Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: April 30, 2024

Citation: Sangani, R., G., et al., 2024. Exploring Histologic Emphysema in a Rural Lobectomy Cohort: Insights and a Review. Medical Research Archives, [online] 12(4). https://doi.org/10.18103/mra.v12i4.5265

DOI: https://doi.org/10.18103/mra.v12i4.5265

ISSN: 2375-1924

REVIEW ARTICLE

Exploring Histologic Emphysema in a Rural Lobectomy Cohort: Insights and a Review

Rahul G. Sangani[1*], Vishal Deepak[1], Bhanusowmya Buragamadagu[1] and Andrew J. Ghio[2]

[1]Division of Pulmonary, Critical Care and Sleep Medicine, Dept. of Medicine, West Virginia University, Morgantown, WV
[2]US EPA, Chapel Hill, NC

[*]rgs4383@gmail.com

ABSTRACT

Exposure to cigarette smoking is extensive in rural Appalachia where one in four adults smokes. The clinical implications of this habit are evident among patients with some of the highest national rates for chronic obstructive pulmonary disease (COPD), lung cancer, and pulmonary fibrosis. Individuals undergoing surgical lung resection for suspicious lung nodules or masses at a major rural academic center in the area demonstrated an excessive burden of histologic emphysema (73.5%). This destructive process of the alveoli was linked to a significant burden of comorbid conditions, various radiologic patterns of interstitial lung diseases and interstitial lung abnormalities, histologic fibrosis, inflammatory processes (respiratory bronchitis, desquamative interstitial pneumonia, peribronchiolar metaplasia), anthracosis, and lung cancer. Physiologically, this combination of injuries imposed substantial limitations. Findings presented may enhance the understanding of concurrent changes occurring in the smoker. The complex inter-relationships and disparities between clinical COPD, radiologic and histologic emphysema are defined. While emphysema remains an irreversible pathology, associated inflammatory and fibrotic conditions are possibly amenable to earlier smoking cessation strategies and available disease-modifying therapies.

Keywords: Cigarette Smoking, Emphysema, Fibrosis, Histology, Radiology, Smoking Cessation.

Introduction

Emphysema, a histologic subtype of chronic obstructive pulmonary disease (COPD), is characterized by abnormal, permanent enlargement of air spaces distal to the terminal bronchioles with destruction of their walls[1]. Despite being defined by changes to lung parenchyma, invasive biopsy for diagnosis is almost never used. Instead, surrogates like documenting noxious exposure, spirometry-based airflow obstruction, and often CT chest imaging are employed. These diagnostic approaches may fail to catch asymptomatic patients with early emphysema, making characterization of early disease challenging.

Identifying a single risk factor for multiple chronic lung injuries, as with cigarette smoke-induced lung diseases, poses a challenge for clinicians. Despite being the primary risk factor, the prevalence of COPD, pulmonary fibrosis, and lung cancer vary significantly in smokers[2,3]. Shared mechanisms of injury starting with cigarette smoke-induced inflammation may lead to distinct phenotypic presentations in patients, influencing the clinical management approach for each chronic lung ailment. However, this approach becomes challenging when proven therapeutics show an inadequate response, raising suspicion of alternative diagnoses or simultaneous pathology remains elusive.

To unravel the paradox of parallel chronic lung injuries associated with cigarette smoking, we examined findings from a lung resection cohort presenting with pulmonary nodules/masses. We describe correlations between histologic emphysema with diverse clinical, physiologic, radiologic, and pathologic findings and conduct a comprehensive review of the available literature on the relationships between emphysema and other smoking-related injuries.

Materials and Methods

Study design: After obtaining the approval of the institutional review board, we retrospectively identified thoracic oncology clinic patients (n=381) who underwent lung resection for suspicious lung nodules/masses at WVUH between January 1, 2017 to December 31, 2020. Electronic medical records were reviewed to collect data regarding demographics, smoking and exposure profile, comorbidities, and pulmonary function tests (PFTs). Detailed methodologies, encompassing radiology and pathology case definitions, and inclusion/exclusion criteria were outlined elsewhere[4,5]. In this investigation, we explored clinical, physiologic, radiologic, and pathologic correlations of histologic emphysema.

Statistical analysis: Standard descriptive statistical measures were applied, including frequencies for categorical variables and means±standard deviations (SD) for continuous variables. Differences between the groups were assessed using Chi-square or Fisher exact test for categorical variables and Student's t-test for continuous variables. Two-tailed tests of significance were utilized, with a significance level set at $p<.05$.

Results and Discussion

In the study cohort, 73.5% (n=280) and 26.5% (n=101) demonstrated the presence and absence of histologic emphysema, respectively. Baseline characteristics including demographics, smoking habits, occupational exposures, comorbidities, and mortality data

were presented in Table 1. Radiological and pathological findings of the groups were described in Table 2. The clinical, radiologic, and histologic impact of smoking cessation was demonstrated in Table 3 with groups of current smokers (40.3%) and former smokers (47.5%). For ex-smokers, the median duration since smoking cessation was 9 years. Figure 1 presents various PFT measures between the groups with and without histologic emphysema. Lastly, Figure 2 provides the complex inter-relationship between different modalities of diagnosis consisting of histologic emphysema (73.49%), radiologic emphysema (84.25%) and clinical COPD (58.06%).

1. EMPHYSEMA AND CIGARETTE SMOKING

Cigarette smoking (CS) is the major recognized risk factor for emphysema. Mechanistic pathways are thought to possibly include reactive oxygen species and inflammatory oxidative stress-induced cell apoptosis[6]. Smoking rates in rural areas, including the Appalachian region, are notably higher than in urban areas, with a prevalence of 33% which is more than double the national average[7]. Our study revealed that patients with histologic emphysema were more likely to be current smokers (47.5% vs. 21.8%, p=<.001), with higher daily cigarette consumption (25.06±13.88 vs.13.89±12.64, p=0) and longer smoking duration (38.94±14.10 vs. 22.17±20.04, p=0), resulting in greater total pack years (51.47±33.84 vs. 23.42±26.20, p=0, Table 1). Consequently, the prevalence of COPD in rural areas, including Appalachia, is alarmingly high[8,9].

Historical autopsy studies have confirmed a dose-dependent relationship between smoking and emphysema[10]. In our rural cohort, we demonstrated a similar response between cigarette smoking and emphysema, including centrilobular and para-septal subtypes[4]. Both duration and intensity of smoking are strongly associated with development of emphysema however, duration of smoking has been implicated significantly more[11,12]. Our findings suggest that histological emphysematous changes may precede radiographic detection, beginning with early smoking exposure of more than 10 pack years[4].

2. EMPHYSEMA AND COMORBID CONDITIONS

Emphysema, as part of COPD often presents with other comorbidities. Various catabolic factors contribute to declining BMI and muscle mass[13]. The severity of emphysema inversely correlates with the body mass index (BMI) with lower BMI values being associated with progression and poorer prognosis[14-16]. In our rural Appalachian cohort, patients with histological emphysema exhibited significantly lower BMI compared to those without emphysema (27.71±6.84 kg/m^2 vs.30.20±6.87 kg/m^2, p=.001, Table 1). Despite lower BMI in emphysema patients in our rural population, it was higher than reported in previous studies, possibly influenced by higher obesity rates in rural Appalachia[16,17].

Emphysema patients often have multiple comorbidities due to shared risk factors. Common comorbidities in COPD patients include hypertension, obesity, hyperlipidemia, gastroesophageal reflux disease (GERD), and coronary artery disease (CAD)[18]. An increased burden of comorbidity has been associated with higher mortality, hospital readmission, and health expenditures[19-21]. In rural areas, the impact of comorbidities on emphysema patients is not well-studied, emphasizing the

need for further population-based research in these regions.

3. EMPHYSEMA AND MONOCYTE INTERACTION

Smoking one cigarette introduces 10-40 mg particulate matter, suspended in a gas, into the respiratory tract. With a mean particle size approximating 0.1 μm, the particles will deposit in the distal airways and the alveolar region[22]. Monocytes, myeloid-derived blood cells, play a crucial role in the human body's innate and adaptive immune systems[23]. These cells can contribute to early inflammatory responses by transforming into classical CD14++CD16- subtypes or expanding into non-classical $CD14^{DIM}CD16+$ subtypes. Alveolar macrophages (AM), as sentinel cells, initiate and resolve immune responses against microbes and inhaled particles. Cigarette smoke exposure has been found to dysregulate AM functions, influencing recruitment, phenotype, immune function, and homeostatic roles[24].

In response to injury, AM can express two polarized states: M1, a pro-inflammatory phenotype, or M2, an anti-inflammatory phenotype, depending on the local environment[24,25]. While resident lung macrophages were traditionally considered self-renewing[26-28], recent literature supports the extravasation of circulating monocytes into the lungs and their differentiation to macrophages in response to ongoing inflammation[29-31]. Following infection or inflammatory stimuli like cigarette smoke, the production of "non-classical" $CD14^{DIM}CD16+$ monocytes (5-8% of blood monocytes) substantially increases[32-34], allowing them to migrate into the lungs, initiate monocyte-to-macrophage programs, and undergo macrophage maturation/polarization[35-38].

Patients with severe COPD show a considerable elevation in circulating monocytes, particularly non-classical monocytes[39]. Elevated blood monocyte counts are correlated with comorbid conditions, including chronic respiratory disorders[40]. An increased monocyte count is reported as a marker for the risk of acute exacerbation of COPD.[41] In our rural lobectomy patient cohort, individuals with emphysema exhibited significantly higher absolute (0.69±0.20 vs. 0.61±0.22 $x10^2/\mu L$, $p<.001$) and percentage (9.18±2.32 vs.7.48±2.42, $p=0$) monocyte counts compared to those without emphysema (Table 1). We have previously demonstrated a positive linear correlation between percentage monocyte, cigarette pack years (CPY), and the accumulation of radiologic and histologic lung injuries, including emphysema[4]. A dose-dependent relationship between smoking and monocytosis has also been reported in a large observational cohort[42]. The observed dose-dependent link between CS, peripheral monocytosis, and the progressive concentration of emphysematous changes over time underscores the significant role of monocytes in the pathogenesis and progression of lung injuries. Additionally, in our rural cohort, a higher absolute monocyte count was associated with increased mortality[4], supporting previous associations between higher monocyte counts and poor prognosis in chronic lung diseases[43-47].

