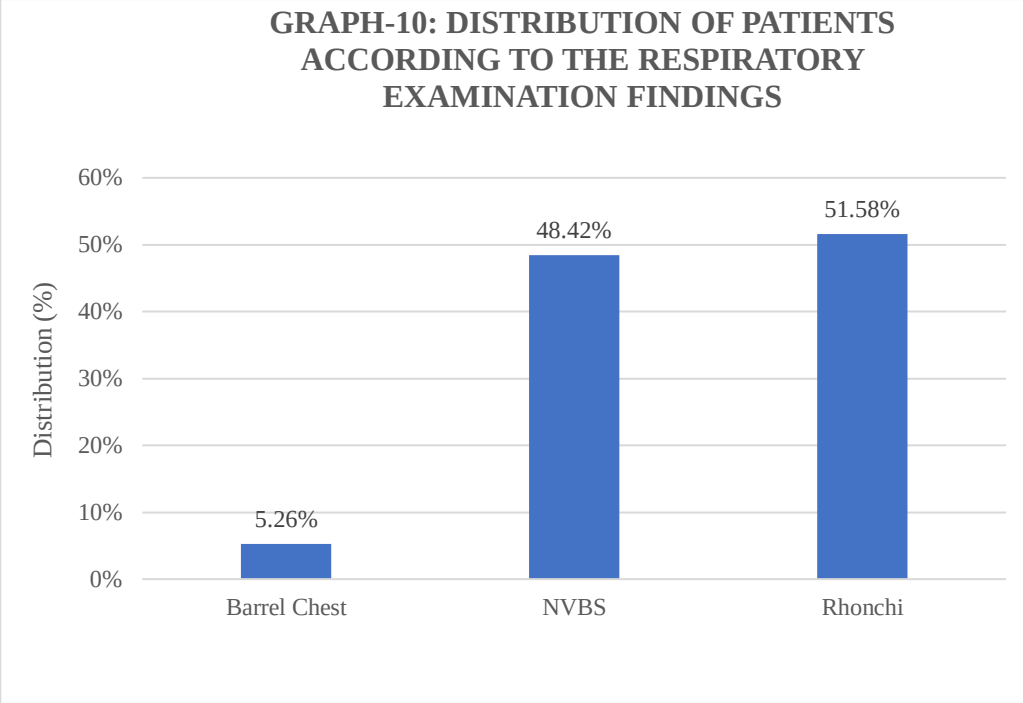
Graph-9: Distribution of patients according to the type of device



- DPI: This segment represents 83.2% of the total devices used.
- MDI (Metered Dose Inhaler): This segment accounts for 16.8% of the total devices used.

Table-14: Distribution of patients according to the respiratory examination findings and its association with GOLD grading

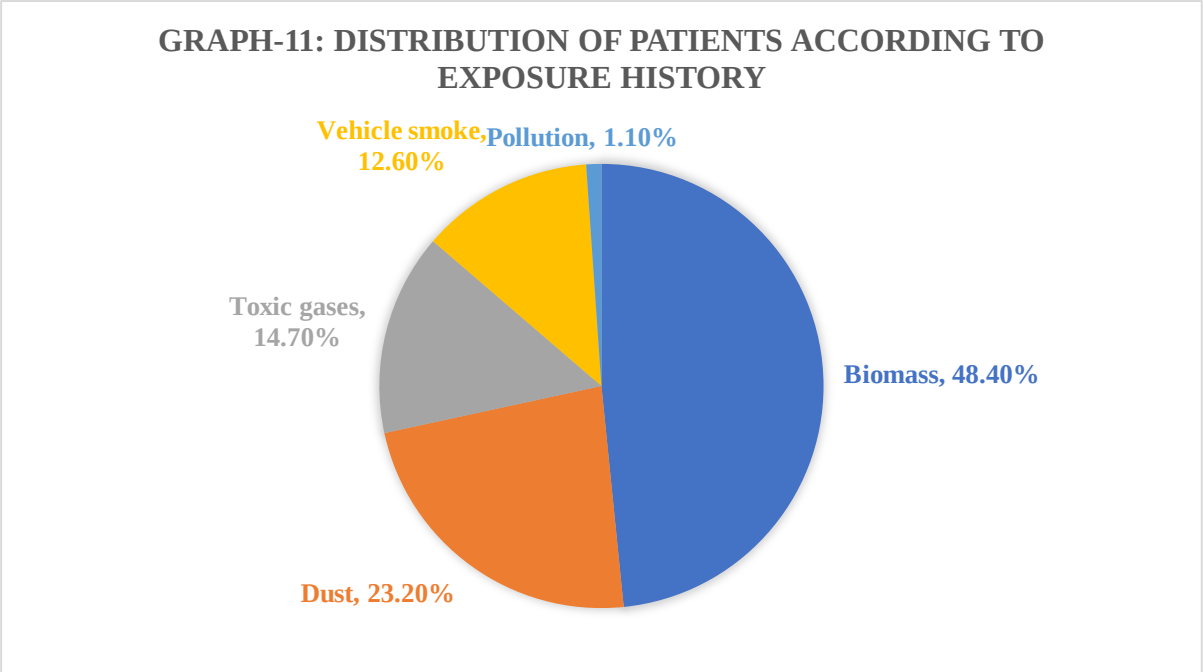
Respiratory examination findings	GOLD grading								Total	
	1		2		3		4		No.	%
	No	%	No	%	No	%	No	%		
Barrel Chest	0	0.00	4	80.00	1	20.00	0	0.00	5	5.26
NVBS	2	4.35	37	80.43	7	15.22	0	0.00	46	48.42
Rhonchi	1	2.04	35	71.43	10	20.41	3	6.12	49	51.58
Total	**3**	3.16	**72**	75.79	**17**	17.89	**3**	3.16	**95**	**100.00**



In this study on physical examination, Barrel Chest was noted in 5.26% of the patients and rhonchi in 51.58%.

Table-15: Distribution of patients according to exposure history

	Frequency	Percent
Biomass	46	48.4
Dust	22	23.2
Toxic gases	14	14.7
Vehicle smoke	12	12.6
Pollution	1	1.1
Total	95	100.0



- This graph categorizes participants based on their exposure to various environmental factors.
- Biomass exposure is the most common (48.4%), followed by dust (23.2%), toxic gases (14.7%), vehicle smoke (12.6%), and pollution (1.1%).

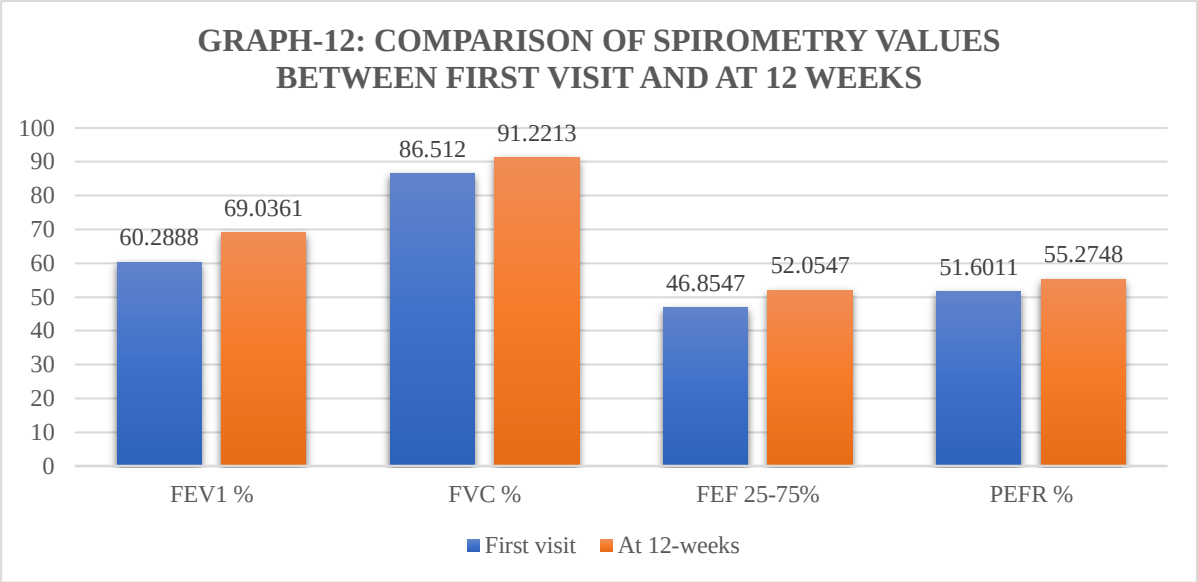
Table-16: Baseline characteristics

	Mean	Std. Deviation
AGE	64.82	8.317
HEIGHT	160.37	6.365
WEIGHT	63.08	9.7
BMI	24.52	3.6
PR	88.65	9.255
SBP (mm Hg)	126.63	8.48
DBP (mm Hg)	76.88	7.28
SPO2	96.78	1.423
FEV1 %	60.2888	12.48108
FVC %	86.512	18.79621
FEV1/FVC	0.6774	0.04251
FEF 25-75%	46.8547	14.82759
PEFR %	51.6011	17.77456
6MWD (metres)	382.74	114.55
MMRC Grade	1.59	0.92
CAT score	27.09	3.17
SGRQ ratio	38.29	12.60
symptoms	66.55	15.20
activity	40.53	13.76
impact	27.26	16.35
BODE TOTAL	3.86	1.67
BODE QUARTILE	n(%)	
I	5(5.3)	
II	40(42.1)	
III	40(42.1)	
IV	10(10.5)	
GOLD GRADING	n(%)	
Mild	3(3.16)	
Moderate	72(75.79)	
Severe	17(17.89)	
Very Severe	3(3.16)	

This table shows mean values and standard deviations for various health parameters.

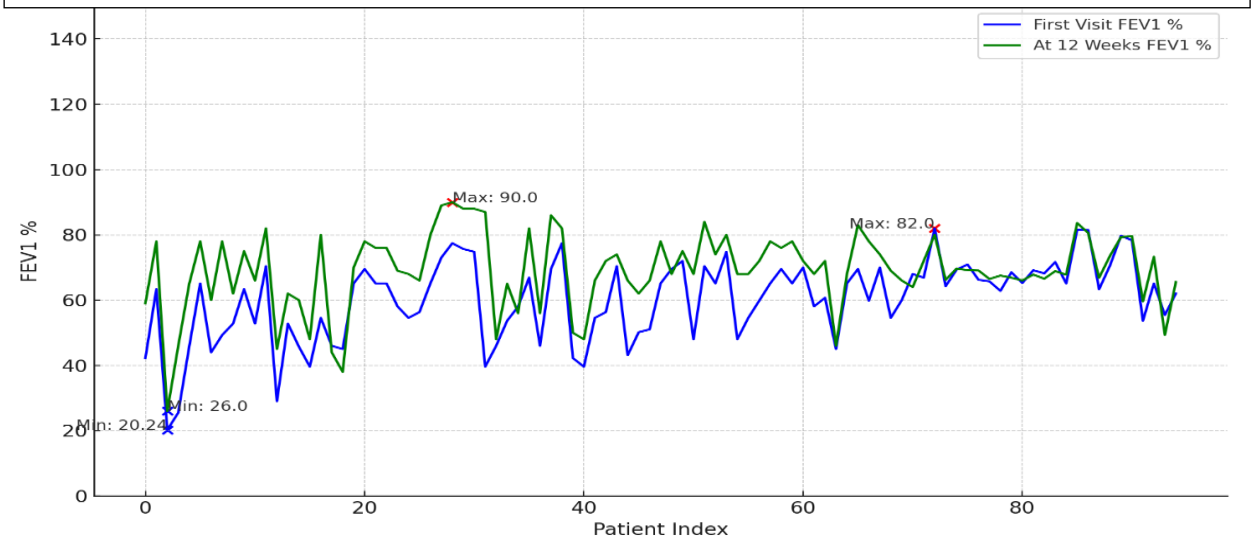
Table-17: Comparison of spirometry values between first visit and at 12 weeks

Variable	First-visit		At 12-weeks		P value
	Mean	SD	Mean	SD	
FEV1 %	60.2888	12.48108	69.0361	11.90893	0.001
FVC %	86.5120	18.79621	91.2213	14.92416	0.001
FEV1/FVC	.6774	.04251	.7488	.07234	0.001
FEF 25-75%	46.8547	14.82759	52.0547	13.63872	0.001
PEFR %	51.6011	17.77456	55.2748	14.95994	0.001

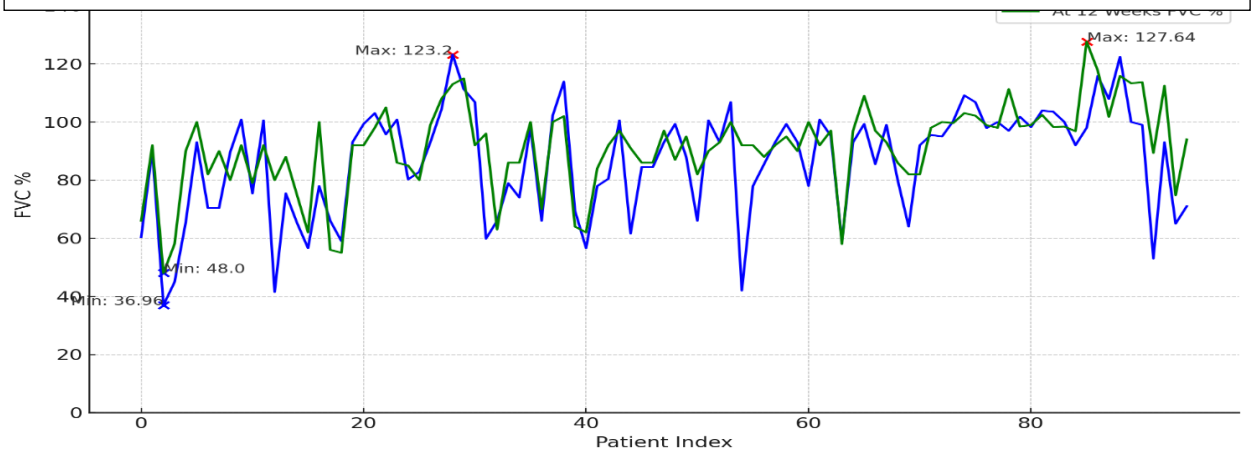


- These tables compare various health parameters between the first and follow-up visits.
- Significant improvements were seen in FEV1%, FVC%, FEV1/FVC, FEF 25-75%, and PEFR% from the first to the follow-up visit, all with p-values of 0.001 indicating statistical significance.

