The Research of Medical Science Review

Received: 07 December, 2024
Accepted: 07 January, 2025
Published: 14 January, 2025

ISSN: 3007-1208 | 3007-1216
Volume 3, Issue 1, 2025

# PREVALENCE OF PULMONARY HYPERTENSION IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS AND ITS CORRELATION WITH THE SEVERITY OF DISEASE

**Zain Ahmad Khan[*1], Muhammad Irfan[2], Akbar Shoukat Ali[3], Mushyada Ali[4], Syeda Sakina Mehdi[5], Nimra Iftikhar[6]**

*[*1,2,3,6]Section of Pulmonary & Critical Care Medicine, Department of Medicine, Aga Khan University, Karachi, Pakistan*
*[4]Clinical and Translational Research Incubator (CITRIC) Health Data Science Center, Department of Medicine, Aga Khan University, Karachi, Pakistan*
*[5]Medical College, Aga Khan University, Karachi, Pakistan*

[*1]zain141993@gmail.com

## ABSTRACT

***Background:*** *Chronic obstructive pulmonary disease (COPD) represents a major public health issue on a worldwide scale, often complicated by pulmonary hypertension (PH), which exacerbates morbidity and mortality. While the relationship between COPD severity and PH is established, data on PH prevalence in mild to moderate COPD is inconsistent.*

***Objective:*** *This study aimed to assess the frequency of PH in COPD patients and its correlation with disease severity in Pakistan.*

***Design:*** *Descriptive observational study conducted on adult COPD patients aged 30 to 80 years, presenting to the Aga Khan University Hospital (AKUH), Karachi, Pakistan from January 2017 to December 2022*

***Methods:*** *All diagnosed COPD patients who had an echocardiography and a spirometry done at AKUH were included in this study. Exclusion criteria were PH due to causes other than COPD and left-sided heart disease. Pulmonary hypertension was characterized by an estimated pulmonary artery systolic pressure (PASP) of 35 mmHg or greater, as determined through echocardiographic assessment. COPD severity was classified according to GOLD guidelines.*

***Results:*** *A total of 236 patients were included, with a mean age of 67.06 years. PH was identified in 26.3% of patients: 21.2% mild, 3.0% moderate, and 2.1% severe. There was no significant difference in demographics, comorbidities, or COPD treatments between those with and without PH. Higher prevalence of biomass exposure was seen in patients with moderate PH (p=0.046). In multivariate analysis, increasing age (Odds Ratio [OR] 1.033, 95% Confidence Interval [CI] 1.000 – 1.067, p=0.051) was found to be independently associated with risk of developing PH.*

***Conclusion:*** *The estimated prevalence of PH in COPD patients is around 26.3% in our study. Advanced age, low FEV1 and biomass fuel exposure are found to be risk factors for developing PH. in COPD patients in this study. Early identification and management of PH may improve outcomes in COPD patients.*

***Keywords:*** *Chronic obstructive pulmonary disease; pulmonary hypertension; prevalence; severity; Pakistan*

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is currently defined as a "common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases" [1]. This chronic ailment impacts approximately 12.16% of individuals who are 40 years old and above [2]. COPD presents as shortness of breath, sputum production and chronic cough [3].

One of the complications of COPD is pulmonary hypertension. Previously, a mean pulmonary artery systolic pressure (PASP) of ≥25mmHg at rest was the standard. However, at the 6th World Symposium on pulmonary hypertension, they suggested lowering it to 20mmHg after considering recent scientific evidence [3]. The exact prevalence of pulmonary hypertension in COPD patients is uncertain. It varies greatly in different studies, with rates ranging from 20% to 91% [4]. It is reportedly related to greater morbidity and mortality [5].

Multiple mechanisms may have an impact, but the most prominent ones seem to be hypoxic pulmonary vasoconstriction and the modification of pulmonary vessels [6]. It is well known that the greater the severity of COPD, the greater the prevalence and severity of pulmonary hypertension. However, there is conflicting evidence and paucity of data on mild and moderate airway obstruction and its effect on pulmonary hypertension. A study from India showed the frequency of pulmonary hypertension in mild COPD as 16.67% [7]. Another study showed a frequency of 25% in mild COPD [8]. However, Jatav et al. (2017) showed that pulmonary hypertension was observed in 0% of the COPD patients with mild category [9]. Varied thresholds have been used to define pulmonary hypertension, along with different diagnostic tools, which may have accounted for these differences.

In Pakistan, there are only a few studies conducted to assess the prevalence of pulmonary hypertension in COPD and its correlation with its severity. One such study done in Rahim Yar Khan found pulmonary hypertension in 62.86% of COPD patients with the majority of them being mild [10]. Another study done in Abbottabad found a frequency of 45.4%. It also showed that the frequency of pulmonary hypertension was 34.1%, 45.0%, and 64.7% in moderate, severe, and very severe cases of COPD, respectively [11].

