QA1

Diagnostic Features in Combined Pulmonary Fibrosis and Emphysema: A Systematic Review

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Combined pulmonary fibrosis and emphysema (CPFE) was initially described as the presence of emphysema with upper zone predominance and diffuse parenchymal lung disease with significant pulmonary fibrosis on computed tomography (CT) (1). Subsequent studies have used heterogeneous definitions and diagnostic criteria for CPFE, which has limited our ability to compare different cohorts and draw firm conclusions about the features, outcomes, and optimal management of these patients. We conducted a systematic review to summarize the definition and diagnostic criteria used in previous studies of CPFE. Our goal was to use these data to support standardization of diagnostic criteria and facilitate future research in this group of patients.

Methods

We searched MEDLINE and EMBASE for all full-text articles published between January 2000 and 2019 that provided a definition and/or diagnostic criteria for CPFE (protocol registered in PROSPERO) (2). Eligible studies included original research published in English that included at least 10 patients with evidence of both pulmonary fibrosis and emphysema. Screening was performed independently by two authors, with disagreements resolved by consensus after assessment by a third reviewer.

Results

The search resulted in 9,118 citations, with a total of 72 publications included for data synthesis (Figure 1). CPFE was diagnosed based on criteria proposed by Cottin and colleagues in 60% (43/72) of all eligible studies (Figure 2) (1). Alternative methods of defining CPFE used values from pulmonary function tests or applied different imaging criteria for emphysema and/or fibrosis.

A diagnosis of idiopathic pulmonary fibrosis (IPF) was required in 34 studies (47%). Five studies specifically focused on patients with connective tissue disease–associated ILD (two systemic sclerosis, two rheumatoid arthritis, and one with various subtypes). The extent of fibrosis was determined visually in 70 studies (97%), with 1 study requiring at least 10% fibrosis on chest CT imaging (Figure 2). Quantitative CT imaging was used to evaluate fibrosis extent in two studies (e.g., percentage of voxels with mean lung attenuation between 0 and −700 Hounsfield units).

Forty-three studies required that emphysema be upper lung predominant, 10 included emphysema in all locations, and 19 did not specify location criteria. The extent of emphysema was assessed visually in 65/72 studies. The majority of studies (72%) diagnosed CPFE if there was any emphysema present on chest CT imaging, whereas 28% used a specific threshold (Figure 2). Nine studies required that emphysema affected ⩾10% of the lung volume, whereas four studies used a threshold of 5%, another four studies used 25%, and single studies each used 15% and 20%. One study required a minimum score of 2 in the upper lungs using the Goddard method of quantifying emphysema (3). Quantitative CT imaging was used to evaluate emphysema extent in seven studies (e.g., percentage of voxels with mean lung attenuation less than −950 Hounsfield units).