GRAPH-13: COMPARISION OF FEV1% OF PATIENTS AT FIRST VISIT AND AT 12 WEEKS



GRAPH-14: COMPARISION OF FVC% OF PATIENTS AT FIRST VISIT AND AT 12 WEEKS



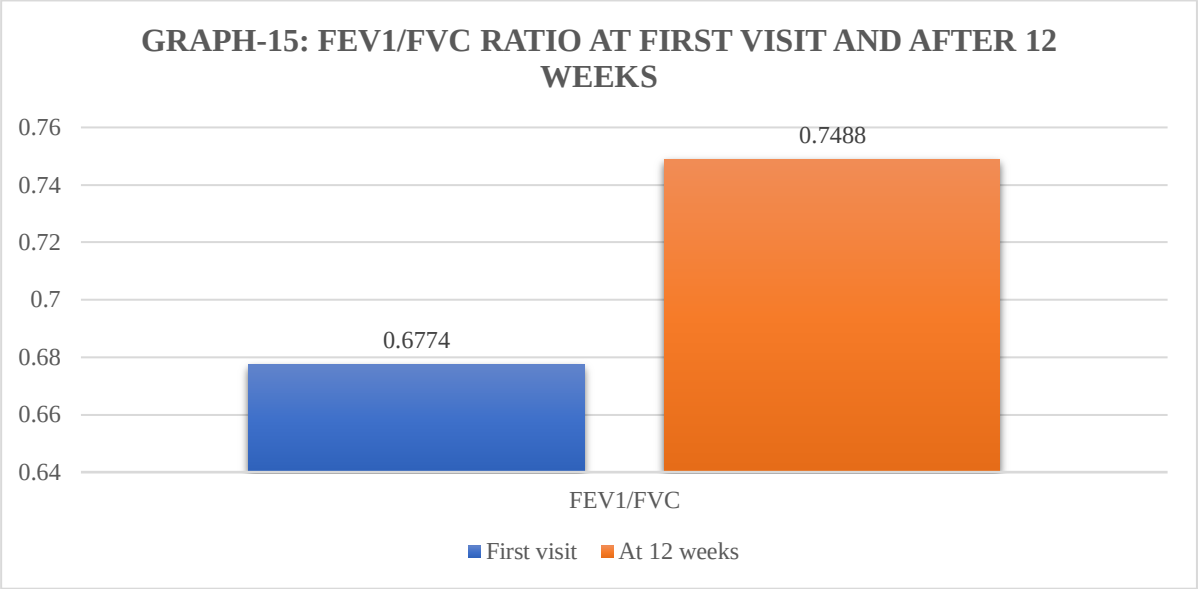
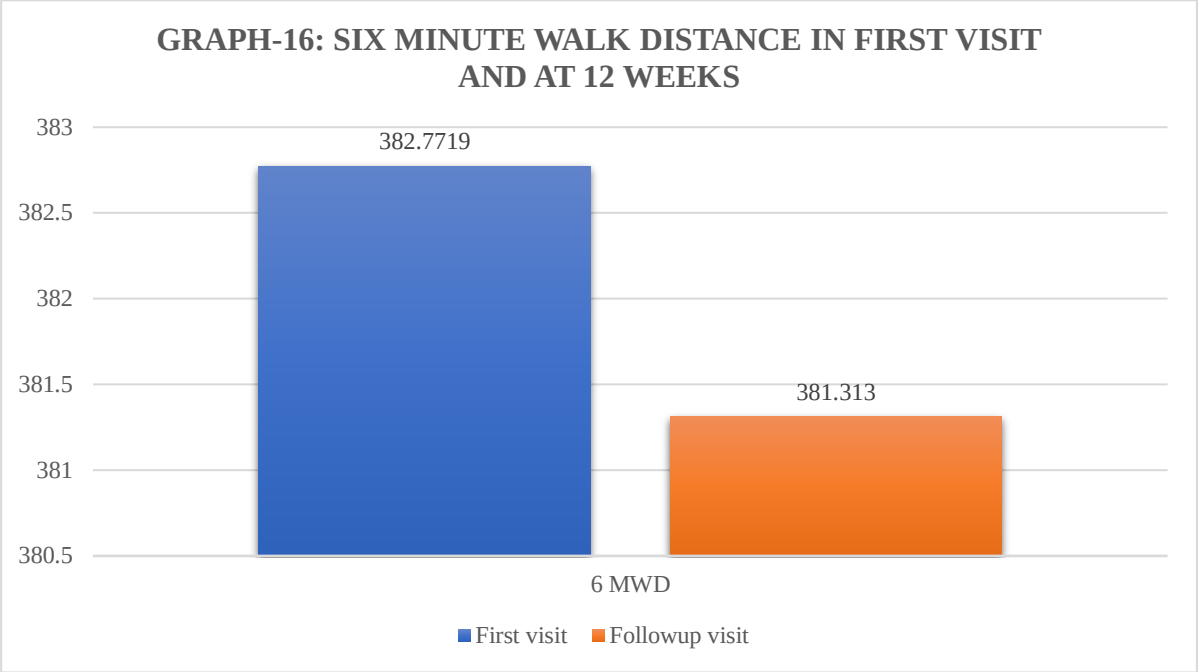


Table-18: 6 minute walk distance in first visit and at 12 weeks

Variable	First-visit		At 12-weeks		P value
	Mean	SD	Mean	SD	
6 MWD	382.7719	114.61198	381.313	106.1933	0.388

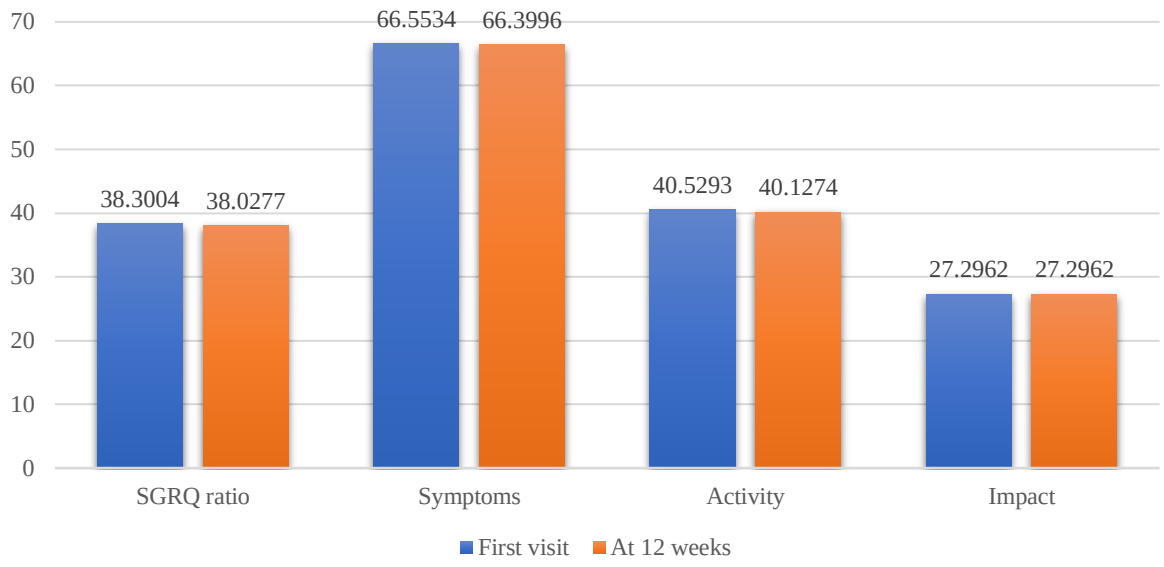


- The comparison of the 6 MWD test results between the first visit and at 12 weeks is shown in this graph
- The mean 6 MWD at the first visit was 382.77 meters with a standard deviation of 114.61 meters, while at 12 weeks, the mean was 381.31 meters with a standard deviation of 106.19 meters.

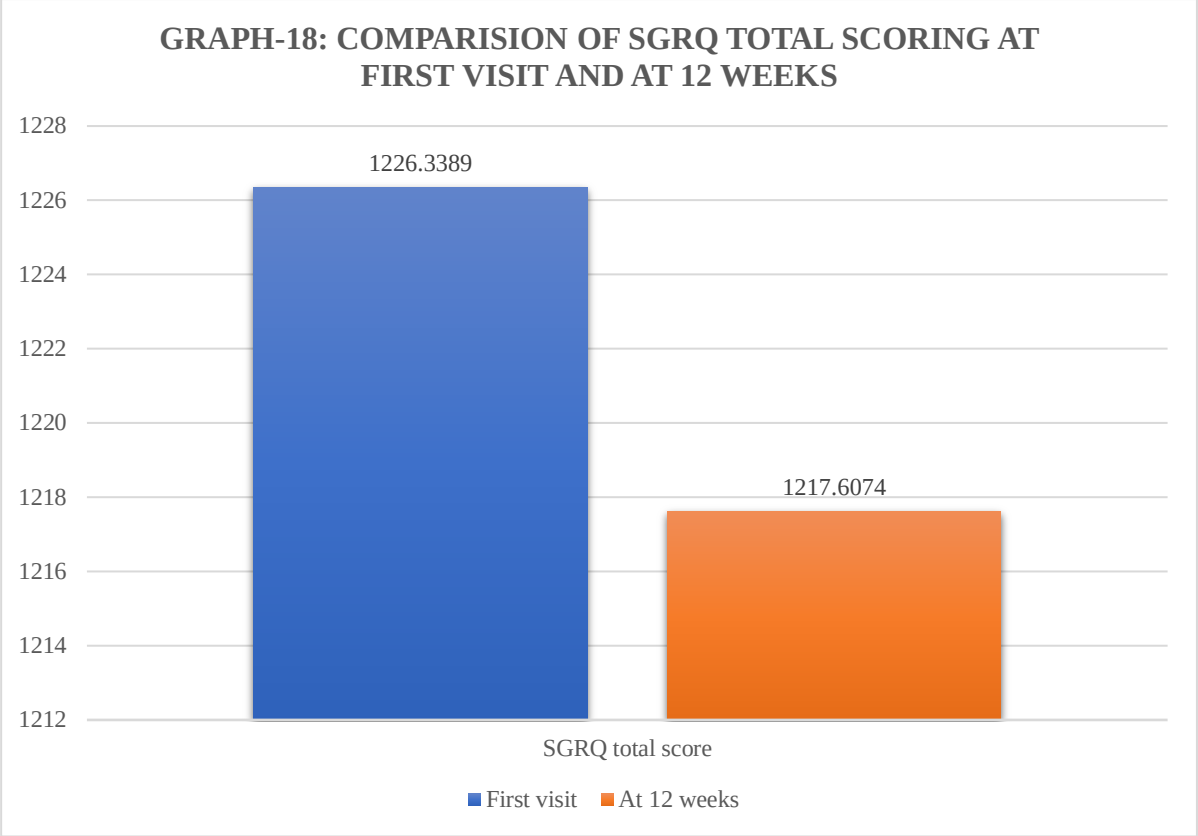
Table-19: SGRQ comparison of ratio and individual parameters first visit and at 12 weeks

Variable	First visit		At 12 weeks		P value
	Mean	SD	Mean	SD	
SGRQ ratio	38.3004	12.59559	38.0277	12.57522	0.006
Symptoms	66.5534	15.20596	66.3996	15.24277	0.164
Activity	40.5293	13.77469	40.1274	13.51881	0.057
Impact	27.2962	16.34385	27.2962	16.34385	
SGRQ total score	1226.3389	403.29808	1217.6074	402.64605	0.006

GRAPH-17: SGRQ COMPARISION OF RATIO AND INDIVIDUAL PARAMETRES FIRST VISIT AND AT 12 WEEKS



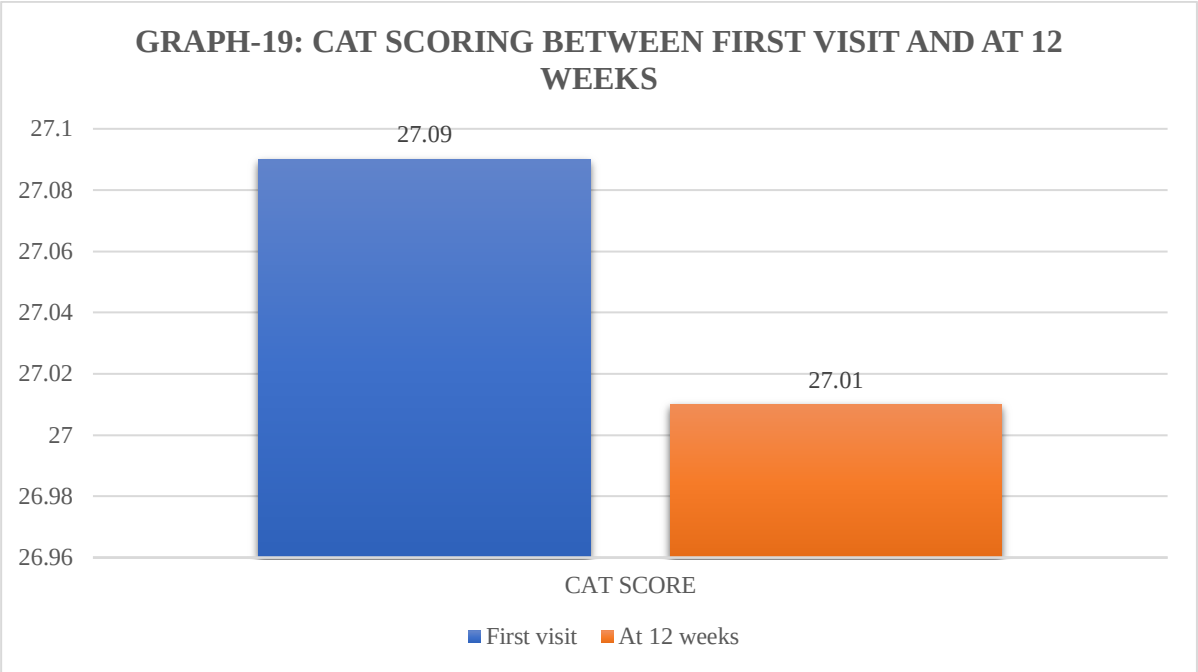
- The graph shows that there were minimal changes in the SGRQ ratio, symptoms, activity, and impact scores over the 12-week period.
- While there are slight improvements in the SGRQ ratio and activity scores, and a stable symptoms score, the impact score did not change.



The decrease in the SGRQ total score from 1226.3389 to 1217.6074 is seen over the 12-week period.

Table-20: CAT scoring between first and at 12 weeks

Variable	First visit		At 12 weeks		P value
	Mean	SD	Mean	SD	
CAT SCORE	27.09	3.173	27.01	3.217	0.778



- This table compares CAT score between the first and follow-up visits.
- The CAT scores between the first visit and at 12 weeks show a negligible change, with the mean scores remaining almost identical (27.09 at the first visit and 27.01 at 12 weeks).

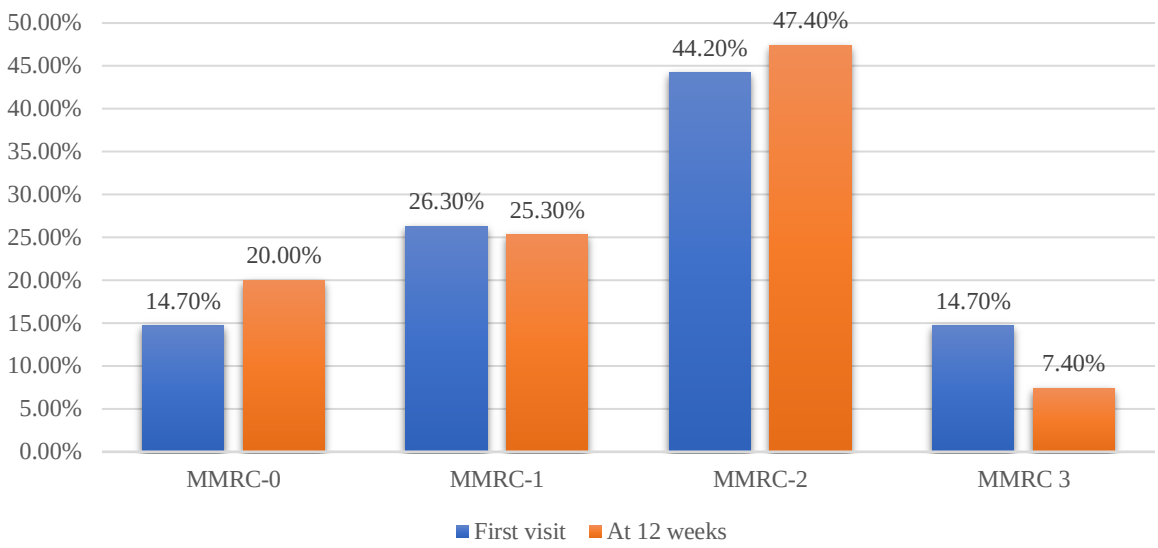
Table-21: Distribution of patients according to the MMRC grading at first visit and at 12 weeks

			Visit		Total
			First	At 12 weeks	
MMRC	0	Count	14	19	33
		%	14.7%	20.0%	17.4%
	1	Count	25	24	49
		%	26.3%	25.3%	25.8%
	2	Count	42	45	87
		%	44.2%	47.4%	45.8%
	3	Count	14	7	21
		%	14.7%	7.4%	11.1%
Total		Count	95	95	190
		%	100.0%	100.0%	100.0%

Chi square = 3.215, P value = 0.360 (NS)

The MMRC dyspnoea scale scores comparing the first visit and 12 weeks show some improvements in patients' breathlessness. The percentage of patients with no breathlessness (MMRC score 0) increased from 14.7% to 20.0%, and those with severe breathlessness (MMRC score 3) decreased significantly from 14.7% to 7.4%. The proportion of patients with moderate breathlessness (MMRC score 2) slightly increased from 44.2% to 47.4%, while those with mild breathlessness (MMRC score 1) remained relatively stable. Overall, these results indicate an improvement in dyspnoea, particularly among those with the most severe symptoms.