Table 1: Baseline characteristics of cohort

Variables % or mean±SD	Group with histologic emphysema (n=280, 73.5%)	Group without histologic emphysema (n=101, 26.5%)	p-value
Demographics			
Age, years	66.70±9.03	64.11±12.38	ns
Body mass index (BMI), kg/m^2	27.71±6.84	30.20±6.87	.001
Male	46.4	37.6	ns
Smoking behavior			
Never smoker	4.6	32.7	0
Current smoker	47.5	21.8	<.001
Ex-smoker	47.9	45.5	ns
Years since smoking cessation	10.21±12.62	14.45±16.48	ns
Cigarette smoked per day	25.06±13.88	13.89±12.64	0
Duration of smoking	38.94±14.10	22.17±20.04	0
Composite pack years	51.47±33.84	23.42±26.20	0
Exposures			
Coal	8.6	5.9	ns
Silica	3.9	3.0	ns
Asbestos	8.9	1.0	ns
Comorbidities			
COPD	66.4	38.6	<.001
Hypertension	68.6	70.3	ns
Hyperlipidemia	60.0	55.4	ns
Coronary artery disease	37.5	29.7	ns
GERD	41.1	39.6	ns
Peripheral arterial disease	14.6	5.9	.021
Non-lung cancer malignancy	10.0	13.9	ns
Hypoxemic respiratory failure	16.4	6.9	.018
Labs			
Absolute monocyte, x10^2/μL	0.69±0.20	0.61±0.22	<.001
Percentage monocyte	9.18±2.32	7.48±2.42	0
Mortality	23.2	15.8	ns

Abbreviations: COPD= chronic obstructive lung disease, GERD= gastro-esophageal reflux disease, ns= non-significant

4. EMPHYSEMA AND ITS PHYSIOLOGICAL EFFECTS:

Emphysema induces numerous changes in various indices of PFTs, yet it's crucial to recognize the low sensitivity of PFTs in diagnosing early-stage emphysema. Over one-fourth of patients may exhibit structural emphysema before a significant decline in

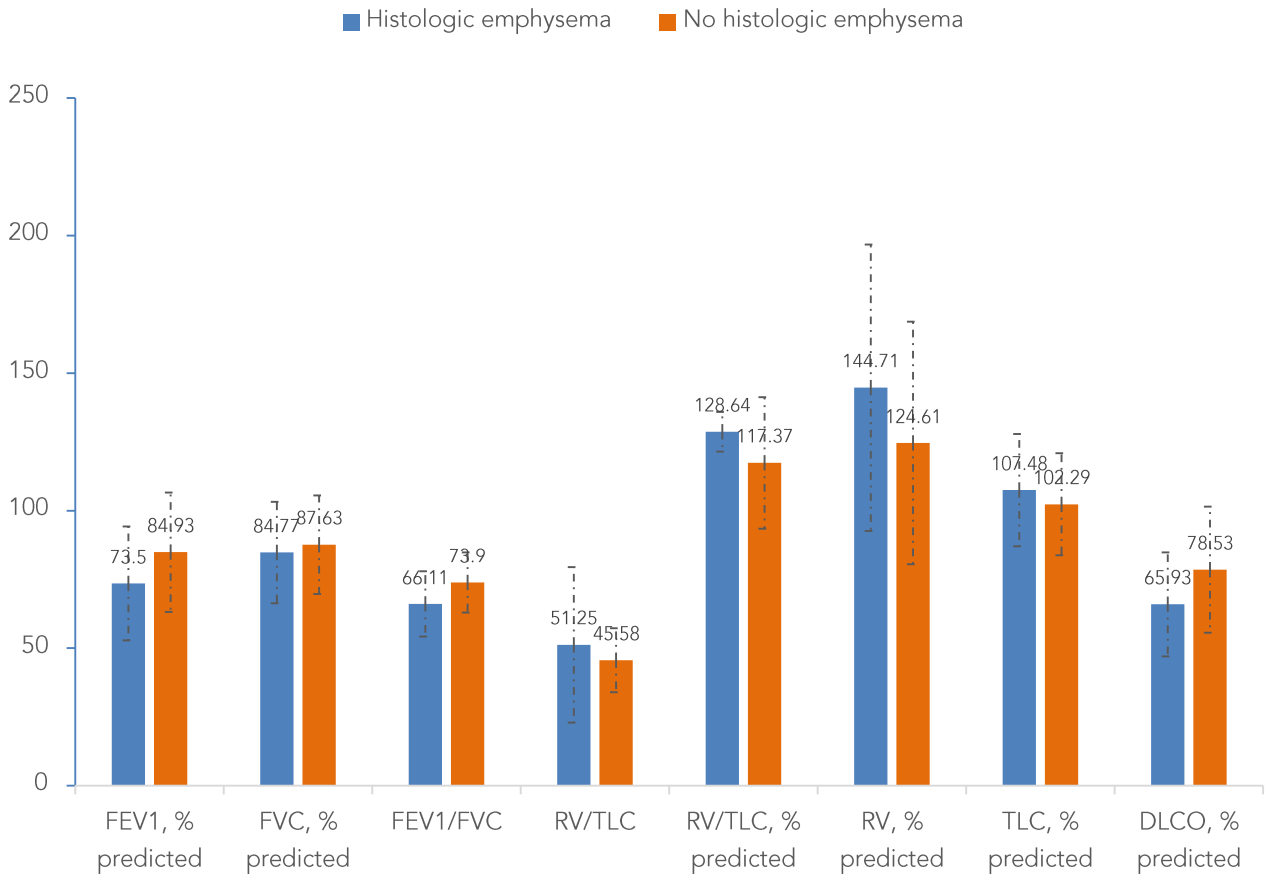
PFTs is evident[48]. As a result of its being a heterogeneous disease with varying severity in different lung regions, emphysema can lead to changes in regional function that are not effectively captured by PFTs[49].

The primary physiological feature in emphysema is expiratory flow limitation due to the destruction of alveoli and small airways. This can impact all three components of PFTs—spirometry, lung volumes, and diffusion capacity for carbon monoxide (DL_{CO}). The classic emphysema pattern includes airflow limitation (reduced forced expiratory volume in one second (FEV_1)/forced (vital capacity (FVC) ratio and reduced percentage predicted FEV_1), air trapping/hyperinflation (elevated residual volume (RV) and/or elevated total lung capacity (TLC), and diffusion impairment (reduced DL_{CO}). These PFT changes are known to occur in a sequential manner, the obstructive ventilatory limitation manifesting earlier, followed by hyperinflation and diffusion impairment[50,51].

a. Changes in Spirometry: Our rural lobectomy patients with histologic emphysema exhibited significantly greater airflow obstruction relative to those without histologic emphysema (ratio FEV_1/FVC: 66.11±11.84 vs. 73.90±10.92, p=0 and lower percentage predicted FEV_1: 73.50±20.71 vs. 84.93±21.70, p=<.001) (Figure 1). The current COPD definitions involve respiratory symptoms and fixed obstructive ventilatory impairment on forced spirometry, but these criteria may misdiagnose approximately 10% of patients with radiologic emphysema[52]. Phenotypic differentiation of COPD patients has provided improved management strategies in recent years[53,54]. While greater severity of radiologic emphysema correlated with spirometry limitation[52,55], but a simplistic predictive ability of respiratory symptoms in addition to a reduced ratio (FEV_1/FVC) has been demonstrated for the same endpoint[54].

b. Changes in Lung Volumes: Small airways injury in emphysema causing flow limitation during expiration leads to air trapping, often termed as hyperinflation of lungs. Multiple PFT indices, including RV, TLC, and RV/TLC ratio, can reflect hyperinflation[56] and abnormally increased values (% predicted RV: 144.71±52.05 vs. 124.61±44.12, p=.040, % predicted TLC: 107.48±20.43 vs. 102.29±18.57, p=.001, and % predicted RV/TLC: 128.64±27.23 vs.117.37±23.88, p=.001) were observed in our cohort in patients with histologic emphysema relative to those without histologic emphysema (Figure 1). An increased number and area of pores of Kohn in smokers' lung tissue are postulated to contribute towards larger residual volume[57]. A percentage predicted ratio RV/TLC >126% (by body plethysmography) has been proposed as a possible threshold value for hyperinflation[58]. Hyperinflation contributes to increased airway resistance, reduced lung elastic recoil and expiratory time, and symptoms of dyspnea and limited exercise tolerance[59,60]. Resting hyperinflation (i.e. an elevated RV/TLC ratio) in association with radiologic emphysema were demonstrated to predict the risk for the exacerbation and mortality in COPD patients[61].

Figure 1: Pulmonary function tests in groups with and without histologic emphysema



Significant difference (p<.05) between the groups existed for all measures except % predicted forced vital capacity.

c. Changes in Diffusion Capacity: DL_{CO}, a functional measure of alveolar-capillary gas exchange, predicts exercise capacity decline in emphysema patients[62]. In our rural cohort, percentage predicted DL_{CO} (65.93±18.94 vs.78.53±22.89, p=0) was significantly reduced in patients with histologic emphysema relative to those without histologic emphysema (Figure 1). Histologic studies evaluating emphysema have shown a significant association with both alveolar unit destruction and reduction in DL_{CO}.[57] The burden of radiologic emphysema, particularly the centrilobular subtype, was associated with an accelerated decline in DL_{CO}[63]. Clinically, these patients have worsening exercise capacity and increased mortality[62,63]. Lastly, diffusing capacity strongly predicted all-cause mortality in individuals with COPD, independent of radiographic emphysema[64,65].

5. EMPHYSEMA AND INTERSTITIAL LUNG ABNORMALITIES:

Interstitial Lung Abnormalities (ILAs) are viewed as precursor lesions that may evolve into early pulmonary fibrosis[66]. They are defined as incidental findings on CT chest scans in non-dependent lung regions affecting over 5% of any lung zone[67]. Notably, cigarette smoking is a recognized risk factor for ILAs[5,66,67]. ILAs are categorized based on distribution and the presence of fibrosis, including subpleural nonfibrotic or subpleural fibrotic. Radiographic features of ILAs can

encompass ground-glass opacities, reticular abnormalities, non-emphysematous cysts, lung distortion, traction bronchiectasis/ bronchiolectasis, and honeycombing[67].

Given their shared risk factor of cigarette smoking, it is reasonable to anticipate a coexistence of emphysema and ILAs and that they may predict each other's presence. In our study of rural patients undergoing lobectomy for suspicious nodules, ILAs were highly prevalent (35.2%), with subpleural reticulation (fibrotic ILA) being the most common finding. The study also demonstrated that diagnoses of COPD, radiographic emphysema, and histologic emphysema predicted the presence of ILA/ILD in our smoking cohort[5]. In a large population cohort, a significant association between ILAs and paraseptal emphysema was observed[68]. When comparing patients with or without histological emphysema, there was no difference in the prevalence of any ILA patterns (44.6% vs. 41.6%, p=.595) (Table 2). However, mixed centrilobular ground glass opacities (CL-GGO) and subpleural reticulation (20.0% vs. 8.9%, p=.013) and isolated traction bronchiectasis/bronchiolectasis (26.8% vs. 16.8%, p=.045) demonstrated significantly higher prevalence in patients with histologic emphysema (Table 2).