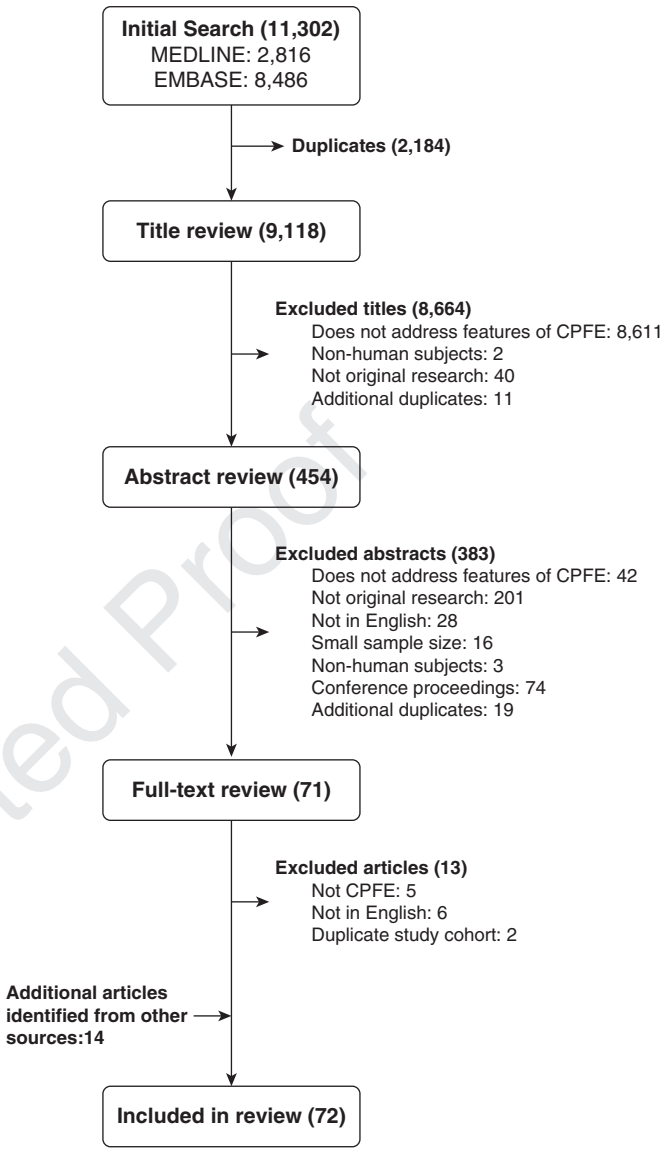

Figure 1. Systematic review search results. Articles were excluded if the study was not original research, not combined pulmonary fibrosis and emphysema–related, had a sample size <10, was non-English, or involved nonhuman subjects. The 14 additional articles were identified by reviewing reference lists of eligible full-text manuscripts. CPFE = combined pulmonary fibrosis and emphysema.

Discussion

There is an appreciation that CPFE possesses unique clinical, radiologic, and physiologic features. However, study of the biology, management, and prognosis of CPFE has been limited by the lack of diagnostic criteria and inability to directly compare study populations. A clear consensus on the definition and diagnosis of CPFE is required to address these knowledge gaps. We conducted a systematic review to identify the heterogeneous definitions and diagnostic criteria previously used in CPFE studies, with the intent

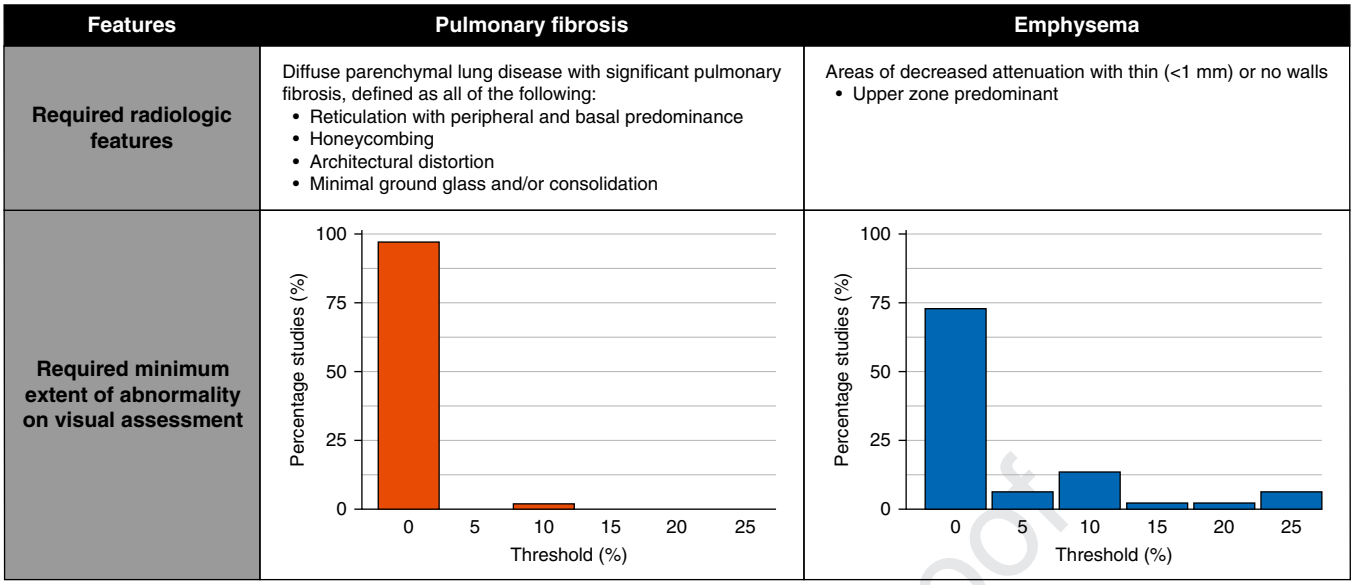

Figure 2. Definition and thresholds used to define combined pulmonary fibrosis and emphysema. A threshold of "0" indicates studies that defined the presence of the abnormality based on patients having any amount of that abnormality.

that this information will facilitate standardization and support future CPFE research.

The majority of studies on CPFE have focused on patients with IPF. IPF and chronic obstructive pulmonary disease share common risk factors of older age and smoking (4–6). Thus, this definition likely captures the largest and most clinically relevant subgroup of patients with ILD who have concurrent emphysema while also ensuring a relatively homogeneous patient population. Conversely, including a variety of ILD subtypes has the advantage of capturing all patients with these two diseases; however, this approach results in a heterogeneous population that can be a source of significant bias and complicates assessment of disease biology that might vary across ILD subtypes. A potential approach would be to carefully and transparently define CPFE in a manner that is appropriate to the main study objectives. For example, studies evaluating prognosis likely require separation of patients with and without IPF, whereas studies evaluating lung physiology may not require such stratification.

