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Synergistic Impact of ICS/LABA and LAMA Therapy on Mortality and Hospitalization in Heart Failure Patients with Asthma-COPD Overlap

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Abstract

The clinical intersection of heart failure (HF) and chronic obstructive airway diseases, particularly asthma and chronic obstructive pulmonary disease (COPD), represents a complex cardiopulmonary phenotype that presents substantial diagnostic and therapeutic challenges. This observational registry-based study analyzed 200 patients to examine the association of combined inhaled corticosteroid/long-acting beta-2 agonist (ICS/LABA) plus long-acting muscarinic antagonist (LAMA) therapy with all-cause mortality, hospitalization frequency, and cardiopulmonary clinical characteristics.

Across the 24-month observation period, patients receiving ICS/LABA + LAMA had lower observed mortality than patients receiving ICS/LABA alone, including within the asthma-COPD overlap (ACO) subgroup. However, because treatment assignment was not randomized, these differences should be interpreted as associations rather than definitive causal treatment effects. Multivariable logistic regression identified higher log-transformed N-terminal pro-B-type natriuretic peptide (NT-proBNP) as the strongest independent predictor of frequent hospitalization in the reported model, whereas the treatment coefficients shown in the available regression output were not independently significant.

The clinical findings are biologically consistent with published evidence showing that effective bronchodilation can reduce pulmonary hyperinflation and improve cardiopulmonary mechanics, while inhaled corticosteroid therapy may provide additional benefit in appropriately selected patients with asthma features or eosinophilic inflammation. No clear cardiovascular safety signal was identified in this cohort, although the observational design does not permit definitive conclusions regarding arrhythmia risk or cardiovascular safety. Overall, the results support coordinated cardiopulmonary assessment and individualized inhaled therapy in patients with HF and coexisting obstructive airway disease, while emphasizing the need for prospective randomized studies to determine whether triple inhaled therapy directly reduces mortality or hospitalization in this specific high-risk population.

Keywords: heart failure, asthma-COPD overlap, COPD, asthma, ICS/LABA, LAMA, triple inhaled therapy, NT-proBNP, hospitalization, mortality

1. INTRODUCTION

The contemporary landscape of cardiovascular and pulmonary medicine is increasingly shaped by the complex interplay of multimorbidity. Among these clinical intersections, the co-occurrence of heart failure (HF) with chronic obstructive airway diseases—namely asthma and chronic obstructive pulmonary disease (COPD)—represents a particularly formidable diagnostic and therapeutic challenge [1, 2]. This cardiopulmonary coexistence involves bidirectional pathophysiological interactions in which cardiac dysfunction can worsen pulmonary gas exchange and airway mechanics, while chronic pulmonary inflammation and mechanical hyperinflation can adversely affect right- and left-ventricular performance [3, 4].

Within this spectrum, patients who exhibit concurrent clinical, spirometric, and inflammatory features of both asthma and COPD—a heterogeneous clinical phenotype commonly described as asthma-COPD overlap (ACO)—constitute a clinically complex subgroup [5]. Epidemiological and registry-based studies indicate that individuals with ACO experience a disproportionately high burden of acute exacerbations, accelerated decline in forced expiratory volume in one second (FEV1), profound impairment in health-related quality of life, and elevated rates of emergency department visits and hospital admissions compared to patients with either condition in isolation [6, 7]. When complicated by concomitant heart failure, the clinical trajectory becomes particularly complex, as symptoms of dyspnea, fatigue, and fluid retention overlap extensively, frequently leading to diagnostic misclassification, delayed therapeutic intervention, and increased mortality [8, 9].

The physiological mechanisms binding heart failure and obstructive airway diseases are intricate and mutually reinforcing. In patients with HF, elevated left ventricular filling pressures lead to pulmonary venous hypertension, interstitial and alveolar edema, and reflex bronchoconstriction, effectively increasing airway resistance and work of breathing [10]. Conversely, chronic airway obstruction and hyperinflation in COPD and asthma elevate intrathoracic pressure swings during the respiratory cycle, imposing an increased inspiratory threshold load and augmented left ventricular afterload, which progressively impairs myocardial relaxation and systolic performance [11, 12]. Furthermore, systemic low-grade inflammation—mediated by C-reactive protein, interleukin-6, tumor necrosis factor-alpha, and various interleukins—characterizes both severe asthma/COPD and advanced heart failure, accelerating systemic endothelial dysfunction, atherosclerosis, and myocardial remodeling [13, 14].

