Monaldi Archives for Chest Disease

eISSN 2532-5264 https://www.monaldi-archives.org/

Monaldi Arch Chest Dis 2025 [Online ahead of print]

To cite this Article:
Para O, Vanetti M, Dibonaventura C, et al. **Chronic obstructive pulmonary disease and heart failure in real life: the tip of the iceberg in the sea of comorbidities. A prospective observational study.** *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2025.3157

Chronic obstructive pulmonary disease and heart failure in real life: the tip of the iceberg in the sea of comorbidities. A prospective observational study

Ombretta Para,[1,2] Marco Vanetti,[3,4] Chiara Dibonaventura,[2] Davide Salerno,[2] Lorenzo Caruso,[2] Christian Carleo,[2] Asim Raza,[2] Carlo Nozzoli,[2] Antonio Spanevello[3,4]

[1]PhD Research Program in "Clinical and Experimental Medicine and Medical Humanities", University of Insubria, Varese; [2]Internal Medicine 1, University Hospital of Careggi, Florence; [3]Respiratory Rehabilitation of the Institute of Tradate, Istituti Clinici Scientifici Maugeri IRCCS, Varese; [4]Department of Medicine and Surgery, University of Insubria, Varese, Italy

Correspondence: Ombretta Para, PhD research program in "Clinical and Experimental Medicine and Medical Humanities", University of Insubria, Varese, Italy.
E-mail: opara@studenti.uninsubria.it

Contributions: all the authors contributed to data interpretation. All the authors participated in the conception and revision of the article, drafted the article and approved the final version to be published.

Conflict of interest: the authors have no potential intellectual or economic conflict of interest.

Ethics approval and consent to participate: the study was performed in accordance with the Declaration of Helsinki and local regulations. The study was approved by local ethical committee (n. 24860_oss).

Informed consent: all patients gave their consent for partecipating in the study.

Patient consent for publication: obtained.

Availability of data and materials: all data analyzed during this study are included in this published article.

Funding: none.

Abstract

Chronic obstructive pulmonary disease (COPD) and heart failure (HF) are two of the most common conditions treated in internal medicine. Although it is known that these diseases often coexist, the specific characteristics of the affected patients and the prognostic implications are not yet well understood. Managing patients with both COPD and HF requires an integrated treatment approach. The aim of the study was to examine the association between COPD and HF. We conducted a prospective observational cohort study. All consenting patients admitted to the Internal Medicine Department from the Emergency Department with known or strongly suspected COPD were enrolled. A total of 144 patients were included, with 47.2% of them also having HF, distributed among the various HF subcategories as follows: 10.4% with HF with reduced ejection fraction (HFrEF), 3.5% with HF with mild-reduced ejection fraction, and 33.3% with HF with preserved ejection fraction (HFpEF). This result is consistent with the literature, which suggests a higher prevalence of COPD in patients with HFpEF compared to HFrEF. A Doppler echocardiography was performed during hospitalization. Some variables showed a statistically significant difference when comparing patients with COPD and HF to those with COPD without HF. Interestingly, the follow-up at 3 and 6 months post-discharge revealed higher mortality in patients with HF, with an odds ratio (95% confidence interval) of 10.0 (1.2-82.2). This study could contribute to a better understanding of the prognostic implications arising from the coexistence of COPD and HF, emphasizing the importance of a patient-centered approach in managing multiple comorbidities.

Key words: heart failure, COPD, bronchitis, ejection fraction, comorbidities.

Introduction

Heart failure and chronic obstructive pulmonary disease (COPD) are two clinical syndromes of significant relevance in terms of global prevalence, morbidity, and mortality, and therefore, they have a considerable impact on the healthcare system [1-4]. Before the 1980s, heart failure was thought to be rare in patients with COPD, and when present, it was considered exclusively as right-sided heart failure. It was later demonstrated that the actual prevalence of right heart dysfunction is lower than previously thought (0.2-0.6%), except in cases of advanced COPD [5]. In subsequent years, an association between left heart dysfunction and COPD emerged [6,7], sparking growing scientific interest in the subject. However, there are no systematic large-scale studies examining cardiac function in patients with COPD or vice versa, pulmonary function in patients with HF.

