# To study 6MWT as a Prognostic Marker in stable COPD Patients & its correlation with Spirometry Grading

**Sameeksha Shringi[1], Mahesh Kumar Mishra[2], Aviral Kumar Singh[3]**

Department of Respiratory Medicine, Mahatma Gandhi medical college, Jaipur – India

**Address for correspondence**
**Mahesh Kumar Mishra**
Department of Respiratory Medicine, Mahatma Gandhi medical college, Jaipur – India
E-mail:
maheshmishradr@gmail.com

**Author Contributions**

SS MKM conceived idea, SS AKS drafted the study, MKM AKS collected data, SS AKS did statistical analysis and interpretation of data, SS MKM critical review manuscript, All approved final version to be published.

**Declaration of conflicting interests**

The authors declare that there is no conflict of interest.

## Abstract

**Background:** 6MWT is non invasive standardized exercise test that measures global and integrated responses of all systems involved during exercises, including pulmonary and cardiovascular, systemic /peripheral circulation, muscle metabolism.

**Objectives:** The study was designed to identify the relationship of desaturation at baseline using 6MWT with spirometry grading and clinical outcomes of acute exacerbation, hospitalizations and mortality in stable COPD patients which is significantly noted in the study.

**Methodology:** One ten patients with stable COPD diagnosed and staged as per the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines underwent 6MWT. A drop in standard pulse oximetry (SpO 2 ) of ≥4% or nadir up to ≤88% was defined as desaturation. Based on Desaturation during 6MWT, two groups were formed: desaturated cases and nondesaturated cases.

**Results:** Out of 110 stable COPD patients, 36 patients desaturated during 6MWT (n = 36/110). Desaturation was significantly more in higher grades of spirometry (very severe, severe) compared to non desaturated cases. Smokers were significantly more prone for desatuartion probably due to dual signergistic action of bio mass fuel exposure and smoking habits. Rate of hospitalization more frequent in very severe and severe. Interpretation and Conclusion: The 6MWT is a safe and sensitive test to access prognosis in stable COPD patients. Desaturation during 6 minute walk test is found to be good predictor of hospitalization, exacerbations and mortality.

**Keywords:** COPD; 6MWT; Desaturation

## Introduction

Chronic Obstructive Pulmonary Disease(COPD) is a common respiratory illness of public health challenge, a important cause of morbidity and mortality globally. Patients of COPD are commonly reported in the clinical practise. (omit please).

Previously, COPD comprised of chronic bronchitis, emphysema, chronic respiratory disease, chronic obstructive airflow limitation depending on combination of patho-physiology and clinical features of chronic cough and airway obstruction. Currently, presented as an umbrella term for a number of clinical disorders with chronic bronchitis on one side and emphysema on other side of spectrum.

COPD, currently 4th leading cause of death globally 3but is projected to be 3rd leading cause of death by 2020 and 5th leading cause of disability adjusted life years (DALY's). According to WHO number of cases of COPD in India raised from 28.1 million in 1990 to 55.3 million in 2016 and prevalence in males and females were found to be 3.4 and 4.4 per 1000.According to WHO, with the increasing prevalence of smoking in developing countries, and aging population in high income countries, prevalence of COPD is expected to rise over in next 30 years and by 2030 there may be over 4.5 million deaths annually from COPD and related conditions.[4]

Exacerbations account for greatest proportion of total COPD burden on healthcare system. There is striking direct relationship between severity of COPD and cost

of care and changes as COPD severity progresses. As per the European Union budget report total direct costs of respiratory disease accounts for 6% of total healthcare system, with COPD accounting for 56% (38.6 billion Euros) of cost of respiratory disease.[5] A single moderate to severe exacerbation, mean annual decline in post bronchodilator lung function is increased when compared with rate of decline before exacerbation (FEV1- 76.5 ml/year vs 39.1 ml/year).[6]

6MWT is a standardized easy and underused clinical parameter. It is sub-maximal type of exercise in normal individuals but near-maximal in patients with compromised lung functions. It evaluates the global and integrated responses of all systems involved during exercises, including pulmonary andcardiovascular, systemic /peripheral circulation, muscle metabolism therefore used as a clinical indicator of functional capacity in patients with various lung diseases.