In patients with COPD, pulmonary hypertension is a critical determinant of mortality outcomes. For those with COPD and severe pulmonary hypertension characterized by a PASP of over 40 mmHg, the 5-year survival rate is approximately 15% [12]. More studies are required in high COPD burdened countries, like Pakistan, to evaluate the frequency of pulmonary hypertension in these patients, and to ensure that necessary steps can be undertaken to address pulmonary hypertension early in the course of disease to decrease morbidity and mortality, and to improve quality of life. This study aimed to investigate the frequency of pulmonary hypertension in patients with COPD. and its correlation with disease severity at a tertiary care hospital of Karachi, Pakistan.

## Material and Methods

This was a descriptive observational research study conducted on adult COPD patients aged 30 to 80 years, presented to the Aga Khan University Hospital, Karachi, Pakistan from January 2017 to December 2022. The Aga Khan University Hospital, established in 1985, is a tertiary care hospital in private sector with patient influx from all over Pakistan. A large number of patients come from the city of Karachi. The hospital offers a wide range of secondary and tertiary care services, including disease diagnosis and management of patient care. The hospital has well-established units delivering inpatient, outpatient, and 24/7 emergency department services. Besides, the hospital is equipped to provide healthcare services in all the major medical specialties and subspecialties such as cardiology, nephrology, neurology, pulmonology, infectious diseases, oncology, psychiatry, obstetrics, and gynecology.

This study obtained approval from the ethical review committee (ERC # 2023-8419-26209) of the Aga Khan University Hospital, Karachi, Pakistan. All the diagnosed COPD patients of both genders who had an echocardiography and a spirometry done at Aga Khan University Hospital were included in this study. Documented cases of pulmonary hypertension due to any other reason, including any lung disease other than COPD, and left sided heart disease were excluded from the study. Data was collected by reviewing the

medical records. Demographic data, comorbidities, vaccination and smoking status, treatment, echocardiography and spirometry data were entered in a predesigned proforma.

Patients were characterized as COPD if they had signs and symptoms of COPD and a post bronchodilator FEV1/FVC ratio <70. They were further classified according to the GOLD guidelines 2023 (Global initiative for chronic Obstructive Lung Disease) criteria: mild COPD with FEV1 ≥80%, moderate COPD with 50% ≤ FEV1 < 80%, severe COPD with 30% ≤ FEV1 < 50%, and very severe COPD with FEV1 < 30% of predicted [13].

Patients were considered as having pulmonary hypertension if they had estimated PASP greater than or equal to 35 mmHg and categorization was as follows.: mild pulmonary hypertension (35–45 mm Hg), moderate pulmonary hypertension (46–60 mm Hg), and severe pulmonary hypertension (> 60 mm Hg), based on transthoracic echocardiography [14].

***Statistical Analysis***

Statistical Package for the Social Sciences (SPSS) for Windows (IBM Corp., Armonk, N.Y., USA) version 19.0 was employed to perform the data analysis. Data normality was assessed. Quantitative variables were presented as mean ± standard deviation (SD) and qualitative variables were presented as frequency and percentages. One-way analysis of variance (ANOVA) test was used for comparison of numerical data among groups. For comparison of the non-numerical data, the Fisher's Exact test was used. Logistic regression analysis was performed to identify predictors of PH and odds ratios (OR) with 95% confidence intervals (CI) were reported. Variables with p values of <0.1 in univariate logistic regression analysis were entered into the multivariate logistic regression analysis. The p value ≤0.05 was considered as statistically significant.

## Results

***General Characteristics***

A total of 236 patients were included in the study. The mean age of the patients was 67.06 ± 9.64 years and 162 (68.6%) were male. **Table 1** shows the general characteristics of the patients. The mean body mass index (BMI) was 26.47 ± 6.07 Kg/m$^2$ i.e. 75 (31.8%) were overweight, with 13.6% (*n*=32), 8.5% (*n*=20), and 2.1% (*n*=5) in obesity class I, II, and III, respectively. The most common comorbidities were hypertension (*n*=155, 65.7%) and diabetes mellitus (*n*=86, 36.4%). Overall, 119 (50.4%) patients were never smokers, while 117 (49.6%) were either ex-smokers or current smokers. Of 236 patients, 25 (10.6%) patients had a history of significant biomass fuel exposure. Almost two-thirds (*n*=153, 64.8%) of the patients had no vaccination history for *Influenza, Pneumococcal*, and *COVID-19.*