Cardiovascular diseases are one of the most common comorbidities in patients with chronic lung disease, significantly contributing to hospitalizations and deaths [8-10].

COPD rarely occurs in isolation and its severity can be influenced by the presence of comorbid conditions, especially cardiovascular. Experts believe that measuring lung function should be integrated with an accurate cardiovascular assessment, a metabolic assessment and the search for the main markers of systemic inflammation [10].

At the same time, COPD is an independent risk factor for cardiovascular morbidity and mortality, with a markedly increased risk in patients with reduced lung function, measured by FEV1, in the lowest fifth percentile [11].

Although the association between COPD and HF is evident, there is limited literature on the actual proportion of this association, the characteristics of patients affected by both conditions, the prognostic consequences, and the factors that most impact prognosis remain to be clearly defined. Our study aims to contribute to this investigation in a real-life setting in the internal medicine department, where these two pathologies are among the most frequently observed [12,13].

Materials and Methods

Endpoint

The primary aim of the study was to evaluate the prevalence of heart failure in a cohort of hospitalized patients in Internal Medicine with a diagnosis of COPD and to analyse their clinical-laboratory and instrumental characteristics to compare patients with HF to those without HF, in order to identify any statistically significant differences.

Secondary endpoints were the evaluation in the two patient groups (patients with HF and those without HF) of in-hospital mortality, need for transfer to higher intensity care settings (intensive care unit, ICU), need for non-invasive ventilation (NIV) during hospitalization, length of

hospital stay, dyspnoea assessed with the Modified British Medical Research Council (mMRC) questionnaire 30 days after discharge, mortality and readmission at 30 days after discharge, mortality and readmission at 3- and 6-months after discharge.

Study design

We conducted a prospective observational cohort study in the Internal Medicine Department 1 at the Careggi University Hospital. Patient enrollment was facilitated using the electronic medical record system (Archimed® medical software version 6.20 by B. Dannaoui, Florence, Italy). After the enrolment two telephone follow-up after one, three and six months since hospital discharge were performed.

The study was performed in accordance with the Declaration of Helsinki and local regulations. The protocol was approved by the Ethics Committee of our center,University Hospital of Careggi, Florence.

The authors declare they have no conflict of interest.

Data collection

We included in the study all patients with suspected or confirmed diagnosis of COPD by lung function test admitted to the Internal Medicine Department 1 from the emergency department between June 2023 and May 2024. In all patients with suspected COPD, lung function tests were planned within 3 months after the hospital discharge and at least one month after the COPD exacerbation.

Exclusion criteria were inability of the patient to provide consent, absence of COPD diagnosis at lung function tests, admission for massive pulmonary embolism, shock of any cause, or acute myocardial infarction.

At admission, the following variables were collected using electronic medical records: anthropometrics data, smoking status, daily consumption of alcoholic units, lung function tests, comorbidities, current therapy, long term oxygen therapy (LTOT) history of exacerbations in the previous year.

Routine blood samples including complete blood cell count, plasma creatinine, C-reactive protein, NT-proBNP levels (at time 0 and after 72 hours), and high-sensitivity Troponin T (TnT-hs) levels (at time 0 and after 24 hours) were performed within 48 hours to the admission into the internal medicine department. Barthel Index [14] was used to evaluate functional status of patients.

During hospitalization, and at discharge questionnaire (mMRC) was used in all patients to assess the dyspnoea and Charlson Comorbidity Index was used to evaluate the impact of concomitant disease.