Despite the profound epidemiological impact of this overlap, cardiovascular and pulmonary guidelines have historically been developed largely within their respective disease-specific frameworks [15, 16]. Cardiologists frequently hesitate to prescribe optimal doses of bronchodilators—particularly long-acting beta-2 agonists (LABA) and long-acting muscarinic antagonists (LAMA)—due to theoretical concerns regarding tachycardia, arrhythmogenesis, and myocardial oxygen demand [17]. Conversely, pulmonologists may underutilize evidence-based heart failure therapies or misinterpret elevated natriuretic peptide levels as purely secondary to acute pulmonary exacerbations [18, 19]. Such therapeutic uncertainty can contribute to undertreatment or fragmented care and may leave patients vulnerable to recurrent decompensation.

Pharmacologically, the management of ACO in the presence of heart failure requires a delicate balance between achieving maximal bronchodilation, mitigating airway inflammation, and preserving cardiovascular stability. Inhaled Corticosteroids (ICS) combined with LABA form a foundational therapeutic pillar, providing bronchodilation through the LABA component and anti-inflammatory activity through the ICS component [20, 21]. However, ICS/LABA therapy may be insufficient in patients with persistent airflow limitation, hyperinflation, or recurrent exacerbations despite treatment [22, 23].

The incremental therapeutic addition of a Long-Acting Muscarinic Antagonist (LAMA)—thereby establishing an ICS/LABA + LAMA triple inhaled regimen that combines dual bronchodilation with anti-inflammatory therapy—has emerged as a major advancement in general obstructive airway management [24]. By simultaneously targeting beta-2 adrenergic receptors and muscarinic M3 receptors, the LABA/LAMA bronchodilator components target complementary adrenergic and muscarinic pathways and can improve airflow and lung deflation, reduces residual volume, and improves inspiratory capacity [25, 26]. Nevertheless, the specific physiological and clinical impacts of this combined regimen on heart failure patients with ACO—particularly regarding the delicate balance between respiratory improvement and cardiac safety—remain insufficiently explored in randomized controlled trials [27, 28].

To address this critical knowledge gap, the present study undertakes a detailed observational investigation of 200 well-characterized patients presenting with heart failure and concurrent obstructive airway disease. By analyzing detailed clinical registries, baseline hemodynamic parameters, comprehensive biomarker profiles (including NT-proBNP), and longitudinal healthcare utilization metrics, this research aims to: (1) evaluate the association of of the ICS/LABA + LAMA regimen versus ICS/LABA monotherapy in reducing all-cause mortality and acute hospitalization frequency; (2) elucidate the physiological mechanisms by which dual bronchodilation influences cardiac afterload and cardiopulmonary stability; (3) assess the cardiovascular safety profile of intensive bronchodilator therapy in failing myocardium; and (4) establish independent predictors of adverse clinical outcomes through sophisticated multivariate logistic regression modeling. Through these efforts, we aim to provide additional evidence for integrated cardiopulmonary care pathways.

2. METHODOLOGY

This investigation was designed as an observational, registry-based cohort study with cross-sectional baseline characterization and longitudinal follow-up encompassing 200 adult patients diagnosed with chronic heart failure and concomitant obstructive pulmonary diseases (asthma, COPD, or Asthma-COPD Overlap). The study protocol was structured in strict adherence to the ethical guidelines outlined in the Declaration of Helsinki and received comprehensive institutional review board approval. Patient data were assembled from retrospective and prospectively recorded clinical data from specialized cardiopulmonary out-patient clinics and inpatient registries over a 24-month observation period.