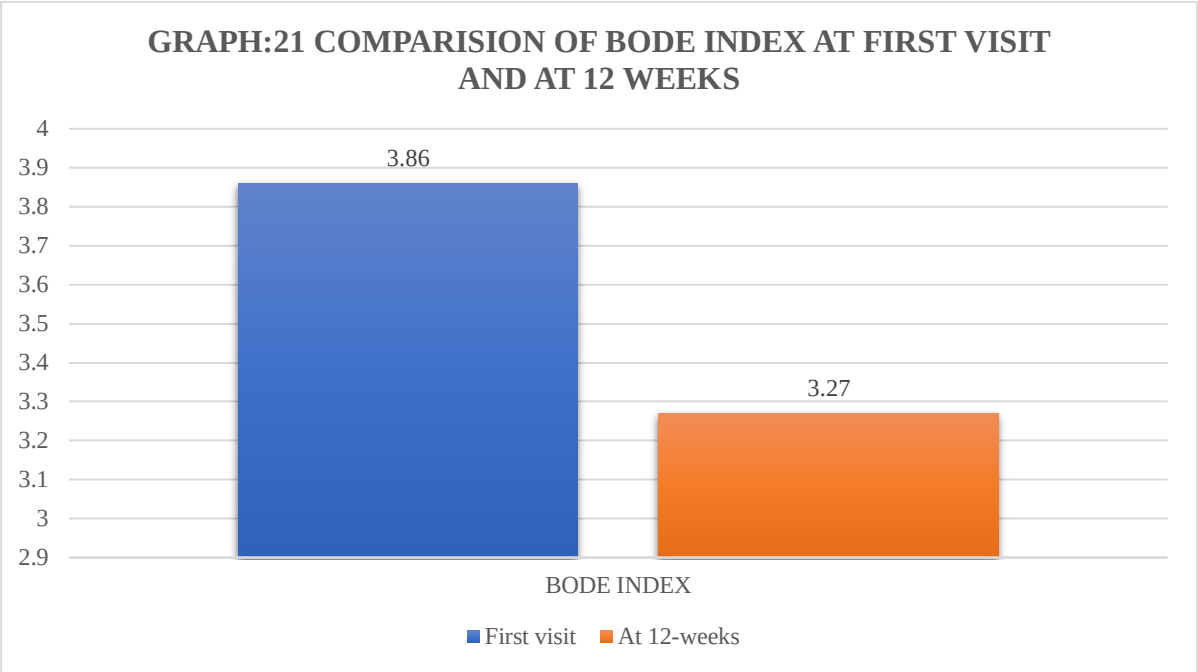
GRAPH-20: DISTRIBUTION OF PATIENTS ACCORDING TO THE MMRC GRADING AT FIRST VISIT AND AT 12 WEEKS



- This table compares MMRC dyspnoea scores between the first and follow-up visits.
- There is no significant change in MMRC scores between visits, with a p-value of 0.360.

Table-22: Comparison of BODE index at first visit and at 12 weeks

Variable	First visit		At 12 weeks		P value
	Mean	SD	Mean	SD	
BODE INDEX	3.86	1.667	3.27	1.425	0.001

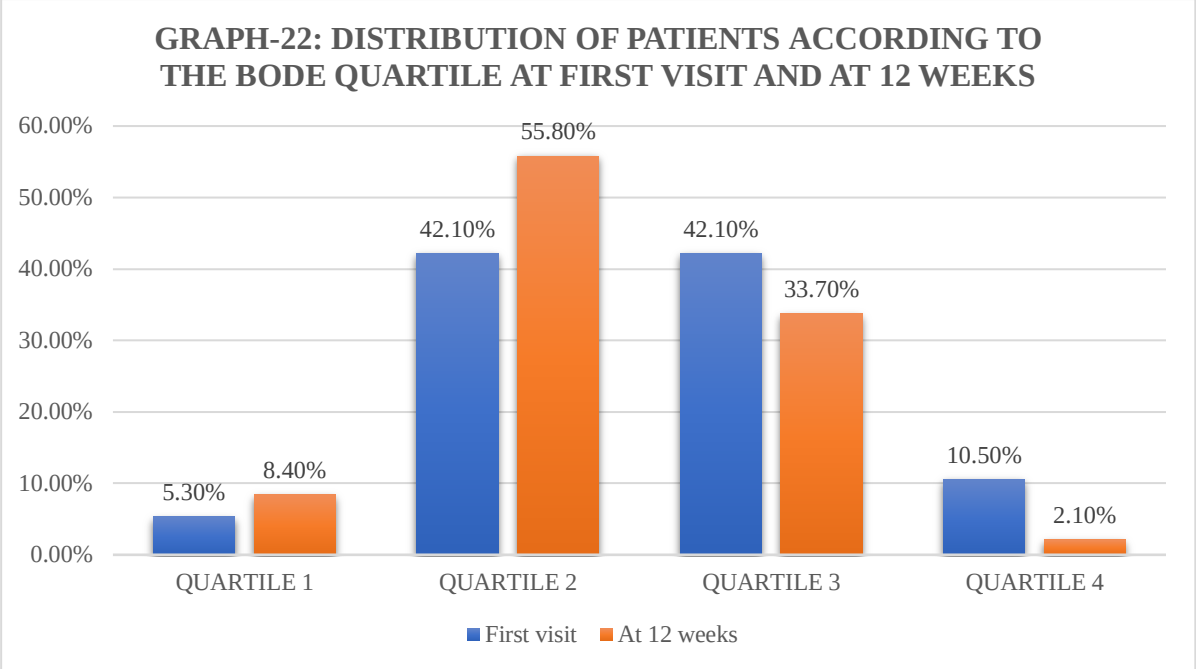


- There is a noticeable decrease in the BODE index from the first visit to the follow-up visit (3.86 to 3.27)

Table-23: Distribution of patients according to the BODE QUARTILE at first visit and at 12 weeks

			Visit		Total
			First	At 12 weeks	
BODE QUARTILE	1	Count	5	8	13
		%	5.3%	8.4%	6.8%
	2	Count	40	53	93
		%	42.1%	55.8%	48.9%
	3	Count	40	32	72
		%	42.1%	33.7%	37.9%
	4	Count	10	2	12
		%	10.5%	2.1%	6.3%
Total		Count	95	95	190
		%	100.0%	100.0%	100.0%

Chi square = 8.732, P value = 0.033 (S)



BODE quartiles corresponding to the BODE index **1:** 0-2, **2:** 3-4, **3:** 5-6, **4:** 7-10

- This table compares BODE index categories between the first and follow-up visits.
- There is a significant reduction in the BODE index, indicating improvement in COPD severity, with a p-value of 0.033.

Table-24: Correlation of occupation and exposure history in patients

OCCUPATION		EXPOSURE HISTORY					Total
		Biomass	Dust	Pollution	Toxic gases	Vehicle smoke	
Bank	Count	0	3	0	0	0	3
	%	0.0%	100.0%	0.0%	0.0%	0.0%	100.0%
Battery shop	Count	0	0	0	3	0	3
	%	0.0%	0.0%	0.0%	100.0%	0.0%	100.0%
Brick factory	Count	3	0	0	1	1	5
	%	60.0%	0.0%	0.0%	20.0%	20.0%	100.0%
Business	Count	1	1	0	1	1	4
	%	25.0%	25.0%	0.0%	25.0%	25.0%	100.0%
Cook	Count	6	0	0	0	0	6
	%	100.0%	0.0%	0.0%	0.0%	0.0%	100.0%
Farmer	Count	10	4	0	0	0	14
	%	71.4%	28.6%	0.0%	0.0%	0.0%	100.0%
Housewife	Count	21	7	0	1	0	29
	%	72.4%	24.1%	0.0%	3.4%	0.0%	100.0%
Labourer	Count	5	5	0	1	1	12
	%	41.7%	41.7%	0.0%	8.3%	8.3%	100.0%
Military	Count	0	1	0	2	0	3
	%	0.0%	33.3%	0.0%	66.7%	0.0%	100.0%
Priest	Count	0	0	0	3	0	3
	%	0.0%	0.0%	0.0%	100.0%	0.0%	100.0%
Stone cutter	Count	0	1	0	0	0	1
	%	0.0%	100.0%	0.0%	0.0%	0.0%	100.0%
Traffic police	Count	0	0	1	2	9	12
	%	0.0%	0.0%	8.3%	16.7%	75.0%	100.0%
Total	Count	46	22	1	14	12	95
	%	48.4%	23.2%	1.1%	14.7%	12.6%	100.0%

Chi square = 134.557, P value = 0.001 (S)

- This table cross-tabulates occupation with different types of exposure.
- Certain occupations, like housewives and farmers, are more exposed to biomass, while labourers and military personnel are more exposed to dust and toxic gases, respectively.

GRAPH-23: CORRELATION OF OCCUPATION AND EXPOSURE HISTORY IN PATIENTS

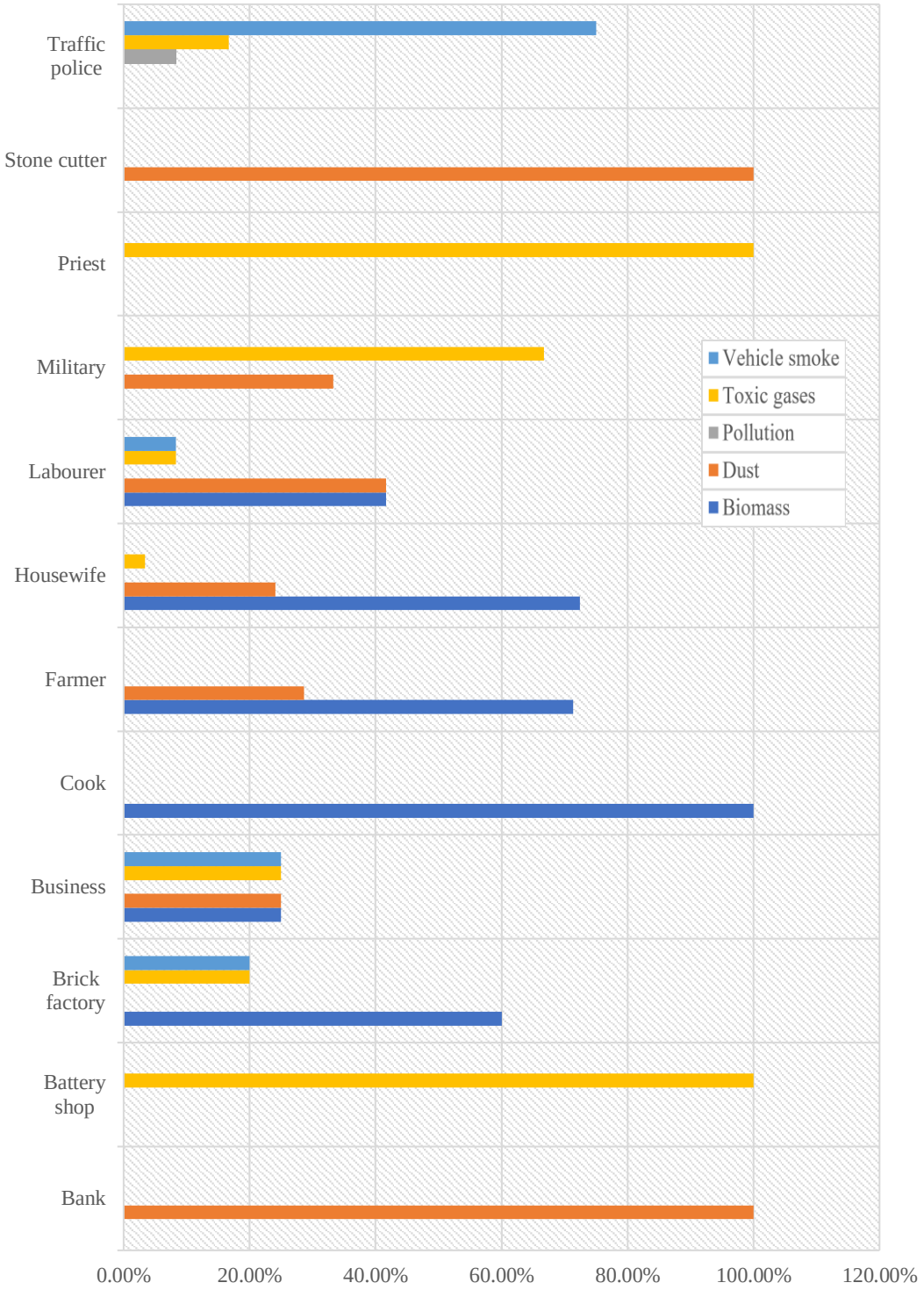


Table-25: Number of adverse effects in the patients during 12 weeks (n=95)

Adverse effects	**frequency**	%
Exacerbations:	**35**	36.8%
Others:	**16**	13%
Dry mouth	6	6.3%
Headache	2	2.1%
Increased cough	4	4.2%
Sinusitis	1	1.0%
URTI	3	3.2%

- The data presents the frequency and percentage of various adverse effects.
- The most common adverse effect is exacerbations, occurring in 36.8% of cases, followed by 13% comprising of other side effects, which includes Dry mouth at 6.31%, Increased cough at 4.21%, URTI at 3.16%, Headache at 2.10%, and Sinusitis at 1.05%.

DISCUSSION

In addition to tobacco smoke, environmental variables are also receiving more attention as risk factors for COPD. We defined COPD by the latest GOLD guidelines. The non-smoking exposures were identified.

The aim of this study was to assess the effectiveness of treatment containing triple drug combination by comparing various health parameters before and after treatment. This analysis encompasses demographic data, comorbidities, past illness history, physical examination findings, exposure history, and several respiratory function metrics. The detailed findings provide insights into the impact of the interventions on patient health outcomes.

The study had 95 participants out of which the majority of patients (47.4%) belonged to the 61-70 age-group, followed by 26.3% in the 71-80 age group the mean age being 64.82± 8.32 indicating a higher prevalence of respiratory conditions in older adults. Natalie T et al reported the mean age of patients in their study to be 65.9±10.6 amongst non-smokers.[10] In another study by Salvi et al mean age was more than 60 years. The higher age group in our study is comparable with other studies.[37]

There were 44 male (46.3%) and 51 female patients (53.7%) in our study. This was consistent with a study done by Jindal et al [11] where 43.5% were males and 56.5% were females. This indicates females are prone to non-smoking factors causing COPD. In a study by Salvi et al a comparable gender ratio was seen with 53% male and 47% female.[37]

The body mass index of all the patients was calculated and they were classified as underweight, normal and overweight and obese with a BMI <18.5, 18.5-24.9, 25-30, >30 respectively. The BMI of all patients were calculated and classified observing that the mean of the patients had 24.52 ±3.60 BMI in the study. Ramirez et al [119] reported that most patients in their study had the BMI of 27±5 which is comparable with our study and denotes that people with higher BMI had an increased risk of developing COPD. Although Salvi et al [37] in their study found BMI to be 21.3 ± 4.4 and 20.0 ± 3.3 in biomass and occupational exposure respectively.

