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RESEARCH ARTICLE

SIGNIFICANCE OF QUANTITATIVE RADIOLOGICAL PHENOTYPE OF COPD AND CORRELATION WITH BODE INDEX

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ABSTRACT

Background - Chronic obstructive pulmonary disease (COPD) is a heterogeneous disorder because of variation in clinical presentation and disease progression. The Role of phenotyping is to identify therapeutic and prognostic characteristics in COPD. Quantitative computed tomography (QHRCT) is non-invasive tool to identify distinct phenotypes in COPD.

Aim-we aimed to evaluate the correlation of Quantitative Radiological Phenotype of COPD with BODE index

Method- 50 COPD subjects meeting Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria for COPD with QHRCT analysis were included. Total lung emphysema was measured using the Density Mask Technique with a −950 Hounsfield unit threshold. An visual Semi-Automated Quantification of segmental wall area percentage wall area percentage (WA%) and square root of the wall area of a theoretical airway of 10 mm internal perimeter (Pi10) in 6 segmental bronchi In six segment bronchi. We compared Emphysema severity and Airway Abnormality on Body-Mass Index, Airflow Obstruction, Dyspnea and Exercise Capacity Index measure

Results- Emphysema percentage (LAA950) with BODE score showed positive correlation (r=0.7095, p-value <0.005). Airway dimension segmental wall area percentage (r=0.32, p-value <0.005) and lumenal perimeter (Pi10) (r=0.34, p-value <0.005), also showed positive correlation. Emphysema severity (low attenuation area percentage) was increased with increasing age (r=0.772, p-value<0.005).Emphysema severity (low attenuation area percentage) was increased with increasing number of pack years (r= 0.663, p-value <0.005).

Conclusion -QHRCT is complimentary tool to evaluate progression of COPD. Emphysema and Airway disease both relate to clinically important parameters. Emphysema is a stronger predictor of BODE and Its systemic components MMRC, 6MWT, and BMI than Airway Abnormalities. It is evident that patients with high BODE scores have a much greater burden of emphysema than airway disease.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease with variable clinical presentation. Heterogeneity is also found in rate of disease progression, and structural deformity. COPD is defined on clinical and physiologic variables. The Global Initiative for Chronic Obstructive Lung Disease classification system for COPD was recently 2016, classifying COPD based on symptoms, pulmonary function test and history of exacerbation. GOLD stratified COPD in different groups. Computed tomography (CT) of Thorax is a useful investigation that can identify different phenotype of COPD, and also establish progression and structural abnormalities in COPD. Thoracic CT is also non- invasive and widely available investigation. CT imaging measure emphysema and airway wall abnormality in COPD. Emphysema and Airway Abnormality in COPD have significant relation with disease progression, number of exacerbation and disease outcome in COPD

We have studied analytic methodologies that quantify emphysema and airways disease as well as focus on how this information can be used to define clinically meaningful phenotypes in COPD.

MATERIALS AND METHODS

Patient selection

We performed a cross sectional study to evaluate all diagnosed COPD patients who attended the Department of TB and respiratory diseases, SS Hospital, IMS, BHU.

If not previously documented/tested, all such patients were documented for COPD with post bronchodilator pulmonary function test confirmation (FEV1 / FVC < 0.7) with irreversible airway obstruction and were screened for other causes of breathlessness like exacerbation of Bronchial Asthma, Interstitial lung diseases, worsening of Dyspnea due to heart failure etc., by channeling through detailed history, thorough physical examination and underwent High resolution Computed Tomography of Thorax .The reproducibility of the airway measurement will preliminary testing by performing examination in a patient with COPD and in a control patient. Difference in airway and lung attenuation measurements between the patient with or without chronic bronchitis will evaluate. During hospital admission, patients were first treated with the standard protocol consisting of Short acting beta-2 agonist, inhaled and injectable corticosteroids and Theophylline as warranted and guided by arterial blood gas analysis. Once the patient stabilized, PFT and Reversibility testing and other relevant investigations were done and accordingly they were included/excluded from the study
All patients included in study underwent evaluation as per pre-standardized protocol

Exclusion criteria

A. Patients who presented with exacerbation not due to COPD but because of other disease like bronchial asthma, bronchiectasis interstitial lung diseases etc.
B. Patients with multiple organ failure
C. Haemodynamic instability
D. Those patients who are not giving consent

Study size: 50 Patients

Clinical Variables

A detailed clinical history was taken, and physical examination performed.