To improve internal validity and clinical relevance, predefined inclusion and exclusion criteria were applied. Inclusion criteria mandated: (1) a confirmed, documented diagnosis of chronic heart failure of any ejection fraction phenotype—including heart failure with reduced ejection fraction (HFrEF, EF $\leq$ 40%), heart failure with mildly reduced ejection fraction (HFmrEF, EF 41-49%), and heart failure with preserved ejection fraction (HFpEF, EF $\geq$ 50%)—diagnosed in accordance with established European Society of Cardiology (ESC) and American Heart Association (AHA) criteria [15, 16]; (2) an established, documented diagnosis of asthma, COPD, or ACO based on clinical history, spirometric demonstration of persistent airflow limitation (post-bronchodilator FEV1/FVC < 0.70 for COPD, and documented reversible airflow obstruction or hyper-responsiveness for asthma/ACO) following GOLD and GINA guidelines [1, 2]; (3) age of 18 years or older; and (4) a minimum of 12 months of continuous clinical follow-up data within the healthcare network. Exclusion criteria comprised: (1) acute pulmonary embolism or acute coronary syndrome within three months preceding enrollment; (2) primary pulmonary arterial hypertension; (3) severe confounding hepatic or renal failure (estimated glomerular filtration rate < 15 mL/min/1.73m^2 or receiving renal replacement therapy); (4) active malignant neoplasms with life expectancy under one year; and (5) incomplete medical records lacking essential biomarker or spirometric data.

Following screening, the cohort of 200 patients was stratified based on pulmonary phenotype and prescribed pharmacological regimens. Pulmonary phenotyping classified the cohort into three distinct clinical subgroups: - *Asthma-COPD Overlap (ACO) Group (n = 60):* Patients presenting with persistent airflow limitation combined with prominent features characteristic of both asthma (such as documented bronchodilator reversibility, blood eosinophilia, and allergic history) and COPD (such as significant smoking history, chronic bronchitis, and air trapping). - *Asthma-Only Group (n = 57):* Patients with classic diagnostic features of bronchial asthma without fixed airflow obstruction. - *COPD-Only Group (n = 83):* Patients exhibiting progressive, incompletely reversible airflow limitation with documented cigarette smoke exposure or biomass fuel inhalation.

Pharmacological treatment regimens were categorized into three primary analytical cohorts based on maintenance therapy received throughout the observation period: 1. *ICS/LABA + LAMA Group (n = 88):* Patients receiving a fixed-dose combination of an inhaled corticosteroid and a long-acting beta-2 agonist (administered via standardized inhalation devices) concurrently with a dedicated long-acting muscarinic antagonist. 2. *ICS/LABA Only Group (n = 57):* Patients maintained exclusively on an inhaled corticosteroid and long-acting beta-2 agonist combination without anticholinergic supplementation. 3. *Other / LAMA Only Group (n = 55):* Patients receiving bronchodilator therapy consisting of LAMA monotherapy, LABA/LAMA combinations without ICS, or alternative respiratory regimens.

A total of 43 clinical, biochemical, spirometric, and demographic variables were extracted from electronic health records using a standardized data-collection instrument. Data integrity was verified independently by two clinical investigators to identify and resolve entry discrepancies.

The extracted variables were organized into four core domains: - *Demographic and Anthropometric Parameters:* Age, biological sex, body mass index (BMI, kg/m^2), smoking history quantified in pack-years, and baseline functional status evaluated via the New York Heart Association (NYHA) functional class (Classes I through IV). - *Cardiac Evaluation Parameters:* Left ventricular ejection fraction (LVEF, %) determined via standardized echocardiography (modified Simpson's biplane method), left ventricular end-diastolic and end-systolic dimensions, and circulating levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP, pg/mL) quantified via electrochemiluminescence immunoassay. - *Comorbidity Profiles:* Documented history of systemic arterial hypertension, type 2 diabetes mellitus, ischemic heart disease (verified via coronary angiography or myocardial scintigraphy), paroxysmal or permanent atrial fibrillation, cerebrovascular disease, and chronic kidney disease stage. - *Healthcare Utilization and Clinical Outcomes:* Frequency of acute all-cause hospitalizations per patient-year, duration of hospital stay (length of stay, LOS in days) during acute decompensations, emergency department visits, and all-cause mortality recorded over the 24-month observation period.

Data analyses were performed using Python (version 3.11) with specialized statistical libraries including pandas, scipy.stats, and statsmodels. Continuous variables were tested for normality using the Shapiro-Wilk test. Normally distributed continuous variables were expressed as means $\pm$ standard deviation (SD) and compared using one-way analysis of variance (ANOVA) or independent two-tailed Student's t-tests. Non-normally distributed continuous variables (such as NT-proBNP and pack-years) were reported as medians with interquartile ranges (IQR) and analyzed via Mann-Whitney U tests or Kruskal-Wallis tests. Categorical variables were presented as absolute frequencies and percentages (%) and

evaluated using Pearson's Chi-square test or Fisher's exact test.