Studies evaluating the association between subclinical ILAs and radiologic emphysema have yielded discordant results. An earlier study by Washko et al. demonstrated an inverse relationship with emphysema, with a prevalence of 8% in the COPD gene cohort[69]. However, they excluded regions with radiographic emphysematous changes, which may include have included smoking-related interstitial fibrosis. These investigations lacked histologic confirmation for ILAs, and a large proportion of patients met criteria for "indeterminate" ILA[70,71]. Recent studies have suggested that ILAs can have a higher prevalence in patients with COPD/ emphysema than the general population (up to 40.5%)[72-74]. Moreover, we previously established an association of mixed CL-GGO and subpleural reticular ILA pattern with histologic evidence of fibrosis[5]. Patients undergoing lobectomy for lung cancer reported a higher prevalence of radiographic interstitial changes and showed a correlation with the histologic pattern of smoking-related interstitial fibrosis (SRIF) with emphysema[75].

The co-occurrence of ILAs in emphysema can have several important clinical implications. These patients were likely to experience excessive respiratory symptoms and limited exercise capacity (reduced 6-minute walk distance; 6MWD)[73]. Among COPD patients, the coexistence of ILAs has been linked with enhanced disease severity and hospital admissions with frequent exacerbations[72,76]. ILAs can modify PFT changes, with studies reporting a differential impact on spirometry and lung volumes, likely reflecting the pseudo-normalization of PFTs from opposing effects of obstructive (emphysema) and restrictive ventilatory impairments (ILAs, associated fibrosis) which warrants further exploration[73,77]. An accelerated decline in diffusion capacity has been increasingly observed among patients with co-existing emphysema and ILAs[5,73,76], suggesting the potential utility of reduced DL_{CO} as an additional early diagnostic endpoint.

6. EMPHYSEMA AND FIBROSIS:

Rather than simply resulting from a destructive process, emphysematous lung

tissue is characterized by active remodeling involving extracellular matrix synthesis, apoptosis, and alveolar cell proliferation[78]. Coexisting interstitial fibrosis is frequently observed in emphysema patients given the robust relationships with risk factors of cigarette smoking and older age for both conditions[79,80]. Recognition of their overlapping clinical, physiological, and radiological features has led to the identification of a distinct syndrome known as combined pulmonary fibrosis emphysema (CPFE)[81]. Additionally, patients with connective tissue diseases often exhibit coexisting fibrotic interstitial lung disease (ILD) and emphysema, suggesting a complex susceptibility of fibrotic patients to develop emphysema[82]. Despite longstanding awareness of the co-occurrence of these distinct pathophysiologic processes[83,84], a lack of clear definitions and a spectrum of morphologic and radiologic variants has hindered understanding. Recent efforts now allow a general definition of the CPFE syndrome[85].

Our heavily smoking rural cohort demonstrated a significant presence of radiologic ILDs (22.9% vs. 6.9%, p=<.001) and histologic fibrosis (27.5% vs. 15.8%, p=.019) and honeycombing (3.9% vs. 0, p=.042) in patients with histologic emphysema. The most common incidental radiologic ILD patterns reported were CPFE and respiratory bronchiolitis (RB)-ILD. In addition, the presence of fibrosis twice more likely to predict emphysema in resected lung specimens[5].

Initial diagnostic criteria for CPFE focused on clinical, physiological, and HRCT patterns[81]. However, a more recent statement supports heterogeneous smoking-related patterns of histologic fibrosis (most commonly usual interstitial pneumonia (UIP), RB, SRIF, Langerhans cell histiocytosis (LCH), and desquamative interstitial pneumonia (DIP) coexisting with emphysema[85]. Despite the classic definition of histologic emphysema definition mentioning permanent enlargement of distal airspaces with the destruction of walls and a lack of obvious gross fibrosis[86], it is evident that some degree of fibrosis accompanies emphysema at the tissue level[87]. To address this concept, classifying fibrotic changes with emphysema based on their clinical importance was suggested. Such fibrosis could include diffuse fibrotic changes (such as UIP and nonspecific interstitial pneumonia (NSIP), which may have significant clinical and functional consequences) vs. localized, clinically occult fibrotic changes (such as RB, RB-ILD, RB-ILD with fibrosis, airspace enlargement with fibrosis (AEF), and SRIF)[88]. Interestingly, they advise against reporting localized fibrosis seen incidentally on lung specimens. Conversely, clinically meaningful outcomes were associated with this form of localized fibrosis in smokers' lungs, prompting the need for further explorative studies[89-91]. Additionally, emphysema was observed to occur in lung zones other than the apices and often admixed with fibrosis or sometimes replaced by thick-walled cysts[92]. The presence of thick-walled large cysts may represent a unique radiologic and histologic finding of CPFE[75,93]. These cysts (>2.5 cm in diameter) tend to locate near the respiratory bronchiole with extension into one or more acini and have dense fibrous walls. The thick-walled cysts variant of CPFE was observed to have a greater extent of emphysema[93], and it is proposed that the cysts result from tractional dilatation of alveoli

(i.e., traction emphysema) within areas of fibrosis[85].

Along with sharing an excessive burden of chronic comorbidities of COPD, CPFE predominantly affects elderly heavy smoking males[85,94]. CPFE patients were noted to have severe dyspnea on exertion, greater supplemental oxygen requirements, higher physician-led diagnosis of COPD, and half of the patients being prescribed inhaled bronchodilator therapy[95,96]. The traditional impact of CPFE on PFTs was known for its relative preservation of spirometry, lung volumes, and an isolated out-of-proportion decline in diffusion capacity[85]. Patients with CPFE confirmed greater impairment of diffusion capacity compared to groups with idiopathic pulmonary fibrosis (IPF) and emphysema alone[93]. A reduced percentage predicted DL_{CO} at the time of diagnosis was a significant predictor of CPFE in a rural Appalachian heavy smoking cohort[94]. Tobacco smoking in ILD was associated with the CPFE phenotype, with quicker lung function decline compared to non-smoking ILD patients[97]. Recent meta-analyses showed that CPFE patients were seven-fold more likely to develop lung cancer compared to those without CPFE, with squamous cell cancer being the most common subtype[98]. Similarly, compared to IPF without emphysema, CPFE was twice more likely to develop lung cancer[99]. Moreover, these patients experienced increased post-operative complications, including respiratory failure, prolonged mechanical ventilation, and the need for home oxygen[100]. Post-transplant complications, such as primary graft dysfunction, acute cellular rejection, and chronic lung allograft dysfunction, were more prevalent in CPFE compared to IPF transplant recipients[101]. Given the notable vascular remodeling in lung tissues affected by both emphysema and fibrosis, 15-55% of CPFE patients reported having pulmonary hypertension (PH)[85,102]. A recent meta-analysis demonstrated a three-fold increased incidence of PH in CPFE compared to patients with emphysema alone[103]. The median survival for CPFE was reported between 2.1 and 8.5 years, with a 5-year survival ranging from 38-55%[95]. CPFE likely predicts worse survival due to the presence of greater extents of fibrosis and emphysema; however, these estimates on mortality varied due to the heterogeneous population studied and inconsistent follow-up time[85,94].

7. EMPHYSEMA AND HISTOLOGIC CHANGES OTHER THAN FIBROSIS:

Accompanying histological findings seen in lung tissue of emphysema patients relative to those without histologic emphysema from our cohort included 1) anthracosis (69.3% vs. 40.6%, $p<.001$), 2) RB (17.5% vs. 4.0%, $p<.001$), 3) DIP (8.2% vs. 1.0%, $p<.001$), and 4) peribronchiolar metaplasia (12.5% vs. 0, $p=0$) (Table 2).

Table 2: Radiological and histological findings of the cohort

Variables % or mean±SD	Group with histologic emphysema (n=280, 73.5%)	Group without histologic emphysema (n=101, 26.5%)	p-value
Radiology findings, %			
Any ILD patterns	22.9	6.9	<.001
Any ILA	44.6	41.6	ns
a. CL-GGO	12.5	11.9	ns
b. SPR	14.3	20.8	ns
c. mixed a+b	20.0	8.9	.013
d. non-emphysematous cysts	7.1	4.9	ns
Isolated traction bronchiectsis/bronchieolectsis	26.8	16.8	.045
Isolated honeycombing	2.5	2.0	ns
Histology findings, %			
Fibrosis	27.5	15.8	.019
Honeycomb changes	3.9	0	.042
Anthracosis	69.3	40.6	<.001
RB	17.5	4.0	<.001
DIP	8.2	1	<.001
PBM	12.5	0	0
Lung cancer	88.6	79.2	.019

Abbreviations: CL-GGO= centrilobular ground glass opacities, DIP= desquamative interstitial pneumonia, ILA= interstitial lung abnormalities, ILD= interstitial lung disease, ns= non-significant, PBM= peribronchiolar metaplasia, RB= respiratory bronchiolitis, SPR= subpleural reticulation.

a. Emphysema and Anthracosis:

Lung injury after smoking can correlated with exposure to particle[104]. Smoking one cigarette exposes the human respiratory tract to a remarkable mass of particle (15,000-40,000 µg). The lungs of cigarette smokers reveal enormous numbers of both intracellular (most frequently being in macrophages) and extracellular particle. Cells become anthracotic with a heavy burden of carbonaceous material described to be brown or black in color. Focal emphysema is an early lesion involving the branches of the terminal bronchiole. This focal emphysema is associated with the observation of anthracosis[105,106]. Centrilobular emphysema following smoking originates in areas of "parenchymal soot deposits", immediately adjacent to retained particle, and severity is dependent on the total quantity of particle[104,107]. In these emphysematous foci, there is a close relationship with particles suggesting a possible participation in the destructive process leading to injury.

b. Emphysema and RB:

The greatest deposition of cigarette smoke particle (CSP, mean diameter of about 0.2-0.5 μm) occurs in the 16th to 19th generations of airways[108]. Accordingly, RB occurs in a large number of smokers[109]. This inflammatory response is characterized histologically by an accumulation of brownish- to blackish-pigmented macrophages (i.e. smokers' macrophages) in the respiratory bronchioles (i.e. that region with the greatest CSP deposition) and a chronic interstitial inflammatory infiltrate in the bronchiole[110]. This is either synonymous with or can progress to include interstitial fibrosis and hyperplasia of the overlying alveolar epithelial cells. These morphologic findings are frequently employed in the description of RB-ILD. Both emphysema and RBILD are almost exclusively associated with smoking. Subsequently, foci of emphysema are commonly observed in patients with RB and RB-ILD[111,112].

c. Emphysema and DIP:

Continued exposure to cigarette smoke can lead to greater particle deposition in the alveolar region, triggering an inflammatory response consistent with DIP. This is characterized by numerous pigmented macrophages within the distal airspaces of the lung[113]. The majority of patients with this lung injury are smokers[114]. While the feature that differentiates RB from DIP is the distribution and extent of macrophage accumulation (that is bronchiolocentric in the former and more diffuse in the later), there are no reliable histologic features to distinguish the two inflammatory responses with certainty and they can be considered different phases of a single response[115]. Emphysema has been demonstrated in patients with DIP[116], likely reflecting the shared pathways of pathogenesis following smoke exposure.

d. Emphysema and Peribronchiolar Metaplasia:

Cigarette smoke-induced lung injury also includes peribronchiolar metaplasia, seen as a simple columnar and cuboidal bronchiole epithelium in adjacent alveolar walls. This phenomenon is associated with other smoking-related lung diseases (RB and DIP)[117]. Peribronchiolar metaplasia on pathologic examination of lung tissue is also increased in patients with either radiographic or histologic evidence of emphysema[117]. The response to inflammatory injury after smoking includes a diffuse epithelial metaplasia, a prominent feature of bronchopulmonary metaplasia[118]. These cells can exhibit surfactant and mucin production reflecting a primitive epithelial phenotype, a consequence of exposure to cigarette smoke with repair[118,119]. The co-existence of emphysema and peribronchiolar metaplasia supports further examination of this relationship in an attempt to understand the chronology of events.