It is performed indoors, over a flat, straight, corridor with hard surface. It gives an objective idea about the changes in performance caused by progression of disease. In addition it is safe, simple to perform, require minimal medical personnel and inexpensive cost effective.[7]

6MWT can be performed as per GUIDELINES of ATS and desaturation evaluation as per guidelines of Royal college of Physicians. Normal 6MWD varies from 450-700 m. Distance > 500 m is a good prognosis of disease, whereas distance walked < 200 m carries poor prognosis.

Oxygen desaturation during 6MWT is defined as per the Royal College of Physicians Guidelines as >4% reduction between arterial oxygen saturation measured by pulse oximetry pre- and post test (change in $spo_2$> 4%) and post-test $Spo_2$ <90%.

Patients who experience oxygen desaturation during 6 MWT have high risk of developing- acute exacerbation, emergency visits, hospitalization, mortality with poor prognosis and have been reported in few studies from the western countries.

Very few studies are available in India as per our search. Scarcity of literature in India prompted us to plan this study to know the various outcomes in patients of COPD having oxygen desaturation.

### Aims & Objectives

The present study was conducted with the aims;

1). To assess the status of oxygen desaturation during 6 minute walk test in patients of COPD of various severity.

2). To estimate the various outcomes i.e. /frequency of emergency visits/hospitalization, acute exacerbations& mortality during 1 year of follow up in COPD patients those desaturated in 6 minute walk test & correlate with grading of severity.

## Methodology

This is a prospective observational follow-up study undertaken in 110 patients of Chronic Obstructive Pulmonary Disease (COPD) attending OPD of Department of Respiratory Medicine, Mahatma Gandhi Medical College and Hospital, Jaipur from January 2011- July 2019. We included those participants with various severity varies mild to very severe. Study cases were included in this study after obtaining the informed consent from. For selection of study cases strict inclusion and exclusion criteria was followed. Inclusion criteria include all patients diagnosed of COPD with various severity from mild to very severe patients of COPD as per Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines 2017-2018, having age equal or more than 40 years. Included patients must show baseline $spo_2$ > 90% at room air and stable patients of mild to very severe COPD with no acute exacerbation for past 6 weeks according to GOLD guidelines, 2011. Whereas exclusion criteria include patient of COPD in moribund condition/non ambulatory/acute exacerbation, corpulmonale, respiratory failure, associated with pulmonary tuberculosis, asthma, or any other chronic disease or unable to do spirometry. This study also exclude those cases who are not willing for signing consent form. Height in centimetres, weight in

Table 1. Profile of Distance in 6MWT with Spirometry Grading

| Spirometry Grading | Mean | Std. Deviation | P value |
|---|---|---|---|
| Mild | 330.667 m | 36.5933 | 0.001 |
| Moderate | 305.136 m | 70.1707 | |
| Severe | 286.535 m | 59.7632 | |
| Very Severe | 208.282 m | 76.0045 | |
| Total | 264.918 m | 79.3514 | |

The above table showing profile of mean distance walked in various grading during 6MWT & is declining as the severity increases which is significant.

kilograms with body mass Index (BMI) was calculated as weight (kg)/height (m2). Blood pressure and saturation were recorded. Spirometry was performed on a computerized spirometer by machine as per European certified (True Flow by ndd, 700-1-01EOPC). Combined assessment test (CAT) of study cases were also performed according to GOLD guidelines. Symptom burden is measured by modified medical Research Council questionnaire (m MRC).[9]

### Technical Aspects of 6MWT

6MWT is performed according to American Thoracic Society (ATS) guidelines (2011).[7]

### Smoking Status

Patients were stratified according to smoking status into following groups

**Current Smoker (CS):** CS had smoked at least 100 cigarettes in their entire life and were still smoking.

**Never Smoke (NS):** NS never smoked a cigarette or who smoked fewer than 100 cigarettes in their entire life.

Statistical Analysis: The data was coded and entered into Microsoft Excel spreadsheet. Analysis was done using SPSS version 20 (IBM SPSS Statistics Inc., Chicago, Illinois, USA) Windows software program. Descriptive statistics included computation of percentages means and standard deviations. Chi square test for qualitative data and ANOVA test for quantitive were used. P value <0.05 was considered to be statistically significant.