BODE index

The BODE Index is a composite marker of disease taking into consideration the systemic nature of COPD (Celli *et al*., 2004).
Imaging Variables- Low attenuation area below 950 HU cutoff in lung (LAA (950), 10 mm of lumenal perimeter (Pi10), Segmental wall percentage area (WA%).

Statistical Analysis

The main outcome of study is to evaluate difference in airway measurement, lung attenuation data and Bode index results of 50 COPD patients were examined. Statistical analysis was performed with SPSS 11. Simple linear and multiple regression analysis were used to investigate the relationship between morphological airway data and BODE index components results in entire group of among COPD patients attending outpatient and inpatient department in S.S. Hospital I.M.S B.H.U. The student test was performed to assess differences in variables P-value <0.05 is considered as statistically significance.

RESULTS

This study was conducted in Sir Sunderlal Hospital, Institute Of Medical Sciences, Banaras Hindu University, Varanasi. We evaluated all diagnosed COPD patients who had attended the Department of TB and respiratory diseases, of above hospital. Newly diagnosed cases were included in study after post bronchodilator Spirometry. Total 50 patients were taken in study. With following sex and age distribution:

Table 1 Frequency table showing sex distribution

SEX	Frequency	Percentage
1-female	18	36.0
2-male	32	64.0
Total	50	100.0

In our study we had male predominance. Earlier it was considered that COPD is a disease limited to males only. Due to increase use of tobacco and BIOMASS fuel in female also caused increase number of females with COPD.

Age

Eight percent of the patients in our study were in between 50 to 70 years of age.

Table 2 Frequency table showing age distribution

Age (in years)	Frequency	Percentage
40-50	3	6.0
51-60	19	38.0
61-70	21	42.0
71-80	7	14.0
Total	50	100.0

Youngest of our patient was 40 year of age and oldest was 80 year with mean age 62.5 years.

Risk factors

Table 3 Frequency table showing risk Factor association

Risk Factor	Frequency	Percentage
Absent	8	16.0
Smoking	35	70.0
Other (biomass fuel, occupational exposure)	7	14.0
Total	50	100.0

Smoking was the most important risk factor as seventy percent of our patients were smoker, fourteen percent patients had risk factors other than smoking like exposure to biomass fuel which was more important in rural India, especially in females and occupational exposure. In our study we had sixteen percent patients which had no identified risk factors

Table 4 Frequency table showing numbers of Pack years

Pack years	Frequency	Percentage
0	15	30.0
1-10	8	16.0
11-20	16	32.0
>20	11	22.0

We use pack year as a quanta of risk factor exposure

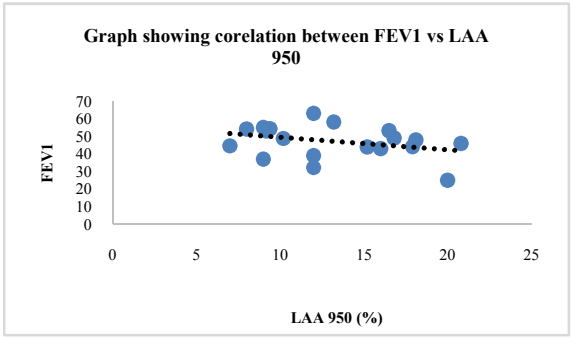
Table 5 Frequency table showing GOLD spirometeric classification

GOLD spirometeric classification	Frequency	Percentage
1	3	6.0
2	29	58.0
3	16	32.0
4	2	4.0
Total	50	100.0

Most of the patients (90%) included in study belong to GOLD Spirometeric class 2 and 3 in our study

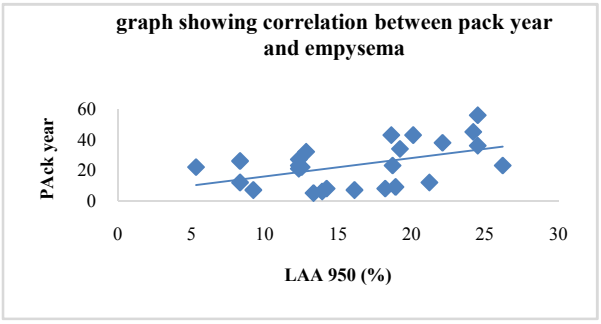
Table 6 Frequency table showing Exacerbation year code

Exacerbation year	Frequency	Percentage
<2	38	76.0
2 or more	12	24.0
Total	50	100.0



