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COMPARISON OF FEV1 REGARDLESS OF RATIO (FRR) WITH FORCED EXPIRATORY RATIO (FER) IN COPD; TO INCORPORATE PRESERVED RATIO IMPAIRED SPIROMETRY (PRISM)

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ABSTRACT

Background: Traditionally spirometric criteria of post-bronchodilator FEV1/FVC is used to define Chronic Obstructive Pulmonary Disease(COPD). This has been termed as forced expiratory ratio(FER)(1). It is however, well observed that people who smoke even if do not fulfill the GOLD definition, still continue to experience symptoms and behave in a similar manner. This indicates that the current criteria of diagnosis of COPD may not be sufficient in all cases. **Objective:** To compare the validity of FEV1 regardless of ratio (FRR) with GOLD defined COPD (Forced expiratory ratio FER) and to identify patients with PRISM as a separate group. **Methods:** It was an analytical type of study undertaken in the Department of Pulmonology, Fauji Foundation Hospital Rawalpindi on 123 stable patients, who presented to the outpatient department (OPD) for evaluation of their symptoms, from July 2015 to August 2017. Data was analyzed by calculating frequencies and percentages using SPSS version 20. Validity of FER, FRR was calculated by checking the sensitivity, specificity, positive and negative predictive values. PRISM was identified as a subgroup. **Results:** The mean age of patients was 63.41 $\pm$10.28. Around 108(87.80%) of patients were male while 15(12.20%) were female. GOLD Defined COPD group and the PRISM groups were comparable with no statistically significant difference in their mean age, smoking status, arterial blood gas values and the six minute walk test. The sensitivity and specificity of GOLD defined COPD is modest (53.50% and 45.50%) and FEV1 regardless of ratio(FRR) has got an improved sensitivity (98.2%) and positive predictive value (91.66%). **Discussion:** The sensitivity of FRR in the present study was more than 90% ; implicating its use in mass screening programs for COPD, in the communities and multiple health care centers of the world. **Conclusion:** Using FEV1 regardless of ratio (FRR) is a an easy and widely available parameter that can be useful in future hence reducing the morbidity and mortality that can be a consequence of missing a diagnosis.

KEY WORDS: Chronic Obstructive Lung Disease, Spirometry, Standards, Forced Expiratory Volume, Validity of Results.

INTRODUCTION

Chronic Obstructive Pulmonary Disease(COPD) is one of the leading cause of deaths throughout the world.[2] It has an overall prevalence of 10%-12%.[1,3] Cigarette smoking is one of the main risk factor for this illness.[4] It is linked with progressive decline in FEV1 with age(5). FEV1 is influenced by reduced elastic recoil of lungs along with alveolar wall destruction. Studies have demonstrated small airway disease in smokers who do not have overt signs of COPD or reduction in FEV1.[5]

Spirometry is the most simple, readily available tool for screening purposes.[2] The definition of COPD is quite complex. Traditionally spirometric criteria of post-bronchodilator FEV1/FVC <70% is used to define this illness. This has been termed as forced expiratory ratio(FER).[1] It is however, well observed that people who smoke even if do not fulfill the GOLD definition, still continue to experience symptoms and behave in a similar manner. This indicates that the current criteria of diagnosis of COPD may not be sufficient in all cases.[4]

Spirometry pattern of FEV1/FVC ratio more than 70% but an FEV1 < 80% is given as a restrictive defect by Global Initiative of Obstructive Lung Disease (GOLD) registry, but numerous studies have demonstrate that smokers who exhibit this feature have evidence of increase in total lung capacity(TLC) as measured by total body plethysmography or CT scan.[5] Preserved ratio impaired spirometry (PRISM) is the term used to describe these patients.[6] Both FEV1 and FVC progressively decline with age, but studies have shown that decline of FEV1 is more rapid and consistent with age and smoking status.[2] Using FEV1 regardless of

ratio(FRR) as a diagnostic criteria may lead to GOLD COPD stage I(FEV1/FVC <70%, FEV1> 80%) to be missed; however, it has been described that patients usually report symptoms when they are in stage II(FEV1< 80%≥50%) and stage III(FEV1 ≥30% <50%), when it is likely to be picked up by FRR.

