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Quantitative Computed Tomography (CT) Assessment of Emphysema in Patients with Severe Chronic Obstructive Pulmonary Disease (COPD) and its Correlation with Age, Sex, Pulmonary Function Tests, BMI, Smoking, and Biomass Exposure

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: To evaluate the role of HRCT in quantifying emphysema in severe COPD patients and to study the variations in the pattern of emphysema in relation to age, sex, FEV_1, smoking index, biomass exposure, and BMI.

Material/Methods: Automatic lung segmentation of HRCT scans in 41 severe COPD patients (GOLD stage III or more) was done using an emphysema protocol. The extent of emphysema was assessed using the density mask method with a threshold of –950 HU (%LAA-950). The percentage of emphysema in each lung lobe and both lungs was correlated with 6 parameters – age, sex, BMI, smoking index, biomass exposure, and FEV_1.

Results: Smoking resulted in homogenously distributed emphysema regardless of the severity of smoking. BMI was inversely correlated with the extent of emphysema. A significant association was found between the percentage of emphysema in the right lower lobe and BMI (P=0.015), between biomass exposure and the percentage of emphysema in RUL, RLL, and both lungs (P values of 0.024, 0.016, and 0.036, respectively). The extent of emphysema was disproportionately low compared to the amount of obstruction on PFTs, indicating an airway predominant variety of COPD with significant biomass exposure.

Conclusions: Smoking is associated with a relatively homogenous distribution of emphysema with no regional predilection. Biomass exposure produces predominantly right-sided emphysema. BMI decreases with increasing levels of emphysema in the right lower lobe. These risk factors of emphysema patterns are helpful in deciding on the management, including surgical options.

MeSH Keywords: Emphysema • Pulmonary Disease, Chronic Obstructive • Smoking • Tomography, Spiral Computed

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Background

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the world and is poised to become the third leading cause of death worldwide in 2030 [1,2]. The most widely used and accepted COPD guidelines is "The Global Initiative for Chronic Obstructive Lung Disease (GOLD)". GOLD defines COPD as "a common preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and lungs to noxious particles and gases. Exacerbations and co-morbidities contribute to overall severity in the individual patient". Smoking remains the major risk factor

for COPD. Biomass exposure is also a significant risk factor, especially in rural areas.

COPD manifests differently in individuals. This has led to the emergence of the concept of "phenotype" in COPD. The term phenotype in the field of COPD refers to the predominant set of disease features that show variations in their presence in different individuals and which are significant enough to affect the prognosis and clinical outcome. Based on this concept, numerous clinical and radiological phenotypes of COPD have been described, which have different prognoses and outcomes and hence merit different treatment approaches.

Once a diagnosis of COPD is made, numerous modalities are used to assess the severity and monitor the progress and treatment response in COPD. These include spirometry, diffusing capacity, arterial blood gas analysis, and radiological modalities like X-ray and computed tomography (CT). CT is superior to chest radiography in the detection of emphysema and in the assessment of its distribution and extent. Morphologically, two main subtypes of emphysema exist. The centrilobular (or centriacinar) form of emphysema results from dilatation or destruction of the respiratory bronchioles and is the type of emphysema most closely associated with cigarette smoking. The panlobular (or panacinar) form of emphysema is associated with α1-antitrypsin deficiency and results in an even dilatation and destruction of the entire acinus. Emphysema will be visible in many conventional CT sections with thicknesses of 5 to 8 mm. However, it is more readily detected on high-resolution CT (HRCT) sections with thicknesses of 1 to 2 mm that are reconstructed with an edge enhancing algorithm. Advances in CT have enabled localizing, quantifying, prognosticating, and phenotyping COPD. Stratification of treatment of COPD into medical and surgical categories is also well accomplished by CT.

In the present study, a quantitative analysis of thoracic HRCT scans was done in patients with stable GOLD stage 3 or 4 COPD, and the percentage of emphysema in each lobe of both lungs and the total extent of emphysema was correlated with 6 parameters – age, sex, BMI, smoking index, biomass exposure, FEV_1.