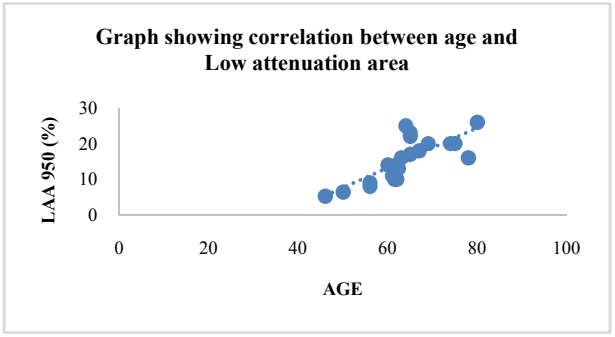
1 Graph showing correlation between Forced Expiratory Volume in 1 second (FEV_1) and emphysema percentage (Area of Low Attenuation 950)

Emphysema (Low attenuation area percentage) showed negative correlation (r= -0.634, p-value <0.005) with FEV_1.



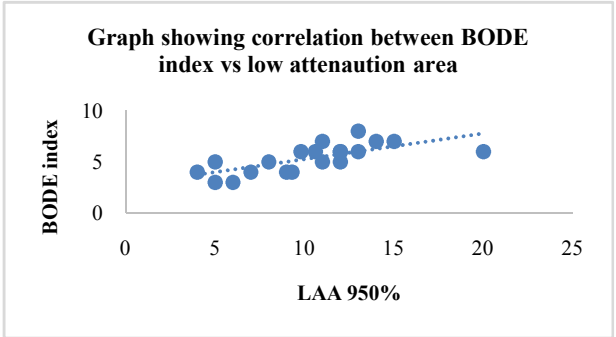
2 Graph showing correlation between Pack year and emphysema percentage Area of Low Attenuation

Emphysema severity (low attenuation area percentage) increased with number of pack years (r= 0.463, p-value <0.005)



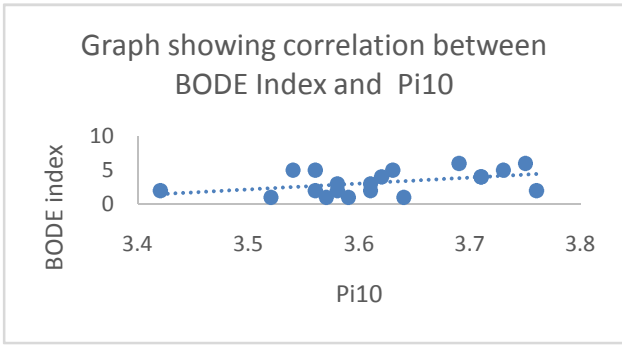
3 Graph showing correlation between Age and emphysema percentage (area of low attenuation)

Emphysema severity (low attenuation area percentage) increased with increasing age (r=0.772, p-value<0.005). Showed that positive correlation



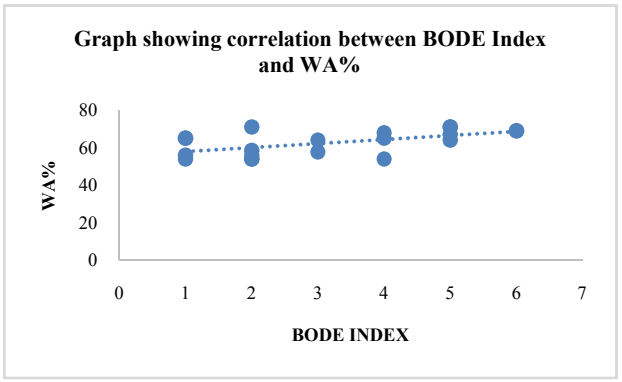
4 Graph showing correlation between BODE index and emphysema percentage (area of low attenuation)

Emphysema percentage (LAA950) with BODE index showed positive correlation (r=0.7095, p-value <0.005)



5 Graph showing correlation between BODE Index and airway dimension Pi10 (10 mm luminal perimeter)

Airway dimension Pi10 (10 mm lumenal perimeter) (r=0.34, p-value <0.005) showed positive correlation with BODE index.



6 Graph showing correlation between BODE Index and airway dimension WA% (Segmental wall percentage Area)

Airway dimension segmental wall percentage area showed positive correlation with BODE index (r=0.32, p-value <0.005).

DISCUSSION

COPD includes emphysema, an anatomically defined condition characterized by destruction and enlargement of the lung alveoli; chronic bronchitis, a clinically defined condition with chronic cough and phlegm; and small airway disease, a condition in which small bronchioles are narrowed.

In our study we assessed whether the High Resolution Computed Tomography (HRCT) of Thorax variables were as good as other known clinical variables in grading emphysema patients. The results showed that our subjects had moderate emphysema. Moreover, all imaging variables in grading emphysema patients were potentially as useful as other known clinical variables.