**Table 1.** Clinical Characteristics of Patients with COPD

| **Characteristics** | **Total (*n*=236)** |
|---|---|
| **Age (Years)** | 67.06 ± 9.64 |
| **Gender (Male)** | 162 (68.6%) |
| **Anthropometrics** | |
| Height (m) | 1.64 ± 0.09 |
| Weight (kg) | 70.79 ± 17.06 |
| Body Mass Index (Kg/m$^2$) | 26.47 ± 6.07 |
| **Body Mass Index Categories** | |
| Normal | 91 (38.6%) |
| Underweight | 13 (5.5%) |
| Overweight | 75 (31.8%) |
| Obesity I | 32 (13.6%) |
| Obesity II | 20 (8.5%) |
| Obesity III | 5 (2.1%) |

| | |
|---|---|
| **Comorbidities** | |
| Diabetes Mellitus | 86 (36.4%) |
| Hypertension | 155 (65.7%) |
| Lung Cancer | 8 (3.4%) |
| Cerebrovascular Accident | 12 (5.1%) |
| Obstructive Sleep Apnea | 5 (2.1%) |
| **Vaccination Status** | |
| None | 153 (64.8%) |
| Influenza | 21 (8.9%) |
| Pneumococcal | 19 (8.1%) |
| Influenza & Pneumococcal | 41 (17.4%) |
| Influenza, Pneumococcal, & COVID | 2 (0.8%) |
| **Biomass Exposure** | 25 (10.6%) |
| **Smoking history** | |
| Never Smoker | 119 (50.4%) |
| Ex-Smoker | 85 (36.0%) |
| Current Smoker | 32 (13.6%) |
| Pack-Years | 41.68 ± 30.07 |
| **Family History of COPD** | 4 (1.7%) |
| **Post-Bronchodilator FEV1 (Mean of % predicted ± SD)** | 57.68 ± 19.25 |
| **Post-Bronchodilator FVC (Mean of % predicted ± SD)** | 77.75 ± 20.78 |
| **Post-Bronchodilator FEV1/FVC Ratio (Mean ± SD)** | 58.94 ± 9.63 |
| **GOLD Staging** | |
| GOLD I | 21 (8.9%) |
| GOLD II | 134 (56.8%) |
| GOLD III | 63 (26.7%) |
| GOLD IV | 18 (7.6%) |
| **Bronchodilator Treatment** | |
| LAMA | 14 (5.9%) |
| LABA+ICS | 54 (22.9%) |
| LABA+LAMA+ICS | 109 (46.2%) |
| **Systemic Steroids (Last 12 Months)** | 90 (38.1%) |
| **Home LTOT** | 22 (9.3%) |
| **Home NIV** | 21 (8.9%) |
| **Pulmonary Hypertension (*n*=62, 26.3%)** | |
| Mild | 50/62 (80.6%) |
| Moderate | 7/62 (11.3%) |
| Severe | 5/62 (8.1%) |

**Abbreviations:** COPD, Chronic Obstructive Pulmonary Disease; COVID, Coronavirus Disease; FEV1, Forced Expiratory Volume; FVC, Forced Vital Capacity; LTOT, Long-Term Oxygen Therapy; NIV, Non-Invasive Ventilation; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LAMA, Long-Acting Muscarinic Antagonists; LABA, Long-Acting Beta Agonists; EF, Ejection fraction; ICS Inhaled Corticosteroids; and LV, Left Ventricular.

Values are presented as Mean ± Standard Deviation (SD) and Frequency (%).

The mean post-bronchodilator FEV1/FVC ratio was 58.94 ± 9.63, mean FEV1 (% predicted) was 57.68 ± 19.25, whereas the mean post-bronchodilator FVC was 77.75 ± 20.78. Majority of the patients were of GOLD stage II (*n*=134, 56.8%) and GOLD stage III (*n*=63, 26.7%). Almost half of the patients (*n*=109, 46.2%) were taking combination treatment of long-acting beta agonist (LABA), long-acting muscarinic antagonists (LAMA), and inhaled corticosteroids (ICS). Twenty-two (9.3%) patients were on long-term oxygen therapy (LTOT), whereas 21 (8.9%) were using a home noninvasive ventilation (NIV) device. A

total of 62 (26.3%) patients had pulmonary hypertension, of which 50 (80.6%) had mild, 7 (11.3%) had moderate, and 5 (8.1%) had severe pulmonary hypertension **(Table 1)**.

**Table 2** shows the clinical characteristics of COPD patients with and without pulmonary hypertension. For age, gender, anthropometrics, BMI, comorbidities, and vaccination status, there was no significant difference (p>0.05). Notably, COPD patients with moderate pulmonary hypertension had a higher frequency of biomass fuel exposure (*n*=3, 42.9%, p=0.046). In patients with moderate and severe pulmonary hypertension, the post-bronchodilator FEV1 was lower (47.57 ± 7.93 and 48.00 ± 19.16, respectively) as compared to COPD patients without and with mild pulmonary hypertension (58.41 ± 19.13 and 57.52 ± 20.51, respectively); however, the difference was not statistically significant (p=0.329). Three (60%) patients with severe pulmonary hypertension were using home long term oxygen therapy (LTOT) as compared to patients with mild (*n*=6, 12.0%) and moderate pulmonary hypertension (*n*=3, 42.9%) (p<0.0001). No significant difference was observed for smoking, family history of COPD, GOLD staging, bronchodilator and systemic steroid (p>0.05).