Conversely FEV1 is found to be reduced in many smokers with normal FEV1/FVC ratio. These patients though classified as having restrictive defect behave in a manner similar to GOLD defined COPD patients.[7] Many alternate criteria had been developed to incorporate these patients with "restrictive defect"; including FEV1/FEV6[8] and the famous 5th percentile criteria proposed by American Thoracic Society.[9] These criteria, however, complicate the diagnosis of COPD. To remain simple, FEV1 as a criteria for diagnosis of COPD is reliable and more predictive of decline in lung function.[2] The main benefit of FEV1 regardless of ratio(FRR) is to incorporate patients missed by FER. This subgroup, termed as "GOLD unclassified smokers" is now recognized as a separate identity known as preserved ratio impaired Spirometry (PRISM). In the famous COPDGene Study, the prevalence of PRISM in population was 12.3%.[6]

The objective of this study was to compare the validity of FEV1 regardless of ratio (FRR) with GOLD defined COPD (Forced expiratory ratio FER) and to identify patients with PRISM as a separate group.

MATERIAL AND METHODS

It was an analytical type of study undertaken in the Department of Pulmonology, Fauji Foundation Hospital Rawalpindi on 123 stable patients, who presented to the outpatient department (OPD) for evaluation of their symptoms. The study duration was 2 years from July 2015 to July 2017.

Sample size was calculated by WHO sample size calculator as 120. According to a study by Johns and colleagues, 80% of patients with COPD are diagnosed by spirometry using FER criteria.[1] Using the sensitivity calculator and an absolute precision of 0.08, sample size was 120. Hence 123 patients were included in the study.

GOLD defined COPD, also named Forced expiratory ratio (FER) was defined on Spirometry as given by Global Initiative of Obstructive Lung Disease (GOLD). Accordingly, those patients on spirometry have FEV1/FVC ratio less than 70%, regardless FEV1.[1,8]

FEV1 regardless of ratio (FRR) was defined as FEV1 less than 80%, not taking into consideration the FEV1/FVC ratio. This has the potential to miss GOLD COPD stage I.[1]

Preserved ratio impaired Spirometry (PRISM), also labeled by some authorities as GOLD unclassified smokers, have been defined as those patients who have clinical and radiological features similar to patients with COPD, but on spirometry their FEV1 is less than 80% predicted with a normal FEV1/FVC ratio.[6]

Validity of a test is calculation of its sensitivity, Specificity, Positive Predictive Value (PPV) and negative predictive value (NPV).

Quantitative CT scan(QCT) was defined as CT scan used to measure the lung volumes in maximal inspiration(total lung capacity TLC) and full expiration(Functional residual capacity FRC); using multi detector CT scan and reconstruction imaging techniques.[10]

Current or former smokers with a smoking history of more than 10 pack years, who came to the ambulatory clinics of Fauji Foundation Hospital for evaluation of their symptoms, were included in the study. Patients between 40-80 years of age were incorporated.

Patients with normal spirometry, radiological evidence of any parenchymal lung disease including tuberculosis and bronchiectasis, non-smokers, huqqa smokers and patients in exacerbation were excluded.

Informed consent was taken. Demographic features including age and sex, and smoking history, patient symptoms, co-morbid diseases, body mass index were recorded. Dyspnea was measured by 6 minute walk test. Arterial oxygen saturation, chest x-ray were performed. Medical International Research (MIR) microlab III spirometer was used. Spirometry was performed at baseline and 10minutes after bronchodilator challenge using salbutamol nebulization. Patients FEV1, FVC and FEV1/FVC ratio were noted. All patients underwent a multi-detector high resolution CT chest (HRCT), to measure the total lung capacity, taken as the gold standard.[11,12]

Data was analyzed by calculating frequencies and percentages using SPSS version 20. Validity of FER, FRR was calculated by checking the sensitivity, specificity, positive and negative predictive values. PRISM was identified as a subgroup.

RESULTS

The mean age of patients was 63.41 ±10.28. Around 108(87.80%) of patients were male while 15(12.20%) were female. A predominant male pattern may be due to a selection bias due to mainly male gender inclined towards cigarette smoking in Pakistan.[13] The mean smoking history was about 35.78± 20.40 pack years.

Approximately 88(71.50%) patients had dyspnea as the only symptom while 35(28.50%) of patients also complaint of cough with sputum. Around 63(51.20%) of patients had no comorbid illness while hypertension, diabetes and ischemic heart disease were concurrent conditions in 34(27.60%), 13(10.60%) and 13(10.60%) of patients respectively.

Results of hyperinflation on CXR and Increased Total lung capacity (TLC) on HRCT chest were consistent (91.10%), with HRCT chest being taken as the gold standard. The demographic features of these patients are depicted in table 1.

Table 1: Demographic features.