The results of this study also suggested that combined analysis of each component of COPD is important not only to assess disease severity but also to understand the pathogenesis of COPD.

The extent of emphysema, as assessed by CT scan, is a good predictor of mortality in patients with COPD, and greater emphysematous destruction is a predictor of a high BODE index.

Our study showed that the severity of emphysema as measured on CT correlated with BODE index as well as with four components of the index, i.e. BMI, FEV1, mMRC and 6MWT. Our study showed that there was a significant inverse relationship between BMI and the extent of emphysema on CT scan in the lungs of male smokers (r= -.695 p-value<0.005) and it is unclear if emphysema predisposes to weight loss among patients who develop COPD or whether low body weight contributes to the development of emphysema. This is similar to the study done by Ogawa E *et al* 2009 who concluded that body mass index in male patients with COPD had negative correlation with low attenuation areas on CT. Body mass index (BMI) was significantly lower in the higher low attenuation area phenotype of COPD than Wall Percentage area of Bronchus. Body mass index (BMI) was significantly lower in the emphysema dominant phenotype than in the airway dominant phenotype. Low BMI could be a consequence of COPD. Basal metabolic rate is increased in moderate to severe COPD. Decramer *et al* (2008) have proposed that the pathogenesis of nutritional depletion in COPD is high energy expenditure and low energy intake. Importantly, low BMI is one of the independent predictors for mortality in patients with COPD. These observations have led to a number of trials to intervene with nutritional support for patients with COPD

The CT measurements revealed that a decreased FEV1 is associated with an increase low attenuation area of emphysema and with an increase of airway wall area. This is similar to the study by Nakano Y *et al* 2000 concluded that emphysema (Low attenuation area percentage) and airway wall thickening negatively correlated with measurements of lung function. Emphysema (Low attenuation area percentage) showed negative correlation (r= -0.634, p-value <0.005) with FEV1 .While airway dimension Pi10 (10 mm lumenal perimeter) also showed negative association with FEV1(r=-0.631 p-value =0.004).Nakano Y *et al* (2000) found that Emphysema (low attenuation area percentage) and airway thickening have inverse relationship with airflow in COPD

Airflow obstruction in COPD is caused by loss of lung recoil and airway narrowing (Gould *et al* 1988). In any one subject it is difficult to define the relative contributions of these mechanisms to the airflow obstruction. Emphysema, and its computed tomography surrogate low attenuation area percentage correlates with loss of recoil in lung of COPD (Mair *et al* 2009). Haraguchi *et al* (1999) showed that the bronchi of patients with COPD had more degenerated cartilage and perichondrial fibrosis than a control group

They also showed that the degree of perichondrial fibrosis correlated with the thickness of the epithelial basement membrane. Tiddens *et al* (2000) evaluated airway wall dimensions in cartilaginous airways of patients with COPD. They found that the wall area of central airways was increased in obstructed patients (FEV1/FVC = 40%) in comparison to non-obstructed patients (FEV1/FVC = 80%). They also showed that the increase in cartilaginous airway wall area correlated significantly with a semiquantitative measure of peripheral airway inflammation.

Grydeland *et al* (2009) studied on Quantitative computed tomography emphysema and airway wall thickness by sex, age and smoking. They concluded that they found significant difference in quantitative HRCT measure of Emphysema and airwall thickness between varying age and smoking groups of both control and COPD subject. In our study also showed that Emphysema severity (low attenuation area percentage) was increased with increasing age (r=0.772, p-value<0.005).

The increasing emphysema score with ageing found in our study. This may have several explanations it could indicate that natural ageing of lung gradually reduces the relative importance of environmental risk factor (Gevenois *et al* 1996)

In our study also showed that Emphysema severity (low attenuation area percentage) was increased with increasing number of pack years (r= 0.463, p-value <0.005).