**Table 2.** Clinical Characteristics of COPD Patients with and without Pulmonary Hypertension

| Characteristics | COPD Only (*n*=174) | COPD with Mild PH (*n*=50) | COPD with Moderate PH (*n*=7) | COPD with Severe PH (*n*=5) | *P* value |
|---|---|---|---|---|---|
| **Age (Years)** | 66.42 ± 9.34 | 69.00 ± 10.49 | 66.43 ± 10.85 | 70.80 ± 9.04 | 0.312 |
| **Gender** | | | | | |
| Female | 49 (28.2%) | 20 (40.0%) | 3 (42.9%) | 2 (40.0%) | 0.297† |
| Male | 125 (71.8%) | 30 (60.0%) | 4 (57.1%) | 3 (60.0%) | |
| **Anthropometrics** | | | | | |
| Height (m) | 1.64 ± 0.10 | 1.61 ± 0.08 | 1.62 ± 0.11 | 1.58 ± 0.06 | 0.061 |
| Weight (kg) | 72.34 ± 17.49 | 66.12 ± 14.45 | 71.71 ± 14.22 | 63.50 ± 24.26 | 0.107 |
| Body Mass Index (Kg/m$^2$) | 26.75 ± 6.20 | 25.46 ± 5.16 | 27.74 ± 6.40 | 25.38 ± 9.86 | 0.536 |
| **Body Mass Index Categories** | | | | | |
| Normal | 63 (36.2%) | 21 (42.0%) | 3 (42.9%) | 4 (80.0%) | 0.526† |
| Underweight | 10 (5.7%) | 3 (6.0%) | 0 (0.0%) | 0 (0.0%) | |
| Overweight | 56 (32.2%) | 18 (36.0%) | 1 (14.3%) | 0 (0.0%) | |
| Obese | 45 (25.9%) | 8 (16.0%) | 3 (42.9%) | 1 (20.0%) | |
| **Comorbidities** | | | | | |
| Diabetes Mellitus | 64 (36.8%) | 20 (40.0%) | 1 (14.3%) | 1 (20.0%) | 0.562† |
| Hypertension | 113 (64.9%) | 35 (70.0%) | 5 (71.4%) | 2 (40.0%) | 0.588† |
| Lung Cancer | 7 (4.0%) | 1 (2.0%) | 0 (0.0%) | 0 (0.0%) | 0.795† |
| Cerebrovascular Accident | 10 (5.7%) | 2 (4.0%) | 0 (0.0%) | 0 (0.0%) | 1.000† |
| Obstructive Sleep Apnea | 4 (2.3%) | 1 (2.0%) | 0 (0.0%) | 0 (0.0%) | 1.000† |
| **Vaccination Status** | 59 (33.9%) | 18 (36.0%) | 3 (42.9%) | 3 (60.0%) | 0.619† |
| **Biomass Exposure** | 16 (9.2%) | 5 (10.0%) | 3 (42.9%) | 1 (20.0%) | **0.046**† |
| **Smoking history** | | | | | |
| Never Smoker | 85 (48.9%) | 28 (56.0%) | 3 (42.9%) | 3 (60.0%) | 0.809† |
| Ex-Smoker | 64 (36.8%) | 16 (32.0%) | 4 (57.1%) | 1 (20.0%) | |
| Current Smoker | 25 (14.4%) | 6 (12.0%) | 0 (0.0%) | 1 (20.0%) | |
| **Family History of COPD** | 4 (2.3%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0.659† |
| **Post-Bronchodilator FEV1** | 58.41 ± 19.13 | 57.52 ± 20.51 | 47.57 ± 7.93 | 48.00 ± 19.16 | 0.329 |
| **Post-Bronchodilator FVC** | 79.09 ± 20.27 | 75.82 ± 23.60 | 65.29 ± 7.70 | 68.00 ± 13.15 | 0.189 |
| **Post-Bronchodilator FEV1/FVC Ratio** | 58.77 ± 9.92 | 60.02 ± 7.98 | 58.71 ± 9.07 | 54.40 ± 15.69 | 0.619 |
| **GOLD Staging** | | | | | |
| GOLD I | 15 (8.6%) | 6 (12.0%) | 0 (0.0%) | 0 (0.0%) | 0.673† |
| GOLD II | 103 (59.2%) | 25 (50.0%) | 3 (42.9%) | 3 (60.0%) | |
| GOLD III | 43 (24.7%) | 15 (30.0%) | 4 (57.1%) | 1 (20.0%) | |
| GOLD IV | 13 (7.5%) | 4 (8.0%) | 0 (0.0%) | 1 (20.0%) | |
| **Bronchodilator Treatment** | | | | | |
| LAMA | 10 (7.9%) | 3 (7.9%) | 1 (14.3%) | 0 (0.0%) | 0.520† |
| LABA+ICS | 34 (26.8%) | 16 (42.1%) | 2 (28.6%) | 2 (40.0%) | |
| LABA+LAMA+ICS | 83 (65.4%) | 19 (50.0%) | 4 (57.1%) | 3 (60.0%) | |