### Results

Majority of participants (77.3%) were males and among study cases, 65.45% were of age groups 51-70 years and 16.36% were of age above 70 years. 81 (74.0%) of study cases were from rural area and 29 (26.0%) were from urban area making a ratio of 3:1. This study also showed that 79% patients belong to lower socioeconomic status.

Mean age of COPD cases that de-saturated was 64.38 years, whereas in non desaturated cases it was 60.47

Table 2. Comparative study between Desaturated & Non Desaturated Cases

| | | Total | NonDesaturated | Desaturated | p value |
|---|---|---|---|---|---|
| Subjects | | 110 | 74 | 36 | |
| Sex | Male | 84 | 57 | 27 | 0.001 |
| | Female | 26 | 17 | 9 | |
| Average Age (years) | | 61.7545 | 60.473 | 64.3889 | 0.04 |
| Smoking profile | | | | | |
| Smoker | | 87 | 56 | 31 | 0.001 |
| Non smoker | | 23 | 18 | 5 | |
| **GOLD Stage I/II/III/IV** | | | | | |
| I | | 6 | 6 | 0 | |
| II | | 22 | 20 | 2 | |
| III | | 43 | 36 | 7 | 0.001 |
| IV | | 39 | 12 | 27 | |
| **Exacerbations in 1 yr. Follow up** | | | | | |
| 0-1 | | 99 | 70 | 29 | |
| 2 to 3 | | 11 | 4 | 7 | |
| >4 | | 0 | 0 | 0 | 0.001 |
| 6MWD | | 264.9182m | 306.6757 m | 179.0833 m | 0.001 |
| **Hospitalization in 1 yr. Follow up** | | | | | |
| 1 | | 108 | 74 | 34 | |
| 2 | | 1 | 0 | 1 | 0.001 |
| 3 | | 1 | 0 | 1 | |
| Mortality in 1 yr. Follow up | | | 0 | 5 | 0.001 |

The above table showing profile of mean distance walked in various grading during 6MWT & is declining as the severity increases which is significant.

year which showed statistically significant results.

79.1% were smokers among which majority were males (90.6%) which were statistically significant. 21% were Non Smokers.

Spirometry status of COPD patients, minimum are- Grade I(5.50%) &Grade II(20.5%).Maximum are- Grade III(39.15%) & Grade IV(35.50%). Making total 74.6%.

Most of patients were in Grade C (48.20%), followed by Grade D(26.40%) & 22.70% in Grade B, Minimum (Grade A) 2.70%.

Out of 110 patients, 36 pts. desaturated (32.70%) and 74 pts.(67.30%) were non desaturated during 6MWD.

The distance profile of distance during 6 minute walk test in COPD cases i.e. maximum subjects (41.80%) were between 200-300 m, followed by 300-400 m (36.40%), <100 m(4.50%), and least in >400 m(0.90%)

Mean distance in 6mwt i.e. desaturated patients 179 +58.04 m & Non desaturated patients 306 +48.84 m which was highly significant.(p=0.001) as shown in table/figure (9write down the number of table or figure)

COPD patient 86.10% than non smoker 13.90% which is highly significant. Out of 110 COPD cases-Among 87 smokers-31 cases. (35.63%) desaturated, 56(64.36%) cases were non desaturated whereas; 23 were non smokers-5 cases (21.73%) desaturated, 18 cases(78.26%) cases did not desaturate.

Table 2 shows majority of cases desaturated in very severe grade 69.23% followed by severe grade 16.27% and minimum in moderate 9.50% and nil in mild grade. Out of 36 desaturated cases– all have acute exacerbations of that maximum cases 29 (80.60%) have 1 episode of acute exacerbation, followed by 6 cases (16.70%) have 2 exacerbation &1 case(2.80%) have 3 exacerbations during follow up of 1 year. While In Non Desaturated 74 COPD cases - 45.90% had acute exacerbations of that,30 patients (40.50%) had 1 episode of A/E, 4(5.40%) had 2 A/E during follow up of 1 year.

Out of 36 desaturated patients 18 (50.00%) had one episode of hospitalization, 1 patient (2.80%) had 2 episodes of hospitalizations,1 patient (2.80%) had 3 episodes of hospitalization. Making total (55.60%) of total hospitalizations during 1 year follow up incomparison to 74 Non Desaturation patients 10patients (13.50%) had 1 episode of hospitalization during 1 year follow up which is significant.