During hospitalization, all patients performed doppler echocardiography for morphological and functional heart assessment, evaluating left ventricular systolic and diastolic function. Heart failure was defined according to 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [15] and was classified in three categories: Hearth Failure with reduced Ejection Fraction (HFrEF) if EF<40%, Harth Failure with mild reduced Ejection Fraction (HFmrEF) if EF 41-49% and Harth Failure with preserved Ejection Fraction (HFpEF) if EF 50%.

Patients with COPD were divided into two groups based on the presence or absence of HF (already present at admission or newly diagnosed) for population comparison.

One, three and six months after hospital discharge, a telephone follow-up was conducted to assess mortality and number of hospital re-admissions. During this evaluation mMRC questionnaire was administered.

All consenting patients over the age of 18 who, between June 2023 and May 2024, were admitted to the Internal Medicine Department 1 from the emergency department with known or strongly suspected COPD based on clinical history and risk factors, regardless of the reasons for admission, were consecutively enrolled. Exclusion criteria included: inability of the patient to provide consent, absence of spirometric confirmation of COPD in scheduled respiratory function tests, admission for massive pulmonary embolism, shock of any cause, or acute myocardial infarction.

The following variables were collected for each patient using electronic medical records: sex, age, body mass index (BMI), Barthel index [14], history of active smoking expressed in pack-years [16], alcohol consumption expressed in daily alcohol units. We investigated any previous spirometric diagnosis of COPD, the number and severity of exacerbations per year, as well as the current exacerbation at the time of admission and the main comorbidities present at admission, particularly: arterial hypertension, ischemic heart disease, previous HF diagnosis, dyslipidemia, diabetes mellitus, peripheral artery disease, atrial fibrillation, moderate or severe valvular disease, chronic kidney disease, previous acute cerebrovascular event (stroke); for each patient, the Charlson Comorbidity Index was calculated [17]. We considered the ongoing therapy at the time of admission, with particular attention to long-term oxygen therapy, inhalation therapy, antihypertensive therapy, gliflozin therapy, and beta-blocker therapy.

The presence of respiratory failure (defined as $PaO_2 < 60$ mmHg on arterial blood gas analysis), signs/symptoms of HF, NYHA class if applicable amd mMRC class were evaluated in all patients at admission, and at hospital discharge.

Blood tests at admission (within the first 48 hours of hospitalization) were included: complete blood count with differential, plasma creatinine, C-reactive protein, NT-proBNP levels (at time

0 and after 72 hours), and high-sensitivity Troponin T (TnT-hs) levels (at time 0 and after 24 hours).

Patients underwent Doppler echocardiography during hospitalization for morphological and functional heart assessment, evaluating left ventricular systolic and diastolic function.

We observed the presence of HF at admission or its development during hospitalization, the need for NIV, the need for transfer to a higher intensity care setting, any death, the length of hospitalization, and the discharge destination (home or long-term care facility). Where not previously performed and if clinical conditions allowed, spirometry was scheduled post-discharge for diagnostic confirmation of COPD. Patients with COPD were divided into two groups based on the presence or absence of HF (already present at admission or newly diagnosed) for population comparison.

If patients had never performed simple spirometry before admission, to confirm the suspected diagnosis of COPD we scheduled simple spirometry at least one month after the exacerbation episode. Patients performed spirometry tests (MIR MiniSpir; MIR, Rome, Italy), and both forced expiratory volume in the 1 sec (FEV1) and forced vital capacity (FVC) were recorded and expressed as absolute values (in litres, L) and as a percentage of a predicted value (% predicted). The FEV1 and FVC values were also recorded as a ratio. At least three measurements were taken for each spirometric test and each lung volume variable to ensure reproducibility of the data.

The assessment of airway obstruction and its severity was carried out in accordance with the 2023 GOLD document [18]. Patients with an FEV1/FVC 70% were excluded from the study.

A follow-up phone call was conducted 30 days after discharge with enrolled patients to assess any readmission, death, or worsening of the mMRC scale compared to discharge. Additional follow-up, limited to readmission and death, were conducted at 3 and 6 months after discharge.