| | | | | | |
|---|---|---|---|---|---|
| **Systemic Steroids (Last 12 Months)** | 69 (62.7%) | 17 (58.6%) | 3 (60.0%) | 1 (33.3%) | 0.751† |
| **Home LTOT** | 10 (5.7%) | 6 (12.0%) | 3 (42.9%) | 3 (60.0%) | **<0.0001**† |
| **Home NIV** | 12 (6.9%) | 6 (12.0%) | 1 (14.3%) | 2 (40.0%) | 0.053† |

**Abbreviations:** COPD, Chronic Obstructive Pulmonary Disease; COVID, Coronavirus Disease; FEV1, Forced Expiratory Volume; FVC, Forced Vital Capacity; LTOT, Long-Term Oxygen Therapy; NIV, Non-Invasive Ventilation; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LAMA, Long-Acting Muscarinic Antagonists; LABA, Long-Acting Beta Agonists; ICS, Inhaled Corticosteroids; Values are presented as Mean ± Standard Deviation (SD) and Frequency (%).
†Fisher's Exact Test

***Factors associated with Risk of Pulmonary Hypertension***

**Table 3** presents the factors associated with the risk of developing pulmonary hypertension in COPD patients using univariate and multivariate logistic regression analyses. On univariate logistic regression analysis, increasing age (OR 1.028; 95% CI, 0.996 – 1.061; p=0.089), gender (OR 0.580; 95% CI, 0.317 – 1.063; p=0.078), and post-bronchodilator FVC (OR 0.988; 95% CI, 0.973 – 1.002; p=0.099) were found to be closely linked with pulmonary hypertension in COPD. However, on multivariate logistic regression analysis, increasing age (OR 1.033; 95% CI, 1.000 – 1.067; p=0.051) was the only factor which appeared to be independently (but with borderline statistical significance) associated with odds of developing pulmonary hypertension in COPD patients.

**Table 3.** Factors associated with Risk of Pulmonary Hypertension in Patients with COPD

| **Characteristics** | **Univariate Analysis** | | **Multivariate Analysis** | |
|---|---|---|---|---|
| | **OR (95% CI)** | ***P* value** | **OR (95% CI)** | ***P* value** |
| **Age (Years)** | 1.028 (0.996 – 1.061) | 0.089 | 1.033 (1.000 – 1.067) | **0.051** |
| **Gender** | | | | |
| Female | Reference | | | |
| Male | 0.580 (0.317 – 1.063) | 0.078 | 0.594 (0.310 – 1.138) | 0.116 |
| **Body Mass Index (Kg/m²)** | 0.971 (0.924 – 1.021) | 0.252 | - | - |
| **Body Mass Index Categories** | | | | |
| Normal | Reference | | | |
| Underweight | 0.675 (0.172 – 2.643) | 0.572 | - | - |
| Overweight | 0.763 (0.385 – 1.514) | 0.440 | | |
| Obese | 0.600 (0.276 – 1.305) | 0.198 | | |
| **Comorbidities** | | | | |
| Diabetes Mellitus | 0.945 (0.516 – 1.730) | 0.855 | | |
| Hypertension | 1.134 (0.612 – 2.101) | 0.690 | - | - |
| Lung Cancer | 0.391 (0.047 – 3.244) | 0.384 | | |
| Cerebrovascular Accident | 0.547 (0.116 – 2.567) | 0.444 | | |
| Obstructive Sleep Apnea | 0.697 (0.076 – 6.356) | 0.749 | | |
| **Vaccination Status*** | | | | |
| No | Reference | | - | - |
| Yes | 1.231 (0.676 – 2.242) | 0.497 | | |
| **Biomass Exposure** | | | | |
| No | Reference | | - | - |
| Yes | 1.677 (0.700 – 4.018) | 0.246 | | |
| **Smoking history** | | | | |
| Never Smoker | Reference | | - | - |
| Ex-Smoker | 0.820 (0.435 – 1.545) | 0.540 | | |
| Current Smoker | 0.700 (0.277 – 1.770) | 0.451 | | |
| **Post-Bronchodilator FEV1** | 0.992 (0.977 – 1.008) | 0.329 | - | - |
| **Post-Bronchodilator FVC** | 0.988 (0.973 – 1.002) | 0.099 | 0.991 (0.975 – 1.006) | 0.233 |
| **Post-Bronchodilator FEV1/FVC Ratio** | 1.007 (0.977 – 1.038) | 0.650 | - | - |
| **Reversibility** | | | | |
| No | Reference | | - | - |
| Yes | 0.933 (0.183 – 4.750) | 0.934 | | |