The study indicates that a significant portion of participants (66.3%) have comorbidities, with the most common being Type 2 Diabetes Mellitus (61.05%), followed by hypertension (41.05%), and ischemic heart disease (9.47%). Despite the high prevalence of these comorbid conditions, the GOLD grading of COPD severity and the presence of comorbidities did not significantly correlate ($p > 0.05$). This suggests that while comorbidities are common among COPD patients, their presence does not necessarily correlate with the severity of COPD as measured by GOLD criteria. This finding highlights the importance of managing comorbid conditions independently of COPD severity to improve overall patient outcomes.

The findings of our study highlight the significant role that occupation plays in determining the type and level of respiratory exposure. Occupations involving biomass fuel usage, dust, and vehicle emissions are particularly hazardous and contribute to the high prevalence of respiratory conditions observed in our study population.

Biomass Exposure (48.4%): Out of the total 95 individuals, 46 (48.4%) are exposed to biomass. The highest exposure is among housewives (72.4%), farmers

(71.4%), and cooks (100%), indicating an increased prevalence due to the use of cooking fuels such as kerosene, coal, wood, hay-stalks, and animal dung manure, as well as the burning of crops, hay, animal manure, and bagasse on farms. Our study shows that burning these materials releases smoke and pollutants, which can be harmful when inhaled over prolonged periods. Several studies have found similar occupational correlation to exposure to biomass which is consistent with our finding. [20,32,34,36,39]

Dust Exposure (23.2%): Predominantly affecting farmers, labourers, and stone cutters, dust exposure can lead to chronic respiratory conditions. The type of dust observed in our study was biological dust like animal dander and waste, pollen, grain dust, sugarcane mold and hay seen in farmers and labourers. The stone cutters had been exposed to silica dust, and other materials like cement, marble, granite etc. Improved occupational safety measures and the use of personal protective equipment (PPE) are essential in mitigating this risk. [27]

Toxic Gases (14.7%): Battery shop workers, military personnel, and priests face significant exposure to toxic gases in the forms of chemical fumes, gunpowder smoke and incense sticks. Adequate ventilation and safety protocols can help reduce exposure to these hazardous substances. Hagstad et al.[27] found that in never-smokers, occupational exposure to gas, dust or fumes was significantly associated with COPD and the prevalence was as high as 24% due to the same.

Vehicle Smoke (12.6%): Traffic police are heavily exposed to vehicle emissions, highlighting the need for protective measures such as face masks and periodic health check-ups to monitor and mitigate respiratory health impacts. Kan et al [44] in their study done on traffic density exposure and decline in lung functions, observed that a

significant decline in Fev1 and FVC was seen with a preserved ratio which is consistent with our study and indicates how traffic related vehicle smoke exposure can lead to respiratory health problems.

The long-term exposure to occupational exposures to biological dusts, mineral dusts and gases/fumes at high levels were associated with increased incidence of moderate COPD in a population of Swiss working adults, particularly in males and in ages ≥40 years supporting existing evidence of a causal relationship between occupational exposures and development of COPD. [28]

FEV1 is a dynamic measure of flow indicating airway obstruction and degree of severity. The patients enrolled in the study had a baseline FEV1 of 60.29% ±12.48 which significantly improved to FEV1 % 69.04% ±11.90. The GOLD grading data at baseline and 12 weeks showed significant improvements with the majority of patients being in the moderate (75.79%) and severe (17.89%) categories at baseline, and with only a small fraction in the mild (3.16%) and very severe (3.16%) categories. At 12 weeks, there was a notable shift: the percentage of patients in the mild category increased to 17.89%, while the moderate category saw a slight decrease to 71.58%. The severe and very severe categories decreased to 9.47% and 1.05%, respectively indicating the treatment effectively reduced the severity of COPD in many patients, with more patients moving to milder categories.

FVC % at baseline was 86.51%±18.79 which statistically increased to 91.22%±14.92 at 12 weeks, indicating better lung function post-treatment. Bardsley et al in his study observed the change in FEV1 was 2.4% after bronchodilator treatment.[6] Baba et al [120] in a study showed the improvement of FEV1 from median

of 73.7(23.2) to 77.7 (23.8) with FVC improvement from median of 91.5(27.6) to 95.8(25.9) in non-smoker COPD patients after bronchodilator treatment.

In pooled analyses of various studies[3,4,7], the triple therapy of (BDP/FF/GP) significantly delayed the time to clinically important deterioration (CID) in patients with symptomatic COPD and FEV1 <50%, compared to dual therapies BDP/FF, tiotropium, and IND/GLY. Similarly, the time to sustained CID was extended with BDP/FF/GP compared to BDP/FF and tiotropium. Lipson et al [5] studied that, fewer patients on (FF/UMEC/VI) experienced significant lung function reduction compared to those on (BUD/FOR), with a median time to CID 5 times longer for triple-therapy than on dual-therapy.

The FEV1/FVC Ratio improved from 0.677 to 0.749, reflecting improved airway patency. In a study by Ramirez et al FEV1/FVC ratio with biomass exposed COPD had a mean of 0.56 ± 0.09[119]

$FEF_{25-75\%}$ is the sensitive measure of airflow in peripheral airways where primary airflow obstruction originates and it is reduced in early bronchial impairment, which is associated with small airway disease.[121] In our study there is a statistically significant improvement in FEF25-75 values from 46.85 ± 14.82 to 52.05 ±13.64 post treatment. Kwon et al in their study found FEF25-75% to be 58.7±10.0 developing COPD.[121] In a study by Knox- Brown et al [60] reduced FEF25-75% was associated with small airway obstruction especially with studied risk factors of increasing age, passive smoking, dust exposure, family history of COPD etc which is consistent with our study. Other studies, done on non-smokers had impaired FEF25-75% values measured by oscillometry indicating the significant involvement

of small airways which thereby suggest non-smoking COPD being a small airway involvement phenotype.[2,31,36,37,120]

PEFR primarily reflects large airway flow and depends on voluntary effort and muscular strength of the patient. The mean improvement in PEFR in our study is from 51.60± 17.77 to 55.27± 14.96 relatively lower as compared with other studies. In a study by Salvi et al PEFR mean was seen to be 29.8 ± 11.2 and 34.9 ± 24.3 in patients exposed to biomass and occupationally exposed COPD patients respectively.[37] Hani A et al [122] conclude in their study of pulmonary function tests including FEV1, FVC, PEFR and FEF25-75% among smokers and non-smokers that mean FVC, FEV1 and PEFR were higher in non-smoker in each age group but significantly reduced values. This effect may be because as PEFR is effort dependent, less value changes recorded in the present study may be caused by a less than maximal effort by the patients. The diurnal and daily variation in the PEFR was not studied and only point of care values were taken.

The slight decrease in the SGRQ ratio reflects an overall minor improvement in quality of life. This ratio, being a composite measure, underscores the marginal but positive effect of the interventions across different aspects of health status. This study confirms that Triple drug therapy improves the quality of life in patients of COPD showing good responsiveness in the questionnaire scores within 12 weeks of administration of treatment. ($p<0.006$) The slight decrease in the total SGRQ score from 1226.34 to 1217.61 suggests an overall improvement in the health-related QOL of the participants. Although this change is statistically significant, it is relatively small, indicating that the interventions had a modest impact on the participants' perceived health status.

The symptoms domain remained unchanged, suggesting interventions did not affect the frequency, severity, or duration of respiratory symptoms like coughing, wheezing, and breathlessness due to their chronic nature and may require prolonged treatment duration to show noticeable improvements. The slight decrease in the activity domain score indicates a minor improvement in physical activities, likely from better respiratory function post-treatment. However, this change is not significant. The impact domain score stayed the same, indicating that the psychosocial and emotional aspects of living with a respiratory condition did not change, likely due to the long-term experience of the disease.

Upon comparing individual parameters of SGRQ scoring, involved in the scoring we found that there is no improvement in symptoms possibly due to the chronic nature requiring prolonged treatment duration to show noticeable improvements and impact of disease, this could be substantiated with other studies like FLAME trial and TRILOGY trial[7] where in change in SGRQ scorings were not observed until 12weeks. Compared to the FLAME trial and the TRILOGY trial, where improvements in the SGRQ total score were not noticed until week 12, the IMPACT study's SGRQ improvements were noticed earlier.[7,123] The mean SGRQ ratios in biomass and occupationally exposed COPD patients were reported to be 60.2 ± 18.1 and 59.7 ± 16.3 in a study by Salvi et al., respectively, which is greater than what we discovered in our study and remained unchanged over a 2-year follow-up period.[37]

Bardsley et al observed significant differences in the patients given triple-therapy for 52 weeks with the mean change from baseline in the SGRQ total score and in the percentage of patients who had a response as defined by a decrease in the SGRQ total score (44.5 to 45.4) of at least 4 points ($P<0.001$).

This pattern was also apparent for all the three domains of SGRQ scores and seen as early as 4 weeks with triple therapy as compared to other studies, which is consistent with our findings.[6] TRINITY trial, a double-blind, randomized trial including 2,691 patients with severe COPD used a combination of beclomethasone dipropionate, formoterol fumarate, and glycopyrronium bromide (BDP/FF/GB) in triple therapy significantly decreasing moderate-to-severe COPD exacerbation rates compared to when given tiotropium alone (0.46 vs. 0.57; p=0.0025) concluding that fixed triple therapy offers superior clinical benefits over tiotropium for patients with symptomatic COPD also showing a significant change in SGRQ scoring reflecting the quality of life after giving triple drug therapy as treatment.[4]

In our study, CAT score increased significantly from 27.09 ± 3.17 to 27.01± 3.22 after treatment. A higher CAT score reflects more severe disease and a greater negative impact on a COPD patient's quality of life and daily functioning. In a study by Salvi et al CAT score was found to be 22.0 ± 6.5 and 25.2 ± 8.8 in biomass and occupational non-smokers which is consistent with our findings but on longitudinal follow up of these patients showed no significant change over 2 years.[37]

Salvi et al. found that for a similar degree of FEV1 impairment (~40% predicted), the mean SGRQ and CAT scores in their study were about 50% higher than the average scores reported in studies from Western nations. This suggests that the QOL for both smoking individuals developing COPD and non-smoking-COPD subjects in India is lower than in high-income countries. Early changes in measures like the SGRQ and CAT are driven by symptom reductions, and the timing of reported changes in HRQoL can be a good indicator of symptom improvements.[6]

In our study no significant change in the 6min walk test(p<0.388) with a mean of 382.77 ± 114.61 seen as a baseline in our study group. In addition, those with occupational exposure manifested statistically significant shorter 6MWDs as observed by Paulin et al ($\beta = -26.0$ m; $P = 0.006$). [124] In a study by Casanova et al the median 6MWD was 380 m (range 160-600 m) which was similar to our study.[125]

The BODE Index and quartile distributions show a significant shift towards lower scores and quartiles post-treatment. The BODE index decreased from 3.86 at the first visit to 3.27 at the follow-up visit, indicating an overall improvement in the prognosis and severity of COPD among the participants (p=0.001). The chi-square test result (p value = 0.033) indicates a statistically significant difference in the distribution of patients across BODE quartiles between the first and follow-up visits. There is a rise in the number of patients in the lower BODE quartiles (1 and 2), indicating an improvement in their condition. Conversely, there is a decrease in the number of patients in the higher BODE quartiles (3 and 4), suggesting fewer patients with severe COPD after treatment. This significant shift in distribution towards lower BODE quartiles reflects an overall improvement in COPD severity post-treatment. This indicates an overall improvement in the participants' respiratory function, dyspnoea, and exercise capacity, leading to better disease management and prognosis. In a study by Nonato et al BODE index for COPD patients was found to be 3.1±2 which is consistent with the findings of our study.[126]

The significant decrease in MMRC scores from 1.59 to 1.42 (p = .048), reflects a reduction in breathlessness among the participants. This is a critically important result because dyspnoea is a significant symptom that lowers the QOL for people with COPD. The number of participants with MMRC 0 increased from 14.7% to

20.0%, indicating an improvement in those with no dyspnoea or breathlessness only with strenuous exercise. The number of participants with MMRC 3 decreased from 14.7% to 7.4%, showing a significant reduction in those with severe breathlessness that stops them from leaving the house.

In our study, the most common adverse effect observed is Exacerbations, affecting 35 individuals, which accounts for 36.8% of the total cases. This high percentage suggests that exacerbations are a significant concern and may require closer monitoring and management. Following exacerbations, 13% of individuals showed various other side effects like dry mouth which was reported by 6 individuals (6.31%); Increased cough in 4 individuals (4.21%), and while less common, it can be a bothersome symptom that might affect daily activities and overall health perception. Upper Respiratory Tract Infections (URTI) were reported by 3 individuals (3.16%), indicating a moderate occurrence rate. Less frequent adverse effects include headache in 2.10%, and sinusitis in 1.05%. Though these effects are relatively rare, they are still important to acknowledge as they can affect patient compliance and overall treatment satisfaction.

In patients with symptomatic COPD, a post-bronchodilator FEV1 of less than 50%, and a history of exacerbations, the TRINITY study showed that extrafine fixed triple therapy—a combination of beclomethasone dipropionate/ formoterol fumarate/ glycopyrronium bromide—offers significant clinical benefits over tiotropium alone. In comparison to tiotropium, the fixed triple treatment was linked to a decreased rate of moderate-to-severe exacerbations and higher improvements in pre-dose FEV1 at week 52. According to these results, fixed triple therapy is a better course of treatment for COPD patients who are at high risk of exacerbations.[4]

The study on triple therapy with (BDP/FF/GB) significantly improved lung function and reduced moderate-to-severe exacerbations in COPD patients compared to dual therapy with (BDP/FF). The triple therapy led to a 23% reduction in exacerbations and improved FEV1 both pre-dose and 2 hours post-dose. Adverse events were similar between the two groups, with 54% in the triple therapy group and 56% in the dual therapy group, and only one serious treatment-related adverse event reported. These results support the use of triple therapy for better management of COPD[7]

These side effects due to triple-drug therapy are similar to those reported in the literature. [3–7]

Limitations:

Despite the valuable insights, this study has several limitations. The sample size is relatively small, which may limit the generalizability of the findings. Additionally, the follow-up period may not be sufficient to capture the long-term outcomes of the interventions. Future studies should aim to include larger and more diverse populations with longer follow-up periods.

Secondly, our study was not a randomized-controlled trial. Hence the use of triple therapy cannot be overemphasized as compared to dual therapy in these groups of patients.

Single-centre study- multicentric trial required to duplicate the results.

CONCLUSION

In conclusion, our study emphasizes the importance of environmental factors, and various non-smoking exposures, as significant contributors to COPD. By following the latest GOLD guidelines and assessing non-smoking exposures, we investigated the effectiveness of triple drug combination therapy on various health parameters before and after treatment.

Our findings indicate that triple therapy significantly improves lung function, as evidenced by increases in FEV1 and FVC, and enhances overall respiratory health, as seen in the improvement of the FEV1/FVC ratio and FEF25-75%.

While the SGRQ and CAT scores showed minor but statistically significant improvements, the impact on the quality of life and symptom severity was modest, suggesting the need for prolonged treatment for more noticeable changes.

The study also highlights the demographic distribution of COPD, with a higher prevalence in older adults and a significant proportion of females, aligning with the observations of non-smoking risk factors.