In our study increased number of pack-years smoked was associated with increasing emphysema score in COPD case. This is in accordance with the study by Soejima *et al* (2000). These data are similar to the findings of previous respiratory physiological studies which reported that pack years are independent predictor of indices of emphysema (Welle *et al* 1998).Number of pack years was related to increasing airwall thickness (Van pelt *et al* 2000) Smoking is the most important risk factor as 70% of our patients were smokers, 14% patients had risk factors other than smoking like exposure to biomass fuel which is more important in rural India and especially in females. When a person who has no history of smoking gets exposed to other risk factors like Post TB Bronchiectasis, biomass fuel exposure, occupational exposure etc. will have 10.5 times more chance of developing COPD. This observation is supported by Künzli *et al* (1997) who said that exposure to outdoor and indoor air pollutants increases the prevalence of COPD by an estimated 2% for each 10 g/m3 increase in particulate matter. This observation is also supported by Halbert *et al* (2003) who told that the use of biomass fuels (e.g. use of wood for cooking and heating) increases the risk of COPD by three to four times contributing significantly to COPD prevalence, especially in rural regions. In our study we had 16% patients which had no identified risk factors so there is requirement of more research to identify factors leading to COPD in such patients. Joint exposure to smoking and occupational factors has been shown to multiply the risk of COPD (Blanc *et al*, 2009.Women seem to be more susceptible to the effects of tobacco smoke, and the same might be true for other harmful inhalational substances. A different dose-response relationship for men and women has been shown, especially at lower levels of smoking (Sorheim *et al*, 2010).

In this analysis we also demonstrated a relationship between emphysema and BODE score. The relationship between emphysema and BODE is stronger than the relationship between airway disease and BODE.

Emphysema percentage (LAA950) with BODE score showed positive correlation (r=0.7095, p-value <0.005).Airway dimension Pi10 (10 mm lumenal perimeter) (r=0.34, p-value <0.005) and segmental wall percentage area (r=0.32, p-value <0.005) also showed positive correlation. But emphysema was strongly associated with BODE.

It is evident that patients with high BODE scores have a much greater burden of emphysema than airway disease.

We now know that COPD is a complex chronic inflammatory disease with multiple dimensions. Celli *et al* (2004) developed a multidimensional index that integrates these principal prognostic determinants. The BODE [body mass index (BMI), airflow obstruction, dyspnea and exercise capacity] index. This

score showed to be more effective than FEV1 as a prognostic variable.

Ong *et al* 2005 found the BODE index to be useful for predicting hospital admission risk. Its predictive capacity being even greater than that of the COPD staging system as defined by the GOLD.

Admission to the hospital and heavy use of health-care resources is a common feature of COPD. The BODE scoring system may prove to be helpful in health-care resource allocation and in guiding therapy for individual patients. This multistage scoring system mean BODE index can provide useful prognostic information of survival and hospitalization (Jose Marin *et al* 2009)

The relationship between emphysema percentage and BODE appears to be driven most strongly by its relationship with FEV1. The FEV1 is essential for the diagnosis and quantification of the respiratory impairment resulting from COPD (Pauwels *et al* 2001). In addition, the rate of decline in FEV1 is a good marker of disease progression and mortality (Burrows B *et al* 1991). However, the FEV1 does not adequately reflect all the systemic manifestations of the disease. For example, the FEV1 correlates weakly with the degree of dyspnea (Mahler *et al* 1984), and the change in FEV1 does not reflect the rate of decline in patients' health (Burge *et al* 2000). Prospective observational studies of patients with COPD have found that the degree of dyspnea (Nishimura *et al* 2002) and health-status scores (Domingo *et al* 2002) are more accurate predictors of the risk of death than FEV1.

Weight loss and hyperinflation are known associations with Emphysema percentage (LAA950), that likely contribute to these relationships.

In the study done by Mair *et al* 2007 showed that exacerbation frequency was not related with emphysema severity , but their subjects' emphysema was less severe, their BMI was higher, and their shorter smoking history. Emphysema percentage was better correlated with clinical variables than PERC15 and MLD .which meant that Emphysema percentage (LAA950) is a better index for emphysema.

Quantitative CT is a good objective method to quantify the percentage of lung having emphysema. We found that emphysema was equally distributed in both the lungs with cluster of collection of emphysematous spaces in lung.

A combined algorithm using CT percentage low attenuation area and lung density along with body mass index, pack-years, and smoking status has also been demonstrated to allow reasonably good predictive value for diagnosis of COPD on CT

CT has particular advantages for assessing the extent of localized morphologic disease in individual patients. In the near future, advancements in CT scanning technology and software may lead to the assessment of the disease on a lobar and segmental basis and to an understanding of the regional heterogeneity and natural history of each disease component of COPD.

CONCLUSION

It is evident that patients with high BODE scores have a much greater burden of emphysema than airway disease. The extent of emphysema, as assessed by CT scan, is a good predictor of mortality in patients with COPD and greater emphysematous destruction is a predictor of a high BODE index. A combined algorithm using CT percent low attenuation area and along with body mass index, pack-years, and smoking status has also been demonstrated to allow reasonably good predictive value for diagnosis of COPD on CT

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