8. EMPHYSEMA AND LUNG CANCER:

Lung cancer stands as a leading cause of cancer-related mortality and morbidity[120]. Emphysema frequently emerges incidentally during CT chest assessments for lung cancer screening, coronary disease risk stratification, or trauma. Both visual and quantitative CT evaluations of radiologic emphysema reveal an elevated risk of developing lung cancer, correlating with regional emphysema severity[121-123]. Notably, the centrilobular emphysema subtype exhibits a significant association with lung cancer[122]. Among patients with emphysema, many progress to COPD, and a reported <10% decrease in FEV_1 reflects a three-fold increase in lung cancer

risk, particularly in women[124]. Concurrent risk factors, such as smoking, inhalational toxin exposure, and reduced alpha-1 antitrypsin levels, further elevate the likelihood of developing lung cancer in these individuals[120,122,125].

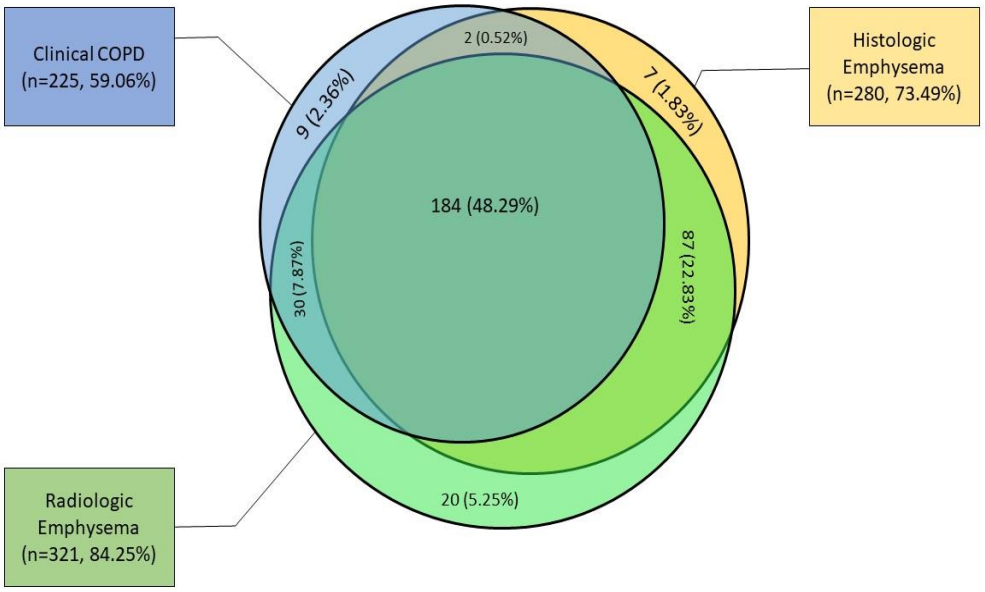
Emphysema's presence in lung cancer significantly influences long-term survival. A substantial cohort study by Oelsner et al. revealed an increased incidence of mortality due to respiratory disease and lung cancer among patients with radiologic emphysema[126]. The degree of airflow obstruction and the severity of emphysema play pivotal roles in determining the surgical treatment approach (lobectomy, segmentectomy) for lung cancer patients. Furthermore, emphysema is associated with a higher risk of postoperative complications and recurrence[127,128].

Cigarette-smoke-induced chronic inflammation, airway epithelial hyperplasia, and apoptosis are argued to represent simultaneous lung injury and aberrant repair, akin to two sides of a coin[129]. Alterations in the tumor microenvironment, including matrix metalloproteinase (MMP), are observed in non-small cell lung tumors arising from emphysematous lungs, suggesting a potential biological link to the clinicopathological aggressiveness of these cancers.[130,131] The upregulation of Transforming Growth Factor (TGF)-β known to regulate essential cellular processes for lung homeostasis, has been associated with major pulmonary diseases, including emphysema, pulmonary fibrosis, and lung cancer[132].

9. HISTOLOGIC EMPHYSEMA, RADIOLOGIC EMPHYSEMA, AND CLINICAL COPD:

Understanding the intricate relationship among histologic emphysema, radiographic emphysema, and their manifestation as clinical COPD is complex. While one might assume these entities commonly coexist, they also have the potential to exist independently. In our rural cohort (Figure 2), clinical COPD was identified in 58.06% (n=225) of patients, while a higher number exhibited radiographic emphysema (84.25%, n=321) and histologic emphysema (73.49%, n=280). Collectively, 48.29% (n=184) of patients presented with all three entities. Individually, 2.36% (n=9) had only clinical COPD, 5.25% (n=20) had only radiographic emphysema, and 1.83% (n=7) had only histologic emphysema. Radiologic emphysema demonstrated a stronger positive correlation with histologic emphysema compared to clinical COPD diagnosis (r^2=0.58, p<.0001 vs. r^2=0.36, p<.0001). HRCT imaging has proven sensitive for detecting low-attenuation areas corresponding to histologic emphysema. Similarly, large cohort studies indicate that radiologic emphysema proportionately increases with GOLD class severity[133,134]. Furthermore, the greater severity of radiographic emphysema is associated with higher mortality[135].

Figure 2: Relationship between histologic emphysema, radiologic emphysema, and clinical COPD



The cohort distribution is illustrated across three domains: histologic emphysema, radiologic emphysema, and clinical COPD. Radiologic emphysema (84.2%) is the most prevalent, followed by histologic emphysema (73.5%) and clinical COPD (59.1%). About half of the cohort exhibits abnormalities in all three domains, with 22.8% having both radiologic and histologic emphysema, and 7.9% showing overlapping radiologic emphysema and clinical COPD. This highlights the relationships between these domains, emphasizing that radiologic emphysema is the most sensitive method for detecting lung parenchymal changes, correlating more with histologic changes than clinical COPD diagnosis.

Diagnosing clinical COPD involves respiratory symptoms and evidence of airway obstruction on spirometry[136]. However, the correlation between spirometry and radiographic emphysema is generally weak[137]. In a COPDGene study, 26% of patients exhibited significant radiographic emphysema or signs of air-trapping without spirometric abnormalities[138]. Emphysema on radiography may not correlate with airflow limitation, but there is a correlation between the severity of lung abnormalities and spirometry parameters without reaching COPD diagnosis cutoffs[139]. Similarly, 30% of smokers with normal spirometry showed some degree of emphysema on HRCT[134]. Clinical COPD is highly heterogeneous, lacking reliable correlation of airflow limitation measures with symptoms, exercise capacity, and disease course. These findings underscore the importance of ongoing emphasis on smoking cessation rather than relying solely on normal spirometry for reassurance[133]. Conversely, COPD can manifest as an airway-predominant phenotype, i.e., chronic bronchitis, without significant radiographic emphysema[54]. Distinguishing between these phenotypes is crucial, as management strategies differ. Patients with airway disease without emphysema tend to be more responsive to inhaled corticosteroids and bronchodilators, while those with predominant emphysema may be candidates for surgical or procedural interventions to reduce lung volumes[54,140].

Similar to radiographic emphysema, histopathologic emphysema can correlate poorly with lung function parameters[141]. As

illustrated, histopathologic emphysematous changes can occur without evidence of clinical COPD or radiographic emphysema. This poor correlation likely arises from emphysema's heterogeneity, with pulmonary function and CT scans evaluating the organ as a whole, while histologic evaluation involves a portion of the lung. In our cohort, surgical lung resection included both upper and lower lobes, and emphysema known to occur predominantly in upper lobes. This offers a plausible explanation for these discrepant findings. We observed histologic emphysema as early as 10 pack-years, challenging the traditional 20-pack-year cutoff for detecting clinical COPD syndrome.

10. EMPHYSEMA AND SMOKING CESSATION: The cessation of smoking significantly impacts the course of COPD, demonstrating well-established benefits over decades, such as relieving respiratory symptoms, enhancing lung function, improving the efficacy of standard therapeutics, reducing exacerbation rates, and decreasing mortality, and comorbid conditions[142]. While limited histologic changes have been evaluated post-smoking cessation, earlier studies indicated reversibility in goblet cell hyperplasia. However, fibrosis in distal airways, pigment deposition, and end-stage alveolar destruction, such as emphysema, demonstrate some persistence[143,144].

In our lobectomy cohort, former smokers exhibited significantly reduced rates of histologic emphysema (86.2% vs. 74.9%, p=.010), RB (22.4% vs. 9.5%, p=.001), and DIP (11.8% vs. 2.8%, p=.001), but not for fibrosis (25.0% vs. 27.4%) or anthracitic pigment deposition (65.1% vs. 65.4%) (Table 3). Current smoking prevalence was higher in emphysema patients according to 2017 National Health Interview Survey data. We previously demonstrated that current smoking status independently predicts histologic RB and emphysema.[4] Evidence of microscopic emphysema and anthracosis began with as little as ten-pack years of smoking, with continued smoking promoting its accumulation over time as the predominant histologic abnormality. RB and DIP are considered part of a spectrum of smoking-related inflammatory lung parenchymal changes, with smoking cessation viewed as the cornerstone of treatment[109].

Alternatively, with the widespread use of CT chest scans, several studies confirm the persistence of radiologic emphysema even after smoking cessation, with ongoing progression in current smokers[134,145-147]. Current smokers in our study exhibited excessive rates of radiologic emphysema (97.4% vs. 91.6%, p=.025), including the centrilobular subtype (90.1% vs. 81.0%, p=.019) (Table 3). Rates of radiologic ILD patterns did not differ based on current smoking status (25.0% vs. 18.4%, p=.147, Table 3). Recent quantitative volumetric CT scans indicated a time-dependent reduction in lung density post-smoking cessation, corresponding to a reversal of smoke-induced inflammatory sequelae within the first two years[148,149]. Ex-smokers from our cohort did not show a significant difference in spirometry compared to current smokers, suggesting airflow limitation stabilization during smoke-free periods (median duration of 9 years for ex-smokers in our cohort) (Table 3). However, measures of air trapping, hyperinflation, and diffusion impairment remained worse in current smokers (Table 3). Decreased

diffusion capacity was associated with a more rapid progression of emphysema in heavy smokers[150]. Precise mechanisms for persistent lung inflammation post-smoking cessation are not well-known, which may include influences of innate immunity and differential, site-specific DNA methylation[143,151-153].