Statistical analysis

After testing for normality using the Shapiro-Wilk test, continuous variables were expressed as mean and standard deviation (SD), while categorical variables were expressed as percentages. Homogeneity between groups was assessed using Pearson's Chi-square test and Fisher's exact test, depending on the event frequency for categorical variables, and the Mann-Whitney U test or Kruskal-Wallis test for continuous variables. These analyses were used both for the comparison between groups for the primary objective and for the univariate analysis of secondary objectives. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. A p-value < 0.05 was considered statistically significant.

Endpoints related to hospitalization (such as the need for transfer to a higher intensity care setting or the need for NIV), except for death, were used as variables in calculating discharge-related endpoints (discharge destination and length of stay). Hospitalization and discharge endpoints were then included as variables in the calculation of later endpoints.

As regards the calculation of the sample size, assuming that in patients with COPD the prevalence of heart failure, of any type, is around 20% and accepting a precision in the estimate of ±10% (95% confidence interval of the estimate), it is necessary to collect a sample of at least 62 patients.

According to the literature, considering the possibility of having incomplete data for approximately 15% of the subjects and the lack of spirometry confirmation in 30% of patients, it is planned to include a total of at least 80 patients.

All analyses were conducted using SPSS Statistics version 25.0 (IBM, Armonk, NY, USA).

Results

A total of 177 patients were consecutively enrolled, of whom 33 met exclusion criteria; thus, 144 patients were included.

Heart failure (HF) was diagnosed in 68 patients (47.2%), of which 15 had reduced ejection fraction (HFrEF) (10.4%), 5 had mildly reduced ejection fraction (HFmrEF) (3.5%), and 48 had preserved ejection fraction (HFpEF) (33.3%) (Figure 1). Of these 68 patients, 51 (75%) had previously received a diagnosis of HF (either in an outpatient setting or during previous hospitalizations), while the remaining 17 patients (25%) were newly diagnosed with HF at the emergency department.

In our patient cohort it was possible to obtain spirometric data in 70% of patients. In the remaining 30% of patients with a clinical sign and/or symptoms strongly suggestive of COPD, it was not possible to perform diagnostic confirmation with spirometry due to lack of compliance with the test.

Patients with COPD and HF, compared to those with COPD without HF, showed a statistically significant difference in age, Charlson index, BMI, Barthel Index, and a history of comorbidities such as ischemic heart disease, atrial fibrillation, and chronic kidney disease. Additionally, there was a significant difference in mMRC class at admission and at discharge between the two populations (Table 1).

Analyzing blood tests, significantly lower values of hemoglobin and lymphocytes were observed in patients with HF, while NT-proBNP and hs-TnT values at admission and NT-proBNP at 72 hours were significantly higher. Patients with HF were more frequently on beta-blocker therapy, and they more frequently presented with typical signs and symptoms of cardiac overload and respiratory failure (Table 2).

Regarding the evaluation of secondary endpoints (Table 3), the population with COPD and HF exhibited a higher in-hospital mortality rate, and non-invasive ventilation (NIV) during hospitalization was required more frequently. However, these differences were not statistically significant. On the other hand, no substantial differences were observed between the two populations in terms of the need for transfer to the ICU and the length of hospital stay.
The 30-day follow-up after discharge showed a significant difference in mMRC class, while the 3- and 6-month follow-up highlighted a higher mortality in patients with HF with an OR of 10.0 (Table 4).

