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Comorbid Chronic Obstructive Pulmonary Disease and Heart Failure: Shared Risk Factors and Opportunities to Improve Outcomes

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Chronic obstructive pulmonary disease (COPD) and heart failure (HF) are highly prevalent conditions, commonly cooccur, and risk for both increases with aging. COPD and HF are associated with significant morbidity and mortality, with poorer outcomes in the setting of comorbid disease. In fact, cardiovascular disease accounts for more than half of all deaths in patients with COPD (1). In a recent analysis of the Clinical Practice Research Datalink, incident HF in patients with COPD was associated with a

threefold higher 1-year mortality than patients with COPD without HF (2). Although symptomatic COPD and HF often coexist in older adults, clinical presentations and outcomes remain poorly defined. Without an improved understanding of the heterogeneous patterns of healthcare utilization and treatment in these high-risk patients, improving health-related quality of life, quality of care, and survival will not be possible.

In this issue of *AnnalsATS*, Gulea and colleagues (pp. 971–980) report on a retrospective cohort study of insured patients in the United States with COPD and HF between 2008 and 2018 (3). The analysis examines differences among HF subtypes based on ejection fraction (EF): 1) HF with preserved EF (HFpEF, $\geq 50\%$); 2) HF with mildly reduced EF (HFmrEF, 40–49%); and 3) HF with reduced EF (HFrEF, $< 40\%$). Of the included sample of 5,419 adults, median age was 74 years. The leading subtype of HF was HFpEF (70%), followed by HFrEF (20%) and HFmrEF (10%). Regardless of the HF subtype, there was a high prevalence of comorbidities (e.g., atrial fibrillation [49%], diabetes [47%], hypertension [97%]). Overall, 38% of patients died in follow-up, with similar crude mortality rates observed among patients with HFrEF, HFmrEF, and HFpEF. Nearly half of patients were hospitalized within 1 year, with similar hospitalization rates among each HF subtype. Overall, the leading cause for hospitalization was acute exacerbation of COPD (36%). However, the

causes for hospitalization differed when examined by HF subtype, with the highest rate of HF-specific hospitalization in patients with COPD and HFrEF (20%) compared with COPD and HFpEF (16%). In contrast, acute exacerbation of COPD was more likely among those with HFpEF (38%) than HFrEF (29%). The amount of guideline-based medical therapy was low in patients with COPD and HFrEF, with 49% on β -blockers and 75% on either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. In all patients with COPD, only 43% were receiving either a short-acting bronchodilator, long-acting bronchodilator, or inhaled corticosteroid regimen at baseline.

The study by Gulea and colleagues is an important contribution to the growing body of literature examining the complex interplay between lung and heart phenotypes. Strengths of the analysis include a relatively large sample of insured adults from the Optum Labs Data Warehouse, which links administrative claims with electronic healthcare records (including data on EF from echocardiography). Although the study focused on patients with COPD and comorbid HF, approximately 40% of all the patients identified with HF in cohort development had concomitant COPD, suggesting that this high-risk subset captures a large proportion of patients with HF. This may be related to the pathophysiologic sequelae of pulmonary vascular abnormalities and hypoxia present in patients with COPD, which may drive right

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Shared Upstream Clinical and Social Factors for Lung and Heart Health

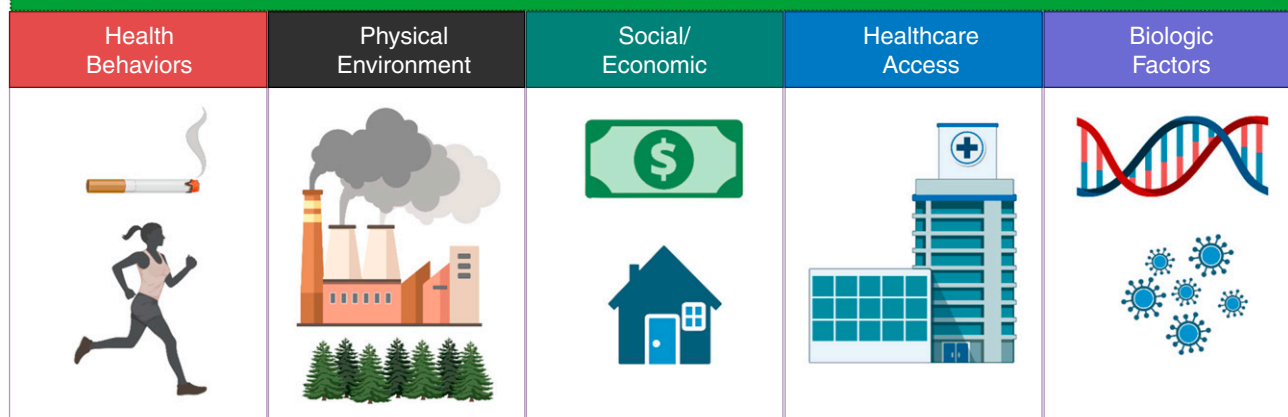


Figure 1. Shared upstream risk factors for chronic obstructive pulmonary disease and heart failure.