Among 36 Desaturated patients at the baseline-5 patients (13.90%) died while no deaths in non desaturated patients in 1 year follow up which is

highly significant(p=0.001).

Mortality is present only in very severe spirometry grading (12.82%) compared toall grading of COPD Cases during 1 year of follow up period. Among all the COPD cases overall mortality is 4.54%

Mortality is present only in very severe spirometry grading (18.51 while no mortality in mild, moderate and severe desaturated COPD Cases during 1 year of follow up period. With overall mortality in all desaturated cases is 13.88% while no mortality in all non desaturated.

Five cases who died during 1 year follow up study,4 patients died in 1st episode of hospitalization with past history of high frequency of A/E(2-3) while 1 patient diedin hospital with 3rd episode of A/E during follow up and only 1 episode of A/E in past 12 months. The cause of death in all 5 cases were A/E with type 2 respiratory failure.

## Discussion

### Demographic Profile of COPD Patients:

#### Gender

In present study male predominance of 77.3% in comparison of females 22.7% with male: female ratio of 3.4:1 in COPD patients. Male predominance is also reported from western and Indian studies i.e. 60% in Waatevik M et al (2016),[10] Tamakuwala G (2017),60% in Dogra A et al (2015)[12] reported similar results. Awareness of disease in females may be the reason of female predominance in this study. While in our study male dominated may be due to of rural predominance of patients.

#### Age

In accordance with age in our study, we found maximum patients in the age group of 40-70 years with mean age of 61.75±9.45 years. Similar results were also reported in studies by Dogra A et al (2015)[12], Tamakuwala G et al (2017)[11] where they reported maximum number of patients of age group 51-70 years.

#### Residence & Socio-Economic Status

In our study 3/4th of patients belongs to rural area, & more than 2/3 rd (69%) patients from lower socio-economic status. Spiromics et al (2017)had same study where rural population where majority of COPD were from rural area.

#### Smoking profile of COPD patients

In regards to smoking we found majority (4/5th)of patients were smokers of that maximum were males with gender ratio of 9:1 M:F. Similar result was reported by study by Dogra et al (2015)[12] where they

found 60 patients were male and 12 females were smokers.

## Spirometry grading of COPD patients:

With regards to Global Initiative for Chronic Obstructive Lung Disease(GOLD) criteria, about 2/3rdpatients were having severe & very severe grade of COPD. Only (20%) had moderate grade & 13% were mild cases. Similar results were founded by Takiagawa N et al (2007) and Waatevik M et al (2016)[10].

## Profile of Distance in 6MWT:

In our study mean distance in 6mwt was 264.91±79.35 m. In western studies by Takigawa N et al[14] (432+103.5 m) and in other Indian studies-Mishra Bet al (2016) and Tamakuwala G et al (2017)[11] reported higher mean distance during 6MWT than ours.

## Distance in 6MWT & Spirometry Grading:

In our study as spirometry grading increased in COPD cases the mean distance covered in 6 minutes was significantly reduced-as per spirometry grading i.e. mild, moderate, severe, and very severe 330.67m, 305.13m, 286.53 m and 208.28 m respectively.Similar Indian study by Tamakuwala G et al (2017)[14] - mild(379.11 m),moderate (261.85 m) & severe (189.27 m).

## Desaturation profile in COPD patients:

In our study, out of110 cases of COPD 1/3 rd cases (36 patients) desaturated during 6 MWT& almost equal ratio in male(32%) and female (34.60%) COPD patients. However Waatevik M et al(2007)[10] reported lower rate of desaturation 23% (1/4th) with equal ratio in male & females patients who desaturated during 6MWT comparable to our study. In other studies reported much higher desaturation during 6MWT- i.e. Dogra A. et al(2015)[12] 55% with insignificant gender ratio.

## Correlation of Smoking with desaturation:

The desaturation was significantly more in smoker COPD patients in comparison to non smokers. In our study, out of 87 smoking COPD patients more than 1/3 rd (31) desaturated and in 23 non smokers 1/5th desaturated. These values significant indicating that smokers COPD patients are more prone to desaturate in comparision to non smokers. Same is supported by Waatewik M et al10 but not significant difference in study of Dogra et al[12].