Demographic Features	Results
Age	Mean 63.41 ±10.28(SD)
Sex **Male** **Female**	 108 (87.80 %) 15 (12.20 %)
Smoking	Mean 35.78± 20.40 pack years
Symptoms **Dyspnea only** **Cough with Sputum**	 88(71.50%) 35(28.50%)
Comorbid illness **None** **HT** **Diabetes** **IHD**	 63(51.20%) 34(27.60%) 13(10.60%) 13(10.60%)
MMRC dyspnea grades	I 2.40% II 58.50% III 31.70% IV 7.30%
Body mass index (BMI)	22.81(± 3.74SD)
Arterial saturation (SaO2)	96.48(± 2.32SD)
Six Minute walk test (6MWT)	417.15(±53.79 SD)
Hyperinflation on CXR **Yes** **No**	 112(91.10%) 11 (8.9%)
Total Lung Capacity **Increased** **Not Increased**	 112(91.10%) 11 (8.9%)

The mean MMRC grade of dyspnea was 2.44(±0.67SD) and body mass index (BMI) was 22.81(±3.74SD). The mean distance travelled by the patients was 410(±53.79) meters. 112 patients out of 123 were confirmed as COPD cases on total lung capacity measurement. Spirometry pattern is illustrated in Figure 1 below:

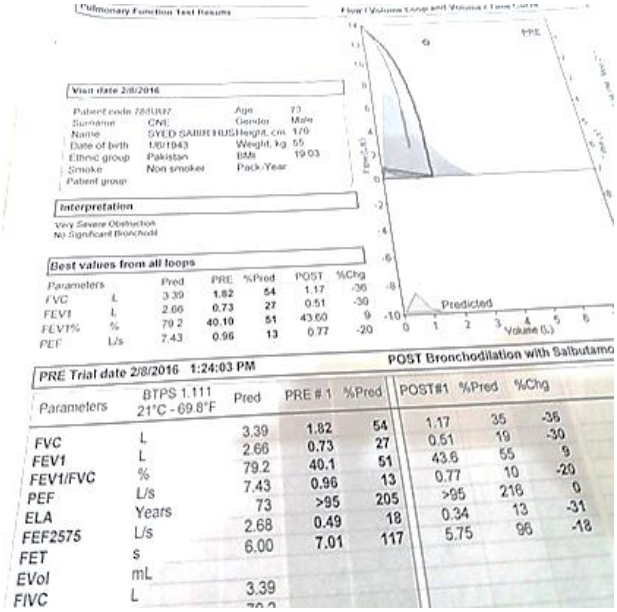

Figure 1: Sample Spirometry using Gold Defined Criteria for COPD.

The two groups identified by our study were Gold Defined COPD as termed as Forced Expiratory Ratio (FER) group and PRISM group. Characteristics of these two groups are described in table 2.

Table 2: Comparison of Means.

Variable	Comparison of Means		
	GOLD Defined COPD group(FER)	Preserved Ratio Impaired Spirometry group(PRISM)	**P value**
Age	64.64(±10.47) years	61.95(±9.961)years	0.15
Smoking status	37.94(±21.36) pack years	33.20(± 19.07) pack years	0.20
BMI	22(±3.99)kg/m2	22(±3.45)kg/m2	0.68
Saturation(SaO2)	96(± 2.73)%	96.59(±2.26)%	0.24
6MWT	413(±55.81)m	421(±51.43)m	0.42

It is evident from table 2, that the GOLD Defined COPD group and the PRISM group are comparable with no statistically significant difference in their mean age, smoking status, arterial blood gas values and the six minute walk test.

The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) using Gold defined COPD criteria (Forced expiratory ratio FER), identifying patients with preserved ratio impaired Spirometry is given in table 3:

Table 3: Validity of Forced Expiratory ratio (GOLD defined COPD).

Subgroup (total 123)	Parameter on Spirometry	TLC	Frequency & percentage n(%)	Sensitivity a/a+c	Specificity d/d+b	PPV a/a+b	NPV d/c+d
Gold defined COPD (FER)	FEV1/FVC <70%	TLC increased (actual COPD) a=60 TLC not increased (False +ive) b=6	66(53.70%)	54.46%	45.45%	91.04%	8.9%
PRISM	FEV1/FVC >70% FEV1<80%	TLC increased (False -ive) c=52 TLC not increased (true -ive) d=5	57(46.30%)				

As is clearly evident from table 3 that the sensitivity and specificity of GOLD defined COPD (Forced Expiratory ratio or FER) is modest (53.50% and 45.50%). It is also evident from this table that preserved ratio impaired Spirometry (PRISM) is an important subgroup identified by measuring the total lung capacity (57 or 46.3% of patients) and is likely to be missed, if FER criteria is only used.

Table 4 describes in detail the validity of FEV1 regardless of ratio(FRR) using Total lung capacity as the gold standard.