Material and Methods

Patients

This study involved 41 stable COPD patients attending the Medicine and Pulmonary Medicine Departments. Only severe COPD (GOLD stage III or more) patients diagnosed by the post-bronchodilator $FEV_1/FVC < 0.7$ and $FEV_1 < 50\%$ of predicted values were included in this study. The approval of the local ethical committee was sought for the study protocol, and the informed consent was taken from all patients before the examination. A brief history, relevant physical examination, and quick review of records, including chest X-rays, was done.

CT scan

CT scans were done on 64-slice MDCT scanner (Lightspeed VCT-XTE, GE medical systems) with the following parameters: kvp: 120 kvp, mAs: 335 mAs, Gantry rotation time: 0.6 secs, Gantry tilt: 0 degree, Slice thickness: 0.6mm, Total radiation dose: 4.498 mSV. The high resolution CT images were acquired at suspended full inspiration using the smallest FOV (Field Of View) that included both lungs. On completion of CT scanning, the data were transferred to a real-time interactive 3D Workstation: Advantage Window version 4.5, GE Healthcare. Images were reconstructed using the recommended reconstruction kernel for thoracic VCAR, which is BONE or STANDARD. In addition, volume rendering (VR), maximum and minimum intensity projections (MIP and minIP) in standard axial, coronal, sagittal, and oblique reformatted images were obtained. Axial source data was analyzed in all cases.

Post-processing

It was done in a pre-installed post-processing application/software, i.e., Thoracic VCAR. Thoracic VCAR is a non-invasive CT image analysis software package, which may be used in conjunction with CT lung images to aid in the assessment of thoracic disease (emphysema, COPD) diagnosis and management. The emphysema protocol within the software provided automatic segmentation of the lungs. The lobe segmentation protocol divided the lungs into several lobes. The software provided quantification of HU values and displayed in color (blue) the thresholds within a segmented region. Thoracic VCAR application supports CT datasets, high resolution scans, or volume scans.

Image analysis

The extent of emphysema was assessed using the density mask method to get the percentage of lung voxels with a density lower than a certain threshold. This was expressed using the term%LAA (percentage low attenuation areas) to describe these low density regions of the lung. A threshold of -950 Hounsfield Units (HU) was used as the primary cut-off (%LAA-950) to obtain color-coded display of abnormal emphysematous regions in both lungs. The volume information of the left lung, right lung, both lungs, and each lobe of each lung was analyzed and displayed in the statistics panel, which was recorded in the final report. Airway analysis was not done due to lack of achieving a uniform level of airway tracking in all patients with the installed version of the software.

Statistical Analysis

The percentage of emphysema in each lobe of both lungs and the total emphysema extent were correlated with 6 parameters – age, sex, BMI, smoking index, biomass exposure, FEV_1. P value was calculated for each association. The test used to determine the statistical significance was ANOVA (analysis of variance).

Results

The age of patients ranged between 42 years to 82 years, with the mean age of 62.53 (SD±10.17) years. There was male predominance in our study. There were 34 (82.92%) males and 7 (17.07%) females in this study. The mean BMI of the patients was 18.14 (SD±3.01). The minimum BMI was 13.67, while the maximum BMI was 25.11. Smoking was the most common associated risk factor and was

Table 1. Lobar and total distribution of emphysema (in percent) in all the cases.

	RUL	RML	RLL	LUL	LLL	Total
Mean	16.02	7.96	7.68	16.94	8.13	13
SD	17.32	12.92	12.85	18.86	11.83	13.05
Maximum	69.29	60.05	65.4	66.37	60.93	45.17
Minimum	0.06	0	0.02	0.01	0.05	0.08

Table 2. P values for statistical association between age, BMI, smoking index, biomass exposure, FEV_1 and percentage of emphysema, both lobar and total.

	RUL	RML	RLL	LUL	LLL	Total
Age	0.519	0.631	0.378	0.098	0.754	0.337
BMI	0.495	0.198	0.015	0.37	0.057	0.240
Smoking Index	0.512	0.398	0.344	0.239	0.208	0.222
Biomass exposure	0.024	0.079	0.016	0.086	0.404	0.036
FEV_1	0.496	0.366	0.203	0.897	0.873	0.589

