**Title:** Differences in outcomes between heart failure phenotypes in patients with coexistent COPD: A cohort study

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**Abstract**

**Aim:** Differences in clinical presentation and outcomes between HF phenotypes in patients with COPD have not been assessed. The aim of this study was to compare clinical outcomes and healthcare resource use (HRU) between patients with COPD and HF with preserved (HFpEF), mildly-reduced (HFmrEF), and reduced ejection fraction (HFrEF).

**Methods and results:** Patients with COPD and HF were identified in the United States (US) administrative claims database OptumLabs® DataWarehouse between 2008-2018. All-cause and cause-specific (HF) hospitalization, acute exacerbation of COPD (AECOPD, severe and moderate combined), mortality and HRU were compared between HF phenotypes. From 5,419 patients with COPD, 70% had HFpEF, 20% had HFrEF and 10% had HFmrEF. All-cause hospitalization did not differ across groups, however patients with COPD and HFrEF had a greater risk of HF-specific hospitalization (HR 1.54, 95%CI 1.29-1.84) and mortality (HR: 1.17, 95%CI 1.03-1.33) compared to patients with COPD and HFpEF. Conversely, patients with COPD and HFrEF had a lower risk of AECOPD compared with those with COPD and HFpEF (HR 0.75, 95%CI 0.66-0.87). Rates of long-term stays (in skilled-nursing facilities) and emergency room visits were lower for those with COPD and HFrEF than for those with COPD and HFpEF.

**Conclusion:** Outcomes in patients with comorbid COPD and HFpEF are largely driven by COPD. Given the paucity in treatments for HFpEF, better differentiation between cardiac and respiratory symptoms may provide an opportunity to reduce the risk of AECOPD. Risk of death and HF hospitalization were highest among patients with COPD and HFrEF, emphasizing the importance of optimizing guideline-recommended HFrEF therapies in this group.

**Keywords: COPD, heart failure**

**Introduction**

Chronic obstructive pulmonary disease (COPD) and left-sided heart failure (HF) commonly co-occur, due to risk factors including smoking and aging (1). COPD has also been shown to be associated with increased risk of hospitalization, death and worse quality of life in patients with concomitant HF (2-6).

Left ventricular ejection fraction (LVEF) is an important determinant of prognosis in HF and directs treatment pathway, as several disease-modifying therapies exist for those with HF with reduced ejection fraction (HFrEF) [LVEF<40%], but are lacking for those with HF with preserved ejection fraction (HFpEF) [LVEF>=50](7). Data on HF with mildly-reduced ejection fraction (HFmrEF) [LVEF 41-49%] are debated. HFrEF medications such as beta-blockers are frequently under-utilized in patients with COPD and HF(8-10), while COPD-targeted medication such as beta-agonists are associated with an increase in adverse cardiovascular events (11) in those with existing HFrEF(12) or precursors such as left ventricular systolic dysfunction(13).

Increasingly, it has been recognized that HF represents a dynamic syndrome, with a spectrum of phenotypes, exhibiting unique patient characteristics and potentially heterogeneous disease trajectories (14). When COPD is present, low-grade systemic inflammation may additionally contribute to the progression of atherosclerosis, ischemia and adverse cardiovascular events (4). The impact of LVEF HF phenotype is poorly described in patients with COPD but may have relevant implications for treatment planning.

We aimed to describe the clinical and sociodemographic characteristics of a cohort of patients with HF and comorbid COPD according to LVEF-based phenotype and assessed the association between HF phenotype and clinical outcomes, including all-cause and HF-specific hospitalization, acute exacerbation due to COPD (AECOPD), all-cause mortality and healthcare utilization.

**Methods**

*Data source*

We used the OptumLabs® Data Warehouse (OLDW)(15) a longitudinal, data asset including de-identified administrative claims linked with electronic healthcare records (EHR) to identify commercially insured (those receiving coverage through their employer) and Medicare Advantage patients (those qualifying for government insurance due to age ≥65 years or long-term disability; includes Part D coverage) at least 18 years old with incident HF in the US. The OLDW compares favorably with the insured population of the country(16) and represents a diverse population regarding age, race and US regions, including sociodemographic information for 73% of enrollees. It has been used to reliably investigate outcomes in HF and other indications(16, 17).

This study involved analysis of de-identified data. In accordance with the Health Insurance Portability and Accountability Act, it was exempt from Institutional Review Board approval.