Occupational exposure, particularly to biomass, dust, toxic gases, and vehicle smoke, was identified as a critical determinant of respiratory health, with housewives, farmers, and cooks being the most affected groups.

Despite the study's limitations, including a small sample size and short follow-up period, the results underscore the necessity of targeted interventions and improved occupational safety measures to mitigate the risk of COPD.

Future research should focus on larger, more diverse populations and extended follow-up periods to validate these findings and explore long-term outcomes.

SUMMARY

- Demographics:
  - The majority of participants were older adults, primarily in the 61-70 age group, with a mean age of 64.82 years, consistent with other studies. Mean age: 64.82 ± 8.32.
- Gender Distribution:
  - The study had a higher proportion of female participants (53.7%) compared to males (46.3%), indicating a significant impact of non-smoking factors on females. Mean BMI: 24.52 ± 3.60.
- Body Mass Index (BMI):
  - The majority of participants had an overweight BMI, which is linked to an increased risk of COPD development.
- Environmental and Occupational Factors:
  - There is an increasing recognition of environmental and non-smoking exposures as significant risk factors for COPD.
  - Occupational exposures, particularly to biomass fuels, dust, toxic gases, and vehicle emissions, plays a critical role in the prevalence of COPD.
- Exposure History:
  - A high prevalence of COPD was associated with biomass exposure (48.4%), dust exposure (23.2%), toxic gases (14.7%), vehicle smoke (12.6%) and pollution (1%)
- Respiratory Function Improvement:

- Significant improvements were observed in FEV1 and FVC post-treatment, indicating better lung function.
- FEV1/FVC ratio and FEF25-75% values also showed significant improvement, reflecting enhanced airway patency and small airway function.

❋ Quality of Life:

- The SGRQ scores showed a minor improvement, indicating a modest positive impact of the interventions on health-related quality of life. ($p < 0.006$).
- CAT scores remained relatively unchanged, suggesting persistent disease impact on daily functioning. ($p < 0.05$).

❋ BODE Index and Quartile Distribution:

- There was a significant shift towards lower BODE scores post-treatment, reflecting an overall improvement in COPD severity and prognosis. Decreased from 3.86 to 3.27 post-treatment.

❋ Dyspnoea Improvement:

- MMRC scores decreased significantly, indicating a reduction in breathlessness among participants. ($p = 0.048$)

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ANNEXURE I

INFORMED CONSENT FORM

Dear Mr. /Mrs. /Dr. _____, you are kindly requested to enroll yourself in a research study tilted, "*Clinical effectiveness of Triple drug therapy combination containing LABA, LAMA and ICS given for 12 weeks in non-smoking Chronic Obstructive Pulmonary Disease patients, Prospective observational study over a period of 1 year*" being conducted by **Reg No:BR0121002**, a post graduate student in M.D. Respiratory Medicine and the study will be carried out under the direct supervision and guidance of

You have been requested to participate in this as you fit into the laid-out criteria for a study 'subject'/ participant.

Your participation in the study is voluntary. During the study you will be subjected to lung function test, 6 minute walk test, and routine chest X-ray after which combination of triple drug therapy will be given for 12 weeks, which will form part of the care required for the seeing the clinical effectiveness of the triple drug therapy. Your decision whether or not to participate in the study will not affect your treatment in any form. If you decide to participate you are free to withdraw at any time.

TITLE OF THE STUDY:

Clinical effectiveness of Triple drug therapy combination containing LABA, LAMA and ICS given for 12 weeks in non-smoking Chronic Obstructive Pulmonary Disease patients, Prospective observational study over a period of 1 year.

PURPOSE OF THE STUDY: To evaluate the clinical effectiveness of triple drug therapy combination containing LABA, LAMA and ICS in non-smoking COPD patients in patients over 12 weeks coming to KLE's Dr.Prabhkar Kore Hospital and MRC.

PROCEDURES INVOLVED: If you agree to enroll yourself in my study, you will be subjected to clinical examination which will involve assessment of your vitals, general physical examination and focused systemic examination. You will then be subjected to Lung function test, 6 minute walk test, Chest X-ray, filling of SGR-Questionnaire, COPD Assessment test, anthropometry evaluation in the start of the study and repeating the same after 12 weeks of triple drug therapy taken by patient

RISKS AND BENEFITS: There are no potential risks involved in this study.

Benefits of taking part in this research: By taking part in this study, the clinical effectiveness of triple drug therapy can be evaluated in non- smoking COPD patients.

VOLUNTARY PARTICIPATION / WITHDRAWAL FROM THE STUDY: Taking part in the study is voluntary. You may choose not to enroll yourself in this study and may choose to leave the study anytime in between.

ALTERNATIVES: Your decision regarding participation in study will not change present or future health care services offered to you at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. You would simply be excluded from the study if you wish to, and all your details shall be kept confidential and you will get the routine line of management.

PRIVACY AND CONFIDENTIALITY: All data collected or disclosed by you during the course of participation of study, will be kept fully confidential. If, however during the course it becomes necessary for the progress of the course to disclose the identity, it would be done so only after your informed & written consent. The only people to know that you are a research subject are members of the research team. No information about you will be disclosed to other without your written permission except:

In emergency to protect your rights AND welfare.

If required by law.

AUTHORIZATION TO PUBLISH RESULT: The results of the study may be used to publish an article. When the results of research are published or discussed in a conference, no information will be displayed that would disclose your identity. Any information obtained in connection with this study and that can be identified with you will remain confidential.

FINANCIAL INCENTIVES FOR PARTICIPATION: No additional costs shall be incurred upon you for the purpose of this study. It is purely being done with the idea of research and all the cost of study will be borne by the investigator.

COMPENSATION: In the event that you become injured as a result of taking part in this study, treatment will be offered to you at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum, or you will be given information about where to receive medical care. However, no reimbursement, compensation or free medical care will be given.

QUESTIONS/CONTACT DETAILS: You shall be free to contact the below mentioned name & addresses anytime during the study period for any clarification or help as you may desire for.

PRINCIPAL INVESTIGATOR: BR0121002

CONSENT STATEMENT

I am making a voluntary decision to participate in the study "*Clinical effectiveness of Triple drug therapy combination containing LABA, LAMA and ICS given for 12 weeks in non-smoking Chronic Obstructive Pulmonary Disease patients, Prospective observational study over a period of 1 year.*" My signature below indicates that I have decided to participate and I have read the information provided above or the information provided above has been read to me in the language that I understand best. I was given the opportunity to ask questions and that they have been answered to my satisfaction.

Name of the participant	Signature or left thumb impression of the participant

Name of the investigator	Signature of the investigator:

ANNEXURE- II

CASE PROFORMA

NAME	
AGE	
SEX	
ADDRESS	
OCCUPATION	

COMPLAINTS AND HISTORY	
PAST HISTORY	
FAMILY HISTORY	
PERSONAL HISTORY ▪ ALCOHOLISM ▪ TOBACCO CHEWING ▪ SMOKING ▪ OTHERS COMORBIDITIES	
EXPOSURE HISTORY	
TREATMENT HISTORY	
ADVISED TREATMENT	

VITALS

	VISIT 1	AT 12 WEEKS
TEMPERATURE		
PULSE		
BLOOD PRESSURE		
SPO2		
RESPIRATORY RATE		
AUSCULTATION		

PHYSICAL EXAMINATION

	VISIT 1		A 12 WEEKS	
	YES	NO	YES	NO
PALLOR				
ICTERUS				
LYMPHADENOPATHY				
CYANOSIS				
CLUBBING				
EDEMA				

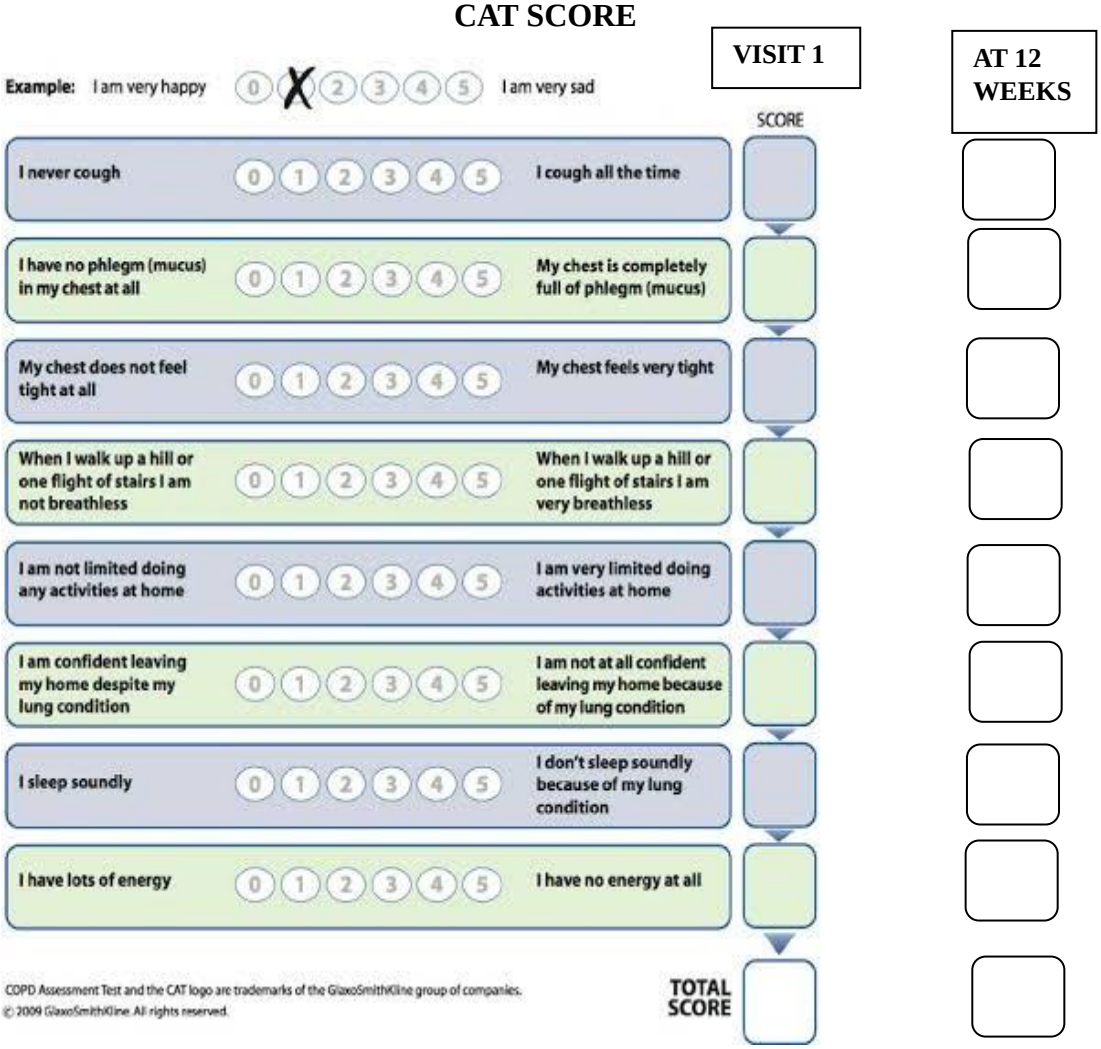
ANTHROPOMETRY

HEIGHT	
WEIGHT	
BMI	

SPIROMETRY

	VISIT 1			AT 12 WEEKS		
	PRE	POST	%	PRE	POST	%
FEV1(L)						
FVC(L)						
FEV1/FVC						
PEFR(L/s)						

CAT SCORE



MODIFIED MRC DYSPNEA SCALE[a]			AT 12 WEEKS
PLEASE TICK IN THE BOX THAT APPLIES TO YOU | ONE BOX ONLY | Grades 0 - 4			
mMRC Grade 0.	I only get breathless with strenuous exercise.	☐	☐
mMRC Grade 1.	I get short of breath when hurrying on the level or walking up a slight hill.	☐	☐
mMRC Grade 2.	I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level.	☐	☐
mMRC Grade 3.	I stop for breath after walking about 100 meters or after a few minutes on the level.	☐	☐
mMRC Grade 4.	I am too breathless to leave the house or I am breathless when dressing or undressing.	☐	☐

6 MINUTE WALK DISTANCE

BODE INDEX

	VISIT 1				AT 12 WEEKS			
	0	1	2	3	0	1	2	3
FEV1(L)								
MMRC								
6MWD								
BMI								

	VISIT 1	AT 12 WEEKS
SGRQ SCORE		

SGRQ QUESTIONNAIRE

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you most problems, rather than what the doctors and nurses think your problems are.

Please ask if you have difficulty understanding the questions. Do not spend too long deciding about your answers.

0c) Please pick one response to show how you describe your current health:

Very good1	Good2	Fair3	Poor4	Very Poor5
☐	☐	☐	☐	☐

The following questions ask about your chest trouble. Please answer as it applies to you.

PART 1

1) I cough:

- ☐ Most days a week1
- ☐ Several days a week2
- ☐ Only with respiratory infections4
- ☐ Not at all5

2) I bring up phlegm (sputum):

- ☐ Most days a week1
- ☐ Several days a week2
- ☐ Only with respiratory infections4
- ☐ Not at all5

3) I have shortness of breath:

- ☐ Most days a week1
- ☐ Several days a week2
- ☐ Not at all5

4) I have attacks of wheezing:

- ☐ Most days a week1
- ☐ Several days a week2
- ☐ A few days a month3
- ☐ Only with respiratory infections4
- ☐ Not at all5

5) How many attacks of chest trouble did you have during the last year?

- ☐ 3 or more attacks1
- ☐ 1 or 2 attacks2
- ☐ None3

6) How often do you have good days (with few respiratory problems)?

- ☐ No good days1
- ☐ A few good days2
- ☐ Most days are good3
- ☐ Every day is good4

7) If you have a wheeze, is it worse when you get up in the morning?

- ☐ No0
- ☐ Yes1

PART 2

8) How would you describe your respiratory problems?

- ☐ Cause me a lot of problems or are the most important physical problem I have1
- ☐ Cause me a few problems2
- ☐ Cause no problems3

9) Questions about what activities usually make you feel breathless. For each statement, please tell me which applies to you these days.

	False0	True1
9a) Washing or dressing yourself	☐	☐
9b) Walking around the house	☐	☐
9c) Walking outside on the level ground	☐	☐
9d) Walking up a flight of stairs	☐	☐
9e) Walking up hills	☐	☐

10) Some more questions about your cough and breathlessness. For each statement, please tell me which applies to you these days.

	False0	True1
10a) Coughing hurts	☐	☐
10b) Coughing makes me tired	☐	☐
10c) I am short of breath when I talk	☐	☐
10d) I am short of breath when I bend over	☐	☐
10e) My cough or breathing disturbs my sleep	☐	☐
10f) I get exhausted easily	☐	☐

11) Questions about other effects that your chest trouble may have on you. For each statement, please tell me which applies to you these days.

	False0	True1
11a) My cough or breathing is embarrassing in public	☐	☐
11b) My respiratory problems are a nuisance to my family, friends, or neighbors	☐	☐
11c) I get afraid or panic when I cannot catch my breath	☐	☐
11d) I feel that I am not in control of my respiratory problems	☐	☐
11e) I have become frail or an invalid because of my respiratory problems	☐	☐
11f) Exercise is not safe for me	☐	☐
11g) Everything seems too much of an effort	☐	☐

12) These are questions about how your activities might be affected by your respiratory problems. For each statement, please tell me which applies to you because of your breathing.