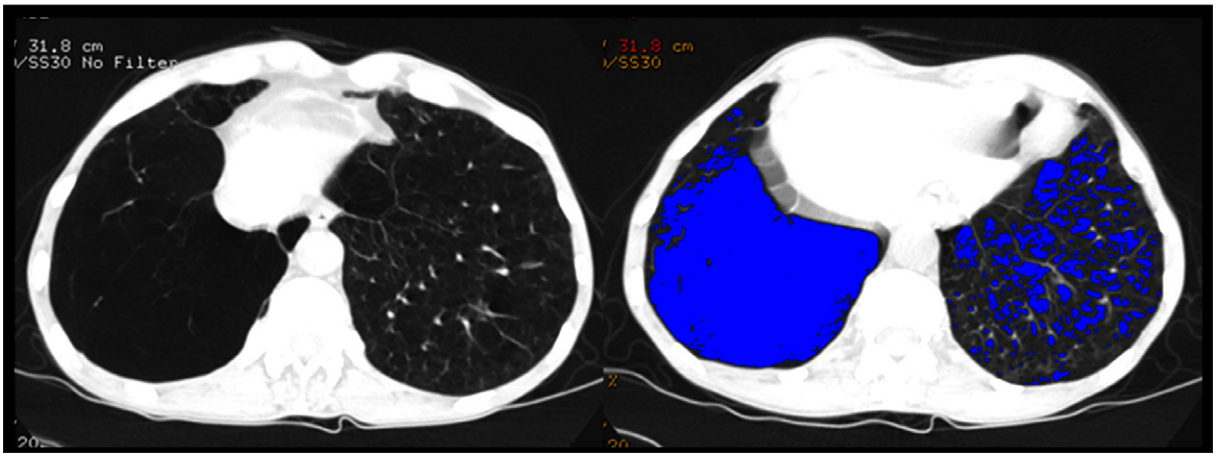

Figure 1. Large emphysematous regions in the right lower lobe on HRCT and post-processed color-coded HRCT images.

present in all 41 patients (100%). Smoking index was used as a measure of severity of smoking and also as a tool for stratifying patients into groups. Smoking index was defined as the number of cigarettes/bidis smoked per day multiplied by the duration of smoking. The mean smoking index was 568.65 (SD±355.12). There was a relatively homogenous distribution of emphysema in both lungs regardless of the severity of smoking. Exposure to smoke from biomass fuels was present in 9 patients (21.95%). Of those exposed, only 2 were males (4.8%), while the remaining 7 were females (17.07%). Minimum FEV_1 was 0.32, while the maximum FEV_1 was 1.47. The mean FEV_1 was 0.74 (SD±0.26).

The range, mean, and the standard deviations of the percentage of emphysema in each lung lobe are depicted in Table 1.

Statistical significance was sought for the relationship between each of the 5 parameters and percentage of emphysema distribution on quantitative HRCT. The P values for these associations are depicted in Table 2.

A statistically significant association was found between the percentage of emphysema in the right lower lobe and BMI (P value=0.015). There was an inverse correlation between BMI and the percentage of emphysema. A statistically significant association was found between biomass exposure and percentage of emphysema in the right upper lobe, right lower lobe, and the total percentage of emphysema in both lungs. P values for these associations were 0.024, 0.016, and 0.036, respectively. The amount of emphysema was disproportionately low compared to the degree of obstruction demonstrated by spirometry. This was suggestive of an airway predominant variety of COPD affecting the patients with significant biomass exposure.

No statistically significant association was found between age, sex, FEV_1, and the percentage of emphysema in any lobe of both lungs.

Below, we present HRCT findings of representative cases in the present study (Figures 1–4).