Table 3: Effects of smoking cessation in the cohort

Variables (% or mean±SD)	Current smokers (40.3%)	Former smokers (47.5%)	p-value
Age, years	63.30±8.90	68.68±9.28	0
Body mass index (BMI), kg/m^2	26.79±6.49	28.76±6.24	.005
Smoking behavior:			
Years since smoking cessation	-	13.08±13.64	-
Cigarettes smoked per day	25.33±11.49	25.14±13.66	ns
Duration of smoking	43.22±10.58	36.13±13.37	0
Composite pack years	55.60±31.87	46.01±31.82	.006
PFT findings			
FEV_1, % predicted	72.35±20.02	75.06±21.11	ns
FVC, % predicted	84.49±18.43	84.40±17.05	ns
FEV_1/FVC	66.34±10.75	66.95±12.78	ns
RV, % predicted	151.16±55.33	136.99±47.54	.022
TLC, % predicted	109.94±20.73	104.29±19.43	.019
RV/TLC, % predicted	132.04±29.18	125.28±23.82	.040
DL_{CO}, % predicted	62.50±15.38	68.66±20.03	.002
Radiology findings			
Any emphysema	97.4	91.6	.025
Centrilobular subtype	90.1	81.0	.019
Paraseptal subtype	39.5	35.7	ns
Any ILD patterns	25.0	18.4	ns
Histology findings			
Emphysema	86.2	74.9	.010
Fibrosis	25.0	27.4	ns
Anthracosis	65.1	65.4	ns
RB	22.4	9.5	.001
DIP	11.8	2.8	.001
PBM	9.2	11.7	ns
Lung cancer	89.5	88.3	ns
Mortality	19.7	26.8	ns

Abbreviations: DLco= diffusion capacity for carbon monoxide, DIP= desquamative interstitial pneumonia, FEV_1= forced expiratory value in one second, FVC= forced vital capacity, ILD= interstitial lung disease, ns= non-significant, PBM= peribronchiolar metaplasia, RB= respiratory bronchiolitis, RV= residual volume, TLC= total lung capacity.

Conclusion:

Distinct heavy smoking habits of this rural Appalachian cohort resulted in excessive rates of emphysema. Subsequently, histologic emphysema showed significant correlations with clinical comorbidities, radiological and histological fibrosis, lung cancer and physiological limitations. Remarkable disparity was observed while employing the diagnostic criteria for histologic emphysema, radiologic emphysema, and clinical COPD, highlighting their complex inter-relationship. Former smokers showed lower rates of cigarette smoke-related inflammatory changes confirming the role of smoking cessation. Continued smoking contributed towards greater emphysematous damage. Fibrosis, anthracosis and related physiologic limitations (hyperinflation and diffusion impairment) persisted despite smoking cessation.

Conflict of Interest:

The authors declare they have no financial or non-financial competing interests.

Funding:

None

Acknowledgements:

None

Declarations:

The study protocol was approved by the institutional review board of West Virginia University (ID 2010131995). The written informed consent was waived by the IRB considering its qualification for exempt research category with minimal to no risk posed to subjects. The data related to study was collected confidentially to maintain HIPAA compliance. All ethical standards were adhered in accordance with the Declaration of Helsinki.

Consent for publication:

Not applicable.

Authors' contributions:

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. RGS takes the primary responsibility of accuracy of data presented.

Abbreviations:

FEV_1: forced expiratory volume in one second
FVC: forced vital capacity
RV: residual volume
TLC: total lung capacity
DL_{CO}: diffusion capacity for carbon monoxide

References:

1. Thurlbeck WM, Muller NL. Emphysema: definition, imaging, and quantification. *AJR Am J Roentgenol*. Nov 1994;163(5):1017-25. doi:10.2214/ajr.163.5.7976869

2. Beghe B, Cerri S, Fabbri LM, Marchioni A. COPD, Pulmonary Fibrosis and ILAs in Aging Smokers: The Paradox of Striking Different Responses to the Major Risk Factors. *Int J Mol Sci*. Aug 27 2021;22(17)doi:10.3390/ijms22179292

3. Ridge CA, McErlean AM, Ginsberg MS. Epidemiology of lung cancer. *Semin Intervent Radiol*. Jun 2013;30(2):93-8. doi:10.1055/s-0033-1342949

4. Sangani RG, Deepak V, Anwar J, Patel Z, Ghio AJ. Cigarette Smoking, and Blood Monocyte Count Correlate with Chronic Lung Injuries and Mortality. *Int J Chron Obstruct Pulmon Dis*. 2023;18:431-446. doi:10.2147/COPD.S397667

5. Sangani RG, Deepak V, Ghio AJ, et al. Interstitial lung abnormalities and interstitial lung diseases associated with cigarette smoking in a rural cohort undergoing surgical resection. *BMC Pulm Med*. Apr 29 2022;22(1):172. doi:10.1186/s12890-022-01961-9

6. Vij N, Chandramani-Shivalingappa P, Van Westphal C, Hole R, Bodas M. Cigarette smoke-induced autophagy impairment accelerates lung aging, COPD-emphysema exacerbations and pathogenesis. *Am J Physiol Cell Physiol*. Jan 1 2018;314(1):C73-C87. doi:10.1152/ajpcell.00110.2016

7. Tobacco Use in West Virginia (2022).

8. Cardarelli K, Westneat S, Dunfee M, May B, Schoenberg N, Browning S. Persistent disparities in smoking among rural Appalachians: evidence from the Mountain Air Project. *BMC Public Health*. Feb 2 2021;21(1):270. doi:10.1186/s12889-021-10334-6

9. Croft JB, Wheaton AG, Liu Y, et al. Urban-Rural County and State Differences in Chronic Obstructive Pulmonary Disease - United States, 2015. *MMWR Morb Mortal Wkly Rep*. Feb 23 2018;67(7):205-211. doi:10.15585/mmwr.mm6707a1

10. Auerbach O, Hammond EC, Garfinkel L, Benante C. Relation of smoking and age to emphysema. Whole-lung section study. *N Engl J Med*. Apr 20 1972;286(16):853-7. doi:10.1056/NEJM197204202861601

11. Bhatt SP, Kim YI, Harrington KF, et al. Smoking duration alone provides stronger risk estimates of chronic obstructive pulmonary disease than pack-years. *Thorax*. May 2018;73(5):414-421. doi:10.1136/thoraxjnl-2017-210722

12. Pleasants RA, Rivera MP, Tilley SL, Bhatt SP. Both Duration and Pack-Years of Tobacco Smoking Should Be Used for Clinical Practice and Research. *Ann Am Thorac Soc*. Jul 2020;17(7):804-806. doi:10.1513/AnnalsATS.202002-133VP

13. Jagoe RT, Engelen MP. Muscle wasting and changes in muscle protein metabolism in chronic obstructive pulmonary disease. *Eur Respir J Suppl*. Nov 2003;46:52s-63s. doi:10.1183/09031936.03.00004608

14. Casanova C, de Torres JP, Aguirre-Jaime A, et al. The progression of chronic obstructive pulmonary disease is heterogeneous: the experience of the BODE cohort. *Am J Respir Crit Care Med*. Nov 1 2011;184(9):1015-21. doi:10.1164/rccm.201105-0831OC

15. Celli BR, Locantore N, Tal-Singer R, et al. Emphysema and extrapulmonary tissue loss in COPD: a multi-organ loss of tissue

phenotype. *Eur Respir J*. Feb 2018;51(2)doi:10.1183/13993003.02146-2017

16. Shaikh M, Sood RG, Sarkar M, Thakur V. 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. *Pol J Radiol*. 2017;82:760-766. doi:10.12659/PJR.903278

17. Health Disparities in Appalachia (2017).

18. Chatila WM, Thomashow BM, Minai OA, Criner GJ, Make BJ. Comorbidities in chronic obstructive pulmonary disease. *Proc Am Thorac Soc*. May 1 2008;5(4):549-55. doi:10.1513/pats.200709-148ET

19. Almagro P, Cabrera FJ, Diez J, et al. Comorbidities and short-term prognosis in patients hospitalized for acute exacerbation of COPD: the EPOC en Servicios de medicina interna (ESMI) study. *Chest*. Nov 2012;142(5):1126-1133. doi:10.1378/chest.11-2413

20. Baty F, Putora PM, Isenring B, Blum T, Brutsche M. Comorbidities and burden of COPD: a population based case-control study. *PLoS One*. 2013;8(5):e63285. doi:10.1371/journal.pone.0063285

21. Lin PJ, Shaya FT, Scharf SM. Economic implications of comorbid conditions among Medicaid beneficiaries with COPD. *Respir Med*. May 2010;104(5):697-704. doi:10.1016/j.rmed.2009.11.009

22. *Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects*. 1986.

23. Guilliams M, Mildner A, Yona S. Developmental and Functional Heterogeneity of Monocytes. *Immunity*. Oct 16 2018;49(4):595-613. doi:10.1016/j.immuni.2018.10.005

24. Lugg ST, Scott A, Parekh D, Naidu B, Thickett DR. Cigarette smoke exposure and alveolar macrophages: mechanisms for lung disease. *Thorax*. Jan 2022;77(1):94-101. doi:10.1136/thoraxjnl-2020-216296

25. Cornwell WD, Kim V, Fan X, et al. Activation and polarization of circulating monocytes in severe chronic obstructive pulmonary disease. *BMC Pulm Med*. Jun 15 2018;18(1):101. doi:10.1186/s12890-018-0664-y

26. van de Laar L, Saelens W, De Prijck S, et al. Yolk Sac Macrophages, Fetal Liver, and Adult Monocytes Can Colonize an Empty Niche and Develop into Functional Tissue-Resident Macrophages. *Immunity*. Apr 19 2016;44(4):755-68. doi:10.1016/j.immuni.2016.02.017

27. Yona S, Kim KW, Wolf Y, et al. Fate mapping reveals origins and dynamics of monocytes and tissue macrophages under homeostasis. *Immunity*. Jan 24 2013;38(1):79-91. doi:10.1016/j.immuni.2012.12.001

28. Guilliams M, De Kleer I, Henri S, et al. Alveolar macrophages develop from fetal monocytes that differentiate into long-lived cells in the first week of life via GM-CSF. *J Exp Med*. Sep 23 2013;210(10):1977-92. doi:10.1084/jem.20131199

29. Byrne AJ, Powell JE, O'Sullivan BJ, et al. Dynamics of human monocytes and airway macrophages during healthy aging and after transplant. *J Exp Med*. Mar 2 2020;217(3)doi:10.1084/jem.20191236

30. Gibbings SL, Goyal R, Desch AN, et al. Transcriptome analysis highlights the conserved difference between embryonic and postnatal-derived alveolar macrophages. *Blood*. Sep 10 2015;126(11):1357-66. doi:10.1182/blood-2015-01-624809

31. Misharin AV, Morales-Nebreda L, Reyfman PA, et al. Monocyte-derived alveolar macrophages drive lung fibrosis and persist in the lung over the life span. *J Exp Med*. Aug 7 2017;214(8):2387-2404. doi:10.1084/jem.20162152

32. Fingerle G, Pforte A, Passlick B, Blumenstein M, Strobel M, Ziegler-Heitbrock HW. The novel subset of CD14+/CD16+ blood monocytes is expanded in sepsis patients. *Blood*. Nov 15 1993;82(10):3170-6.