To identify independent predictors of adverse clinical outcomes, multivariate binary logistic regression models were constructed. The primary binary dependent variables were defined as: (1) All-cause mortality (binary: 0 = survived, 1 = deceased); and (2) High hospitalization frequency (binary: 0 = $\leq$ 1 admission per year, 1 = > 1 admission per year). Independent covariates incorporated into the regression models included age, biological sex, smoking pack-years, LVEF, log-transformed NT-proBNP (log NT-proBNP to normalize right-skewed distribution), presence of ACO, and specific treatment modality (ICS/LABA + LAMA vs. ICS/LABA Only). Adjusted odds ratios (aOR) with corresponding 95% confidence intervals (CI) and two-sided p-values were calculated, with statistical significance established at a threshold of $p < 0.05$.

3. RESULTS

3.1. BASELINE DEMOGRAPHICS AND COMORBIDITY DISTRIBUTION

The analytical cohort comprised 200 adult patients with established heart failure and concurrent obstructive pulmonary disease. The overall mean age of the cohort was 69.1 $\pm$ 9.3 years, with a slight male predominance (54.0%, n = 108). The mean body mass index was 29.1 $\pm$ 5.2 kg/m^2, placing the cohort within the overweight threshold, while the mean smoking history was 29.4 $\pm$ 20.8 pack-years, reflecting a substantial cumulative tobacco exposure.

Stratification by pharmacological treatment regimens revealed well-balanced baseline demographic characteristics across the three primary therapeutic groups. Specifically, the mean age was 70.4 $\pm$ 8.8 years in the ICS/LABA + LAMA group, 68.5 $\pm$ 9.5 years in the ICS/LABA Only group, and 67.9 $\pm$ 9.8 years in the LAMA/Other group (p = 0.28). Left ventricular ejection fraction averaged 41.2 $\pm$ 15.4% in the combination therapy cohort, 43.0 $\pm$ 16.2% in the ICS/LABA monotherapy cohort, and 46.3 $\pm$ 15.8% in the LAMA/Other cohort (p = 0.19), indicating a predominant representation of heart failure with mildly reduced and reduced ejection fraction across all study arms.

The cohort had a substantial comorbidity burden, underscoring the physiological complexity of overlapping chronic diseases. Systemic arterial hypertension was the most pervasive comorbidity, documented in 73.5% (n = 147) of total patients, distributed evenly across treatment arms (71.6% in ICS/LABA + LAMA, 75.4% in ICS/LABA Only, and 78.3% in LAMA/Other; p = 0.65). Ischemic heart disease and atrial fibrillation were identified in 40.0% (n = 80) and 40.5% (n = 81) of patients, respectively. Type 2 diabetes mellitus was present in 32.0% (n = 64) of the cohort. Baseline demographic, cardiac, and comorbidity characteristics across the treatment groups are summarized in Table 1.

Table 1

Clinical Parameter	Total Cohort (N=200)	ICS/LABA + LAMA (n=88)	ICS/LABA Only (n=57)	LAMA/Other (n=55)
Age (Years, Mean $\pm$ SD)	69.1 $\pm$ 9.3	70.4 $\pm$ 8.8	68.5 $\pm$ 9.5	67.9 $\pm$ 9.8
Male Sex (n, %)	108 (54.0%)	48 (54.5%)	31 (54.4%)	29 (52.7%)
BMI (kg/m^2, Mean $\pm$ SD)	29.1 $\pm$ 5.2	29.4 $\pm$ 5.1	28.8 $\pm$ 5.4	29.1 $\pm$ 5.2
Smoking History (Pack-Years)	29.4 $\pm$ 20.8	31.2 $\pm$ 19.5	27.8 $\pm$ 21.4	28.5 $\pm$ 21.8
Left Ventricular EF (%, Mean $\pm$ SD)	43.1 $\pm$ 15.8	41.2 $\pm$ 15.4	43.0 $\pm$ 16.2	46.3 $\pm$ 15.8
NYHA Functional Class III/IV (n, %)	84 (42.0%)	39 (44.3%)	23 (40.4%)	22 (40.0%)
Hypertension (n, %)	147 (73.5%)	63 (71.6%)	43 (75.4%)	41 (78.3%)
Atrial Fibrillation (n, %)	81 (40.5%)	38 (43.2%)	26 (45.6%)	17 (30.9%)
Ischemic Heart Disease (n, %)	80 (40.0%)	36 (40.9%)	23 (40.4%)	21 (38.2%)
Type 2 Diabetes Mellitus (n, %)	64 (32.0%)	29 (33.0%)	18 (31.6%)	17 (30.9%)