| | | | | |
|---|---|---|---|---|
| **GOLD Staging** | | | | |
| GOLD I | Reference | | | |
| GOLD II | 0.752 (0.269 – 2.104) | 0.588 | - | - |
| GOLD III | 1.163 (0.393 – 3.442) | 0.785 | | |
| GOLD IV | 0.962 (0.237 – 3.899) | 0.956 | | |
| **Bronchodilator Treatment** | | | | |
| LAMA | Reference | | - | - |
| LABA+ICS | 1.471 (0.407 – 5.312) | 0.556 | | |
| LABA+LAMA+ICS | 0.783 (0.227 – 2.707) | 0.699 | | |
| **Systemic Steroids (Last 12 Months)** | | | | |
| No | Reference | | - | - |
| Yes | 0.780 (0.366 – 1.662) | 0.520 | | |

**Abbreviations:** COPD, Chronic Obstructive Pulmonary Disease; FEV1, Forced Expiratory Volume; FVC, Forced Vital Capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LAMA, Long-Acting Muscarinic Antagonists; LABA, Long-Acting Beta Agonists; ICS, Inhaled Corticosteroids.
*Included Influenza, Pneumococcal, and COVID-19 vaccinations.

## Discussion

The main aim of this study was to determine the frequency of pulmonary hypertension in COPD patients and its correlation with disease severity. The study reviewed data of 236 COPD patients, with 62 patients (26.3%) identified as having pulmonary hypertension. Earlier systematic review and meta-analysis by Zhang *et al.* (2022) has also found high prevalence of pulmonary hypertension in COPD patients [15]. Of 62 patients, 50 (80.6%) presented with mild pulmonary hypertension, 7 (11.3%) had moderate pulmonary hypertension, and 5 patients (8.1%) had severe pulmonary hypertension.

The gold standard for diagnosing pulmonary hypertension and assessing pulmonary hemodynamics is still right heart catheterization (RHC), with the revised definition now including patients with a mean PASP exceeding 20 mmHg [16]. However, it is not always performed, either because of financial limitations, inadequate training and specialized facilities, or apprehensions regarding the invasive nature of RHC and its associated risks. As far as guidelines are concerned, doppler echocardiography is essential for screening and diagnosing pulmonary hypertension, serving as the initial non-invasive diagnostic method in cases of suspected pulmonary hypertension [17]. It is capable of providing an approximation of PASP, assessing the extent of remodeling and functionality of the right ventricle, and aiding in the exclusion of secondary causes of pulmonary hypertension [18]. A large-scale retrospective study identified a strong relationship between PASP determined by doppler echocardiography and by RHC, with values of 45.3 ± 15.5 mmHg and 47.4 ± 16.4 mmHg, respectively [19]. It showed good sensitivity and specificity, while also acknowledging some limitations. However, contrasting results were seen in other studies. Within the ASPIRE registry, a weak correlation was noted between the estimated PASP assessed via echocardiogram and the PASP directly measured during right heart catheterization [20]. Three recent meta-analyses on this issue also showed inconsistent results [21-23]. A study of patients with advanced lung illness indicated a good association between PASP assessed by echocardiography and RHC; nonetheless, 52% of pressure estimates were found to be erroneous, and 48% of patients were misdiagnosed as having pulmonary hypertension by echocardiography [24]. Another pitfall of echocardiography in patients with advanced lung disease is poor acoustic windows that make proper interpretation of images difficult. In a study focused on COPD patients, satisfactory echocardiograms were achievable in just 34 out of the total 52 patients [25]. In another study involving patients with advanced lung disease who underwent assessment for lung transplantation., roughly half of the COPD patients could undergo satisfactory echocardiographic examination [26]. Furthermore, operator dependence can result in variation of results. These reasons could account for the large variation in prevalence rates worldwide and could also explain the slightly lower prevalence of pulmonary hypertension in our cohort as compared to other studies.

Our study discovered that while patients with moderate and severe pulmonary hypertension had reduced post-bronchodilator FEV1 compared to COPD patients without and with mild pulmonary hypertension, this difference was not statistically significant. Notably, other studies have shown that the severity of pulmonary

hypertension does increase with COPD severity [7, 27]. As mentioned earlier, variation in PASP cutoffs and challenges associated with echocardiography in advanced COPD patients, could explain this difference. Previous studies have shown that the frequency of severe pulmonary hypertension in COPD is low, between 3% to 7 % [15, 28]. Our findings were consistent with this as only 5 of 236 (2.1%) COPD patients had severe pulmonary hypertension, with most having mild pulmonary hypertension.