33. Nockher WA, Scherberich JE. Expanded CD14+ CD16+ monocyte subpopulation in patients with acute and chronic infections undergoing hemodialysis. *Infect Immun*. Jun 1998;66(6):2782-90. doi:10.1128/IAI.66.6.2782-2790.1998

34. Ziegler-Heitbrock L. Blood Monocytes and Their Subsets: Established Features and Open Questions. *Front Immunol*. 2015;6:423. doi:10.3389/fimmu.2015.00423

35. Auffray C, Sieweke MH, Geissmann F. Blood monocytes: development, heterogeneity, and relationship with dendritic cells. *Annu Rev Immunol*. 2009;27:669-92. doi:10.1146/annurev.immunol.021908.132557

36. Geissmann F, Jung S, Littman DR. Blood monocytes consist of two principal subsets with distinct migratory properties. *Immunity*. Jul 2003;19(1):71-82. doi:10.1016/s1074-7613(03)00174-2

37. Hoogsteden HC, van Dongen JJ, van Hal PT, Delahaye M, Hop W, Hilvering C. Phenotype of blood monocytes and alveolar macrophages in interstitial lung disease. *Chest*. Mar 1989;95(3):574-7. doi:10.1378/chest.95.3.574

38. Tacke F, Randolph GJ. Migratory fate and differentiation of blood monocyte subsets. *Immunobiology*. 2006;211(6-8):609-18. doi:10.1016/j.imbio.2006.05.025

39. Barnes PJ. Similarities and differences in inflammatory mechanisms of asthma and COPD. *Breathe*. March 1, 2011 2011;7(3):229-238. doi:https://doi.org/10.1183/20734735.026410

40. Kapellos TS, Bonaguro L, Gemund I, et al. Human Monocyte Subsets and Phenotypes in Major Chronic Inflammatory Diseases. *Front Immunol*. 2019;10:2035. doi:10.3389/fimmu.2019.02035

41. Lin CH, Li YR, Lin PR, et al. Blood monocyte levels predict the risk of acute exacerbations of chronic obstructive pulmonary disease: a retrospective case-control study. *Sci Rep*. Dec 6 2022;12(1):21057. doi:10.1038/s41598-022-25520-8

42. Pedersen KM, Colak Y, Ellervik C, Hasselbalch HC, Bojesen SE, Nordestgaard BG. Smoking and Increased White and Red Blood Cells. *Arterioscler Thromb Vasc Biol*. May 2019;39(5):965-977. doi:10.1161/ATVBAHA.118.312338

43. Hai Y, Chen N, Wu W, et al. High postoperative monocyte indicates inferior Clinicopathological characteristics and worse prognosis in lung adenocarcinoma or squamous cell carcinoma after lobectomy. *BMC Cancer*. Oct 22 2018;18(1):1011. doi:10.1186/s12885-018-4909-1

44. Hlapcic I, Dugac AV, Popovic-Grle S, et al. Influence of disease severity, smoking status and therapy regimes on leukocyte subsets and their ratios in stable chronic obstructive pulmonary disease. *Arch Med Sci*. 2022;18(3):672-681. doi:10.5114/aoms.2020.100720

45. Min B, Grant-Orser A, Johannson KA. Peripheral blood monocyte count and

outcomes in patients with interstitial lung disease: a systematic review and meta-analysis. *Eur Respir Rev*. Sep 30 2023;32(169) doi:10.1183/16000617.0072-2023

46. Kreuter M, Lee JS, Tzouvelekis A, et al. Monocyte Count as a Prognostic Biomarker in Patients with Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care Med*. Jul 1 2021;204(1): 74-81. doi:10.1164/rccm.202003-0669OC

47. Scott MKD, Quinn K, Li Q, et al. Increased monocyte count as a cellular biomarker for poor outcomes in fibrotic diseases: a retrospective, multicentre cohort study. *Lancet Respir Med*. Jun 2019;7(6):497-508. doi:10.1016/S2213-2600(18)30508-3

48. Gurney JW, Jones KK, Robbins RA, et al. Regional distribution of emphysema: correlation of high-resolution CT with pulmonary function tests in unselected smokers. *Radiology*. May 1992;183(2):457-63. doi:10.1148/radiology.183.2.1561350

49. Li K, Gao Y, Pan Z, et al. Influence of Emphysema and Air Trapping Heterogeneity on Pulmonary Function in Patients with COPD. *Int J Chron Obstruct Pulmon Dis*. 2019;14:286 3-2872. doi:10.2147/COPD.S221684

50. Ferguson GT. Why does the lung hyperinflate? *Proc Am Thorac Soc*. Apr 2006;3 (2):176-9. doi:10.1513/pats.200508-094DO

51. McDonough JE, Yuan R, Suzuki M, et al. Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. *N Engl J Med*. Oct 27 2011;365(17):1567-75. doi:10.1056/NEJMoa1106955

52. Lutchmedial SM, Creed WG, Moore AJ, Walsh RR, Gentchos GE, Kaminsky DA. How Common Is Airflow Limitation in Patients With Emphysema on CT Scan of the Chest? *Chest*. Jul 2015;148(1):176-184. doi:10.1378/chest. 14-1556

53. Kahnert K, Jobst B, Biertz F, et al. Relationship of spirometric, body plethysmographic, and diffusing capacity parameters to emphysema scores derived from CT scans. *Chron Respir Dis*. Jan-Dec 2019;16:1479972318775423. doi:10.1177/1479972318775423

54. Kellerer C, Jorres RA, Schneider A, et al. Prediction of lung emphysema in COPD by spirometry and clinical symptoms: results from COSYCONET. *Respir Res*. Sep 9 2021;22(1):2 42. doi:10.1186/s12931-021-01837-2

55. Cheng T, Li Y, Pang S, et al. Emphysema extent on computed tomography is a highly specific index in diagnosing persistent airflow limitation: a real-world study in China. *Int J Chron Obstruct Pulmon Dis*. 2019;14:13-26. doi:10.2147/COPD.S157141

56. de Weger WW, Klooster K, Ten Hacken NH, van Dijk M, Hartman JE, Slebos DJ. Determining Static Hyperinflation in Patients with Severe Emphysema: Relation Between Lung Function Parameters and Patient-Related Outcomes. *Lung*. Aug 2020;198(4):62 9-636. doi:10.1007/s00408-020-00368-9

57. Yoshikawa A, Sato S, Tanaka T, et al. Breakdown of lung framework and an increase in pores of Kohn as initial events of emphysema and a cause of reduction in diffusing capacity. *Int J Chron Obstruct Pulmon Dis*. 2016;11:2287-2294. doi:10.2147 /COPD.S114281

58. Diez Herranz A. RV/TLC% ratio: alternative criteria of normality. *Eur Respir J*. Oct 1995;8(10):1812-3. doi:10.1183/0903193 6.95.08101812

59. Cooper CB. The connection between chronic obstructive pulmonary disease symptoms and hyperinflation and its impact on exercise and function. *Am J Med*. Oct 2006;119(10 Suppl 1):21-31. doi:10.1016/j.amjmed.2006.08.004

60. Garcia-Rio F, Lores V, Mediano O, et al. Daily physical activity in patients with chronic obstructive pulmonary disease is mainly associated with dynamic hyperinflation. *Am J Respir Crit Care Med*. Sep 15 2009;180(6):506-12. doi:10.1164/rccm.200812-1873OC

61. Kim YW, Lee CH, Hwang HG, et al. Resting hyperinflation and emphysema on the clinical course of COPD. *Sci Rep*. Mar 6 2019;9(1):3764. doi:10.1038/s41598-019-40411-1

62. Diaz AA, Pinto-Plata V, Hernandez C, et al. Emphysema and DLCO predict a clinically important difference for 6MWD decline in COPD. *Respir Med*. Jul 2015;109(7):882-9. doi:10.1016/j.rmed.2015.04.009

63. Shiraishi Y, Tanabe N, Shimizu K, et al. Stronger Associations of Centrilobular Than Paraseptal Emphysema With Longitudinal Changes in Diffusing Capacity and Mortality in COPD. *Chest*. Aug 2023;164(2):327-338. doi:10.1016/j.chest.2023.01.034

64. Balasubramanian A, Putcha N, MacIntyre NR, et al. Diffusing Capacity and Mortality in Chronic Obstructive Pulmonary Disease. *Ann Am Thorac Soc*. Jan 2023;20(1):38-46. doi:10.1513/AnnalsATS.202203-226OC

65. de-Torres JP, O'Donnell DE, Marin JM, et al. Clinical and Prognostic Impact of Low Diffusing Capacity for Carbon Monoxide Values in Patients With Global Initiative for Obstructive Lung Disease I COPD. *Chest*. Sep 2021;160(3):872-878. doi:10.1016/j.chest.2021.04.033

66. Hata A, Schiebler ML, Lynch DA, Hatabu H. Interstitial Lung Abnormalities: State of the Art. *Radiology*. Oct 2021;301(1):19-34. doi:10.1148/radiol.2021204367

67. Hatabu H, Hunninghake GM, Richeldi L, et al. Interstitial lung abnormalities detected incidentally on CT: a Position Paper from the Fleischner Society. *Lancet Respir Med*. Jul 2020;8(7):726-737. doi:10.1016/S2213-2600(20)30168-5

68. Araki T, Nishino M, Zazueta OE, et al. Paraseptal emphysema: Prevalence and distribution on CT and association with interstitial lung abnormalities. *Eur J Radiol*. Jul 2015;84(7):1413-8. doi:10.1016/j.ejrad.2015.03.010

69. Washko GR, Hunninghake GM, Fernandez IE, et al. Lung volumes and emphysema in smokers with interstitial lung abnormalities. *N Engl J Med*. Mar 10 2011;364(10):897-906. doi:10.1056/NEJMoa1007285

70. Butler MW, Fabre A, Dodd JD. Smokers with interstitial lung abnormalities. *N Engl J Med*. Jun 23 2011;364(25):2465; author reply 2466. doi:10.1056/NEJMc1104014