*Study population*

Incident HF was defined as having minimum one episode of acute HF resulting in hospitalization, or two outpatient claims on different dates within the study period (1/1/2008 to 1/1/2018) containing International Classification of Diseases, Ninth or Tenth Revision(ICD9/ICD10) HF codes in any position and availability of LVEF data from linked EHR. Additional criteria were a COPD diagnosis (based on ICD codes) before HF (**Fig. 1, S1 Table, S1 Fig).**

*Covariates*

We assessed age, sex, race, insurance status, place of diagnosis, education and atrial fibrillation [AF], coronary artery disease [CAD], peripheral artery disease [PAD], cerebrovascular accident [CVA], hypertension, diabetes mellitus, obesity, depression, alcohol misuse disorder, dementia, cancer, peptic ulcer, liver disease and renal failure; identified using ICD9 or ICD10 codes recorded any time before HF (obesity and anemia were assessed in the previous 12 months). We identified pharmacy prescription claims, using National Drug Codes for: beta-blockers, angiotensin-converting-enzyme inhibitors [ACEi], angiotensin receptor blockers [ARBs], mineralocorticoid receptor antagonists [MRA], thiazide, potassium sparing and loop diuretics, short and long-acting beta-agonists and inhaled corticosteroids (ICS) containing regimens (**S2 Table**).

*Outcomes*

Our main outcome was all-cause hospitalization, defined as the first non-elective admission with at least one overnight stay, occurring within one year of, but not including the date of HF diagnosis. Secondary outcomes included HF-specific hospitalization, AECOPD, mortality, in-patient/outpatient healthcare resource use and costs. AECOPD was defined as either an inpatient admission with a primary diagnosis of COPD (severe), or an outpatient visit with a COPD code in any position and a procedure code for administration of a steroid or antibiotic, or a pharmacy claim for oral corticosteroid or antibiotic within 10 days of the visit (moderate).

*Statistical analysis*

Differences in baseline characteristics between HF groups were presented using chi-squared and Kruskall-Wallis tests with Bonferroni correction for multiple testing. Hospitalization, AECOPD and mortality were analyzed using Cox proportional-hazard regressions to calculate hazard ratios (HRs) and 95% confidence intervals (CI). For hospitalization and AECOPD analyses, patients were followed up for 12 months after HF diagnosis or censored at disenrollment or death. For mortality, patients were followed-up to a censoring date of 01/01/2019, or to disenrollment, whichever came first. This resulted in a maximum follow-up time of 120 months (median 27 months, IQR 16.95–42.36). An analysis to assess the competing risk of death before HF-hospitalization and AECOPD, was performed with a Fine-Gray model(18). Negative binomial regression models were used to assess the association between LVEF group and the rate of outpatient, office and emergency room (ER) visits, long-term stays, inpatient admissions and length of stay during one-year follow-up. Rate ratios and 95% CI were calculated. Confounders were added cumulatively in all analyses: first we added age, sex, race, education, medical insurance status, place of diagnosis, comorbidities and HF medications. Second, we added COPD medications and the finally adjusted models included smoking status. Statistical analyses were performed using R v3.6.2.

**Results**

*Baseline characteristics*

Of 5,419 patients with COPD and incident HF and LVEF recorded in OLDW, 70% had HFpEF, 20% had HFrEF and 10% had HFmrEF **(Fig 1)**. An assessment of patient characteristics of HF patients with and without LVEF measurement in OLDW is available in **S3 Table**.

The median age was 74 years [interquartile range (IQR) 67–80] and 50.1% of patients were males. Patients with COPD and HFpEF had a higher overall prevalence of comorbidities compared with either COPD and HFmrEF or COPD and HFrEF patients, except for CAD, which was more frequent in HFrEF and HFmrEF. 62% of patients in the COPD with HFpEF group were diagnosed with HF in an inpatient setting, compared with 56.3% patients with reduced and 52.8% of patients with mildly-reduced LVEF.

*Hospitalization*

In total, 1,980 (50.5%) of patients were admitted to hospital within one-year of HF diagnosis; Overall, 35.6% of all patients experienced either a moderate or severe AECOPD, making this the most frequent outcome in our cohort. 16.4% of all patients were admitted for HF, while a higher proportion of patients with HFrEF experienced this outcome compared to HFpEF (20% vs. 15.5%). Between-group differences revealed AECOPD prevalence among those with HFrEF was similar to HFmrEF, but lower compared to patients with HFpEF (29.4% in HFrEF and 29.9% in HFmrEF vs. 38% in HFpEF). Stratification by severity revealed moderate AECOPD was observed in similar proportions across all categories while severe AECOPD admissions occurred less frequently in the HFrEF group compared with HFpEF (7.2% vs 11.6%) **(Table 2)**.

There was an incremental rise in the risk of AECOPD associated with use of short, long-acting bronchodilators and ICS-regimens, compared to lack of COPD medication use. HF-admission was not impacted by COPD medication use (**S4 Table**).