Discussion

Chronic obstructive pulmonary disease and heart failure are two of the most frequently observed conditions in Internal Medicine, whether they are the direct cause of hospitalization or not. Although their association is well-documented, the characteristics of patients with both conditions and the potential prognostic implications remain poorly understood. This is crucial for promoting a patient-centred approach to multi-morbidity rather than focusing solely on a single condition [10,18-20]. This study was designed to prospectively investigate the association between COPD and heart failure.
The collected data provide some interesting insights. Heart failure was identified in 47.2% of patients with COPD hospitalized in Internal Medicine, predominantly with preserved ejection fraction. This aligns with the literature, which indicates a higher prevalence of COPD among patients with HFpEF compared to those with HFrEF [21-23]. The prevalence of heart failure in COPD patients varies from 20% to 70% according to the literature, with an annual incidence estimated between 3% and 4% [24]. It is noteworthy that in 25% of cases, heart failure was diagnosed for the first-time during hospitalization, due to the presence or development of compatible signs and symptoms, elevated NT-proBNP levels, and echocardiographic findings. When respiratory symptoms worsen in a COPD patient, it is crucial to distinguish between an exacerbation of the disease and the manifestation of a new intercurrent condition, such as heart failure, as the boundaries between these conditions are not always clear-cut [25].
Exacerbations of COPD and acute HF are triggered by different factors: for instance, respiratory infections and pollutants in COPD, and arrhythmias, acute coronary syndrome, and hypertension in acute HF [26,27].
This differential diagnosis becomes even more complex during the disease's stable phase, especially between COPD and HFpEF, further complicated by the frequent inadequacy of the acoustic window in echocardiography for COPD patients. In our sample, 39.4% of patients had a poor acoustic window due to chest configuration or obesity. In this context, second-level tests, whether invasive or non-invasive, may be useful: reduced exercise tolerance,

reflected by increased left atrial pressure under stress, is a typical sign of HFpEF patients and may facilitate early diagnosis [28,29].

Once the diagnosis is confirmed, what are the benefits? Management of comorbidities has long been the only therapeutic strategy for patients with HFpEF, given the lack of specific therapies due to patient heterogeneity [30]. This approach is supported by evidence that causes of hospitalization in HFpEF patients are often non-cardiac [15,23].

COPD is a frequent cause of hospitalization in adults due to the fact that, over the course of the disease, patients with COPD develop a worsening of respiratory symptoms, which sometimes requires hospital admission for their clinical stabilization.

However, the 2023 ESC guidelines update recommends with class IA the use of SGLT2 inhibitors (dapagliflozin or empagliflozin) to reduce the risk of hospitalization or cardiovascular death in patients with HFpEF and HFmrEF [15,18,31]. Diagnosing heart failure in COPD patients can significantly impact therapeutic choices. Only 11.8% of our population with HF, regardless of ejection fraction, was on an SGLT2 inhibitor at the time of hospitalization [30,31]. Despite potential contraindications related to renal function, there is a significant group of patients who could benefit from this treatment.

Therefore, it is crucial to consider the frequent association between COPD and heart failure and to actively search for the presence of HF, regardless of ejection fraction, in COPD patients to enable more comprehensive treatment with benefits for quality of life, hospitalization frequency, and cardiovascular mortality.

In our Internal Medicine inpatient population, patients with COPD and HF are significantly younger (average 80 years vs. 76 years in the HF-free population), with higher BMI and Charlson index, and a lower Barthel index. They also more frequently have at least three comorbidities (94.1%); among these, the significantly more frequent conditions in patients with HF were ischemic heart disease, moderate-severe valvulopathy, atrial fibrillation, peripheral artery disease, and chronic kidney disease (CKD). However, it is interesting to note that other conditions, such as hypertension, dyslipidemia, and diabetes mellitus, were also more common in this population, although not statistically significant. It is clear that this is a more frail and less autonomous population.

Patients with HF were more frequently on beta-blocker therapy and more frequently presented typical signs and symptoms of cardiac overload (both during hospitalization and at discharge) and respiratory insufficiency (at admission, during hospitalization, and at discharge). The difference in mMRC class at admission and discharge between the two populations, as well as the difference in NYHA class at discharge, was significant. These differences reflect a greater impact of the combination of the two conditions on quality of life and the degree of respiratory insufficiency.

Blood tests showed significantly lower hemoglobin and lymphocyte levels in patients with HF, while NT-proBNP and hs-TnT levels at admission and NT-proBNP at 72 hours were higher on average.

