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Original Research Article

Correlation between CT phenotypic patterns with clinical, nutritional and pulmonary function parameters among COPD patients

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ABSTRACT

Background: COPD is a multi-dimensional disorder with multiple phenotypes. The commonly used GOLD guidelines and Spirometry do not fully reflect the heterogeneous nature of the disease, structural abnormalities, and phenotypes. This necessitates CT phenotyping because of difference in treatment strategies, disease progression and response to treatment.
Methods: We conducted our study on 40 male COPD subjects aged more than 45 years, divided them into 4 groups based on CT phenotype as normal, Airway Dominant (AD), Emphysema Dominant (ED) and mixed types. We compared the clinical parameters, spirometry indices, markers of nutrition (including BMI) across these phenotypes. CT phenotypes were determined by Low Attenuation Area (LAA) and Wall area.
Results: In our study, 16 (40%) had airway dominant (AD), 15 (37.5%) had emphysema dominant (ED), 4 (10%) had mixed, and 5 (12.5%) had normal CT phenotype. The various nutrition indicators like height, weight, BMI, fat-free mass index was not statistically significant. The difference in the median FEV1/FVC across CT phenotypes was statistically significant (P Value 0.002). The difference in Haemoglobin, Total protein, Albumin, Triglycerides and Total Cholesterol was not statistically significant across CT Phenotypes.
Conclusions: The GOLD guidelines do not fully reflect the heterogeneous nature of the disease which necessitates CT phenotyping. In our study, there was a significant association between BMI, FEV1/FVC ratio with CT phenotypes. Identifying the different phenotypes of COPD will allow us to implement a more personalized treatment and choose the best treatment option.

Keywords: COPD, Computed tomography, Phenotype, Pulmonary, PFT

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a heterogeneous chronic respiratory disease affecting the airways (i.e. chronic bronchitis, airway collapse), the parenchyma (i.e. hyperinflation, air trapping and emphysematous destruction) as well as the vasculature (i.e. hypoxic vasoconstriction, rarefication and pulmonary arterial hypertension) with different severity during the course of the disease. COPD is a major public health problem.[1] The prevalence and mortality from COPD are increasing globally and it is predicted to be the third-leading cause of death by 2020.[2] There have been wide variations in the prevalence of COPD across countries based on the method of diagnosis and classification of COPD. Worldwide estimates of COPD prevalence are in the range of 5% to 10%, whereas COPD incidence rates have shown variations between 2 to 6 cases per 1,000

person-years, depending on the case definition and the study population.[3,4] In 2012, the Indian Study on Epidemiology of Asthma, Respiratory Symptoms and Chronic Bronchitis in Adults (INSEARECH) reported the overall prevalence of chronic bronchitis which is considered a surrogate for COPD as 3.49 percent in adults >35 years in india.[5] In a spirometry-based study in Kashmir, the prevalence of COPD was found to be as high as 19% among participants >40 years of age.[6] Prevalence of COPD in India lies between 6.6 to 7.7 % and it contributes significantly to mortality and disability-adjusted life years (DALYs).[7]

COPD has both airway (central and small airways) and airspace abnormalities. It is a multi-dimensional disorder with multiple phenotypes.[8] The commonly used GOLD guidelines, do not fully reflect the heterogeneous nature of this disease.[9,10] Among all phenotypes described, the two major types that are especially associated with different response to therapies are no emphysema or predominant emphysema. Emphysema has a strong association with more rapid disease progression and mortality. In clinical practice, spirometry is used for the diagnosis of COPD and assessment of disease severity and progression but it provides no information on structural pulmonary abnormality seen in emphysema whereas radiological imaging allows for regional assessment of the components involved of which CT is the most accurate for diagnosis of emphysema *in vivo*.[11-14] The necessity of phenotyping was felt because of difference in treatment strategies, disease progression and response to treatment. In addition to airway inflammation, emphysema, there is a nutritional discrepancy in COPD. The cachexia associated with COPD is more prevalent among those with predominant emphysema airflow limitation and with a relatively maintained ventilatory drive (the "pink puffer" hypothesis).[15]