**Table 3** highlights the main results. In the two partially adjusted models (model 1 and 2) and the fully adjusted model 3, there were no significant differences in all-cause admission across all patient groups. Cause-specific outcome analyses suggested patients in the COPD and HFrEF group, were, on average, more likely to experience a HF-specific admission versus patients with COPD and HFpEF (model 3,HRadj 1.54, 95%CI 1.29–1.84). The opposite relationship was observed for AECOPD: patients with COPD and HFrEF were less likely to have an AECOPD admission, compared with patients with COPD and HFpEF (model 3,HRadj 0.75 95%CI 0.66–0.87, **Fig 2**).

Results from the competing risk analysis indicated patients with COPD and HFrEF had a higher incidence of HF-admission and lower incidence of AECOPD, compared to those with COPD and HFpEF, when the competing risk of death was accounted for (**Fig. 3**).

*Mortality*

Crude mortality estimates did not differ significantly across LVEF groups (**S5 Table**), however the fully adjusted model revealed that patients with COPD and HFrEF were at an increased risk of death compared to those with COPD and HFpEF (HRadj 1.16, 95%CI 1.03-1.32), with a median survival of 27 months (IQR 16.9–42.3) (**S2** **Fig.**).

*Healthcare resource utilization*

Median costs for outpatient visits were higher for COPD and HFrEF compared to the other groups **(S6 Table).** In unadjusted analyses, rates of outpatient visits, long-term care stays, inpatient stays and associated length of stay and ER admissions, differed by EF group. After adjusting for potential confounders, differences remained in the rates of long-term hospital stays in skilled-nursing facilities (with an overall decreased rate of events for patients with COPD and HFrEF compared with those with COPD and HFpEF, RRadj, 0.76, 95%CI 0.62-0.94) and ER visits, which were lower for both COPD and HFrEF (RRadj 0.86, 95%CI 0.76 - 0.97) and COPD and HFmrEF patients (RRadj 0.85, 95%CI 0.76 - 0.93) compared with the COPD and HFpEF group. Patients COPD and HFrEF experienced shorter lengths of inpatient stay compared with those with COPD and HFpEF (**S7 Table**).

*Medication*

Patients with COPD and HFrEF saw the highest increase in HF-related medication from baseline to one-year follow-up. ACEi/ARB prescriptions increased from 54.6% to 74.7% and non-cardioselective beta-blockers prescriptions from 26.7% to 49.4%. The COPD and HFrEF and HFmrEF groups had lower levels of short-acting and long-acting beta-agonists and steroids prescribed compared with the COPD and HFpEF group. However, levels of COPD pharmacotherapy remained overall low, as not more than 44% of patients in any group had a prescription (**S3 Fig**).

**Discussion**

This is the largest study to date to describe characteristics of patients with concomitant COPD and HF according to LVEF-based phenotype. The most common HF phenotype in this COPD population was HFpEF. Patients with coexisting COPD and HFrEF had a lower overall burden of comorbidities, and prescriptions for COPD-specific medication, compared to patients with COPD and HFpEF. Individuals with COPD and HFrEF also had lower risk of AECOPD, and lower rates of long-term and ER visits and longer inpatient stays. In contrast, patients with COPD and HFrEF were at increased risk of HF-specific admission and had poorer survival compared to patients with COPD and HFpEF.

*Baseline characteristics*

A lower prevalence of HFrEF compared to HFpEF in COPD cohorts has been shown previously (2, 4, 19, 20), however, while prior studies have evaluated characteristics and outcomes of patients with COPD and HFrEF (21, 22), we provide the largest comparison to date across all HF phenotypes. A previous, smaller study conducted in a population of patients with COPD reported a distinct pattern of baseline characteristics associated with HFpEF versus HFrEF, compared with our report. Kuown and colleagues(23) included 184 highly selected outpatients from South Korea, excluding those with serious comorbidities and thus limiting generalizability to the larger population of patients with comorbid COPD and HF. Their use of a single LVEF cut-off of 50% EF value to categorize patients as either HFrEF (<50%) or HFpEF (>=50%), may have masked potentially distinct findings for HFmrEF. Comorbidity patterns differed across their study and ours, likely due to differences in study design, sample size and geographical location. For example, cardiovascular disease (AF: 49.3% OLDW vs. 38% Kwon et al, hypertension: 97.3% vs. 49%) and non- cardiovascular comorbidities (diabetes: 47.1% vs. 32%) were more prevalent in our sample while anemia was more prevalent in the Asian sample (53% Kwon vs. 32.5% OLDW). The overall prevalence of comorbid conditions in our study was also higher than rates previously reported. In comparison to Kuown and colleagues(23), those with COPD and HFpEF had a higher uptake of COPD medications, particularly ICS-containing regimens, which are prescribed to severe cases, according to the GOLD guidelines(24). Thus, our results suggest there was a higher proportion of severe COPD patients with HFpEF compared with HFrEF.