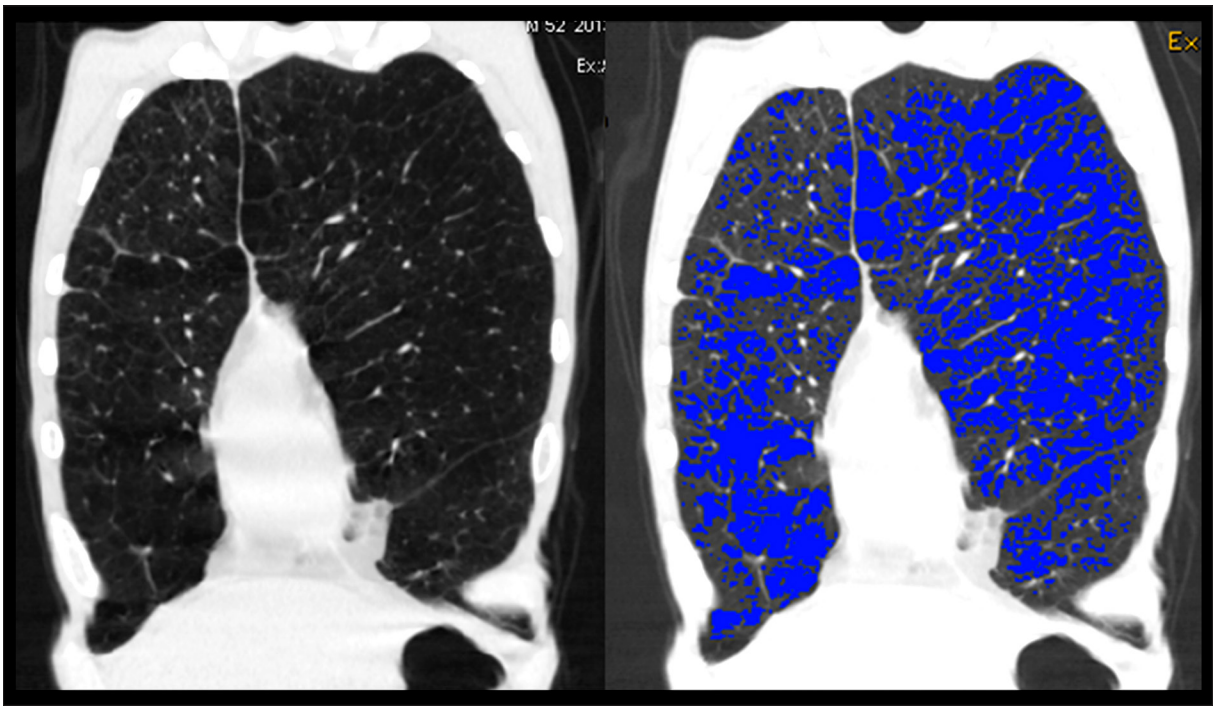

Figure 2. Comparative assessment of non-color-coded and color-coded HRCT images in severe COPD.

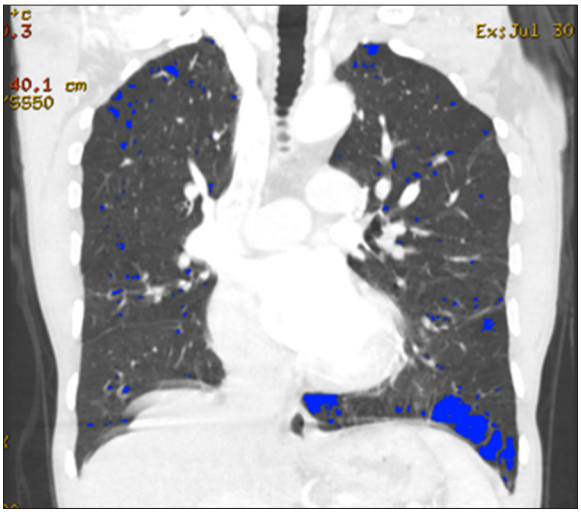

Figure 3. Scantily distributed areas of emphysema are shown in blue.

Discussion

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality worldwide. COPD is characterized by irreversible airflow obstruction. It is a complex disease affecting the airways (e.g. chronic bronchitis, airway collapse), the parenchyma (e.g. hyperinflation, air trapping, and emphysematous destruction) as well as the vasculature (e.g. hypoxic vasoconstriction, pulmonary arterial hypertension) with differing severity during the course of the disease.

Spirometry has been the workhorse for the diagnosis of COPD for decades. However, its inherent limitation of not being able to distinguish airway from parenchyma as the source of disease has led to the use of imaging modalities like CT in COPD. Advances in CT have enabled localizing, quantifying, prognosticating, and phenotyping COPD. Stratification of treatment of COPD into medical and surgical categories is also well accomplished by CT. This study was undertaken to identify the various risk factors and their association with CT-based assessment of emphysema extent. Correlation between spirometric and quantitative CT results was also tested for any detectable pattern. Subjective evaluation was done by color coding (blue) of the emphysematous regions and comparing it with non-color-coded lung window images. This was followed by generating tabulated quantitative estimates of emphysema in each lobe of both lungs. This quantitative data were used for statistical analysis in order to derive meaningful relationship between the distribution of emphysema and other parameters like age, sex, smoking, biomass exposure, PFTs, and BMI. These relationships are discussed further.