## Correlation of Desaturation with Gender Smoking:

In our study, out of 87 smoker COPD patients of that 77 were male to whom 25 cases (1/3rd) had desaturation in comparison to 10 females, 6 had

(2/3rd) had desaturation during 6MWT. This indicates that female smokers are significantly more to desaturate (p=0.02) then male smokers. This significant higher desaturation in female smokers possibly could be due to dual synergistic effect of biomass exposure and smoking habits. In study by Waatevik Metal[10] out of 284 cases who desaturated were male (22.9%) and female (23.8%)

## Desaturation profile in relation to Severity of diseases

In present study desaturated patients were of higher grades of spirometry i.e. 3/4th patients were in the very severe,1/4th cases were severe (19%), moderate (5.6%) & no desaturation in mild cases of COPD. Other studies also reported higher desaturation in severe to very severe by Dogra et al[12].

## Risk of Development of A/E in Desaturated v/s Non Desaturated COPD patients in 1 year follow up:

In present study, therisk of development of frequency of A/E (1-3) in desaturated patients of COPD was significantly more (100%) than (1-2) frequency in non desaturated cases i.e. (46.00%) during 1 year follow up. Waatevik et al[10] reported less frequency of A/E in less than 1/4 thin desaturated cases which is markedly lesser than ours(100%).

## Risk of hospitalizations in Desaturated v/s Non desaturated COPD patients in 1 year follow up:

In our study hospitalization was more than ½ (55%) of 36 desaturated COPD patients-18 patients (50.00%) had one episode of hospitalization, 1 patient (2.80%) had 2 episodes of hospitalizations, 1 patient (2.80%) had 3 episodes of hospitalization making a total 55.60% hospitalizations during 1year follow-up.In 74 Non Desaturation patients, 10 patients (13.50%) had 1 episode of hospitalization during 1 year follow up the values are significant. Study by J Garcia et al (2003)[16] observed 63% of COPD patients were hospitalized during 1 year of follow up study period.

## Desaturation and Mortality:

In our present study the outcome of mortality during 1 year follow up were compared in desaturated v/s non desaturated COPD cases at baseline. Among the 36 desaturated patients during 6MWT of that 5 patients (13.90%) died during follow up of 1 year, whereas there was no mortality in patients who did not desaturate in follow up, this value is significant. In the study from Japan, by Takigawaet al[14] the risk of mortality increased 2 fold times among the patients who desaturated during 6MWT; comparable to our study. Golpe et al (2013)[17] also reported that oxygen desaturation is a significant predictor of death(10.6%)

but it is not an independent predictor in multivariate analysis. Study by Casanova C et al (2007)[18] also reported 2 fold risk of deaths among desaturated patients association between COPD patients who desaturated during 6MWT and higher mortality than patients without desaturation (67% vs 38%).

Relationship of Mortality with Spirometry Gradingin Desaturated v/s Non desaturated COPD patients:

In the present study mortality was significantly associated with severity of spirometrygrading, as all the cases who died during the study period were of very severe grading (5/39) 12.82%. In 36 desaturated COPD cases all the deaths were of very severe grade (5/27) 18.51% as compared no deaths in 74 non desaturated of all grades in 1 year follow up. All the deaths had predominant type 2 respiratory failure. Similar study by Gedebjerg A et al[59] reported mortality rates highest in group D mainly due respiratory cause 18% in 3 year follow up. Anthonisen NR et al (1986)[19] reported greater mortality in patients with FEV 1<40%, similar MIDSPAN study, Mannino et al (2006)[21] demonstrated that death rate in COPD patients depends significantly on degree of severity as the grade increases severity of mortality rises.

## Conclusion

Our study concluded that about 1/3 rd patients of COPD are having desaturation during 6minute walk test which is highly prevalent in smokers and significantly more in female smokers possibly due to dual effect of biomass exposure and smoking. The high prevalence of desaturation is related with severe and very severe spirometry grading.

In our study desaturation during 6 minute walk test is found to be good predictor of hospitalization, exacerbations and mortality.

## References

1. Jindal SK. COPD: the unrecognized epidemic in India. The Journal of the Association of Physicians of India 2012:60:14

2. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030.PLoS Med 2006; 3(11): e442.