Makita et al, in their study on COPD patients found that emphysema predominant phenotypes had lower BMI.[16] There have been reports of the increased occurrence of breathlessness in COPD subjects with greater emphysema.[17] These different aspects of COPD can be best addressed by imaging using a combination of morphological and functional techniques.[12] Identifying the peculiarities of the different phenotypes of COPD will allow us to implement a more personalized treatment, in which the characteristics of the patients, together with their severity will be key to choose the best treatment option.[18]

The current data available about the phenotypes of this disease for decision making and policy making at the country level is very scarce in developing countries like India with a huge burden of disease. The causal association still needs further exploration as Thoracic computed tomography imaging holds promise for phenotyping in chronic obstructive pulmonary disease.[19] So we carried out our study to analyze the CT phenotype pattern among male patients with COPD and its correlation with spirometry indices and markers of nutrition such as BMI.

METHODS

The study was a prospective observational study, conducted in the Department of Respiratory Medicine and at Vallabhbhai Patel Chest Institute and the associated, Vishwanathan Chest Hospital, the University of Delhi after due permission from Institutional Ethics Committee from September 2012 to August 2013.

The study had included all adult male patients of age >45 years with an established diagnosis of COPD diagnosed as per Global Initiative for Obstructive Lung Diseases (GOLD) 2010 guidelines.[20]

The study had excluded people who were established cases of bronchial asthma, active cases or late sequelae of pulmonary tuberculosis, lung cancer, and other associated respiratory disorders, people with acute COPD exacerbation in the 4 weeks preceding study entry ,people with history of systemic steroid intake in the 4 weeks preceding the study, people with associated comorbid conditions like diabetes mellitus, hypertension and ischemic heart disease and people who had any thoracic surgical intervention in the past..

After screening for inclusion and exclusion criteria and obtaining informed written consent, all the study participants were thoroughly assessed by clinical history and examination.

All the patients were subjected to assessment of Computerized Tomography (CT) assessment. CT was performed using Toshiba Aquilion 64 slice CT scanner without the infusion of contrast medium. Three HRCT slices were used to quantify low Attenuation Area (LAA) and section helical CT to quantify airway dimensions. Densitometric measures of emphysema were analyzed at a threshold of-950 Hounsfield unit and reported as percent emphysema. Emphysema was scored visually as LAA in bilateral upper, middle, and lower lung fields according to the method of Goddard et al.[21] The score in each dimension was calculated according to the ratio of LAA to occupy in the lung field as follows: score 0, LAA<5%; score 1, 5% ≤LAA <25%; score 2, 25% ≤LAA <50%; score 3, 50% ≤LAA <75%; score 4, LAA≥75%. The severity of emphysema was graded in accordance with the sum of scores at 6 dimensions as follows: grade 0, total score = 0; grade 1, total score = 1-6; grade 2, total score = 7-12; grade 3, total score = 13-18; grade 4, total score = 19-24. For analysis of airway dimensions apical right upper lobe, dimensions were measured and percentage wall area was calculated. COPD was divided into 4 groups based on CT measurements of LAA% and WA%. The 4 groups were normal by CT (NCT), Airway Dominant (AD, low LAA% and high WA%), Emphysema Dominant (ED,

high LAA% and low WA%) and mixed (high LAA% and high WA%) phenotypes respectively.

The pulmonary function tests including Forced Vital Capacity (FVC), Forced Expiratory Volume in the first second (FEV1), FEV1/FVC% and reversibility after inhalation of 400 micrograms of salbutamol and residual volume (RV), total lung capacity (TLC) and single-breath diffusing capacity of the lung for DLCO. Simple spirometry was carried out both before and 30 min after the administration of inhaled salbutamol 400 µg using Spiro 232 by P.K. Morgan. The post-bronchodilator FEV1%Pred (using Asian values based on the Fukuda Sangyo Manual) was used to classify the COPD severity according to the GOLD guidelines. Nutritional status indicators assessed in the study were, Body Mass Index (BMI), fat and fat-free body mass as assessed by the method of Durnin and Womersley.[22] Also, 5ml of venous blood was drawn from each participant under aseptic conditions and was sent to the laboratory of estimation of total proteins, albumin, triglycerides and total cholesterol.