	False0	True1
12a) I take a long time to get washed or dressed	☐	☐
12b) I cannot take a bath or shower, or I take a long time to do it	☐	☐

	False0	True1
12c) I walk slower than other people, or I stop to rest	☐	☐
12d) Jobs such as house chores take a long time, or I have to stop to rest	☐	☐
12e) If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
12f) If I hurry or walk fast, I have to stop or slow down	☐	☐
12g) My breathing makes it difficult to do things such as walk up hills, carry things up stairs, do light gardening such as weeding, dance, bowl, or play golf	☐	☐
12h) My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk briskly (5 miles per hour), play tennis, or swim	☐	☐

13) We would like to know how your chest usually affects your daily life. For each statement, please tell me which applies to you because of your breathing.

	False0	True1
13a) I cannot play sports or do other physical activities	☐	☐
13b) I cannot go out for entertainment or recreation	☐	☐
13c) I cannot go out of the house to do the shopping	☐	☐
13d) I cannot do household chores	☐	☐
13e) I cannot move far from my bed or chair	☐	☐

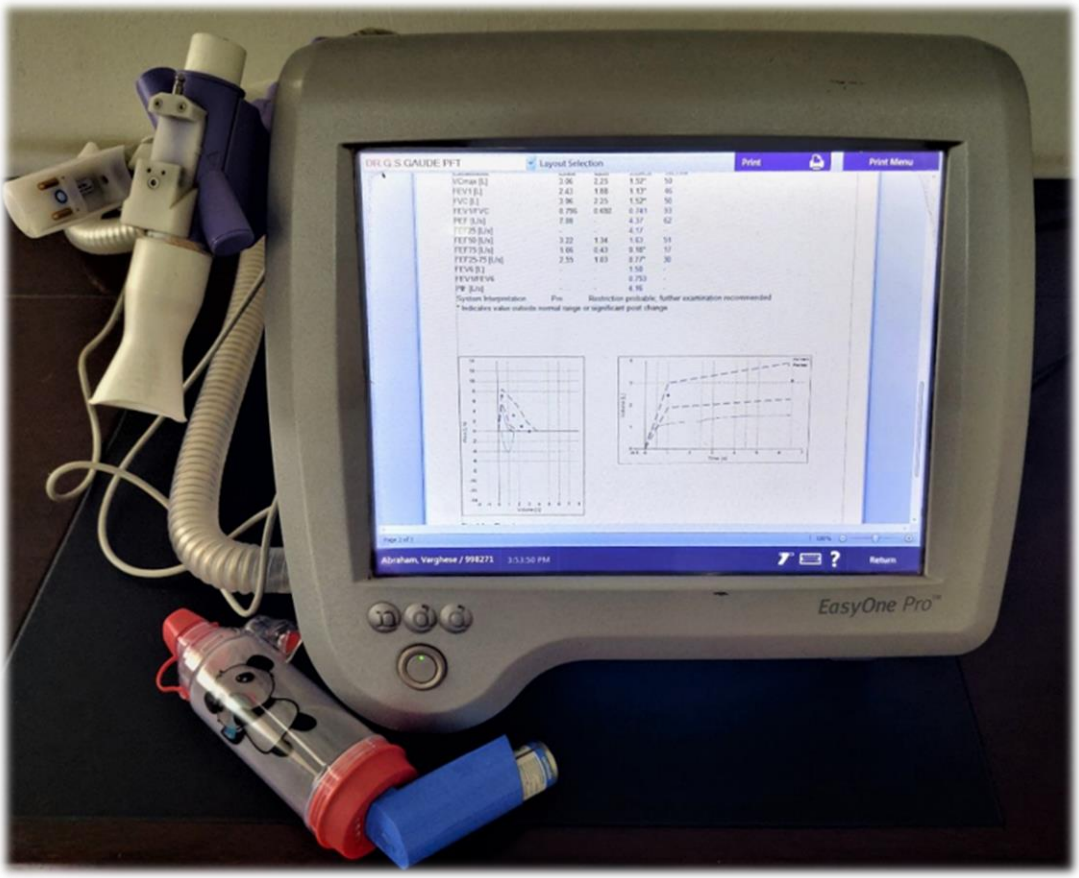
14) How do your respiratory problems affect you? Please pick one response.

- ☐ They do not stop me from doing anything I would like to do1
- ☐ They stop me from doing one or two things I would like to do2
- ☐ They stop me from doing most of the things I would like to do3
- ☐ They stop me from doing everything I would like to do4

ANNEXURE III

PHOTOGRAPH

1. Spirometer



ANNEXURE IV

KEY TO MASTERCHART

M	Male
F	Female
BMI	Body Mass Index
HTN	Hypertension
TDM	Type 2 Diabetes Mellitus
IHD	Ischemic Heart Disease
WNL	Within Normal Limits
PR	Pulse Rate
BP	Blood Pressure
SPO2	Peripheral capillary oxygen saturation
RS	Respiratory System- auscultation
FEV1	Forced Expiratory Volume In 1 Second
FVC	Forced Vital Capacity
FEF 25-75	Forced Expiratory Flow 25-75%
PEFR	Peak Expiratory Flow Rate
6MWD	6 Minute Walk Distance
CXR	Chest X ray
MMRC	Modified Medical Research Council Dypnoea Grading Scale
BODE	BMI, Obstruction Of Airways, Dyspnoea Scale, Exercise Capacity
SGRQ	St. George Respiratory Questionnaire