Compared with a general HFrEF population(25), uptake across all HF-recommended medication classes was lower in patients with COPD and HFrEF, both at baseline and at one-year follow up, as has been shown previously(26). Treatment rates captured in our study are significantly lower compared with registry data(27), perhaps due to more restrictive inclusion criteria in such studies which exclude frail or more severe patients. This suggests a potential link between COPD and underuse of HF medications, particularly in our sample drawn from and administrative databases which captures a comprehensive and diverse cohort of patients. *Admission*

Patients with COPD had similar risk of all-cause hospitalization, regardless of EF phenotype reflecting findings from the general HF population(19, 28). Those with COPD and HFrEF were more likely to experience a HF hospitalization, compared with those with COPD and HFpEF, even after accounting for the competing risk of death. However, HF hospitalization definition did not include events recorded in ambulatory settings; thus, this analysis excluded less severe HF decompensation events.

The higher prevalence of CAD in for patients with COPD and HFrEF may be associated with a higher propensity towards adverse cardiovascular outcomes(29, 30) compared with COPD and HFpEF. Conversely, those with COPD and HFrEF were less likely to experience an AECOPD compared with patients with COPD and HFpEF (**Tables 2-3**). This suggests differences in COPD disease burden or presentation depending on the LVEF phenotype in patients with concomitant HF.

That patients with COPD and HFpEF, respectively HFrEF exhibited different cause-specific outcomes despite having similar rates of any-cause hospitalization may be underlined by the distinct pathophysiology of HFrEF (driven by myocardial processes) versus HFpEF, believed to be triggered by comorbidities such as hypertension, obesity and COPD, which interact to cause a systemic inflammatory state, resulting in HFpEF(31-33).

We found that, on average, the clinical trajectory of patients with COPD and HFpEF appears to be dominated by COPD outcomes. One explanation is the presence of more severe COPD(34) in this subgroup, compared with COPD and HFrEF, evidenced by a higher requirement for COPD-related medication. It is also possible that some misclassification of the cause of admission may have affected results, related to coding practices (i.e., lack of documentation of HF decompensation during admission in the presence of AECOPD treatment, or assigning HF as a secondary cause of admission, thereby potentially underestimating HF admission risk in those with COPD and HFpEF). However, an analysis exploring the relationship between COPD-medication regimens and cause-specific outcomes revealed steroid use was associated with a three-fold increased risk of AECOPD but not HF-admission suggestive of a possible association of COPD severity rather than misclassification in our cohort.

HFpEF is a notoriously difficult diagnosis to make(35), due to a lack of standard criteria and non-specific symptoms that require validation and clinical interpretation from several investigations(4, 19). This may be even more challenging in the presence of COPD, particularly in studies relying on ICD codes for cohort identification such as ours. The tendency to attribute respiratory symptoms to an underlying pulmonary disease rather than a cardiac one may be more prevalent in situations where echocardiography quality is limited, as may occur in patients with COPD(4). There is ongoing debate regarding the optimal diagnostic workup for HF in the context of COPD (36). Future prospective studies including clinical adjudication of diagnoses are needed to investigate the degree to which COPD symptoms may be misclassified as HFpEF (and vice versa), as well as whether the increase in AECOPD risk observed in those with HFpEF is true versus misattribution of cardiac events.

The proportion of patients diagnosed with HFpEF inpatient was higher compared to those with HFrEF. Due to high heterogeneity in clinical characteristics and the existence of many comorbidities, patients with COPD and HFpEF may be more difficult to accurately diagnose or manage in outpatient, generalist settings as compared with COPD and HFrEF. Misdiagnosis or delay in diagnosis may be further exacerbated by the presence of COPD, with greater diagnostic uncertainty for HFpEF versus HFrEF (for which more robust diagnostic criteria are defined(37). Alternatively, HFpEF patients may have less contact with primary care services, as documented previously, providing less opportunities for diagnosis in outpatient settings (38).

*Mortality*

We report a 16% increase in mortality for patients diagnosed with COPD and HFrEF compared with those with COPD and HFpEF, within a median follow-up of 27 months. Data regarding mortality rates between HF phenotypes are conflicting(39), with most observational data in the general HF population suggesting that there is no overall difference between the two HF phenotypes(19), while a large meta-analysis, driven mainly by clinical trial results, revealed a (7)50% lower risk of death for HFpEF compared to HFrEF(40). Our data suggest that in patients with COPD, HFrEF is associated with a poorer overall survival as compared to with a diagnosis of HFpEF. As there are proven prognostic therapies for patients with HFrEF (regardless of presence of other comorbidities), the low uptake of guideline recommended medication in our cohort may underlie this result. Management of HFpEF is currently based on symptom alleviation and comorbidity management only, as there are no approved evidence-based disease-modifying treatments(7). Surprisingly, these patients fared better than those with HFrEF, suggesting that in patients with COPD, HFrEF may carry a heavier mortality burden compared to with a diagnosis of HFpEF. This interpretation is in agreement with the observation that those with HFpEF experience a higher proportion of deaths due to non-cardiovascular causes versus those with HFrEF, as a consequence of a higher burden of non-cardiovascular comorbidities(41).