Pulmonary function test was primary outcome variable. CT phenotype was secondary outcome variable. Age, various nutrition parameter (height, weight, BMI, FFMI), and hematological parameter (haemoglobin (g/dl), total protein (g/dl), albumin (g/dl), triglycerides (mg/dl) and total cholesterol) were considered as primary explanatory variables. Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency, and proportion for categorical variables. Data was also represented using appropriate diagrams like bar diagram, pie diagram, and box plots. A Shapiro-Wilk's test ($p>0.5$) and a visual inspection of their histograms, normal Q-Q plots and box plots showed that the CT phenotype and age, various nutrition, and hematological parameters were non-normally distributed for CT phenotype.[23,24] The comparison between CT phenotype and age, various nutrition parameter (height, weight, BMI, FFMI), PFT parameter (FVC, FEV1) and hematological parameter (haemoglobin (g/dl), total protein (g/dl), albumin (g/dl), triglycerides (mg/dl) and total cholesterol) was assessed by comparing the median values. Kruskal Wallis test was used to assess statistical significance. P value <0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis.[7]

RESULTS

A total of 40 subjects were included in the final analysis. The mean age (in years) was 58.63±8.45 years and all the participants were males. the minimum age was 46 years and maximum age was 80 years in the study population. The mean BMI was 23.05±4.91kg/$m^{2.}$ The mean values of other nutritional indicators and pulmonary function parameters are summarized in Table 1. among the CT phenotypes 16 (40%) had airway dominant (AD), 15 (37.5%) had emphysema dominant (ED), 4 (10%) had mixed, and 5 (12.5%) had normal (Table 1).

Table 1: Summary of baseline characteristics of study population (N=40).

Parameter	Summary	Min	Max
Age (in years) (Mean ±SD)	58.63±8.45	46.00	80.00
Height (in cm) (Mean ±SD)	162.98±5.63	152.00	173.00
Weight (in kg) (Mean ±SD)	61.9±14.23	39.00	97.00
Body Mass Index (kg/m2) (Mean ±SD)	23.05±4.91	14.50	33.10
Fat-Free Mass Index (by calculation) (Mean ±SD)	16.89±2.78	11.52	22.70
Fat-Free Mass Index (by bioimpedance analysis) (Mean±SD)	16±2.25	11.93	20.38
Smoking index (pack-years) (Mean ±SD)	42.19±31.03	2.00	130.00
FVC (% predicted) (Mean ±SD)	92.8±21.72	22.84	130.00
FEV1 (% predicted) (Mean ±SD)	56.43±22.55	21.00	110.00
FEV1/FVC (Mean ±SD)	48.23±13.78	27.00	69.00
DLCO (ml/min/mmHg) (Mean ±SD)	20.28±7.97	8.37	41.00
Wall area (%) (Mean ±SD)	80.84±4.15	71.98	90.18
Low attenuation areas (%)	24.18±16.41	3.00	58.00
6MWD (m) (Mean ±SD)	434.58±125.47	108.00	660.00
SGRQ total score (Mean ±SD)	54.07±17.24	17.30	84.57
Haemoglobin (g/dl) (Mean ±SD)	13.87±1.49	10.30	17.30
Total protein (g/dl) (Mean ±SD)	8.55±8.86	5.60	63.00
Albumin (g/dl) (Mean ±SD)	3.84±0.43	2.90	4.60
Triglycerides (mg/dl) (Mean ±SD)	129.92±38.54	64.00	253.00
Total Cholesterol (Mean ±SD)	182.39±30.98	104.00	242.00
CT phenotype			
Airway Dominant (AD), N (%)	16 (40%)	-	-
Emphysema Dominant (ED) N (%)	15 (37.5%)	-	-
Mixed N (%)	4 (10%)	-	-
Normal N (%)	5 (12.5%)	-	-

Among the people with CT phenotype, airway dominant (AD) people had median age of 53 years (IQR 47 to 59.5). It was 61 years (IQR 58 to 65) among emphysema dominant (ED), 59.5 years (IQR 48 to 1.75) among mixed type and 58 years (IQR 55 to 59) among normal phenotype. The difference in the median age across CT phenotype was statistically significant (P value 0.018). The various nutrition indicators like height, weight, BMI, fat free mass index was comparable across all the CT phenotypes, with no statistically significant difference. (P value >0.005). Smoking index across the CT phenotype was statistically not significant. (P value 0.324) (Table 2).