The emphysema component of CPFE has predominantly been evaluated by imaging and can be determined visually (typically by an experienced chest radiologist) or quantitatively using computer-based analysis based on lung density. Visual assessment is readily available and has moderate interrater agreement (intraclass correlation 0.77; 95% confidence interval, 0.72–0.81) (7). Quantitative methods generally have less interobserver and intraobserver variability; however, its use is currently prohibited by

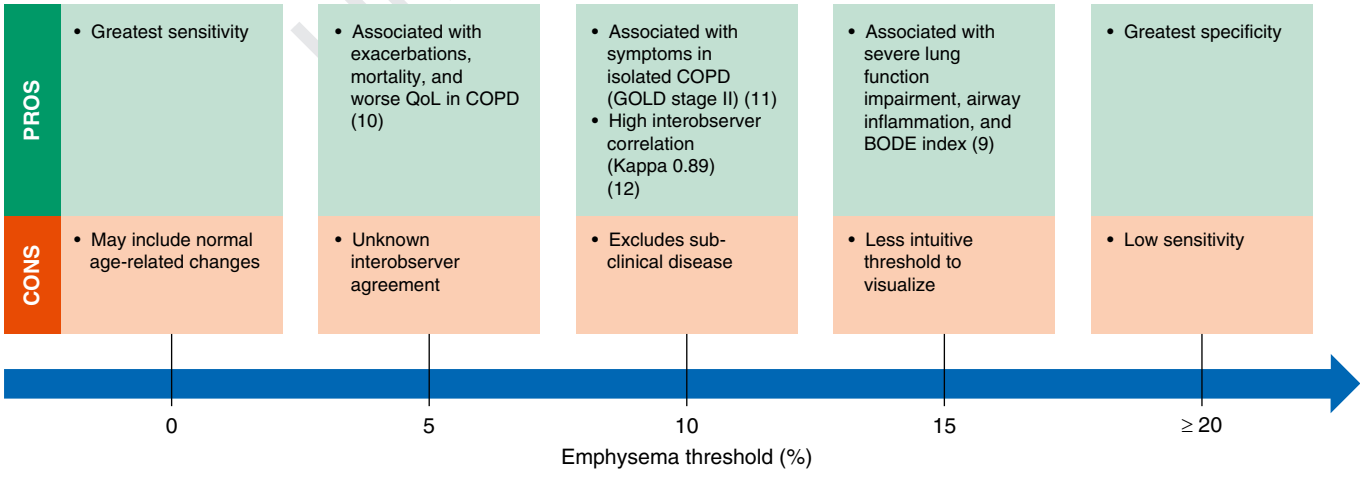

Figure 3. Advantages and disadvantages of thresholds used for the minimum extent of emphysema required to be diagnosed with combined pulmonary fibrosis and emphysema (9–12). COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; QoL = quality of life.

the inability to reliably distinguish emphysema and honeycomb cysts, particularly in areas in which fibrosis and emphysema are admixed. In addition, quantitative CT analysis is not widely available in most clinical settings, resulting in the presence of emphysema being determined by gestalt visual inspection.

Some studies required that a threshold be exceeded to define CPFE, with advantages and disadvantages of such thresholds summarized in Figure 3. Thresholds increase specificity for CPFE and identify cases in which both emphysema and fibrosis are considered to be clinically relevant but at the expense of excluding patients with lesser extents of each component. Criteria using pulmonary function measurements may help refine diagnostic criteria for CPFE (8); however, evidence-based criteria are lacking. Studying patients with early disease (e.g., with interstitial lung abnormalities) offers the best opportunity to learn more about the natural history of CPFE. It is therefore important that future definitions and diagnostic criteria allow for identification and study of these patients with early disease, particularly when studying biological mechanisms.

Conclusions

A major limitation of previous CPFE research is the heterogeneity of study populations, prohibiting direct comparison of different cohorts and validation of key findings. These issues indicate the need to establish specific criteria for CPFE, including standardized and reproducible methods of describing and perhaps quantifying both emphysema and fibrosis. Diagnostic criteria will also need to consider how aspects such as airflow obstruction, type of ILD, and pathological features should be applied when identifying patients with CPFE. We anticipate that the findings of this systematic review will support the efforts of an upcoming joint American Thoracic Society/ERS/JRS Task Force that will produce a consensus definition and diagnostic criteria for CPFE that will enable future research in this area.

Author disclosures are available with the text of this letter at www.atsjournals.org.

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*C.J.R. is Deputy Editor of *AnnalsATS*. His participation complies with American Thoracic Society requirements for recusal from review and decisions for authored works.
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