Table 4: Validity of FEV1 regardless of ratio (FRR).

Subgroup (total 123)	Parameter on Spirometry	TLC	Frequency & percentage n (%)	Sensitivity a/a+c	Specificity d/d+b	PPV a/a+b	NPV d/c+d
FEV1 regardless of ratio (FRR)	FEV1 <80%	TLC increased (actual COPD) a=110 TLC not increased (False +ive) b=10	120(97.6%)	98.21%	9.09%	91.66%	33.33%
No COPD based on FRR	FEV1>80%	TLC increased (False -ive) c=2 TLC not increased (true -ive) d=1	3(2.4%)				

It is evident from the table 4, that FRR has got an improved sensitivity (98.2%) and positive predictive value (91.66%). However, the specificity remains low (9.09%). The sensitivity of FRR to diagnose COPD is much higher than that of FER, tool currently recommended by GOLD guidelines(14). Specificity is a problem, as is the case with FER. However, in population studies and COPD screening in the hospitals, FEV1 regardless of ratio (FRR) is sensitive enough to replace FEV1/FVC ratio (Forced expiratory ratio FER).

DISCUSSION

The results of this study demonstrate that the sensitivity of Gold defined COPD (FEV1/FVC ratio < 70%) also known as forced expiratory ratio (FER) is modest around 53.6%. Numerous studies show that if we rely only on FER criteria, many cases with clinical, radiological and pathological diagnosis of emphysema are likely to be missed. In the COPD Gene study, these missed cases were termed as GOLD unclassified smokers (GOLD-U) and their frequency was found to be 8-14%.[15] In a later article by the same investigators, a new term was coined for these patients; preserved ratio impaired Spirometry(PRISM) with a prevalence of 12.3%.[6]

In the present study, the frequency of PRISM was quite high around 46.3%. The reasons may include a selection bias, hospital setting as compared to community, predominance of male patients, high frequency of patients with MMRC grade II and III dyspnea, racial differences and a higher BMI in our study population, features specifically portrayed for PRISM. Future randomized controlled trials are required. The present study also demonstrates the specificity of FER is also low (45.45%). This is an indication that those patients, who are labeled as COPD on Spirometry, may have a false positive result. It has also been demonstrated in a study by Hansen and colleagues who advocated use of the 5th percentile rather than fixed FEV1/FVC ratio< 70%, a criteria for COPD diagnosis in the general population.[9]

To overcome the problems with Forced expiratory ratio (FER; FEV1/FVC<70%), and to avoid the difficulties in calculating the 5th percentile, the author has advocated use of FEV1 regardless of ratio(FRR) for screening of COPD cases. The sensitivity of FRR in the present study was more than 90%; implicating its use in mass screening programs for COPD, in the communities and multiple health care centers of the world.

Another advantage of FRR is incorporation of patients with preserved ratio impaired Spirometry (PRISM). As is evident from this study and numerous other studies, this important subgroup of patients with clinical and

pathologically similar disease are likely to be missed if older criteria of FER is used to diagnose COPD.[15,6]

There are few limitations of this study. Recruitment of smokers suspected of having COPD was done in a hospital based setting. This needs to be further verified in community based studies.

Another limitation was the use of CT scan to predict total lung capacity in our study. This was primarily done because of feasibility issues and non-availability of total body plethysmography or Helium Dilution techniques in our center. Studies however, has shown good correlation between total lung capacity(TLC) measured by quantitative CT scan(QCT), as compared to traditional methods.[11,10]

This study has many implications. If found sensitive enough in future randomized controlled trials, FRR is likely to replace FER criteria for diagnosis of COPD. It is cheap, readily available and likely to have a wider utility in ambulatory settings. It will also incorporate patients who were previously named as unclassified smokers or patients with preserved ratio impaired Spirometry.

Studies are also required to link PRISM representing specific genotype or phenotype of COPD. Their cellular mechanisms and the predominant cellular types need to be explored. Whether this subtype requires a different treatment regimen or a combination of inhaled therapy needs further more well designed trials.

CONCLUSIONS

This study shows that GOLD defined COPD (Forced Expiratory Ratio) and Preserved ratio impaired spirometry (PRISM) are different spectrum of the same disease. Though the gold standard for COPD diagnosis is measurement of Total Lung capacity (TLC) by either Total body plethysmography or Quantitative CT (QCT), but this TLC evaluation is neither mandatory nor required in ambulatory hospital and population screening programs. Using FEV1 regardless of ratio (FRR) is a an easy and widely available parameter that can be useful in future hence may reduce the morbidity and mortality that can be a consequence of missing a diagnosis.

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