71. King TE, Jr. Smoking and subclinical interstitial lung disease. *N Engl J Med*. Mar 10 2011;364(10):968-70. doi:10.1056/NEJMe1013966

72. Lee TS, Jin KN, Lee HW, et al. Interstitial Lung Abnormalities and the Clinical Course in Patients With COPD. *Chest*. Jan 2021;159(1):128-137. doi:10.1016/j.chest.2020.08.017

73. Liu Y, Tang J, Sun Y. Impact of Interstitial Lung Abnormalities on Disease Expression and Outcomes in COPD or Emphysema: A Systematic Review. *Int J Chron Obstruct*

Pulmon Dis. 2023;18:189-206. doi:10.2147/COPD.S392349

74. Ohgiya M, Matsui H, Tamura A, Kato T, Akagawa S, Ohta K. The Evaluation of Interstitial Abnormalities in Group B of the 2011 Global Initiative for Chronic Obstructive Lung Disease (GOLD) Classification of Chronic Obstructive Pulmonary Disease (COPD). *Intern Med*. Oct 15 2017;56(20):2711-2717. doi:10.2169/internalmedicine.8406-16

75. Otani H, Tanaka T, Murata K, et al. Smoking-related interstitial fibrosis combined with pulmonary emphysema: computed tomography-pathologic correlative study using lobectomy specimens. *Int J Chron Obstruct Pulmon Dis*. 2016;11:1521-32. doi:10.2147/COPD.S107938

76. Ash SY, Harmouche R, Ross JC, et al. Interstitial Features at Chest CT Enhance the Deleterious Effects of Emphysema in the COPDGene Cohort. *Radiology*. Aug 2018;288(2):600-609. doi:10.1148/radiol.2018172688

77. Menon AA, Putman RK, Sanders JL, et al. Interstitial Lung Abnormalities, Emphysema, and Spirometry in Smokers. *Chest*. Apr 2022;161(4):999-1010. doi:10.1016/j.chest.2021.10.034

78. 7 How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General. (CDC (US)) (2010).

79. Huie TJ, Solomon JJ. Emphysema and pulmonary fibrosis: coincidence or conspiracy? *Respirology*. Nov 2013;18(8):1163-4. doi:10.1111/resp.12187

80. Selman M, Martinez FJ, Pardo A. Why Does an Aging Smoker's Lung Develop Idiopathic Pulmonary Fibrosis and Not Chronic Obstructive Pulmonary Disease? *Am J Respir Crit Care Med*. Feb 1 2019;199(3):279-285. doi:10.1164/rccm.201806-1166PP

81. Cottin V, Nunes H, Brillet PY, et al. Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. *Eur Respir J*. Oct 2005;26(4):586-93. doi:10.1183/09031936.05.00021005

82. Antoniou KM, Walsh SL, Hansell DM, et al. Smoking-related emphysema is associated with idiopathic pulmonary fibrosis and rheumatoid lung. *Respirology*. Nov 2013;18(8):1191-6. doi:10.1111/resp.12154

83. Auerbach O, Garfinkel L, Hammond EC. Relation of smoking and age to findings in lung parenchyma: a microscopic study. *Chest*. Jan 1974;65(1):29-35. doi:10.1378/chest.65.1.29

84. Wells AU, King AD, Rubens MB, Cramer D, du Bois RM, Hansell DM. Lone cryptogenic fibrosing alveolitis: a functional-morphologic correlation based on extent of disease on thin-section computed tomography. *Am J Respir Crit Care Med*. Apr 1997;155(4):1367-75. doi:10.1164/ajrccm.155.4.9105081

85. Cottin V, Selman M, Inoue Y, et al. Syndrome of Combined Pulmonary Fibrosis and Emphysema: An Official ATS/ERS/JRS/ALAT Research Statement. *Am J Respir Crit Care Med*. Aug 15 2022;206(4):e7-e41. doi:10.1164/rccm.202206-1041ST

86. The definition of emphysema. Report of a National Heart, Lung, and Blood Institute, Division of Lung Diseases workshop. *Am Rev Respir Dis*. Jul 1985;132(1):182-5. doi:10.1164/arrd.1985.132.1.182

87. Cardoso WV, Sekhon HS, Hyde DM, Thurlbeck WM. Collagen and elastin in human pulmonary emphysema. *Am Rev Respir Dis*. Apr 1993;147(4):975-81. doi:10.1164/ajrccm/147.4.975

88. Wright JL, Tazelaar HD, Churg A. Fibrosis with emphysema. *Histopathology*. Mar 2011; 58(4):517-24. doi:10.1111/j.1365-2559.2010.03648.x

89. Katzenstein AL, Mukhopadhyay S, Zanardi C, Dexter E. Clinically occult interstitial fibrosis in smokers: classification and significance of a surprisingly common finding in lobectomy specimens. *Hum Pathol*. Mar 2010;41(3):316-25. doi:10.1016/j.humpath.2009.09.003

90. Kawabata Y, Hoshi E, Murai K, et al. Smoking-related changes in the background lung of specimens resected for lung cancer: a semiquantitative study with correlation to postoperative course. *Histopathology*. Dec 2008;53(6):707-14. doi:10.1111/j.1365-2559.2008.03183.x

91. Yousem SA. Respiratory bronchiolitis-associated interstitial lung disease with fibrosis is a lesion distinct from fibrotic nonspecific interstitial pneumonia: a proposal. *Mod Pathol*. Nov 2006;19(11):1474-9. doi:10.1038/modpathol.3800671

92. Kinoshita Y, Watanabe K, Ishii H, Kushima H, Fujita M, Nabeshima K. Distribution of emphysema and fibrosis in idiopathic pulmonary fibrosis with coexisting emphysema. *Histopathology*. Jun 2019;74(7):1103-1108. doi:10.1111/his.13831

93. Inomata M, Ikushima S, Awano N, et al. An autopsy study of combined pulmonary fibrosis and emphysema: correlations among clinical, radiological, and pathological features. *BMC Pulm Med*. Jun 28 2014;14:104. doi:10.1186/1471-2466-14-104

94. Sangani R, Ghio A, Culp S, Patel Z, Sharma S. Combined Pulmonary Fibrosis Emphysema: Role of Cigarette Smoking and Pulmonary Hypertension in a Rural Cohort. *Int J Chron Obstruct Pulmon Dis*. 2021;16:1873-1885. doi:10.2147/COPD.S307192

95. Papaioannou AI, Kostikas K, Manali ED, et al. Combined pulmonary fibrosis and emphysema: The many aspects of a cohabitation contract. *Respir Med*. Aug 2016;117:14-26. doi:10.1016/j.rmed.2016.05.005

96. Ryerson CJ, Hartman T, Elicker BM, et al. Clinical features and outcomes in combined pulmonary fibrosis and emphysema in idiopathic pulmonary fibrosis. *Chest*. Jul 2013;144(1):234-240. doi:10.1378/chest.12-2403

97. Douglas D, Keating L, Strykowski R, et al. Tobacco smoking is associated with combined pulmonary fibrosis and emphysema and worse outcomes in interstitial lung disease. *Am J Physiol Lung Cell Mol Physiol*. Aug 1 2023;325(2):L233-L243. doi:10.1152/ajplung.00083.2023

98. Koo HJ, Do KH, Lee JB, Alblushi S, Lee SM. Lung Cancer in Combined Pulmonary Fibrosis and Emphysema: A Systematic Review and Meta-Analysis. *PLoS One*. 2016;11(9):e0161437. doi:10.1371/journal.pone.0161437

99. Chen Q, Liu P, Zhou H, Kong H, Xie W. An increased risk of lung cancer in combined pulmonary fibrosis and emphysema patients with usual interstitial pneumonia compared with patients with idiopathic pulmonary fibrosis alone: a systematic review and meta-analysis. *Ther Adv Respir Dis*. Jan-Dec 2021; 15:17534666211017050. doi:10.1177/17534666211017050

100.Hata A, Sekine Y, Kota O, Koh E, Yoshino I. Impact of combined pulmonary fibrosis and emphysema on surgical complications and long-term survival in patients undergoing

surgery for non-small-cell lung cancer. *Int J Chron Obstruct Pulmon Dis*. 2016;11:1261-8. doi:10.2147/COPD.S94119

101.Takahashi T, Terada Y, Pasque MK, et al. Clinical Features and Outcomes of Combined Pulmonary Fibrosis and Emphysema After Lung Transplantation. *Chest*. Nov 2021;160(5):1743-1750. doi:10.1016/j.chest.2021.06.036

102.Gredic M, Blanco I, Kovacs G, et al. Pulmonary hypertension in chronic obstructive pulmonary disease. *Br J Pharmacol*. Jan 2021;178(1):132-151. doi:10.1111/bph.14979

103.Ni H, Wei Y, Yang L, Wang Q. An increased risk of pulmonary hypertension in patients with combined pulmonary fibrosis and emphysema: a meta-analysis. *BMC Pulm Med*. Jun 21 2023;23(1):221. doi:10.1186/s12890-023-02425-4

104.Ghio AJ, Hilborn ED, Stonehuerner JG, et al. Particulate matter in cigarette smoke alters iron homeostasis to produce a biological effect. *Am J Respir Crit Care Med*. Dec 1 2008;178(11):1130-8. doi:10.1164/rccm.200802-334OC

105.Mitchell RS, Vincent TN, Filley GF. Cigarette Smoking, Chronic Bronchitis, and Emphysema. *JAMA*. Apr 6 1964;188:12-6. doi:10.1001/jama.1964.03060270018004

106.You R, Lu W, Shan M, et al. Nanoparticulate carbon black in cigarette smoke induces DNA cleavage and Th17-mediated emphysema. *Elife*. Oct 5 2015;4:e09623. doi:10.7554/eLife.09623

107.Pratt PC, Jutabha P, Klugh GA. The relationship between pigment deposits and lesions in normal and centrilobular emphysematous lungs. *Am Rev Respir Dis*. Feb 1963;87:245-56. doi:10.1164/arrd.1963.87.2.245

108.Lippmann M, Yeates DB, Albert RE. Deposition, retention, and clearance of inhaled particles. *Br J Ind Med*. Nov 1980;37(4):337-62. doi:10.1136/oem.37.4.337

109.Margaritopoulos GA, Vasarmidi E, Jacob J, Wells AU, Antoniou KM. Smoking and interstitial lung diseases. *Eur Respir Rev*. Sep 2015;24(137):428-35. doi:10.1183/16000617.0050-2015

110.Rao RN, Goodman LR, Tomashefski JF, Jr. Smoking-related interstitial lung disease. *Ann Diagn Pathol*. Dec 2008;12(6):445-57. doi:10.1016/j.anndiagpath.2008.10.001

111.Churg A, Muller NL, Wright JL. Respiratory bronchiolitis/interstitial lung disease: fibrosis, pulmonary function, and evolving concepts. *Arch Pathol Lab Med*. Jan 2010;134(1):27-32. doi:10.5858/134.1.27

112.Sieminska A, Kuziemski K. Respiratory bronchiolitis-interstitial lung disease. *Orphanet J Rare Dis*. Jul 11 2014;9:106. doi:10.1186/s13023-014-0106-8

113.Godbert B, Wissler MP, Vignaud JM. Desquamative interstitial pneumonia: an analytic review with an emphasis on aetiology. *Eur Respir Rev*. Jun 1 2013;22(128):117-23. doi:10.1183/09059180.00005812

114.Yousem SA, Colby TV, Gaensler EA. Respiratory bronchiolitis-associated interstitial lung disease and its relationship to desquamative interstitial pneumonia. *Mayo Clin Proc*. Nov 1989;64(11):1373-80. doi:10.1016/s0025-6196(12)65379-8

115.Desai SR, Ryan SM, Colby TV. Smoking-related interstitial lung diseases: histopathological and imaging perspectives.