*Healthcare resource utilization*

Patients with comorbid COPD and HFrEF were less likely to experience long-term stays and ER visits, but not inpatient visits; however, when they were admitted, they had a shorter length of stay, on average, compared to those with COPD and HFpEF. These results highlight different clinical trajectories between the two groups and may reflect the lower prevalence of comorbidities and higher levels of guideline-recommended prescription medication for those with COPD and HFrEF as well as potential management uncertainty for those with COPD and HFpEF. This may induce a vulnerability towards longer hospitalization duration compared with the COPD and HFrEF group. Additionally, higher overall healthcare costs observed in the COPD and HFpEF group also reflect the overall greater disease burden seen in this group (i.e., higher prevalence of diabetes, renal failure, depression).

**Strengths and limitations**

Our sample is generalizable to the commercially insured and Medicare Advantage US population with COPD and HF. Diagnoses were based on ICD codes though these have been validated(42-44) and to ensure validity of LVEF categories, we limited our sample to patients with echocardiographic data. While patients were largely similar on key variables such as age, sex, most sociodemographic factors and other comorbidities, comparison with previous data from OLDW(45) suggests patients with HF with LVEF recorded had increased prevalence of obesity and AF and were more often insured by Medicare or White, compared with those without LVEF recorded. However, only a minority of patients had LVEF data available in the OLDW, which may reflect a “system-wide” missingness of this variable throughout the database. Still, there may be other factors which may help establish the exact pattern of LVEF missingness.

Using LVEF to categorize HF comes with limitations as this determinant is not always measured accurately, and measurement can vary across technology used(46). However, we used the most recent recent classification(47), with the caveat that we were not able to distinguish improved EF due to lack of data.

Spirometry was not documented for this cohort, however, use of validated COPD codes, which have up to 85% accuracy (48) and assessment of COPD-related medication improved the precision of diagnosis, which is difficult in HF. This is due to potential obstruction related to cardiac decompensation (4), which can confound pulmonary testing and therefore, COPD diagnosis(4, 8, 49). Overdiagnosis of COPD due to underlying, but unrecognized HF cannot be excluded(50). Nevertheless, the assessment of COPD as a prevalent disease in addition to HF limited potential misclassification. Future studies where lung function measurements are performed on euvolemic patients with HF are needed to validate COPD diagnosis.

As we used claims data, we were unable to capture prescriptions not submitted to insurance, therefore, we cannot rule out an underestimation of prescription rates. We did not assess use of sacubitril/valsartan due to low prevalence of this medication in a previous cohort using the same data source (45). However, other studies identifying patients using prescription rather than diagnosis claims have shown sacubitril/valsartan is underused due to slow adoption of the drug due to high cost(51). Regardless of design, previous data suggest that uptake of guideline-recommended medication is low for patients with either HF(17, 52), COPD(53-55) or those with both diseases(23).

We did not adjust for duration or severity of COPD in analyses, however, we controlled for use of diuretics, which may be considered a proxy for the presence of congestion, and COPD medication regimens, which may serve as a proxy for severity of disease (or GOLD stage). Cause-specific outcomes are dependent on ICD coding which are subject to misclassification.

Education and race information was based on public or imputed predictive data in OLDW, which was not validated with self-report data (56-58); however methods for imputing race have shown to have moderate positive predictive value (71%) for identifying race(59).

We did not account for mortality as a competing risk to hospitalization beyond one-year follow-up, due to limitations in recording of death in OLDW(45).Finally, while adjusted for potential confounders, we cannot exclude residual confounding.

**Conclusion**

Among patients with COPD and HF, HFpEF is the most common HF-phenotype. Outcomes in the COPD-HFpEF group were largely driven by COPD, as AECOPDs were more frequent compared with the COPD-HFrEF group, perhaps due to more severe COPD.

While improvements have been observed with emerging therapies such as SGLT2is and sacubitril/valsartan for subgroups of patients with HFpEF, management strategies to treat the the significant multi-morbidity burden in these patients are still needed. A more comprehensive primary care assessment to differentiate between cardiac and respiratory symptoms with greater precision and emphasis on the recognition and management of COPD, may provide an opportunity to reduce AECOPD and improve outcomes for these patients. Conversely, patients with COPD-HFrEF were more likely be admitted to hospital for a HF decompensation, and had overall poorer survival, compared with COPD-HFpEF, emphasizing the importance of optimizing guideline-directed HF medication in this group.