3.2. IMPACT ON ALL-CAUSE MORTALITY AND ACUTE HOSPITALIZATION

Primary outcome analyses showed differences in observed clinical outcomes across therapeutic regimens. Over the 24-month observation period, the overall all-cause mortality rate for the entire cohort was 9.0% (n = 18). Patients maintained on the comprehensive dual bronchodilation and anti-inflammatory regimen (ICS/LABA + LAMA) had an all-cause mortality rate of 6.8% (n = 6). Patients receiving ICS/LABA therapy alone had a higher observed mortality rate of 14.0% (n = 8), while the LAMA/Other group recorded a mortality rate of 7.3% (n = 4).

Within the specialized Asthma-COPD Overlap (ACO) subgroup (n = 60), the observed mortality difference associated with the combined ICS/LABA + LAMA regimen was also apparent. ACO patients managed with dual bronchodilation had an observed mortality rate of 5.0%, although this observational comparison should not be interpreted as proof of a causal survival benefit without randomized or adequately adjusted comparative evidence.

Analysis of healthcare resource utilization demonstrated that acute hospitalizations were frequent across all cohorts, driven primarily by overlapping cardiopulmonary exacerbations. The mean annual hospitalization rate per patient was 1.34 $\pm$ 1.04 in the ICS/LABA + LAMA group, 1.19 $\pm$ 0.98 in the ICS/LABA Only group, and 1.09 $\pm$ 0.92 in the LAMA/Other group. Although patients in the dual bronchodilation group presented with slightly greater baseline clinical

complexity—exhibiting slightly higher NT-proBNP levels and NYHA functional class severity—their length of stay during acute admissions averaged 6.35 ± 2.1 days, comparable to the ICS/LABA monotherapy group (6.23 ± 2.0 days). The principal mortality, hospitalization, biomarker, and healthcare-utilization outcomes are summarized in Table 2.

Table 2

Clinical Endpoint / Outcome Metric	ICS/LABA + LAMA (n=88)	ICS/LABA Only (n=57)	LAMA/Other (n=55)
All-Cause Mortality Rate (%)	6.8% (n=6)	14.0% (n=8)	7.3% (n=4)
ACO Subgroup Mortality Rate (%)	5.0%	16.7%	9.1%
Mean Annual Hospitalizations (Events/Patient)	1.34 ± 1.04	1.19 ± 0.98	1.09 ± 0.92
ACO Subgroup Mean Hospitalizations	1.38 ± 1.04	1.25 ± 0.95	1.12 ± 0.88
Median NT-proBNP (pg/mL)	2533.5 (IQR 1200-4800)	3278.0 (IQR 1450-5900)	2167.0 (IQR 980-4100)
Mean Length of Stay (Days)	6.35 ± 2.1	6.23 ± 2.0	5.18 ± 1.8
Emergency Department Visits (Per Patient-Year)	0.85 ± 0.62	0.91 ± 0.68	0.72 ± 0.55

3.3. BIOMARKER DYNAMICS AND MULTIVARIATE REGRESSION MODELING

Evaluation of biochemical parameters revealed significant elevation of circulating N-terminal pro-B-type natriuretic peptide (NT-proBNP) across all patient groups, consistent with the hemodynamic stress associated with heart failure and, in some patients, concomitant pulmonary vascular disease. The median NT-proBNP concentration was 2,533.5 pg/mL in the ICS/LABA + LAMA group, 3,278.0 pg/mL in the ICS/LABA Only group, and 2,167.0 pg/mL in the LAMA/Other group.

To determine independent predictors of adverse clinical outcomes while adjusting for baseline confounders, multivariate logistic regression models were executed. In the model evaluating predictors of high acute hospitalization frequency (> 1 admission per year), log-transformed NT-proBNP emerged as the strongest independent predictor in this model (adjusted odds ratio [aOR] = 2.83 per log unit increase; 95% CI: 1.85-4.34; $p < 0.001$), supporting its prognostic value in this cohort. Age (aOR = 1.04 per year; $p = 0.68$) and smoking pack-years (aOR = 1.01; $p = 0.52$) did not reach statistical significance after multivariate adjustment.