CAT	COPD Assessment Test
MDI	Metered Dose Inhaler
DPI	Dry-Powder Inhaler

ANNEXURE V

MASTERCHART

ANNEXURE VI- MASTERCHART

SI NO.	AGE	SEX	OCCUPATION	HEIGHT (cm)	WEIGHT (kg)	BMI (kg/m2)	COMORBIDITIES	PAST ILLNESS	FAMILY H/O	PHYSICAL EXAMINATION	EXPOSURE HISTORY	PR(bpm)	BP(mmhg)	SPO2	RS	GOLD grading	FEV1 FIRST VISIT	FVC % FIRST VISIT	FEV1/FVC FIRST VISIT	FEF25-75% FIRST VISIT	PEFR (%) FIRST VISIT	6MWD FIRST VISIT	CXR FIRST VISIT	MMRC FIRST VISIT	CAT SCORE (40)	SGRQ ratio FIRST VISIT	symptoms	activity	impact	SGRQ total score	BODE TOTAL FIRST VISIT	BODE QUARTILE FIRST VISIT	INHALER	ADVERSE EVENTS	SPO2	RS	GOLD grading	FEV1 % AT 12 WEEKS	FVC % AT 12 WEEKS	FEV1/FVC AT 12 WEEKS	FEF25-75% AT 12 WEEKS	PEFR (%) AT 12 WEEKS	6MWD AT 12 WEEKS	CXR AT 12 WEEKS	MMRC AT 12 WEEKS	CAT SCORE AT 12 WEEKS	SGRQ ratio AT 12 WEEKS	symptoms	activity	impact	SGRQ total score AT 12 WEEKS	BODE TOTAL AT 12 WEEKS	BODE CATEGORY AT 12 WEEKS
1	68	M	Farmer	166	62	22.50	HTN, TDM, IHD	NIL	Nil	wnl	dust	77	140/90	98	NVBS	3	42.24	60.34	0.7	52	42	221.6	normal	2	28	37.74	77.64	52.33	15.39	1208.4	7	3	MDI	Increased Cough	98	NVBS	2	59	66	0.89	60	44	220	normal	2	28	37.74	77.64	52.33	15.39	1208	6	2
2	70	M	Farmer	163	56	21.08	nil	NIL	Nil	wnl	dust	65	120/80	98	NVBS	2	63.36	90.5	0.7	66	52	332.5	normal	3	22	50.73	62.54	44.87	50.17	1624.3	6	2	DPI	NIL	98	NVBS	2	78	92	0.84	68	54	330.2	normal	2	22	46.98	53.99	37.58	50.17	1504	4	2
3	72	M	Farmer	154	58	24.46	nil	NIL	COPD	wnl	biomass	78	120/80	95	RHONCHI	4	20.24	36.96	0.55	25	23	208.5	copd changes	2	26	33.16	67.13	37.23	19.11	1061.9	8	3	MDI	NIL	95	RHONCHI	4	26	48	0.54	38	25	210	normal	2	26	33.16	67.13	37.23	19.11	1062	8	3
4	71	M	labourer	147	45	20.82	HTN, TDM	NIL	Nil	wnl	biomass	90	140/70	94	RHONCHI	4	25.52	44.88	0.57	13	42	230.7	copd changes	1	30	21.42	39.65	22.65	14.44	685.7	7	3	MDI	Exacerbation	94	NVBS	3	46	58	0.79	18	44	231.3	copd changes	0	30	21.42	39.65	22.65	14.44	685.7	5	2
5	82	M	labourer	168	56	19.84	nil	NIL	COPD	wnl	dust	89	120/80	98	NVBS	3	45.76	65.37	0.7	24	28	318.7	copd changes	3	24	40.88	72.39	60.44	18.45	1309	7	3	DPI	NIL	98	NVBS	2	65	90	0.72	24	26	316.4	copd changes	2	24	38.56	72.39	52.86	18.45	1235	4	2
6	55	F	housewife	170	60	20.76	HTN, TDM	NIL	Nil	wnl	biomass	99	130/60	98	NVBS	2	65.12	93.03	0.7	52	40	321.4	normal	0	32	21.42	39.65	22.65	14.44	685.7	2	1	DPI	NIL	98	NVBS	2	78	100	0.78	50	42	323.3	normal	0	32	21.42	39.65	22.65	14.44	685.7	2	1
7	58	M	traffic police	168	55	19.49	nil	NIL	Nil	wnl	vehicle smoke	78	130/70	98	RHONCHI	3	44	70.4	0.63	33	40	441.3	normal	3	28	27.87	48.46	0.00	37.40	892.5	5	2	DPI	NIL	98	NVBS	2	60	82	0.73	39	42	440	normal	2	28	25.34	48.46	0.00	37.40	811.4	3	1
8	44	M	traffic police	157	40	16.23	TDM	NIL	Nil	wnl	vehicle smoke	89	130/70	97	NVBS	3	49.28	70.4	0.7	25	27	400	normal	3	22	36.30	72.39	45.51	18.45	1162.2	6	2	DPI	Exacerbation	97	NVBS	2	78	90	0.86	30	32	405	normal	2	22	32.68	66.34	37.23	18.45	1047	3	1
9	59	M	cook	166	66	23.95	TDM	NIL	Nil	wnl	biomass	88	130/78	98	RHONCHI	2	52.8	89.6	0.59	38	52	300.3	normal	1	26	52.83	76.90	46.27	48.48	1691.5	4	2	DPI	NIL	98	NVBS	2	62	80	0.77	60	58	301.3	normal	1	26	52.83	76.90	46.27	48.48	1692	4	2
10	71	M	Farmer	159	58	22.94	HTN, TDM	NIL	COPD	wnl	biomass	78	120/70	97	NVBS	2	63.36	100.8	0.63	50	30	321.6	normal	2	25	54.79	74.71	46.57	52.86	1754.3	5	2	DPI	NIL	97	NVBS	2	75	92	0.81	58	36	320	copd changes	2	25	54.79	74.71	46.57	52.86	1754	4	2
11	69	M	traffic police	156	66	27.12	HTN, TDM	NIL	Nil	wnl	toxic gases	77	130/80	97	RHONCHI	2	52.8	75.43	0.7	28	32	330	normal	2	27	34.48	67.13	37.23	21.67	1104.1	5	2	MDI	NIL	97	NVBS	2	66	79	0.83	30	38	330.2	normal	2	27	34.48	67.13	37.23	21.67	1104	4	2
12	69	F	cook	157	47	19.07	TDM	NIL	Nil	wnl	biomass	89	120/72	98	NVBS	2	70.4	100.57	0.7	20	22	322.6	normal	1	32	52.64	76.88	37.87	53.13	1685.6	3	1	DPI	NIL	98	NVBS	1	82	92	0.8	28	27	330.5	normal	1	32	52.64	76.88	37.87	53.13	1686	3	1
13	66	F	labourer	143	39	19.07	TDM	NIL	Nil	wnl	biomass	99	120/60	95	RHONCHI	4	29.04	41.49	0.7	15	6	209.4	normal	1	33	36.30	72.39	45.51	18.45	1162.2	7	3	MDI	Exacerbation	95	RHONCHI	3	45	80	0.56	19	20	210.1	normal	1	33	36.30	72.39	45.51	18.45	1162	6	2
14	61	M	Priest	170	70	24.22	HTN	RIC	ASTHMA	wnl	toxic gases	69	130/60	98	NVBS	2	52.8	75.43	0.7	36	40	393.4	normal	3	26	42.37	67.13	37.23	36.94	1356.5	5	2	DPI	Exacerbation	98	NVBS	2	62	88	0.7	40	44	400.3	copd changes	3	26	42.37	67.13	37.23	36.94	1357	5	2
15	62	M	labourer	162	60	22.86	nil	NIL	Nil	wnl	biomass	99	110/70	94	RHONCHI	3	45.76	65.37	0.7	38	40	330	normal	1	28	39.06	77.64	52.33	17.95	1250.6	5	2	MDI	Increased Cough	94	NVBS	2	60	75	0.8	60	52	326.8	normal	0	28	39.06	77.64	52.33	17.95	1251	3	1
16	60	M	Priest	165	60	22.04	HTN, TDM	RIC	COPD	wnl	toxic gases	74	140/70	96	NVBS	3	39.6	56.57	0.7	22	27	280.1	normal	3	22	42.37	67.13	37.23	36.94	1356.5	7	3	MDI	NIL	96	NVBS	3	48	62	0.77	28	32	283.7	copd changes	2	22	42.50	67.13	37.23	36.94	1361	6	2
17	70	F	housewife	147	42	19.44	Nil	NIL	Nil	wnl	biomass	75	140/70	97	NVBS	2	54.56	77.94	0.7	52	43	250.5	normal	2	27	34.23	82.90	37.87	15.39	1096	5	2	DPI	NIL	97	NVBS	1	80	100	0.8	58	55	260	normal	2	27	34.23	82.90	37.87	15.39	1096	4	2
18	66	F	housewife	165	70	25.71	HTN, TDM, IHD	NIL	ASTHMA	wnl	biomass	83	130/80	95	RHONCHI	3	46	66	0.69	28	38	311.6	normal	3	22	38.10	92.14	45.15	15.39	1219.9	7	3	DPI	Exacerbation	95	RHONCHI	3	44	56	0.78	20	60	312.9	normal	3	22	38.10	92.14	45.15	15.39	1220	7	3
19	69	M	bank	157	76	30.83	nil	NIL	Nil	wnl	dust	85	130/70	97	RHONCHI	3	45	59	0.69	34	28	260.7	copd changes	2	26	41.97	63.95	60.49	23.43	1343.9	6	2	DPI	Exacerbation	97	RHONCHI	3	38	55	0.69	40	28	263.4	normal	2	26	41.97	63.95	60.49	23.43	1344	6	2
20	62	F	cook	154	80	33.73	nil	NIL	Nil	wnl	biomass	92	130/78	97	NVBS	2	65.12	93.03	0.7	42	40	303	normal	0	30	35.41	82.90	37.41	17.95	1133.7	2	1	DPI	Increased Cough	97	NVBS	2	70	92	0.7	42	40	302.6	copd changes	0	30	35.41	82.90	37.41	17.95	1134	2	1
21	51	M	battery shop	164	68	25.28	HTN, TDM	RIC	PTB	wnl	toxic gases	98	120/80	97	NVBS	2	69.52	99.31	0.7	56	59	392	normal	2	24	47.72	67.13	45.51	42.39	1528	3	1	DPI	Exacerbation	97	NVBS	2	78	92	0.84	56	60	398	normal	1	24	47.72	67.13	45.51	42.39	1528	2	1
22	56	M	bank	160	78	30.47	nil	NIL	PTB	wnl	dust	85	130/74	98	NVBS	2	65.12	103.04	0.63	40	59	398.4	normal	2	26	34.48	67.13	37.23	21.67	1104.1	3	1	DPI	URTI	98	NVBS	2	76	98	0.77	47	58	400.6	normal	2	26	34.48	67.13	37.23	21.67	1104	3	1
23	53	M	military	163	52	19.57	TDM	NIL	ASTHMA	wnl	dust	92	128/72	98	NVBS	2	65.12	95.76	0.68	31	48	401.1	normal	3	24	40.88	72.39	60.44	18.45	1309	4	2	DPI	Dry Mouth	98	NVBS	2	76	105	0.73	43	72	402.4	copd changes	3	24	40.88	72.39	60.44	18.45	1309	4	2
24	61	M	cook	155	57	23.73	TDM	NIL	Nil	wnl	biomass	98	128/78	98	RHONCHI	2	58.08	100.8	0.58	72	40	410.5	copd changes	2	28	35.41	82.90	37.41	17.95	1133.7	4	2	DPI	Dry Mouth	98	RHONCHI	2	69	86	0.8	77	53	411	copd changes	2	28	35.41	82.90	37.41	17.95	1134	3	1
25	60	F	housewife	160	56	21.88	HTN, TDM	NIL	Nil	wnl	biomass	88	140/90	97	NVBS	2	54.56	80.24	0.68	52	43	389.9	normal	2	25	54.79	74.71	46.57	52.86	1754.3	4	2	DPI	NIL	97	NVBS	2	68	85	0.8	55	60	385.9	normal	2	25	54.79	74.71	46.57	52.86	1754	3	1
26	49	F	housewife	153	73	31.18	HTN, TDM, IHD	RIC	Nil	wnl	biomass	86	120/80	98	NVBS	2	56.32	82.82	0.68	47	88	408	normal	2	24	24.44	39.65	22.65	20.29	782.4	4	2	DPI	Dry Mouth	98	NVBS	2	66	80	0.8	50	80	407.8	normal	2	24	24.44	39.65	22.65	20.29	782.4	3	1
27	61	M	Priest	160	61	23.83	TDM	NIL	ASTHMA	BC	toxic gases	102	130/80	96	RHONCHI	2	65.12	93.03	1	66	50	309.3	copd changes	0	32	21.13	38.03	22.65	14.44	676.5	2	1	DPI	NIL	96	RHONCHI	1	80	99	0.8	66	54	309	normal	0	32	21.13	38.03	22.65	14.44	676.5	2	1
28	47	M	Farmer	146	73	34.25	TDM	NIL	Nil	wnl	dust	98	128/72	98	NVBS	2	73.04	104.34	0.7	48	39	409.2	normal	0	30	20.54	34.69	22.65	14.44	657.6	1	0	DPI	NIL	98	NVBS	1	89	108	0.8	48	58	408	normal	0	30	20.54	34.69	22.65	14.44	657.6	1	0
29	52	M	traffic police	155	66	27.47	HTN	NIL	PTB	wnl	pollution	90	128/78	98	NVBS	2	77.44	123.2	0.63	50	68	392	normal	1	28	39.06	77.64	52.33	17.95	1250.6	2	1	DPI	NIL	98	NVBS	1	90	113	0.79	52	72	390	normal	1	28	39.06	77.64	52.33	17.95	1251	2	1
30	62	F	housewife	168	72	25.51	HTN, TDM, IHD	NIL	ASTHMA	wnl	biomass	89	120/70	98	NVBS	2	75.68	111.29	0.68	72	75	399.8	normal	0	34	21.42	39.65	22.65	14.44	685.7	1	0	DPI	Exacerbation	98	NVBS	1	88	115	0.76	74	78	387.3	normal	0	34	21.42	39.65	22.65	14.44	685.7	1	0
31	61	M	Farmer	160	71	27.73	Nil	RIC	PTB	wnl	biomass	99	120/80	97	NVBS	2	74.8	106.86	0.7	55	60	445	normal	2	26	41.98	67.13	37.23	36.18	1344	3	1	DPI	NIL	97	NVBS	1	88	92	0.95	77	79	446.1	normal	2	26	41.98	67.13	37.23	36.18	1344	3	1
65	69	M	military	169	70	24.51	nil	NIL	COPD	wnl	toxic gases	78	110/70	96	RHONCHI	3	39.6	59.84	0.66	17	28	228.6	normal	3	25	33.16	67.13	37.23	19.11	1061.9	8	3	MDI	Dry Mouth	96	RHONCHI	1	87	96	0.9	60	62	229.1	normal	3	25	33.16	67.13	37.23	19.11	1062	6	2
33	55	F	housewife	147	55	25.45	TDM	NIL	Nil	wnl	biomass	87	120/80	98	RHONCHI	3	46	66	0.69	28	38	270.1	copd changes	3	24	37.74	77.64	52.33	15.39	1208.4	7	3	MDI	NIL	98	RHONCHI	3	48	63	0.76	28	39	269.1	copd changes	2	24	37.74	77.64	52.33	15.39	1208	6	2
34	72	F	housewife	157	60	24.34	TDM	NIL	PTB	wnl	biomass	89	140/90	97	RHONCHI	2	53.68	78.94	0.68	35	49	308	copd changes	2	27	33.96	64.16	37.23	21.67	1087.3	5	2	MDI	Exacerbation	97	RHONCHI	2	65	86	0.75	39	66	310	copd changes	2	27	33.96	64.16	37.23	21.67	1087	4	2
35	75	M	brick factory	168	50	17.72	TDM	RIC	ASTHMA	wnl	toxic gases	98	140/80	94	RHONCHI	2	58	74	0.6	24	28	356	copd changes	2	26	43.12	70.47	60.49	23.43	1380.8	4	2	DPI	NIL	94	NVBS	2	56	86	0.65	60	32	357.2	copd changes	2	26	43.12	70.47	60.49	23.43	1381	4	2
36	70	M	Farmer	170	74	25.61	TDM	NIL	Nil	wnl	biomass	88	140/80	96	RHONCHI	2	66.88	98.35	0.68	54	68	384.5	copd changes	0	32	21.42	39.65	22.65	14.44	685.7	1	0	DPI	Dry Mouth	96	NVBS	1	82	100	0.8	66	70	384.2	copd changes	0	32	21.42	39.65	22.65	14.44	685.7	1	0
37	68	M	Farmer	158	70	28.04	HTN, TDM, IHD	NIL	Nil	wnl	biomass	78	120/80	94	RHONCHI	3	46	66	0.69	28	38	300.1	copd changes	0	33	19.19	39.65	15.38	14.44	614.3	3	1	DPI	Exacerbation	94	RHONCHI	2	56	70	0.8	49	50	301.1	copd changes	0	33	19.19	39.65	15.38	14.44	614.3	2	1
38	72	M	traffic police	169	70	24.51	nil	NIL	Nil	wnl	toxic gases	97	120/80	97	NVBS	2	69.52	102.24	0.68	56	59	288	copd changes	2	24	29.86	46.38	37.11	19.89	956.1	4	2	DPI	Exacerbation	97	NVBS	1	86	100	0.8	70	64	288.2	copd changes	2	24	29.86	46.38	37.11	19.89	956.1	4	2
39	75	F	brick factory	160	47	18.36	HTN, TDM	RIC	PTB	wnl	biomass	108	120/70	98	NVBS	2	77.44	113.88	0.7	77	80	338.4	copd changes	2	28	39.06	77.64	52.33	17.95	1250.6	4	2	DPI	NIL	98	NVBS	1	82	102	0.8	87	75	336.5	copd changes	1	28	39.06	77.64	52.33	17.95	1251	3	1
40	60	F	Farmer	155	63	26.22	HTN, TDM	NIL	Nil	wnl	biomass	88	140/90	98	NVBS	3	42.24	69.44	0.61	52	42	401.4	normal	0	30	40.88	72.39	60.44	18.45	1309	3	1	MDI	NIL	98	NVBS	2	50	64	0.7	77	42	402.4	normal	1	25	40.88	72.39	60.44	18.45	1309	3	1
41	62	M	stone cutter	163	65	24.46	HTN	NIL	Nil	wnl	dust	103	120/80	92	RHONCHI	3	39.6	56.57	0.7	22	27	356.7	normal	2	25	22.61	46.38	22.65	14.44	723.8	5	2	MDI	Exacerbation	92	NVBS	3	48	62	0.77	34	38	356	normal	2	24	22.61	46.38	22.65	14.44	723.8	5	2
42	66	F	housewife	168	72	25.51	nil	NIL	COPD	wnl	biomass	88	120/80	95	RHONCHI	2	54.56	77.94	0.7	52	43	375	normal	1	32	21.42	39.65	22.65	14.44	685.7	3	1	DPI	NIL	95	NVBS	2	66	84	0.78	56	44	372	normal	2	28	21.42	39.65	22.65	14.44	685.7	3	1
43	54	F	labourer	160	60	23.44	HTN, TDM	NIL	Nil	wnl	biomass	86	140/92	98	NVBS	2	56.32	80.46	0.7	47	88	358.9	normal	2	24	57.32	74.71	46.57	57.76	1835.3	4	2	DPI	Dry Mouth	98	NVBS	2	72	92	0.78	50	72	360.1	normal	1	26	57.32	74.71	46.57	57.76	1835	2	1
44	80	M	business	160	50	19.53	nil	NIL	COPD	wnl	vehicle smoke	102	140/90	94	RHONCHI	2	70.4	100.57	0.7	42	66	349	copd changes	1	32	48.79	73.19	45.51	42.39	1562.3	3	1	DPI	Exacerbation	94	NVBS	2	74	97	0.76	53	60	350.1	copd changes	1	22	48.79	73.19	45.51	42.39	1562	2	1
45	66	M	traffic police	147	55	25.45	TDM	NIL	Nil	BC	vehicle smoke	86	120/80	94	RHONCHI	3	43.12	61.6	0.7	24	36	278.4	normal	3	22	33.47	71.95	37.41	17.95	1071.7	7	3	DPI	NIL	94	NVBS	2	66	91	0.72	33	42	278.6	normal	2	27	33.47	71.95	37.41	17.95	1072	4	2
46	68	M	business	157	65	26.37	HTN, TDM, IHD	NIL	Nil	wnl	dust	66	120/80	96	NVBS	2	50.16	84.48	0.59	32	72	309	normal	2	26	72.49	83.42	69.83	70.33	2321.1	5	2	DPI	NIL	96	NVBS	2	62	86	0.72	39	68	309.2	normal	0	30	72.49	83.42	69.83	70.33	2321	3	1