**Competing interests**

CG and RZ have nothing to declare. Prof. Quint’s research group has received funds from AZ, GSK, The Health Foundation, MRC, British Lung Foundation, IQVIA, Chiesi, and Asthma UK outside the submitted work; grants and personal fees from GlaxoSmithKline, Boehringer Ingelheim, AstraZeneca, Bayer, Insmed outside the submitted work.

**Data availability**

The data that support the findings of this study are available from OptumLabs, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of OptumLabs. Access to these data is only available through entering into an exclusive institutional partnership agreement with OptumLabs, under which this study was conducted.

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**Author contributions**

Conceptualization & Methodology: CG, JKQ, RZ. Original draft: CG. Editing and final approval: CG, JKQ, RZ; Data curation & Formal data analysis: CG; Data acquisition: JKQ.

**Figure legends**

**Fig 1** Study flow (inclusion of patients) *[COPD= chronic obstructive pulmonary disease; HF= heart failure; EF= ejection fraction; HFpEF= heart failure with preserved ejection fraction; HFmEF= heart failure with mildly-reduced ejection fraction; HFpEF= heart failure with reduced ejection fraction]*

**Fig 2** Association between LVEF phenotype and risk of A) AECOPD and B) HF-admission, in a population of patients with COPD-HF, within one-year of HF diagnosis *[LVEF=left ventricular ejection fraction; HF= heart failure, AECOPD= acute exacerbation due to COPD, No.= number; CI= confidence intervals]*

**Fig 3** Cumulative incidence for competing risk events (HF-admission, AECOPD, death) in a cohort of patients with COPD-HF, within one-year of HF diagnosis *[AECOPD= acute exacerbation due to COPD; HF=heart failure; HFpEF= heart failure with preserved ejection fraction; HFmrEF= heart failure with mid-range ejection fraction; HFrEF= heart failure with reduced ejection fraction]*