Finally, echocardiographic evaluation revealed more frequent left atrial dilation (73.4% vs. 31.3%) and diastolic dysfunction (48.4% vs. 23.5%) in patients with HF, as well as a lower average ejection fraction (51.7 vs. 59.5).

No significant differences were found in mortality, transfer to a higher level of care, or the need for NIV between the two groups, although there was a higher trend in the HF group.

The 30-day follow-up showed a significant difference in mMRC class, while the 3 and 6-month follow-up revealed higher mortality in patients with HF, with an odds ratio (OR) of 10.0 (95% CI: 1.2-82.2).

Obtaining reliable data for comparison between subpopulations based on ejection fraction (EF) was more complex due to reasons such as the small sample size, especially for patients with moderately reduced EF (n = 5). Patients with HFrEF, compared to those with EF > 40%, were more frequently male and showed a higher average NT-proBNP value at 72 hours. The HFmrEF group, on the other hand, had a positive history of ischemic heart disease in all cases (100.0%) and a higher average value of hs-TnT at 24 hours. None of these patients had a spirometric diagnosis of COPD or a history of COPD exacerbations in the past year. Finally, comparing HFpEF patients with those with EF < 50%, the former were more frequently female (62.5%), had a higher average BMI (27.5 vs 24.3), and more frequently had a spirometric diagnosis of COPD. Laboratory tests also showed a lower average NT-proBNP level at admission and at 72 hours, and lower hs-TnT at 24 hours. It is known that stable COPD patients have higher NT-proBNP values compared to the general population, with values seemingly increasing according to 2023 GOLD stage [18,32]. However, the natriuretic peptide maintains its value in diagnosing left ventricular dysfunction in exacerbated COPD patients, although with cut-off values likely higher than those expressed in ESC guidelines for HF [15]. Our analysis results are therefore consistent with the literature.

An additional clarification regarding our analysis context is necessary: the study population consists of patients admitted to Internal Medicine with a spirometric diagnosis of COPD performed in the past or after discharge in 62.5% of cases. The remaining 37.5% are patients with a clinical picture strongly suggestive of COPD who did not undergo pulmonary function tests, due to documented impossibility in past attempts or clinical conditions at the time of discharge. As highlighted by Schneider et al. in 2005, not all patients with a COPD diagnosis recorded in clinical documentation have undergone spirometry for diagnostic confirmation [33].

The diagnostic pathway proposed by the GOLD document often clashes with the clinical conditions of hospitalized Internal Medicine patients, who are often elderly and present a degree of cognitive decline that makes spirometry execution very difficult, requiring understanding of the steps and full cooperation from the patient [34]. This is certainly an open problem, not only for our analysis or clinical studies in general, but also in daily clinical practice. Various alternative diagnostic tools have been proposed to facilitate early diagnosis and treatment of the disease; however, none of these have reached a level of reliability to be used as an alternative to spirometry [35].

The strength of our real-life study is its prospective nature, which allowed for the assessment of blood tests, spirometry and echocardiography for all enrolled patients.

Clarifying the association between COPD and heart failure is essential to reach a real prognostic impact: the association between COPD severity and cardiovascular disease is well known in the literature.

Some studies have shown a strong link between the likelihood of cardiovascular disease (CVD) and the severity of pulmonary dysfunction [36-38]. This association has been observed across the entire spectrum of CVD—including cerebrovascular disease, congestive heart failure (CHF), and arrhythmias—and is evident even in the early stages of the disease. A significant proportion of patients with mild and moderate COPD die from CVD, which is more common than death from respiratory insufficiency in the same group. COPD patients experience higher rates of hospitalization and mortality, primarily due to coronary heart disease (CHD), stroke, and CHF [39].

Since there is a close relationship between smoking, COPD and heart failure, optimizing the diagnosis and treatment of these patients necessarily includes considering all interventions aimed at smoking cessation. Stop smoking is useful to improve symptoms, respiratory function and metabolic parameters in the short term in this patients 'population [40].