3. Salvi S, Kumar GA, Dhaliwal RS,Paulson K, Agarwal A, Koul PA, Mahesh PA et al. The Burden of Chronic respiratory diseases and their heterogeneity across the states of India: the Global Burden of Disease Study 1990-2016. The Lancet Global Health. 2018 ;6(12):e1363-74.

4. World Health Organization.Projections of mortality and cause of death, 2015 and 2030 http://www.who.int/healthinfo/global_burden_disease/projections/en

5. American Thoracic Society Foundation. The Global Burden of Lung Disease.2014 http://foundation.thoracic.org/news/global-burden.php

6. Silverman EK. Exacerbations in chronic obstructive pulmonary disease: do they contribute to disease progression?.Proc Am Thorac Soc. 2007;4(8):586–590. doi:10.1513/pats.200706-068TH.

7. American Thoracic Society Statement: Guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002 Jul 1;166(1):111-7.

8. Wedzicha JA. Domiciliary oxygen therapy services: clinical guidelines and advice for prescribers. Summary of a report of the Royal College of Physicians. J R Coll Physicians Lond 1999; 33: 445–447.

9. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of COPD, 2018. Available from: http://www.goldcopd.org

10. Waatevik M, Johannessen A, Real FG, Aanerud M, Hardie JA, Bakke P. Oxygen desaturation in 6-min walk test is a risk factor for adverse outcomes in COPD European Respiratory Journal 2016 48: 82-91.

11. Tamakuwala G, Shamaliya K, Patel MZ, Patel B. A study of correlation of 6 Minutes Walk Test (6MWT) and Spirometry findings in COPD patients. Int J Res Med 2017; 6(3); 12-20

12. Dogra AC, Gupta U, Sarkar M, Padam A. Exercise-induced desaturation in patients with chronic obstructive pulmonary disease on six-minute walk test. Lung India 2015;32(4):320-5

13. Burkes RM, Gassett AJ, Ceppe AS, Anderson W, O'Neal WK, Wooodruff PG et al; on behalf of SPIROMICS Investigations. Rural residence and chronic obstructive pulmonary disease exacerbations: analysis of the SPIROMICS cohort. Ann Am Thoracic Soc 2018; 15:808-816.

14. Takigawa N, Tada A, Soda R, Date H, Yamashita M, Endo S, Takahashi S, Kawata N, Shibayama T, Hamada N, Sakaguchi M, Hirano A, Kimura G, Okada C, Takahashi K. Distance and oxygen desaturation in 6-min walk test predict prognosis in COPD patients. Respir Med. 2007;101(3):561-7.

15. Mishra BK, Sinha A. A Comparative Study of Six Minute Walk Test (6 MWT) amongst healthy

individuals and COPD patients.International Journal of Science and Research (IJSR) 2016;79.57.

16. Garcia-Aymerich J, Farrero E, Félez MA, Izquierdo J, Marrades RM, Antó JM et al. Risk factors of readmission to hospital for a COPD exacerbation: a prospective study, Thorax 2003;58:100-5

17. Golpe R, Pérez-de-Llano LA, Méndez-Marote L, Veres-Racamonde A. Prognostic value of walk distance, work, oxygen saturation, and dyspnea during 6-minute walk test in COPD patients. Respir Care 2013;58(8):1329-34.

18. Casanova C, Cote CG, Marin JM, de Torres JP, Aguirre-Jaime A, Mendez R, Dordelly L, Celli BR. The 6-min walking distance: long-term follow up

in patients with COPD. Eur Respir J 2007;29(3):535-40.

19. Anthonisen NR, Wright EC, Hodgkin JE. Prognosis in chronic obstructive pulmonary disease. Am Rev Respir Dis 1986;133:14–20.

20. Hole DJ, Watt GCM, DaveySmith G, Hart CL, Gillis CR, Hawthorne VM. Impaired lung function and mortality risk in men and women:findings from the Renfew and Paisley prospective population study. BMJ 1996;313:711–5.

21. Mannino DM, Doherty DE, Sonia Buist A. Global Initiative on Obstructive Lung Disease (GOLD) classification of lung disease and mortality: findings from the Atherosclerosis Risk in Communities (ARIC) study. Respir Med 2006;100(1):115–122.