Range Name	Range values	Right Lung				Left Lung			Total Lung Volume
		Right Lung	Upper Lobe	Middle Lobe	Lowrer Lobe	Left Lung	Upper Lobe	Middle Lobe	Combined Lungs
–950 HU	[–1024/–950]	3.1865%	3.7348%	5.2485%	1.4865%	11.9009%	9.3548%	14.9098%	7.5335%/0.396 L
>–950 HU	[–950/3071]	96.8135%	96.2652%	94.7515%	98.5135%	88.0991%	90.6452%	85.0902%	92.4665%/4.8605 L
	Total	**2.6344 L**	**1.3394 L**	**0.39 L**	**0.905 L**	**2.6221 L**	**1.4202 L**	**1.2019 L**	**5.2565 L**

Figure 4. Computer generated quantitative CT report.

Age

The incidence of centrilobular and panacinar emphysema increases with age and is most frequently found in patients in the seventh decade of life. Consequently, there is a decrease in the incidence of centrilobular emphysema [3]. There was no significant association between the distribution or severity of emphysema and any particular age group in this study. The contemporary literature on COPD indicates an increasing age as a significant predictor of morbidity in COPD. The largest study on COPD to date, the COPDGene study, studied CT scans and spirometric results of 9,317 participants, and it helped in formulating a score called EMPHASIZE (EMPHysema, Age, Smoking, SIZE). This score incorporates age as one the factors in predicting the presence of clinically significant COPD and future morbidity [4]. The likely reason for the discordance between the present study and COPDGene study with regard to the association between age and severity of COPD may be the inclusion of airway wall measurements along with parenchymal changes in the latter, while our study included only parenchymal emphysematous changes.

Sex distribution

COPD predominantly affects males [5]. This is believed to be due to a relatively increased incidence of smoking in males rather than to any gender driven susceptibility. Jain et al. (2011) studied the impact of gender on the expression of COPD in the Indian population. They concluded that, in comparison to males, females were younger, had more dyspnea, more severe bronchial obstruction, more exacerbations, and a higher prevalence of systemic features. Tobacco smoke in the form of bidi smoking was the predominant smoke exposure in males, whereas smoke from biomass fuel burning was the predominant exposure in females. Males were more likely than females to have an emphysema-predominant phenotype, while airway-predominant disease was more common among females [6].

Our study also resonates with the majority of these findings. All female patients in this study had significant biomass exposure (for at least 20 years). Of the 9 patients with biomass exposure, 7 were females. The mean percentage of emphysema was small in all lobes in females (3.61%) than males (12.94%) despite equally severe obstruction on PFTs in both males and females. This indirectly points towards a large proportion of airway predominant abnormality in females when compared to males, which would require quantitative airway evaluation for confirmation. There was no gender predilection for emphysema in any specific lung lobe in both groups.

Smoking

Smoking is the commonest risk factor for COPD. Airway inflammation does not resolve in COPD patients even after smoking abstinence, and it can even increase in some aspects [7]. A recently suggested hypothesis is that COPD may have an autoimmune component which contributes to the airway inflammation even after smoking cessation [8]. These auto-antibodies may be directed against antigens present in tobacco or against endogenous auto-antigens that result from smoking-induced inflammatory and oxidative lung injury [9].

One recent study addressing this issue reported that 50% of smokers eventually develop COPD, as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. This finding is of major clinical significance in that it provides a scientific basis for the advice that can now be given to smokers that if they continue smoking lifelong, they have at least a one in two chances of developing COPD [10]. All 41 patients in our study had history of smoking. Quantification of smoking for grading the severity of exposure in the Indian population was done as early as 1988 by Jindal et al., wherein they formulated a smoking index to express cumulative smoking exposure. This is especially useful in defining the risk of a smoking-related disease. The parameter is similar to "Pack Year" but more suitable to Indian subjects [11].

It was widely believed that the main emphysema subtype among smokers, CLE (centrilobular emphysema), is primarily located in the upper lung zones. However, most of the references for this statement were based on subjective scoring of the extent of emphysema [12]. With the advent of quantitative CT, the studies based on objective and quantitative CT measurements indicate a homogeneous distribution or lower lobe distribution of emphysema in smokers [13]. In our study, there was no significant predilection for emphysema in any specific lobe in smokers, thereby suggesting a relatively homogenous distribution.