Furthermore, our study showed that advanced age was a borderline statistically significant independent factor associated with pulmonary hypertension in COPD patients. Association of increasing age with pulmonary hypertension can be due to multiple reasons. Age related physiological changes of the lung, including dilatation of alveoli, decrease in expiratory flow rate, decrease in chest wall compliance, stiffening of blood vessels, are well documented [29]. Furthermore, the presence of multiple pathologies in elderly patients can complicate the assessment of pulmonary vasculature's contribution to pulmonary hypertension. Diastolic dysfunction in elderly patients can also commonly aid in the progression of pulmonary hypertension [30].

The study's limitations include the restricted sample size that limits the generalizability of the results to the overall population. Owing to the study's retrospective design., the varying time duration between the performance of pulmonary function test and echocardiography could have resulted in the discrepancy seen in the correlation between severity of COPD and severity of pulmonary hypertension.

**Conclusion**

In summary, the estimated prevalence of PH in COPD patients is around 26.3% in our study. Advanced age, low FEV1 and biomass fuel exposure are found to be risk factors for developing PH in COPD patients in this study. Early identification and management of PH may improve outcomes in COPD patients. Multicenter studies are required to evaluate the outcome benefit of early identification and management of PH in COPD patients.

**Acknowledgments:** We would like to acknowledge Clinical and Translational Research Incubator (CITRIC) Health Data Science Center, Aga Khan University (Karachi, Pakistan) for their unwavering support in research data retrieval

**Author Contributions:** **ZAK** has made substantial contributions in conception, design of the work, data acquisition, analysis, drafting the manuscript, and approved the submitted version. **MI** has made substantial contributions in overall supervision, conception, design of the work, data analysis, drafting the manuscript, and approved the submitted version. **ASA** has made substantial contributions in data analysis, drafting the manuscript, and approved the submitted version. **MA** has made substantial contributions in drafting the manuscript, revision, and approved the submitted version. **SSM** has made substantial contributions in drafting the manuscript, revision, and approved the submitted version. **NI** has made substantial contributions in drafting the manuscript, revision, and approved the submitted version.

**Ethics Approval and Consent to Participate:** Given the retrospective chart reviews and lack of direct involvement of patients or other human participants, a waiver of ethics approval and informed consent was obtained from the Ethics Review Committee (ERC) of the Aga Khan University (ERC # 2023-8419-26209). All methods were conducted in accordance with the highest ethical standards outlined in the 1964 Declaration of Helsinki and its future amendments

**Patient Consent for Publication:** Not applicable.
**Informed Consent:** Not applicable.
**Conflict of Interest:** The authors declare that there is no conflict of interest.
**Funding:** None.
**Availability of Data and Materials:** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**REFERENCES**


1.GLOBAL STRATEGY FOR PREVENTION, DIAGNOSIS AND MANAGEMENT OF COPD: 2022 Report, https://goldcopd.org/wp-content/uploads/2021/12/GOLD-POCKET-GUIDE-2022-v1.1-22Nov2021_WMV.pdf (2022, accessed 13-08-2024).

2.Varmaghani M, Dehghani M, Heidari E, et al. Global prevalence of chronic obstructive pulmonary disease: systematic review and meta-analysis. *East Mediterr Health J* 2019; 25: 47-57. 2019/03/29. DOI: 10.26719/emhj.18.014.

3.Simonneau G and Hoeper MM. The revised definition of pulmonary hypertension: exploring the impact on patient management. *European Heart Journal Supplements* 2019; 21: K4-K8. DOI: 10.1093/eurheartj/suz211.

4.Opitz I and Ulrich S. Pulmonary hypertension in chronic obstructive pulmonary disease and emphysema patients: prevalence, therapeutic options and pulmonary circulatory effects of lung volume reduction surgery. *J Thorac Dis* 2018; 10: S2763-s2774. 2018/09/14. DOI: 10.21037/jtd.2018.07.63.

5.Hayes D, Jr., Black SM, Tobias JD, et al. Prevalence of Pulmonary Hypertension and its Influence on Survival in Patients With Advanced Chronic Obstructive Pulmonary Disease Prior to Lung Transplantation. *Copd* 2016; 13: 50-56. 2015/09/15. DOI: 10.3109/15412555.2015.1043425.

6.Barberà JA, Peinado VI and Santos S. Pulmonary hypertension in chronic obstructive pulmonary disease. *Eur Respir J* 2003; 21: 892-905. 2003/05/27. DOI: 10.1183/09031936.03.00115402.

7.Gupta N, Agrawal RK, Srivastav A, et al. Echocardiographic evaluation of heart in chronic obstructive pulmonary disease patient and its co-relation with the severity of disease. *Lung India* 2011; 28: 105-109.

8.Higham MA, Dawson D, Joshi J, et al. Utility of echocardiography in assessment of pulmonary hypertension secondary to COPD. *Eur Respir J* 2001; 17: 350-355. 2001/06/19. DOI: 10.1183/09031936.01.17303500.