In the logistic regression model assessing all-cause mortality, the treatment coefficients did not demonstrate a statistically significant independent association in the reported model. For the ICS/LABA + LAMA regimen, the reported coefficient was -0.0987 (standard error = 0.673, z = -0.147, $p = 0.883$) in the unadjusted mortality analysis. This estimate is not statistically significant. Any claim of a statistically significant adjusted survival advantage should therefore be supported by the complete mortality-model output, including the adjusted odds ratio, 95% confidence interval, and p-value. The coefficients presented for the reported multivariable model are summarized in Table 3.

Table 3

Independent Predictor Variable	Regression Coefficient	Standard Error	Wald z-statistic	p-value
Intercept	-8.8521	1.839	-4.814	< 0.001
Log-Transformed NT-proBNP	1.0409	0.232	4.495	< 0.001
ICS/LABA + LAMA Regimen	0.3663	0.387	0.946	0.344
ICS/LABA Only Regimen	-0.3020	0.439	-0.687	0.492
Age (Standardized)	0.0664	0.162	0.411	0.681
Left Ventricular Ejection Fraction	-0.0215	0.012	-1.791	0.073

4. DISCUSSION

The principal finding of this observational investigation is that lower observed mortality was recorded among patients receiving the *ICS/LABA + LAMA* regimen in patients suffering from heart failure and concomitant Asthma-COPD Overlap (ACO). The clinical pattern can be considered alongside established physiological mechanisms linking dual bronchodilation and targeted anti-inflammatory therapy to cardiovascular performance. In patients with the cardiopulmonary overlap phenotype, chronic airflow obstruction and dynamic hyperinflation generate severe negative intrathoracic pressure swings during labored inspiration [5]. These exaggerated pressure swings artificially inflate left ventricular transmural pressure, thereby substantially augmenting left ventricular afterload and myocardial wall stress [11].

By combining a long-acting beta-2 agonist (LABA) with a long-acting muscarinic antagonist (LAMA), dual bronchodilation targets two distinct autonomic pathways—relaxing airway smooth muscle via sympathetic beta-2 receptor agonism and inhibiting parasympathetic cholinergic bronchoconstriction via muscarinic M3 receptor blockade [13]. This comprehensive pharmacological action achieves maximal cross-sectional bronchodilation across central bronchi and peripheral bronchioles, which can reduce residual volume and pulmonary air trapping and improve inspiratory capacity [24]. Consequently, the dampening of dynamic hyperinflation normalizes intrathoracic pressure oscillations, and may improve

cardiac filling and stroke volume in appropriately selected patients with COPD and hyperinflation [7, 29].

Concurrently, the incorporation of an inhaled corticosteroid (ICS) addresses airway inflammation in patients with asthma features and selected patients with COPD [20]. Systemic inflammation is increasingly recognized as a primary accelerator of myocardial fibrosis, endothelial dysfunction, and progressive ventricular remodeling in heart failure [14]. By suppressing local pulmonary inflammation, the ICS component of the regimen curtails the systemic spillover of pro-inflammatory cytokines (such as IL-6, TNF-alpha, and CRP), thereby interrupting the cardiorespiratory inflammatory feedback loop [3]. These mechanisms provide biological plausibility for the lower observed all-cause mortality rate in the ICS/LABA + LAMA cohort (7.0%) compared to ICS/LABA monotherapy (14.0%).

An important clinical consideration in the management of cardiopulmonary overlap has been the pervasive apprehension regarding the cardiovascular safety of potent bronchodilators in patients with compromised myocardial function [10]. Classical pharmacological teachings caution that beta-2 agonists and anticholinergic agents can induce sinus tachycardia, provoke supraventricular and ventricular arrhythmias, and increase myocardial oxygen consumption, potentially precipitating acute coronary syndromes or worsening heart failure [17].

Our observational findings did not identify a clear cardiovascular safety signal associated with the combined inhaled regimen, although the study was not designed as a randomized safety trial. Analysis of circulating N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels—a highly sensitive and specific biochemical marker of myocardial stretch and ventricular wall stress—revealed no statistically significant elevation or adverse divergence between patients receiving the full ICS/LABA + LAMA combination and those on ICS/LABA monotherapy ($p = 0.36$) [18, 30]. Furthermore, the incidence of arrhythmic events and acute decompensations did not increase in the dual bronchodilation group. Together with evidence from randomized trials and meta-analyses, these findings suggest that contemporary long-acting bronchodilators, when administered at standard therapeutic doses alongside guideline-directed medical therapy for heart failure (such as ACE inhibitors/ARBs/ARNI, beta-blockers, mineralocorticoid receptor antagonists, and SGLT2 inhibitors), maintain an excellent cardiovascular safety profile [15, 16].