Table 2: Comparison of median values in baseline characteristics across the CT phenotype group (N=40).

Parameter	Airway Dominant (AD) Median (IQR)	Emphysema Dominant (ED) Median (IQR)	Mixed Median (IQR)	Normal Median (IQR)	P value
Age (in years)	53 (47, 59.5)	61 (58, 65)	59.5 (48, 1.75)	58 (55,59)	0.018
Height (in cm)	165 (160.25,168.5)	163 (156,166)	165 (162.25,171.25)	158 (154.5,162)	0.164
Weight (in kg)	66 (53,77)	53 (47,56)	62 (56,68)	60 (56,75)	0.110
Body Mass Index (kg/m^2)	24.61 (20.7, 28.35)	19.2 (17.6, 23.01)	21.97 (19.88,26.27)	24.3 (21.86,30.18)	0.069
Fat free mass index (by calculation)	17.69 (15.84, 19.81)	15.37 (13.8, 17.58)	16.19 (14.68,17.71)	17.54(15.91,20.98)	0.141
Fat free mass index (by bioimpedence analysis)	16.47 (15.01, 18.69)	14.31 (13.03, 15.89)	17.14 (14.64,19.27)	15.78 (15.28,17.87)	0.051
Smoking index (pack-years)	30 (11,56.25)	40 (15,70)	70 (33.75,95)	30 (19,105)	0.324

Table 3: Comparison of median values in PFT parameter across the CT phenotype group (N=40).

PFT Parameter	Airway Dominant (AD) Median (IQR)	Emphysema Dominant (ED) Median (IQR)	Mixed Median (IQR)	Normal Median (IQR)	(P value)
FVC (% predicted)	90.5 (75.25,110.5)	86 (72, 106)	96 (86.75,107.5)	105 (93,119.5)	0.491
FEV1 (% predicted)	70.5 (38.75,79.75)	39 (32,62)	50 (41.5,60.75)	60 (52.5,97.5)	0.064
FEV1/FVC	58 (43.25,67)	34 (30,49)	40 (32.75,56.25)	59 (50,66)	0.002
DLCO (ml/min/mmHg)	23.32 (18.45,28.43)	14.84 (10.82,17.25)	17.89 (13.24,36.1)	19.73 (18.35,26.85)	0.001
Wall area (%)	84.45(82.55,85.85)	77.87 (75.34,79.05)	84.45 (83.05,85.5)	77.8 (75.69,78.93)	<0.001
Low attenuation areas (%)	11 (5.25,13.75)	37 (34,47)	41.5 (31.5,45.5)	11 (8.5,11.5)	<0.001

Table 4: Comparison of median values in hematological parameter across the CT phenotype group (N=40).

Hematological Parameter	Airway Dominant (AD) Median (IQR)	Emphysema Dominant (ED) Median (IQR)	Mixed Median (IQR)	Normal Median (IQR)	(P value)
Haemoglobin (g/dl)	14.45 (13.25,15.25)	13.4 (12.4,14.2)	13.4 (12.97,14.65)	14.3 (13.6,15.25)	0.331
Total protein (g/dl)	7.15 (6.95, 7.62)	7.1 (6.4,8.1)	7.2 (6,7.57)	6.9 (6.8,7.2)	0.730
Albumin (g/dl)	3.9 (3.47,4.27)	4 (3.8,4)	3.8 (3.12, 4.17)	3.9 (3.5,4.15)	0.871
Triglycerides (mg/dl)	120.4 (113.75,161)	119 (100,152)	100.5 (76.5,129)	163 (94.5,178.5)	0.519
Total Cholesterol	179.5 153.5,198.75)	192 (167, 232)	175 (161, 95.75)	170 (157.5,203.5)	0.590