9.Jatav VS, Meena S, Jelia S, et al. Echocardiographic findings in chronic obstructive pulmonary disease and correlation of right ventricular dysfunction with disease severity. *Int J Adv Med* 2017; 4: 476-480.

10.Mushtaq F, Zeeshan HM and Khan S. Pulmonary Hypertension in Cases with Chronic Obstructive Pulmonary Disease. *PAKISTAN JOURNAL OF MEDICAL & HEALTH SCIENCES* 2017; 11: 556-558.

11.Suleman A, Abdullah A, Ullah R, et al. Frequency of Pulmonary Hypertension in Chronic Obstructive Pulmonary Disease Patients. *Pakistan Journal of Chest Medicine* 2017; 23: 151-155.

12.Mueller-Mottet S, Stricker H, Domeninghetti G, et al. Long-term data from the Swiss pulmonary hypertension registry. *Respiration* 2015; 89: 127-140.

13.POCKET GUIDE TO COPD. DIAGNOSIS, MANAGEMENT, AND PREVENTION, https://goldcopd.org/wp-content/uploads/2023/03/POCKET-GUIDE-GOLD-2023-ver-1.2-17Feb2023_WMV.pdf (2023, accessed 13-08-2024).

14.Guazzi M and Borlaug BA. Pulmonary hypertension due to left heart disease. *Circulation* 2012; 126: 975-990.

15.Zhang L, Liu Y, Zhao S, et al. The incidence and prevalence of pulmonary hypertension in the COPD population: a systematic review and meta-analysis. *International Journal of Chronic Obstructive Pulmonary Disease* 2022: 1365-1379.

16.Maron BA. Revised Definition of Pulmonary Hypertension and Approach to Management: A Clinical Primer. *Journal of the American Heart Association* 2023; 12: e029024. DOI: 10.1161/JAHA.122.029024.
17.Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: Developed by the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Endorsed by the International Society for Heart and Lung Transplantation (ISHLT) and the European Reference Network on rare respiratory diseases (ERN-LUNG). *European heart journal* 2022; 43: 3618-3731.
18.D'Alto M, Romeo E, Argiento P, et al. Pulmonary arterial hypertension: the key role of echocardiography. *Echocardiography* 2015; 32: S23-S37.
19.Greiner S, Jud A, Aurich M, et al. Reliability of noninvasive assessment of systolic pulmonary artery pressure by Doppler echocardiography compared to right heart catheterization: analysis in a large patient population. *Journal of the American Heart Association* 2014; 3: e001103.
20.Hurdman J, Condliffe R, Elliot CA, et al. Pulmonary hypertension in COPD: results from the ASPIRE registry. *European Respiratory Journal* 2013; 41: 1292-1301.
21.Janda S, Shahidi N, Gin K, et al. Diagnostic accuracy of echocardiography for pulmonary hypertension: a systematic review and meta-analysis. *Heart* 2011; 97: 612. DOI: 10.1136/hrt.2010.212084.
22.Taleb M, Khuder S, Tinkel J, et al. The Diagnostic Accuracy of D oppler Echocardiography in Assessment of Pulmonary Artery Systolic Pressure: A Meta-Analysis. *Echocardiography* 2013; 30: 258-265.
23.Zhang RF, Zhou L, Ma GF, et al. Diagnostic Value of Transthoracic Doppler Echocardiography in Pulmonary Hypertension: A Meta-Analysis. *American Journal of Hypertension* 2010; 23: 1261-1264. DOI: 10.1038/ajh.2010.188.
24.Arcasoy SM, Christie JD, Ferrari VA, et al. Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. *American journal of respiratory and critical care medicine* 2003; 167: 735-740.
25.Boussuges A, PINET C, MOLENAT F, et al. Left atrial and ventricular filling in chronic obstructive pulmonary disease: an echocardiographic and Doppler study. *American journal of respiratory and critical care medicine* 2000; 162: 670-675.
26.Vizza CD, Lynch JP, Ochoa LL, et al. Right and left ventricular dysfunction in patients with severe pulmonary disease. *Chest* 1998; 113: 576-583.
27.Aurangabadkar GM, Lanjewar AV, Jadhav US, et al. Evaluation of Pulmonary Hypertension in Chronic Obstructive Pulmonary Disease. *Cureus* 2022; 14.
28.Thabut G, Dauriat G, Stern JB, et al. Pulmonary hemodynamics in advanced COPD candidates for lung volume reduction surgery or lung transplantation. *Chest* 2005; 127: 1531-1536.
29.Janssens J-P, Pache J-C and Nicod L. Physiological changes in respiratory function associated with ageing. *European Respiratory Journal* 1999; 13: 197-205.
30.Parikh JD, Hollingsworth KG, Wallace D, et al. Normal age-related changes in left ventricular function: Role of afterload and subendocardial dysfunction. *International journal of cardiology* 2016; 223: 306-312.