**Table 1. Baseline characteristics of patients with COPD-HF stratified by LVEF phenotype.**

|  | **HFpEF (N=3843)** | **HFmrEF (N=562)** | **HFrEF (N=1014)** | **Overall (N=5419)** |
| --- | --- | --- | --- | --- |
| **Age (years)** |  |  |  |  |
| Median [IQR] | 75 [67, 81] | 73 [66.3, 79] | 72 [65, 79] | 74 [67., 80] |
| Male | 1684 (43.8%) | 365 (64.9%) | 668 (65.9%) | 2717 (50.1%) |
| **Comorbidities at baseline** |  |  |  |  |
| AF | 1911 (49.7%) | 278 (49.5%) | 481 (47.4%) | 2670 (49.3%) |
| Alcohol misuse disorder | 175 (4.6%) | 33 (5.9%) | 41 (4.0%) | 249 (4.6%) |
| Anemia | 1368 (35.6%) | 133 (23.7%) | 258 (25.4%) | 1759 (32.5%) |
| CAD | 2909 (75.7%) | 493 (87.7%) | 896 (88.4%) | 4298 (79.3%) |
| CVA | 1949 (50.7%) | 257 (45.7%) | 449 (44.3%) | 2655 (49.0%) |
| Liver disease | 625 (16.3%) | 89 (15.8%) | 118 (11.6%) | 832 (15.4%) |
| Cancer | 984 (25.6%) | 141 (25.1%) | 227 (22.4%) | 1352 (24.9%) |
| Dementia | 284 (7.4%) | 24 (4.3%) | 49 (4.8%) | 357 (6.6%) |
| Depression | 939 (24.4%) | 122 (21.7%) | 149 (14.7%) | 1210 (22.3%) |
| Diabetes | 1905 (49.6%) | 249 (44.3%) | 400 (39.4%) | 2554 (47.1%) |
| PAD | 2327 (60.6%) | 330 (58.7%) | 520 (51.3%) | 3177 (58.6%) |
| Hypertension | 3747 (97.5%) | 546 (97.2%) | 978 (96.4%) | 5271 (97.3%) |
| Renal failure | 1169 (30.4%) | 154 (27.4%) | 209 (20.6%) | 1532 (28.3%) |
| Peptic ulcer | 322 (8.4%) | 38 (6.8%) | 54 (5.3%) | 414 (7.6%) |
| Obesity | 1733 (45.1%) | 194 (34.5%) | 347 (34.2%) | 2274 (42.0%) |
| **Place of diagnosis** |  |  |  |  |
| Outpatient | 1461 (38.0%) | 265 (47.2%) | 443 (43.7%) | 2169 (40.0%) |
| Inpatient | 2382 (62.0%) | 297 (52.8%) | 571 (56.3%) | 3250 (60.0%) |
| **COPD medications at baseline** |  |  |  |  |
| No COPD treatment | 2127 (55.3%) | 354 (63.0%) | 630 (62.1%) | 3111 (57.4%) |
| Short-acting bronchodilator | 560 (14.6%) | 83 (14.8%) | 144 (14.2%) | 787 (14.5%) |
| Long-acting bronchodilator | 198 (5.2%) | 19 (3.4%) | 51 (5.0%) | 268 (4.9%) |
| ICS containing regimen | 958 (24.9%) | 106 (18.9%) | 189 (18.6%) | 1253 (23.1%) |
| **HF-medications at baseline** |  |  |  |  |
| ACEIs/ARBs | 1896 (49.3%) | 301 (53.6%) | 554 (54.6%) | 2751 (50.8%) |
| Beta-blockers | 2203 (57.3%) | 388 (69%) | 612 (60.4%) | 3203 (59.1%) |
| MRA | 185 (4.8%) | 28 (5.0%) | 64 (6.3%) | 277 (5.1%) |
| Thiazide diuretics | 596 (15.5%) | 77 (13.7%) | 109 (10.7%) | 782 (14.4%) |
| Loop diuretics | 1511 (39.3%) | 171 (30.4%) | 309 (30.5%) | 1991 (36.7%) |
| **Sociodemographic variables** |  |  |  |  |
| **Smoking status** |  |  |  |  |
| Current smoker | 828 (21.5%) | 146 (26.0%) | 303 (29.9%) | 1277 (23.6%) |
| Never smoked | 749 (19.5%) | 85 (15.1%) | 126 (12.4%) | 960 (17.7%) |
| Not currently smoking | 380 (9.9%) | 46 (8.2%) | 85 (8.4%) | 511 (9.4%) |
| Previously smoked | 1555 (40.5%) | 248 (44.1%) | 400 (39.4%) | 2203 (40.7%) |
| Missing | 331 (8.6%) | 37 (6.6%) | 100 (9.9%) | 468 (8.6%) |
| **Education\*\*** |  |  |  |  |
| Bachelor’s degree Plus | 406 (10.6%) | >42 (>7.4%)\* | >98 (>9.7%)\* | 560 (10.3%) |
| High School Diploma | 1259 (32.8%) | 182 (32.4%) | 364 (35.9%) | 1805 (33.3%) |
| Less than bachelor’s degree | 2160 (56.2%) | 327 (58.2%) | 541 (53.4%) | 3028 (55.9%) |
| Missing | 18 (0.5%) | <11 (<2%)\* | <11 (<2%)\* | 26 (0.5%) |
| **Income (U.S dollars)** |  |  |  |  |
| <$40,000 | 1386 (36.1%) | 184 (32.7%) | 349 (34.4%) | 1919 (35.4%) |
| $40,000-$74,000 | 1083 (28.2%) | 158 (28.1%) | 274 (27.0%) | 1515 (28.0%) |
| $75,000-$124,999 | 633 (16.5%) | 121 (21.5%) | 194 (19.1%) | 948 (17.5%) |
| $125,000-$199,999 | 189 (4.9%) | 25 (4.4%) | 53 (5.2%) | 267 (4.9%) |
| $200,000+ | 67 (1.7%) | 16 (2.8%) | 23 (2.3%) | 106 (2.0%) |
| Missing | 485 (12.6%) | 58 (10.3%) | 121 (11.9%) | 664 (12.3%) |
| **Race\*\*\*** |  |  |  |  |
| White | 3037 (79.0%) | 456 (81.1%) | 815 (80.4%) | 4308 (79.5%) |
| Black | 491 (12.8%) | 59 (10.5%) | 114 (11.2%) | 664 (12.3%) |
| Hispanic | 92 (2.4%) | 13 (2.3%) | 27 (2.7%) | 132 (2.4%) |
| Asian | 36 (0.9%) | < 11 <2%)\* | <11 (<1%)\* | 48 (0.9%) |
| Missing | 187 (4.9%) | > 23 (>4.1%)\* | >47 (>4.6%)\* | 267 (4.9%) |
| \* Exact numbers not presented in order to comply with OptumLabs DataWarehouse cell size suppression policy.  \*\*Education is derived from US Census Bureau’s American Community survey data. The median level of education obtained by individuals within a specified census group is assigned to each enrollee.  \*\*\* Derived from public information from a national supplier of marketing data, using a proprietary algorithm.  Abbreviations ACEis= angiotensin-converting-enzyme inhibitors; AF= atrial fibrillation; ARB = angiotensin receptor blockers; CAD=coronary artery disease; COPD= chronic obstructive pulmonary disease; CVA= cerebrovascular disease; HFmrEF= heart failure with mid-range ejection fraction; HFpEF= heart failure with preserved ejection fraction HFrEF= heart failure with reduced ejection fraction; ICS= inhaled corticosteroids; IQR= inter-quartile range; PAD= peripheral artery disease; MRA= mineralocorticoid receptor antagonists; U.S= United States. | | | | |