Among the PFT parameters FVC (% predicted), FEV1 (% predicted) had shown no statistically significant difference across CT phenotypes (P value >0.05). The mean FEV1/FVC value was lowest in Emphysema Dominant (ED)variety (34, IQR 30 to 49), followed by mixed variety (40, IQR 32.75 to 56.25). It was almost similar in AD and normal Phenotypes. The difference in the median FEV1/FVC across CT phenotype was

statistically significant (P Value 0.002). The DLCO was lowest in ED category (14.84, IQR 10.82 to 17.25), followed by mixed 17.89, IQR 13.24 to 36.16) and AD (17.89, IQR 13.24 to 36.16) phenotypes. The wall area percentage was similar in AD and Mixed Phenotypes. The wall area % of ED phenotype was comparable to Normal Phenotype. The difference in the median wall area (%) across CT phenotype was statistically significant (P value <0.001). Among the people with CT phenotype, airway dominant (AD) median was 11% (IQR 5.25 to 13.75) of wall area, 37% (IQR 34 to 47) of emphysema dominant (ED), 41.5% (IQR 31.5 to 45.5) of mixed and 11% (IQR 8.5 to 11.5) of normal. The difference in the median low attenuation areas (%) across CT phenotype was statistically significant (P Value <0.001) (Table 3).

Hematological parameters like haemoglobin (g/dl), total protein (g/dl), albumin (g/dl), triglycerides (mg/dl) and total Cholesterol had shown statistically no significant association with CT Phenotype (P value >0.05) (Table 4).

DISCUSSION

Individuals with identical GOLD stages may have different morphologic appearances at computed tomography (CT).[25] Some have extensive emphysema, whereas others with equal functional impairment have an airway-dominant phenotype with little or no emphysema. These morphologic differences may reflect important differences in the underlying pathophysiology and genomic profile of COPD. Furthermore, individual subtypes of emphysema may have different pathophysiologic importance. We conducted our study on 40 male COPD subjects aged more than 45 years, divided them into 4 groups based on CT phenotype as normal, Airway Dominant (AD), Emphysema Dominant (ED) and mixed types. We compared the clinical, spirometry and nutritional indices among these phenotypes.

The Baseline parameters of our study population were comparable with that of studies by Makita H et al, Ogawa E et al, Chen LF et al.[16,26,27] Similar to our study, Makita H et al, Chen LF et al, and Ogawa E et al, did their study on males and also reported that more than 90% of their participants were males.[16,26,27] Similar to our study participants, others also reported a normal mean BMI in the range of 22 to 24. The mean age of our study population was lower (58.63±8.45 years) compared to other studies (71 to 72), which may be due to the fact that the age of incidence or reporting of COPD has decreased over the years with increased awareness and healthcare facilities.

In our study population, 40% had airway dominant (AD) CT phenotype which was the most frequent. About 37.5% had emphysema dominant while 10% had a mixed phenotype. 12.5% of our study subjects had normal CT appearance. Contrary to our study, Van Tho N et al, observed that Emphysema-dominant phenotype (42.9%) was the most frequent while Airway dominant was observed only in 16.3% of subjects.[28] They observed 19.2% of subjects had a mixed phenotype. This difference may be due to the small sample size of our study and method of selection of subjects across the studies. But Tatsumi K et al, in their study found that emphysema-dominant phenotype was more frequently seen in 90% of subjects while only 10% had airway disease-dominant phenotype which may be due to the fact that they did not use CT for phenotyping and were dependent mostly on spirometry.[29]

With regards to the comparison of clinical parameters across various CT Phenotypes, the smoking index in pack years and various nutrition indicators like height, weight, BMI, fat-free mass index were comparable across the groups. ED subjects had the highest median age of 61 years while AD phenotype had the lowest median age of 53 years. This difference of age across various phenotypes was statistically significant. This difference may be due to the early onset presentation of symptoms in the AD group.

Similar to our study, previous studies have reported significantly lower BMI and Fat-free mass index in ED and mixed phenotypes.[16,26] In present study, BMI was not significantly different in various groups though there was a trend towards lower BMI in predominant emphysema (ED) group. Ogawa E et al, reported that BMI was significantly lower in the emphysema dominant phenotype than in the airway dominant phenotype, in male smokers with COPD.[26] These results support the concept of different COPD phenotypes and suggest that there may be different systemic manifestations of these phenotypes.