Clin Radiol. Apr 2003;58(4):259-68. doi:10.1016/s0009-9260(02)00525-1

116.Diken OE, Sengul A, Beyan AC, Ayten O, Mutlu LC, Okutan O. Desquamative interstitial pneumonia: Risk factors, laboratory and bronchoalveolar lavage findings, radiological and histopathological examination, clinical features, treatment and prognosis. *Exp Ther Med*. Jan 2019;17(1):587-595. doi:10.3892/etm.2018.7030

117.Sangani RG, Deepak V, Ghio AJ, Patel Z, Alshaikhnassir E, Vos J. Peribronchiolar Metaplasia: A Marker of Cigarette Smoke-Induced Small Airway Injury in a Rural Cohort. *Clin Pathol*. Jan-Dec 2023;16:2632010X231209878. doi:10.1177/2632010X231209878

118.Brown KP. *Histopathology of diffuse lung parenchyma epithelial metaplasia in COPD*. University of Leicester; 2010. Accessed January 31, 2024. https://hdl.handle.net/2381/9199

119.Higham A, Quinn AM, Cancado JED, Singh D. The pathology of small airways disease in COPD: historical aspects and future directions. *Respir Res*. Mar 4 2019;20(1):49. doi:10.1186/s12931-019-1017-y

120.Leiter A, Veluswamy RR, Wisnivesky JP. The global burden of lung cancer: current status and future trends. *Nat Rev Clin Oncol*. Sep 2023;20(9):624-639. doi:10.1038/s41571-023-00798-3

121.Hohberger LA, Schroeder DR, Bartholmai BJ, et al. Correlation of regional emphysema and lung cancer: a lung tissue research consortium-based study. *J Thorac Oncol*. May 2014;9(5):639-45. doi:10.1097/JTO.0000000000000144

122.Yang X, Wisselink HJ, Vliegenthart R, et al. Association between Chest CT-defined Emphysema and Lung Cancer: A Systematic Review and Meta-Analysis. *Radiology*. Aug 2022;304(2):322-330. doi:10.1148/radiol.212904

123.Yong PC, Sigel K, de-Torres JP, et al. The effect of radiographic emphysema in assessing lung cancer risk. *Thorax*. Sep 2019;74(9):858-864. doi:10.1136/thoraxjnl-2018-212457

124.Zhang X, Jiang N, Wang L, Liu H, He R. Chronic obstructive pulmonary disease and risk of lung cancer: a meta-analysis of prospective cohort studies. *Oncotarget*. Sep 29 2017;8(44):78044-78056. doi:10.18632/oncotarget.20351

125.Sun Z, Yang P. Role of imbalance between neutrophil elastase and alpha 1-antitrypsin in cancer development and progression. *Lancet Oncol*. Mar 2004;5(3):182-90. doi:10.1016/S1470-2045(04)01414-7

126.Oelsner EC, Carr JJ, Enright PL, et al. Per cent emphysema is associated with respiratory and lung cancer mortality in the general population: a cohort study. *Thorax*. Jul 2016;71(7):624-32. doi:10.1136/thoraxjnl-2015-207822

127.Sato S, Nakamura M, Shimizu Y, et al. The impact of emphysema on surgical outcomes of early-stage lung cancer: a retrospective study. *BMC Pulm Med*. Apr 4 2019;19(1):73. doi:10.1186/s12890-019-0839-1

128.Shin S, Park HY, Kim H, et al. Joint effect of airflow limitation and emphysema on postoperative outcomes in early-stage nonsmall cell lung cancer. *Eur Respir J*. Dec 2016;48(6):1743-1750. doi:10.1183/13993003.01148-2016

129.Goldkorn T, Filosto S. Lung injury and cancer: Mechanistic insights into ceramide

and EGFR signaling under cigarette smoke. *Am J Respir Cell Mol Biol*. Sep 2010;43(3):259-68. doi:10.1165/rcmb.2010-0220RT

130.Mittal V, El Rayes T, Narula N, McGraw TE, Altorki NK, Barcellos-Hoff MH. The Microenvironment of Lung Cancer and Therapeutic Implications. *Adv Exp Med Biol*. 2016;890:75-110. doi:10.1007/978-3-319-24932-2_5

131.Murakami J, Ueda K, Sano F, Hayashi M, Nishimoto A, Hamano K. Pulmonary emphysema and tumor microenvironment in primary lung cancer. *J Surg Res*. Feb 2016;200(2):690-7. doi:10.1016/j.jss.2015.09.004

132.Saito A, Horie M, Nagase T. TGF-beta Signaling in Lung Health and Disease. *Int J Mol Sci*. Aug 20 2018;19(8)doi:10.3390/ijms19082460

133.Agusti A, Calverley PM, Celli B, et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. *Respir Res*. Sep 10 2010;11(1):122. doi:10.1186/1465-9921-11-122

134.Dhariwal J, Tennant RC, Hansell DM, et al. Smoking cessation in COPD causes a transient improvement in spirometry and decreases micronodules on high-resolution CT imaging. *Chest*. May 2014;145(5):1006-1015. doi:10.1378/chest.13-2220

135.Johannessen A, Skorge TD, Bottai M, et al. Mortality by level of emphysema and airway wall thickness. *Am J Respir Crit Care Med*. Mar 15 2013;187(6):602-8. doi:10.1164/rccm.201209-1722OC

136.Qaseem A, Wilt TJ, Weinberger SE, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. *Ann Intern Med*. Aug 2 2011;155(3):179-91. doi:10.7326/0003-4819-155-3-201108020-00008

137.Tylen U, Boijsen M, Ekberg-Jansson A, Bake B, Lofdahl CG. Emphysematous lesions and lung function in healthy smokers 60 years of age. *Respir Med*. Jan 2000;94(1):38-43. doi:10.1053/rmed.1999.0690

138.Regan EA, Lynch DA, Curran-Everett D, et al. Clinical and Radiologic Disease in Smokers With Normal Spirometry. *JAMA Intern Med*. Sep 2015;175(9):1539-49. doi:10.1001/jamainternmed.2015.2735

139.Yasunaga K, Cherot-Kornobis N, Edme JL, et al. Emphysema in asymptomatic smokers: quantitative CT evaluation in correlation with pulmonary function tests. *Diagn Interv Imaging*. Jun 2013;94(6):609-17. doi:10.1016/j.diii.2013.02.013

140.Kitaguchi Y, Fujimoto K, Kubo K, Honda T. Characteristics of COPD phenotypes classified according to the findings of HRCT. *Respir Med*. Oct 2006;100(10):1742-52. doi:10.1016/j.rmed.2006.02.003

141.Robbesom AA, Versteeg EM, Veerkamp JH, et al. Morphological quantification of emphysema in small human lung specimens: comparison of methods and relation with clinical data. *Mod Pathol*. Jan 2003;16(1):1-7. doi:10.1097/01.MP.0000043519.29370.C2

142.Smoking Cessation: A Report of the Surgeon General (Department of Health and Human Services, Centers for Disease Control and Prevention) (2020).

143.Willemse BW, Postma DS, Timens W, ten Hacken NH. The impact of smoking cessation on respiratory symptoms, lung function, airway hyperresponsiveness and inflammation. *Eur Respir J*. Mar 2004;23(3):464-76. doi:10.1183/09031936.04.00012704

144.Wright JL, Hobson JE, Wiggs B, Pare PD, Hogg JC. Airway inflammation and peribronchiolar attachments in the lungs of nonsmokers, current and ex-smokers. *Lung*. 1988;166(5):277-86. doi:10.1007/BF02714058

145.Miller M, Cho JY, Pham A, Friedman PJ, Ramsdell J, Broide DH. Persistent airway inflammation and emphysema progression on CT scan in ex-smokers observed for 4 years. *Chest*. Jun 2011;139(6):1380-1387. doi:10.1378/chest.10-0705

146.Pompe E, Strand M, van Rikxoort EM, et al. Five-year Progression of Emphysema and Air Trapping at CT in Smokers with and Those without Chronic Obstructive Pulmonary Disease: Results from the COPDGene Study. *Radiology*. Apr 2020;295(1):218-226. doi:10.1148/radiol.2020191429

147.Mohamed Hoesein FA, Zanen P, de Jong PA, et al. Rate of progression of CT-quantified emphysema in male current and ex-smokers: a follow-up study. *Respir Res*. May 20 2013;14(1):55. doi:10.1186/1465-9921-14-55

148.Ashraf H, Lo P, Shaker SB, et al. Short-term effect of changes in smoking behaviour on emphysema quantification by CT. *Thorax*. Jan 2011;66(1):55-60. doi:10.1136/thx.2009.132688

149.Scanlon PD, Connett JE, Waller LA, et al. Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease. The Lung Health Study. *Am J Respir Crit Care Med*. Feb 2000;161(2 Pt 1):381-90. doi:10.1164/ajrccm.161.2.9901044

150.Mohamed Hoesein FA, Zanen P, van Ginneken B, van Klaveren RJ, Lammers JW. Association of the transfer coefficient of the lung for carbon monoxide with emphysema progression in male smokers. *Eur Respir J*. Nov 2011;38(5):1012-8. doi:10.1183/09031936.00050711

151.Roos-Engstrand E, Ekstrand-Hammarstrom B, Pourazar J, Behndig AF, Bucht A, Blomberg A. Influence of smoking cessation on airway T lymphocyte subsets in COPD. *COPD*. Apr 2009;6(2):112-20. doi:10.1080/15412550902755358

152.Wan ES, Qiu W, Baccarelli A, et al. Cigarette smoking behaviors and time since quitting are associated with differential DNA methylation across the human genome. *Hum Mol Genet*. Jul 1 2012;21(13):3073-82. doi:10.1093/hmg/dds135

153.Wan ES, Qiu W, Carey VJ, et al. Smoking-Associated Site-Specific Differential Methylation in Buccal Mucosa in the COPDGene Study. *Am J Respir Cell Mol Biol*. Aug 2015;53(2):246-54. doi:10.1165/rcmb.2014-0103OC