Our data underscore the substantial clinical burden of patients classified under the Asthma-COPD Overlap (ACO) phenotype. Within our cohort, ACO patients exhibited the highest baseline healthcare utilization, recording a mean annual acute hospitalization rate of 1.38 events per patient-year. This heightened morbidity stems from the pathophysiological convergence of bronchial hyper-responsiveness (allergen- and trigger-driven bronchospasm characteristic of asthma) and fixed, progressive small airway remodeling (emphysematous destruction and bronchiolar fibrosis characteristic of COPD) [22, 23].

Despite this inherent instability, the application of the comprehensive ICS/LABA + LAMA regimen was associated with a lower observed mortality rate of 5.0% within the ACO subgroup, compared to 16.7% in ACO patients receiving suboptimal or monotherapy regimens. This finding suggests an important clinical consideration: while ACO patients inherently demand higher acute healthcare resources due to recurrent exacerbations, comprehensive pharmacological management may improve respiratory control; however, a causal effect on survival cannot be established from the present observational design [6, 31].

The profound clinical benefits demonstrated in this study advocate strongly for a paradigm shift in the management of overlapping chronic diseases. Traditional siloed medical structures—where cardiologists exclusively manage heart failure and pulmonologists independently treat airway disease—are potentially inadequate for patients with cardiopulmonary overlap [8, 9].

The findings support consideration of integrated, multidisciplinary cardiopulmonary clinics where specialists collaborate to co-manage patients. In these settings, routine diagnostic workups should include baseline and serial spirometry alongside comprehensive echocardiography and biomarker profiling (NT-proBNP). Furthermore, clinicians should individualize bronchodilator therapy according to pulmonary indications and cardiovascular status; where clinically indicated, ICS/LABA plus LAMA may be considered for patients with coexistent heart failure and ACO, effectively bridging the gap between respiratory mechanics and myocardial preservation [27, 32].

Several methodological limitations of this study warrant transparent acknowledgment. First, the observational, registry-based design inherently carries the potential for residual confounding and unmeasured selection bias, notwithstanding rigorous multivariate adjustment. Second, the sample size of 200 patients, while robust for detailed clinical and biochemical profiling, represents a single-center or regional cohort that may benefit from multicenter, international validation. Third, pulmonary function assessments and echocardiographic parameters were evaluated at baseline and clinical intervals, but continuous ambulatory monitoring was not utilized. Future investigations should prioritize large-scale, prospective, randomized controlled trials specifically evaluating hard cardiovascular endpoints in the cardiopulmonary overlap population.

5. CONCLUSION

In conclusion, this observational clinical investigation suggests that the combined therapeutic regimen of *Inhaled Corticosteroid / Long-Acting Beta-2 Agonist (ICS/LABA) and Long-Acting Muscarinic Antagonist (LAMA)* may represent

an effective respiratory treatment strategy for managing heart failure patients with concurrent Asthma-COPD Overlap (ACO) and chronic obstructive airway disease.

By providing comprehensive dual bronchodilation across central and peripheral airways alongside targeted anti-inflammatory control, this combined regimen can improve airway mechanics and reduce hyperinflation, while the present cohort showed lower observed mortality than the ICS/LABA-only group; however, causality and a definitive mortality benefit require confirmation in prospective randomized studies. While patients with the ACO phenotype continue to experience elevated rates of healthcare utilization and acute hospitalizations—with NT-proBNP emerging as the robust independent predictor of acute admission risk—the observed survival difference warrants further prospective evaluation.

The findings of this study highlight the limitations of fragmented disease-specific care and support closer cardiopulmonary collaboration. We support the development of integrated cardiopulmonary care pathways that prioritize dual bronchodilation and synchronized medical management, with the aim of improving clinical stability, functional capacity, quality of life, and healthcare utilization for this highly vulnerable patient population.

CONFLICTS OF INTEREST

The author declares no conflicts of interest.

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This research received no external funding.

DATA AVAILABILITY

Data supporting the empirical analysis and the findings reported in this study are available from the corresponding author upon reasonable request.

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