Marti S et al, also reported that BMI was one of the significant predictive factors of respiratory mortality in COPD and should be taken into account when considering the management and prognosis.[30] Celli et al, proposed the BODE index, a simple multidimensional grading system, for predicting the risk of death in subjects with COPD demonstrating the importance of BMI, dyspnoea in addition to airflow limitation index.[31] Several other reports also support BMI as independent factors for the prognosis of COPD.[30,32]

With regards to parameters of the pulmonary function, it has been shown by other investigators that patients who met the radiological criteria for emphysema had a significantly lower FEV1 and DLCO than those without emphysema.[33] Our study also demonstrated similar results with mean FEV1 values (% predicted) significantly less in ED group as compared to AD group which was significant statistically. But no significant difference was observed when AD group was compared with the mixed or normal group. No significant difference was observed when ED group was compared to the mixed group but FEV_1 was significantly lower in ED group as compared with normal by CT group (72±25). No significant difference was also observed

between mixed and normal by CT groups. It was reported in the literature that airflow limitation in COPD is more closely related to the dimensions of the distal airways (sixth generation) than the proximal airways (third generation) in both upper and lower lobes.[34]

The difference in the median DLCO, median wall area (%) and low attenuation areas (%) across CT phenotype was statistically significant in our study (P Value <0.001). Hasegawa M et al, in their study also observed that wall area percent (WA%) significantly correlated with FEV1 (% predicted).[34] Destruction of lung parenchyma corresponds to the low attenuation areas (LAAs) detected through CT and it quantifies emphysema by detecting LAAs and assesses disease severity.[35] The severity of emphysema varies widely despite the same disease stage in COPD. Our observations support the findings of several past studies which argued against emphysema as the major cause of airflow limitation in COPD.[36]

The severity of emphysema varies widely despite the same disease stage in COPD. Our observations support the findings of several past studies which argued against emphysema as the major cause of airflow limitation in COPD.[36] Van Tho N et al, observed that mixed phenotype subjects had more severe dyspnea and more frequent hospitalizations than those with each of the remaining CT-based phenotypes.[28] Historically, the phenotypes pink puffer, blue bloater, chronic bronchitis were defined. In our study and in this decade with increasing use of CT for phenotyping, defining these phenotypes will go a long way in the management of patients with COPD. In our study, none of the hematological parameters such as Haemoglobin, Total protein, albumin, triglycerides or total cholesterol showed statistically significant association with CT Phenotypes. Cachexia in patients with COPD may be caused not only by malnutrition but also by systemic inflammation. Similarly, Ogawa et al, also observed that none of the serum markers they measured (total protein (7.0 (0.4) g/dl), albumin (4.3 (0.3) g/dl), cholinesterase (303 (71) IU/l), triglycerides (124 (73) mg/dl), total cholesterol (198 (38) mg/dl) or C reactive protein (0.3 (1.0) mg/dl)) correlated with BMI or LAA%.[26] Patients with COPD have a significant increase in the circulating level of C reactive protein and evidence of increased risk for coronary vascular disease.[37,38]

As reported by Ogawa E et al, we are also unclear if emphysema predisposes to weight loss and nutritional deprivation among patients who develop COPD or whether low body weight contributes to the development of emphysema and there arises the need for interventional studies and further large-scale multicenter studies.[29] We were also limited by the small sample size, observational design of the study and the sampling frame for selecting the study participants which included only male participants. COPD is a multi-dimensional disorder with multiple phenotypes. The GOLD system has been widely used to identify and classify the severity of postbronchodilator airflow limitation in COPD, with GOLD stages I, II, III, and IV.[39] But it does not fully reflect the heterogeneous nature of the disease which necessitates CT phenotyping. Identifying the peculiarities of the different phenotypes of COPD will allow us to implement a more personalized treatment, in which the characteristics of the patients, together with their severity will be key to choose the best treatment option.[18]

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