**Table 2. Frequency of clinical outcomes in a cohort of patients with COPD-HF, according to LVEF phenotype, within one-year of HF diagnosis**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Outcome** | **HFpEF (n=3843)** | **HFmrEF (n=562)** | **HFrEF (n=1014)** | **Overall (n=5419)** | ***P*-value\*\*** |
| All-cause admission | 1980 (51.5%) | 269 (47.9%) | 485 (47.8%) | 2734 (50.5%) | 0.555 |
| HF-specific admission | 595 (15.5%) | 89 (15.8%) | 203 (20.0%) | 887 (16.4%) | <0.01 |
| Any AECOPD\* | 1462 (38%) | 168 (29.9%) | 298 (29.4%) | 1928 (35.6%) | <0.001 |
| Severe AECOPD | 446 (11.6%) | 52 (9.3%) | 73 (7.2%) | 571 (10.5%) | <0.001 |
| Moderate AECOPD | 1265 (32.9%) | 138 (24.6%) | 254 (25.0%) | 1657 (30.6%) | 0.639 |
| Abbreviations: AECOPD= acute exacerbation of COPD; COPD= chronic obstructive pulmonary disease; HF= heart failure; HFpEF= heart failure with preserved ejection fraction; HFmrEF= heart failure with mid-range ejection fraction; HFrEF= heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction.  \*Only first AECOPD counted (moderate or severe)  \*\*Overall p-value, corrected for multiple testing using the Bonferroni correction. | | | | | |

**Table 3. Association between LVEF phenotype and all-cause admission, HF-admission and AECOPD in a cohort of patients with COPD-HF, within one-year of HF diagnosis.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Outcome and LVEF group** | **Unadjusted HR (95% CI)** | **Model 1\* HR (95% CI)** | **Model 2**† **HR (95% CI)** | **Model 3**‡ **HR (95% CI)** |
|  |  |  |  |  |
| **All-cause admission**  **(N=5,126)** |  |  |  |  |
| **HFpEF** | Ref. | Ref. | Ref. | Ref. |
| HFmrEF | 0.91 (0.80 - 1.04, p=0.168) | 1.01 (0.88 - 1.15, p=0.924) | 1.01 (0.88 - 1.15, p=0.925) | **1.01 (0.88 - 1.16, p=0.888)** |
| HFrEF | 0.91 (0.82 - 1.01, p=0.064) | 1.05 (0.95 - 1.17, p=0.343) | 1.05 (0.95 - 1.17, p=0.352) | **1.07 (0.96 - 1.20, p=0.224)** |
|  |  |  |  |  |
| **HF-hospitalization**  **(N=5,126)** |  |  |  |  |
| **HFpEF** | Ref. | Ref. | Ref. | Ref. |
| HFmrEF | 1.03 (0.82-1.28, p=0.812) | 1.09 (0.87-1.38, p=0.451) | 1.09 (0.86 - 1.38, p=0.609) | **1.03 (0.81-1.32, p=0.799)** |
| HFrEF | 1.34 (1.14-1.57, p<0.001) | 1.54 (1.30-1.83, p<0.001) | 1.53 (1.29 - 1.82, p<0.05) | **1.54 (1.29-1.84, p<0.001)** |
|  |  |  |  |  |
| **AECOPD**  **(N=5,126)** |  |  |  |  |
| **HFpEF** | Ref. | Ref. | Ref. | Ref. |
| HFmrEF | 0.74 (0.63-0.86, p<0.001) | 0.78 (0.66-0.92, p=0.003) | 0.83 (0.71-0.99, p=0.033) | **0.82 (0.69-0.97, p=0.024)** |
| HFrEF | 0.72 (0.64-0.82, p<0.001) | 0.75 (0.66-0.86, p<0.001) | 0.78 (0.68-0.89, p<0.001) | **0.75 (0.65-0.97, p<0.001)** |
| Abbreviations: AECOPD= acute exacerbation due to chronic obstructive pulmonary disease; CI= confidence intervals; HR= hazard ratio; HF= heart failure; HFmrEF= heart failure with mildly-reduced ejection fraction; HFpEF= heart failure with preserved ejection fraction; HFrEF= heart failure with reduced ejection fraction; LVEF= left ventricular ejection fraction; ref= reference.  \*Adjusted for: age, sex, race, education, medical insurance status, whether diagnosis was gained in-patient or in out-patient and HF medications; patients with missing data on race were excluded (267) and education (26)  †Adjusted for age, sex, race, education, medical insurance status, whether diagnosis was gained in-patient or in out-patient and HF medications, COPD medications; patients with missing data on race were excluded (267) and education (26)  ‡Adjusted for age, sex, race, education, medical insurance status, whether diagnosis was gained in-patient or in out-patient and HF medications, COPD medications; smoking status; patients with missing data on race were excluded (267) and education (26) | | | | |

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