ventricular enlargement and subsequent decline in left ventricular (LV) size, given the ventricles' mechanical interdependence (4). In addition, hyperinflation and subsequent increases in intrathoracic pressure may lead to declines in venous return that have been postulated to contribute to LV underfilling resulting in a smaller LV cavity as well as increased LV wall stress and greater LV mass (5, 6). This adverse cardiac remodeling may specifically predispose patients with COPD to certain HF subtypes (e.g., HFpEF vs. HFrEF). Indeed, HFpEF was observed to be the predominant phenotype in this sample of patients with COPD.

The present study must be interpreted in the context of the known limitations of analyses from electronic health records and administrative claims. Misdiagnosis of both COPD and HF is common, given the overlapping symptoms (e.g., shortness of breath) and similar demographics of patients experiencing both of these conditions (e.g., older adults). The natural history of COPD and HF encompasses intermittent exacerbations. Shared acute triggers such as viral illness (e.g., influenza) may result in simultaneous exacerbation of both COPD and HF, which can contribute to diagnostic challenges. However, during an acute exacerbation for either COPD or HF, diagnostic testing may have similar and nonspecific findings, including on chest radiography, echocardiography, and spirometry. Although brain natriuretic

peptide is a commonly used biomarker that is incorporated into the universal definition of HF (7), multiple studies have demonstrated that approximately one-third of patients with HFpEF have normal brain natriuretic peptide concentrations despite elevated left-sided filling pressures contributing to underdiagnosis of this subtype of HF (8).

The study also highlights persistent gaps in guideline-directed medical therapy for both HF and COPD. Although much progress has been made in the past decade in the availability of novel disease-modifying therapies for HFrEF, and such therapies are now emerging for HFpEF, there continues to be substantial underutilization of these life-saving therapies. Recent data from the Change the Management of Patients with Heart Failure registry reported similar suboptimal rates of β -blockers (67%) and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (60%) in patients with HFrEF (9). Innovative and effective healthcare delivery strategies are needed to bridge the implementation gap of proven effective strategies, which may include nudges in the electronic health record, polypill, and gamification.

The study raises key questions about the pathobiology of comorbid COPD and HF. Shared mechanisms between COPD and HF (particularly HFpEF) may underlie their concurrent

evolution and explain the predisposition for comorbid disease. Specifically, cumulative exposures to shared clinical and social risk factors (e.g., health behaviors [e.g., tobacco exposure], environment, socioeconomic, healthcare access, and biologic factors [e.g., respiratory viral infections]) are important modifiable factors associated with risk of both COPD and HF (Figure 1) (10). Emerging evidence suggests that lung disease may contribute directly to the pathogenesis of HF, in part, through activation of systemic inflammatory pathways (11, 12). Although the current article focused on patients with a known diagnosis of COPD, there is evidence to support heart–lung interactions among those with impaired respiratory health, even in the absence of spirometric evidence of COPD or radiologic evidence of emphysema. Data from the Coronary Artery Risk Development in Young Adults study demonstrated that impaired lung function was associated with adverse cardiac remodeling on echocardiography and incident HF events (10, 13). Although symptomatic COPD and HF often occur in the elderly, many younger adults have relatively asymptomatic impairment in lung health and cardiac structure and function. These subclinical cardiopulmonary abnormalities that may develop from young adulthood to midlife support this period as a key

modifiable window for preventive interventions in asymptomatic or presymptomatic stages, when intervention may be of greatest benefit.

Based on the high incidence and poor prognosis of comorbid HF in patients with COPD, comprehensive chronic disease management for HF and COPD needs to

be prioritized. In addition to growing calls to close the persistent implementation gap for guideline-directed medical therapy for both conditions (14), prevention of HF in patients with COPD before the development of overt signs and symptoms needs to be addressed and may include targeting of shared risk factors and

mechanistic pathways. Shifting focus upstream to optimize both respiratory and heart health earlier in the life course is urgently needed to curb the growing burden of COPD and HF. ■

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

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Lung Transplantation Disparities among Patients with IPF: Recognition and Remedy

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In 1963, after decades of experiments on laboratory animals, the first lung transplantation in a human being was performed at the University of Mississippi. The procedure can hardly be considered a

success (the patient survived a mere 18 days), and for the next 2 decades, pulmonary transplantation led to consistently poor outcomes (1). In the 1980s, however, the introduction of cyclosporine, together with refined surgical techniques, revolutionized the field, and for the first time, some patients experienced long-term survival after pulmonary transplantation (1). By 1992–2001, median survival after adult lung transplant was 4.7 years, and by 2010–2017, it had risen to 6.7 years (2). These amount to precious years of added life, and improved

quality of life, for some patients with end-stage lung disease.

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