Pulmonary function tests

Although PFTs are both short- and long-term reproducible tests, they represent global measurements of obstruction of small airways in emphysema. Autopsy studies have shown that up to one third of lungs can be destroyed without changes in respiratory function [14]. Our study did not find any statistically significant association between FEV_1 and the percentage of emphysema in any specific lobe of both lungs. There are two possible reasons for this discordance. One is the relative insensitivity of PFTs towards low levels of lung parenchymal destruction, as discussed earlier. Secondly, this study did not include assessment of airways in quantitative CT evaluation, which could have been the predominant cause of severe obstruction on PFTs and relatively less severe on CT. In the COPDGene study, CT measures of air trapping correlated best with the FEV_1 and the FEV_1/FVC [4]. In 2014, Firdaus et al. found that FEV_1 and the FEV_1/FVC correlated best with airway wall thickness and emphysema, respectively [15].

Biomass exposure

Exposure to smoke from biomass fuels was present in 9 patients (21.95%) in our study. Of those exposed, only 2 were males (4.8%), while the remaining 7 were females (17.07%). There was a statistically significant correlation between biomass exposure and percentage of emphysema in the right upper and lower lobe. The reason for this localized association could not be determined.

Although information is scarce, over the past few years, a clear picture of the main characteristics of biomass smoke-associated COPD (BSCOPD) has emerged. This allows for comparison with many aspects of the better understood COPD caused by tobacco/cigarette smoking (TSCOPD), thus forming two clearly separate COPD phenotypes. Bronchial hyperreactivity, airflow obstruction, chronic bronchitis, and unusually low levels of emphysema are the predominant features of BSCOPD. Thus, BSCOPD is an airway predominant phenotype of COPD [16].

Body mass index

Body mass index is a universal measure of nutritional status of an individual. Hence, it has been used extensively in numerous studies to demonstrate any association between the nutritional status and the disease under consideration. COPD is no exception. There has been a resounding uniformity in the conclusions of multiple studies comparing BMI and emphysema. Quantity of emphysema is inversely proportional to BMI [17–19].

In our study, the mean BMI was 18.14 (SD±3.01) kg/m^2. The lowest BMI was 13.67 kg/m^2, while the highest BMI was 25.11 kg/m^2. There was a statistically significant association between BMI and the percentage of emphysema in the right lower lobe (p=0.015). However, the exclusive predilection for the right lower lobe could not be explained.

An accepted explanation of weight loss is excess energy expenditure due to the increased energy needed for breathing secondary to COPD. Atrophy of skeletal muscles is generally the main cause of weight loss in established COPD. COPD has recently been recognized as a systemic disease. Systemic inflammation may be a pathogenic factor that could explain the loss of weight in our subjects. The inflammation in the lungs due to cigarette smoking may induce emphysema and weight loss before the airflow limitation is measurable by spirometry [18].

Dose reduction strategies in COPD quantification – A standard dose CT-based emphysema quantification (150 mAs) was compared with a low-dose CT (25 mAs) protocol coupled with adaptive iterative dose reduction using 3D processing by Nishio et al. in 2012 [20]. They found greater consistency in quantification of emphysema by low-dose CT than standard-dose CT due to the use of adaptive iterative dose reduction using 3D processing in the former. This is definitely encouraging in addressing the issues of radiation risk associated with CT and needs a worthy look in future.

Quantitative CT in emphysema harbors the potential to understand the heterogeneity of the disease process based on risk factors and is being studied for its utility in categorizing disease phenotype and thus stratifying patients into better candidates for treatment options like novel pharmaceutical agents and surgery [21].

Conclusions

Quantitative HRCT is an emerging and powerful tool to quantify, prognosticate, and stratify patients into categories which acknowledge the exact severity and distribution of emphysema. Biomass exposure produces predominantly right-sided emphysema. BMI decreases in proportion to increasing levels of emphysema in the right lower lobe. Smoking remains the most common risk factor for emphysema and displays relatively homogenous emphysema distribution with no specific predilection for any particular lobe. These risk factors of emphysema patterns can be helpful in selecting proper management.

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