47	80	M	bank	158	58	23.23	HTN, TDM	RIC	Nil	wnl	dust	78	130/90	96	NVBS	2	51.04	84.48	0.60	62	66	289	normal	1	30	41.84	64.16	37.23	36.94	1339.7	4	2	DPI	NIL	96	NVBS	2	66	86	0.76	68	68	289.5	normal	2	25	41.84	64.16	37.23	36.94	1340	4	2
48	72	F	brick factory	169	68	23.81	TDM	NIL	Nil	wnl	biomass	88	120/80	97	NVBS	2	65.12	93.03	0.7	42	40	346.8	normal	2	32	20.54	34.69	22.65	14.44	657.6	4	2	DPI	Exacerbation	97	NVBS	2	78	97	0.8	57	46	356	normal	0	32	20.54	34.69	22.65	14.44	657.6	1	0
49	62	F	cook	154	55	23.19	HTN	RIC	COPD	wnl	biomass	98	130/70	97	NVBS	2	69.52	99.31	0.7	56	59	343	normal	1	26	56.59	70.84	45.96	58.03	1812	3	1	DPI	Exacerbation	97	NVBS	2	68	87	0.78	60	63	345.1	normal	2	24	56.59	70.84	45.96	58.03	1812	4	2
50	52	F	housewife	160	60	23.44	HTN, TDM	NIL	Nil	wnl	biomass	95	130/74	98	NVBS	2	72	88	0.7	50	46	392.4	normal	1	30	35.41	82.90	37.41	17.95	1133.7	2	1	DPI	Exacerbation	98	NVBS	2	75	95	0.78	58	44	399.2	normal	2	32	35.41	82.90	37.41	17.95	1134	3	1
51	66	M	traffic police	157	65	26.37	Nil	NIL	Nil	wnl	vehicle smoke	92	128/72	98	NVBS	3	48	66	0.72	66	40	452	normal	2	24	35.61	70.91	44.98	17.95	1140.2	5	2	DPI	Exacerbation	98	NVBS	2	68	82	0.82	60	44	454	normal	1	26	35.61	70.91	44.98	17.95	1140	2	1
52	68	F	labourer	167	72	25.82	Nil	NIL	Nil	wnl	dust	100	128/78	98	NVBS	2	70.4	100.57	0.7	20	22	389.2	copd changes	1	32	64.93	76.90	61.59	62.82	2079.1	2	1	DPI	Exacerbation	98	NVBS	1	84	90	0.93	40	49	389.6	copd changes	1	26	64.93	76.90	61.59	62.82	2079	2	1
53	77	M	business	170	78	26.99	nil	NIL	Nil	wnl	toxic gases	90	110/90	98	NVBS	2	65.12	93.03	0.7	58	73	441.1	normal	2	24	35.41	82.90	37.41	17.95	1133.7	3	1	DPI	NIL	98	NVBS	2	74	93	0.79	59	62	443.5	normal	1	22	35.41	82.90	37.41	17.95	1134	2	1
54	62	M	military	154	44	18.55	Nil	NIL	Nil	wnl	toxic gases	98	130/82	98	NVBS	2	74.8	106.86	0.7	43	44	342.8	normal	0	31	36.30	72.39	45.51	18.45	1162.2	2	1	DPI	NIL	98	NVBS	1	80	100	0.8	46	50	346.1	normal	1	32	36.30	72.39	45.51	18.45	1162	3	1
55	58	M	business	160	55	21.48	HTN, TDM	NIL	COPD	wnl	biomass	97	120/80	98	RHONCHI	3	48	42	0.7	60	49	286.1	normal	2	26	64.93	76.90	61.59	62.82	2079.1	6	2	DPI	Headache	98	NVBS	2	68	92	0.73	60	44	292	normal	3	22	64.93	76.90	61.59	62.82	2079	5	2
56	66	F	brick factory	160	60	23.44	nil	NIL	Nil	wnl	biomass	99	120/80	98	NVBS	2	54.56	77.94	0.7	54	47	342	normal	1	25	31.88	82.90	30.23	15.39	1020.9	4	2	DPI	NIL	98	NVBS	2	68	92	0.7	60	52	356	normal	2	26	31.88	82.90	30.23	15.39	1021	3	1
57	67	F	housewife	160	50	19.53	nil	NIL	COPD	wnl	biomass	94	120/80	98	NVBS	2	59.84	85.49	0.7	62	58	278.3	normal	1	27	21.73	41.42	22.65	14.44	695.7	4	2	DPI	NIL	98	NVBS	2	72	88	0.8	53	46	282.3	normal	1	30	21.73	41.42	22.65	14.44	695.7	3	1
58	70	M	traffic police	156	50	20.55	HTN, TDM	NIL	Nil	wnl	vehicle smoke	97	140/90	94	RHONCHI	2	65.12	93.03	0.7	50	40	356.1	normal	0	32	31.23	71.95	30.13	17.95	1000.1	1	0	DPI	Exacerbation	94	NVBS	2	78	92	0.8	52	48	348.1	normal	0	30	28.60	71.95	30.13	17.95	915.9	2	1
59	73	F	cook	155	63	26.22	nil	NIL	Nil	wnl	biomass	90	110/70	97	RHONCHI	2	69.52	99.31	0.7	56	59	285.2	copd changes	0	33	38.17	54.93	53.31	23.43	1222.2	2	1	DPI	Exacerbation	97	NVBS	2	76	95	0.8	66	72	296.4	copd changes	2	24	38.17	54.93	53.31	23.43	1222	4	2
60	75	F	housewife	163	65	24.46	HTN, TDM	RIC	COPD	wnl	biomass	89	120/80	96	RHONCHI	2	65.12	93.03	0.7	40	59	410.1	copd changes	1	26	35.41	82.90	37.41	17.95	1133.7	2	1	DPI	NIL	96	NVBS	2	78	90	0.8	45	64	408.7	copd changes	1	32	35.41	82.90	37.41	17.95	1134	2	1
61	72	F	housewife	169	70	24.51	HTN, TDM, IHD	RIC	Nil	wnl	dust	99	120/70	97	RHONCHI	2	70	78	0.7	31	48	372.5	normal	1	22	41.97	63.95	60.49	23.43	1343.9	2	1	DPI	Exacerbation	97	RHONCHI	2	72	100	0.7	46	48	357.6	normal	2	24	41.97	63.95	60.49	23.43	1344	3	1
62	55	F	labourer	157	60	24.34	TDM	NIL	COPD	wnl	biomass	78	110/80	97	RHONCHI	2	58.08	100.8	0.58	72	40	267.6	normal	2	27	18.31	34.69	15.38	14.44	586.2	4	2	DPI	Exacerbation	97	NVBS	2	68	92	0.7	66	48	302	normal	0	31	18.31	34.69	15.38	14.44	586.2	1	0
63	58	F	housewife	158	55	22.03	TDM	NIL	Nil	wnl	biomass	89	120/72	98	NVBS	2	60.72	95.2	0.64	38	30	327.3	normal	2	28	33.16	67.13	37.23	19.11	1061.9	5	2	DPI	NIL	98	NVBS	2	72	97	0.7	40	38	337	normal	2	26	33.16	67.13	37.23	19.11	1062	4	2
64	79	M	traffic police	154	80	33.73	nil	NIL	Nil	wnl	vehicle smoke	78	140/80	98	NVBS	3	45	59	0.69	34	28	342	copd changes	1	28	56.59	70.84	45.96	58.03	1812	5	2	DPI	NIL	98	NVBS	3	46	58	0.7	38	53	347.5	copd changes	0	25	52.64	70.84	45.96	58.03	1686	4	2
65	70	F	Farmer	164	68	25.28	HTN, TDM	NIL	Nil	wnl	biomass	77	120/80	95	RHONCHI	2	65.12	93.03	0.7	42	40	320	normal	1	25	36.30	72.39	45.51	18.45	1162.2	3	1	DPI	Headache	95	RHONCHI	2	68	97	0.7	42	45	325.2	normal	1	27	36.30	72.39	45.51	18.45	1162	3	1
66	68	F	Farmer	169	68	23.81	nil	NIL	Nil	wnl	biomass	89	120/80	94	RHONCHI	2	69.52	99.31	0.7	56	59	267	normal	2	24	35.41	82.90	37.41	17.95	1133.7	4	2	DPI	Exacerbation	94	RHONCHI	1	83	109	0.76	58	63	269.9	normal	0	32	35.41	82.90	37.41	17.95	1134	2	1
67	67	F	Farmer	154	55	23.19	HTN, TDM	NIL	COPD	wnl	biomass	94	120/80	97	NVBS	2	59.84	85.49	0.7	60	77	220.8	copd changes	2	25	19.19	39.65	15.38	14.44	614.3	5	2	DPI	Sinusitis	97	NVBS	2	78	97	0.8	66	62	234.1	copd changes	0	33	19.19	39.65	15.38	14.44	614.3	2	1
68	74	F	labourer	160	60	23.44	HTN, TDM	NIL	Nil	wnl	vehicle smoke	83	130/70	98	NVBS	2	70	99	0.7	72	74	244.3	normal	2	26	64.93	76.90	61.59	62.82	2079.1	5	2	DPI	NIL	98	NVBS	2	74	93	0.79	67	71	248.2	normal	2	28	64.93	76.90	61.59	62.82	2079	5	2
69	78	M	traffic police	159	66	26.11	TDM	RIC	Nil	BC	vehicle smoke	77	120/80	94	RHONCHI	2	54.56	80.24	0.68	52	43	363	normal	1	26	40.88	72.39	60.44	18.45	1309	3	1	DPI	Exacerbation	94	NVBS	2	69	86	0.8	66	45	367.1	normal	1	25	36.27	72.39	45.42	18.45	1161	2	1
70	66	F	Farmer	166	80	29.03	TDM	NIL	Nil	wnl	dust	89	140/80	96	RHONCHI	2	60	64	0.78	47	88	347.6	normal	2	22	35.41	82.90	37.41	17.95	1133.7	5	2	DPI	NIL	96	NVBS	2	66	82	0.8	46	80	356.3	normal	1	26	35.41	82.90	37.41	17.95	1134	2	1
71	62	F	housewife	158	82	32.85	HTN	NIL	Nil	wnl	dust	99	120/80	96	NVBS	2	68	92	0.7	53	27	365	normal	2	27	31.88	82.90	30.23	15.39	1020.9	3	1	DPI	NIL	96	NVBS	2	64	82	0.78	55	32	368.2	normal	2	26	31.88	82.90	30.23	15.39	1021	4	2
72	64	F	housewife	160	72	28.13	HTN, TDM, IHD	NIL	Nil	wnl	toxic gases	95	140/90	97	RHONCHI	2	66.88	95.54	0.7	38	52	342.5	copd changes	2	28	36.30	72.39	45.51	18.45	1162.2	4	2	DPI	NIL	97	NVBS	2	72	98	0.73	44	58	338.8	normal	1	28	36.30	72.39	45.51	18.45	1162	3	1
73	71	F	housewife	162	75	28.58	nil	NIL	Nil	wnl	biomass	99	130/70	96	RHONCHI	1	82	95	0.8	50	30	335.7	normal	0	30	31.23	71.95	30.13	17.95	1000.1	2	1	DPI	NIL	96	NVBS	1	80	100	0.8	56	38	338	normal	1	30	28.60	71.95	30.13	17.95	915.9	3	1
74	61	F	housewife	169	70	24.51	nil	NIL	Nil	wnl	biomass	88	130/78	98	RHONCHI	2	64.255	100.28	0.64	50	78	676.41	copd changes	1	32	48.79	73.19	45.51	42.39	1562.3	3	1	DPI	NIL	98	NVBS	2	66.2	99.6	0.66	50	78	670	copd changes	1	22	48.79	73.19	45.51	42.39	1562	2	1
75	60	M	traffic police	160	47	18.36	HTN, TDM	NIL	Nil	wnl	vehicle smoke	78	120/70	97	RHONCHI	2	69.342	109.15	0.64	56	77	540.02	copd changes	3	22	33.47	71.95	37.41	17.95	1071.7	4	2	DPI	Exacerbation	97	NVBS	2	69.7	103.0	0.68	56	77	500	copd changes	2	27	33.47	71.95	37.41	17.95	1072	3	1
76	49	F	housewife	155	63	26.22	HTN, TDM	RIC	COPD	wnl	biomass	77	130/80	97	RHONCHI	2	70.931	106.82	0.66	62	55	597.87	copd changes	2	26	72.49	83.42	69.83	70.33	2321.1	3	1	DPI	NIL	97	NVBS	2	69.2	102.2	0.68	62	55	555	copd changes	0	30	72.49	83.42	69.83	70.33	2321	1	0
77	61	F	housewife	163	65	24.46	nil	NIL	Nil	BC	biomass	89	120/72	98	RHONCHI	2	66.234	97.90	0.68	46	60	724.09	normal	1	30	41.84	64.16	37.23	36.94	1339.7	2	1	DPI	NIL	98	RHONCHI	2	69.1	98.9	0.70	46	60	730	normal	2	25	41.84	64.16	37.23	36.94	1340	3	1
78	47	F	housewife	168	77	27.28	TDM	RIC	Nil	wnl	dust	99	120/60	95	RHONCHI	2	65.738	99.98	0.66	60	82	686.76	normal	2	32	20.54	34.69	22.65	14.44	657.6	3	1	DPI	NIL	95	NVBS	2	66.5	98.0	0.68	60	82	650	normal	0	32	20.54	34.69	22.65	14.44	657.6	1	0
79	52	F	housewife	160	60	23.44	TDM	NIL	Nil	wnl	dust	69	130/60	98	NVBS	2	62.823	96.97	0.65	66	49	402.27	normal	1	26	56.59	70.84	45.96	58.03	1812	3	1	DPI	URTI	98	NVBS	2	67.5	111.3	0.61	66	49	450	normal	2	24	56.59	70.84	45.96	58.03	1812	3	1
80	62	F	labourer	160	50	19.53	nil	NIL	Nil	wnl	dust	99	110/70	94	NVBS	2	68.522	101.82	0.67	50.72	75.372	595.01	copd changes	2	26	34.48	67.13	37.23	21.67	1104.1	3	1	DPI	Exacerbation	96	NVBS	2	66.9	98.4	0.68	50.72	75.37	566	copd changes	2	26	34.48	67.13	37.23	21.67	1104	3	1
81	61	F	housewife	158	70	28.04	HTN, TDM	RIC	Nil	wnl	biomass	74	140/70	96	RHONCHI	2	65.25	98.24	0.66	61.13	68	484.86	copd changes	3	24	40.88	72.39	60.44	18.45	1309	4	2	DPI	Exacerbation	96	RHONCHI	2	66.0	99.0	0.67	61.13	68	498	copd changes	3	24	40.88	72.39	60.44	18.45	1309	4	2
82	54	F	housewife	169	67	23.46	HTN, TDM	NIL	PTB	wnl	dust	75	140/70	97	RHONCHI	2	69.156	103.92	0.67	46.45	78	489.68	copd changes	2	28	35.41	82.90	37.41	17.95	1133.7	3	1	DPI	NIL	97	NVBS	2	67.8	102.4	0.66	46.45	78	496	copd changes	2	28	35.41	82.90	37.41	17.95	1134	3	1
83	66	M	traffic police	160	78	30.47	nil	RIC	ASTHMA	wnl	vehicle smoke	83	130/80	95	RHONCHI	2	68.193	103.54	0.66	38.89	60	541.06	normal	2	25	54.79	74.71	46.57	52.86	1754.3	3	1	DPI	NIL	96	NVBS	2	66.6	98.3	0.68	38.89	60	533.4	normal	2	25	54.79	74.71	46.57	52.86	1754	3	1
84	66	F	labourer	155	63	26.22	TDM	NIL	Nil	wnl	dust	85	130/70	97	RHONCHI	2	71.677	100	0.72	67	70	514.4	normal	2	24	24.44	39.65	22.65	20.29	782.4	3	1	MDI	Exacerbation	97	NVBS	2	68.9	98.4	0.7	67	70	500	normal	2	24	24.44	39.65	22.65	20.29	782.4	3	1
85	68	F	housewife	163	65	24.46	TDM	NIL	Nil	wnl	biomass	92	130/78	97	RHONCHI	2	65.099	92	0.7	62	70.37	645.43	normal	0	32	21.13	38.03	22.65	14.44	676.5	1	0	MDI	NIL	97	RHONCHI	2	67.8	96.8	0.7	62	70.37	623	normal	0	32	21.13	38.03	22.65	14.44	676.5	1	0
86	73	M	brick factory	168	72	25.51	HTN, TDM, IHD	NIL	Nil	wnl	vehicle smoke	98	120/80	97	NVBS	1	81.57	98	0.7	55	62	576.1	normal	1	26	52.83	76.90	46.27	48.48	1691.5	2	1	DPI	Exacerbation	97	NVBS	1	83.6	127.6	0.66	55	62	52	normal	1	26	52.83	76.90	46.27	48.48	1692	5	2
87	75	F	labourer	168	72	25.51	HTN, TDM	NIL	PTB	wnl	toxic gases	85	130/74	98	NVBS	1	81.485	115.85	0.70	58	66	512.17	copd changes	2	25	54.79	74.71	46.57	52.86	1754.3	3	1	DPI	URTI	98	NVBS	1	80.6	117.7	0.68	58	66	500	copd changes	2	25	54.79	74.71	46.57	52.86	1754	3	1
88	72	F	housewife	160	71	27.73	nil	NIL	Nil	wnl	biomass	92	128/72	98	RHONCHI	2	63.326	107.92	0.59	50	66	544.39	normal	2	27	34.48	67.13	37.23	21.67	1104.1	4	2	DPI	Exacerbation	98	NVBS	2	66.8	101.8	0.66	50	66	490	normal	2	27	34.48	67.13	37.23	21.67	1104	3	1
89	66	F	labourer	169	70	24.51	Nil	NIL	Nil	wnl	dust	98	128/78	98	RHONCHI	2	70.638	122.41	0.58	47	80	533.37	normal	3	24	37.74	77.64	52.33	15.39	1208.4	4	2	DPI	NIL	98	RHONCHI	2	73.6	115.9	0.64	47	80	512	normal	2	24	37.74	77.64	52.33	15.39	1208	3	1
90	68	F	housewife	147	55	25.45	HTN, TDM	RIC	PTB	wnl	dust	88	140/90	97	RHONCHI	2	79.718	100	0.7	60	57	649.41	copd changes	2	27	33.96	64.16	37.23	21.67	1087.3	3	1	DPI	Increased Cough	97	NVBS	2	79.3	113.3	0.7	60	57	600	copd changes	2	27	33.96	64.16	37.23	21.67	1087	3	1
91	80	M	battery shop	157	60	24.34	HTN, TDM	NIL	ASTHMA	wnl	toxic gases	86	120/80	98	RHONCHI	2	78.322	99	0.7	55	67	479.48	normal	2	26	43.12	70.47	60.49	23.43	1380.8	3	1	DPI	Exacerbation	98	RHONCHI	2	79.6	113.7	0.7	55	67	456	normal	2	26	43.12	70.47	60.49	23.43	1381	3	1
92	72	F	housewife	166	66	23.95	nil	RIC	Nil	wnl	biomass	102	130/80	96	RHONCHI	2	53.651	53	0.67	62	70.37	531.31	normal	0	31	36.30	72.39	45.51	18.45	1162.2	2	1	MDI	Exacerbation	96	RHONCHI	2	59.6	89.3	0.67	62	70.37	532	normal	1	32	36.30	72.39	45.51	18.45	1162	3	1
93	62	F	housewife	159	66	26.11	TDM	NIL	Nil	BC	dust	98	128/72	98	NVBS	2	65.12	93.03	0.7	55	62	414.59	normal	2	26	64.93	76.90	61.59	62.82	2079.1	3	1	DPI	Exacerbation	98	NVBS	2	73.3	112.5	0.65	55	62	404	normal	3	22	64.93	76.90	61.59	62.82	2079	4	2
94	52	M	battery shop	156	66	27.12	TDM	NIL	Nil	wnl	toxic gases	90	128/78	98	NVBS	2	55.426	65	0.67	58	66	244.7	normal	1	25	31.88	82.90	30.23	15.39	1020.9	5	2	DPI	Exacerbation	98	NVBS	3	49.3	74.8	0.66	58	66	305	normal	2	26	31.88	82.90	30.23	15.39	1021	6	2
95	72	F	Farmer	166	67	24.31	nil	NIL	Nil	wnl	biomass	86	120/80	98	RHONCHI	2	62	71	0.7	49	52	565.36	normal	1	27	21.73	41.42	22.65	14.44	695.7	3	1	MDI	Exacerbation	98	NVBS	2	65.5	94.0	0.70	49	52	570	normal	1	30	21.73	41.42	22.65	14.44	695.7	2	1