However, our study has some limitations that need to be mentioned: it is a single-centre study with a limited sample size. In approximately 30% of patients, spirometry confirmation could not be obtained, although this data is in agreement with the literature and with the advanced age of our population of fragile and complex patients. Further prospective multicentric studies with larger populations will be necessary to deepen the link between COPD and heart failure to optimize the diagnostic and therapeutic pathway for patients.

Conclusions

Given the recognized association between COPD and HF, the marked heterogeneity among populations studied in the existing literature—often numerous and contradictory—makes their conclusions difficult to generalize. Despite its limitations, our study highlights the essential

need to explore the still unclear aspects concerning the characteristics and short- and long-term prognostic implications of HF in COPD patients. Recognizing the potential presence of HF in COPD patients from the early stages of the disease could enable more appropriate treatment, with potential benefits for quality of life and survival.

References

1. Adeloye D, Chua S, Lee C, et al. Global and regional estimates of COPD prevalence: Systematic review and meta–analysis. J Glob Health 2015;5:020415.
2. Ntritsos G, Franek J, Belbasis L, et al. Gender-specific estimates of COPD prevalence: a systematic review and meta-analysis. Int J Chron Obstruct Pulmon Dis 2018;13:1507-14.
3. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;385:117-71.
4. Shahim B, Kapelios CJ, Savarese G, Lund LH. Global public health burden of heart failure: an updated review. Card Fail Rev 2023;9:e11.
5. Naeije R. Pulmonary hypertension and right heart failure in chronic obstructive pulmonary disease. Proc Am Thorac Soc 2005;2:20-2.
6. McCullough PA, Hollander JE, Nowak RM, et al. Uncovering heart failure in patients with a history of pulmonary disease: rationale for the early use of B-type natriuretic peptide in the emergency department. Acad Emerg Med 2003;10:198-204.
7. Rutten FH, Cramer M-JM, Grobbee DE, et al. Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease. Eur Heart J 2005;26:1887-94.
8. Bernabeu-Wittel M, Para O, Voicehovska J, et al. Competences of internal medicine specialists for the management of patients with multimorbidity. EFIM multimorbidity working group position paper. Eur J Intern Med 2023;109:97-106.
9. Kotlyarov S. Analysis of the comorbid course of chronic obstructive pulmonary disease. J Pers Med 2023;13:1179.
10. Fabbri LM, Celli BR, Agustí A, et al. COPD and multimorbidity: recognising and addressing a syndemic occurrence. Lancet Respir Med 2023;11:1020-34.
11. Sin DD. Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. Proc Am Thorac Soc 2005;2:8-11.
12. Güder G, Störk S. COPD and heart failure: differential diagnosis and comorbidity. Herz 2019;44:502-8.
13. De Miguel-Díez J, Chancafe Morgan J, Jimenez-Garcia R. The association between COPD and heart failure risk: a review. Int Chron Obstruct Pulmon Dis 2013;305-12.

14. Shah S, Vanclay F, Cooper B. Improving the sensitivity of the Barthel Index for stroke rehabilitation. J Clin Epidemiol 1989;42:703-9.
15. McDonagh TA, Metra M, Adamo M, et al. 2023 Focused update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. G Ital Cardiol 2024;25:202-13. [Article in Italian].
16. National Cancer Institute. Definition of pack year. 2011. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/pack-year.
17. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.
18. GOLD. 2023 GOLD report. Global Initiative for Chronic Obstructive Lung Disease - GOLD. Available from: https://goldcopd.org/2023-gold-report-2/.
19. Chiumeo F, Folloni S. Chronic obstructive pulmonary disease and heart failure: research and clinical practice in primary care. Ital J Med 2015;9:346-8.
20. Nozzoli C, Anastasio L, Fabbri LM, et al. Complexity of patients with chronic obstructive pulmonary disease hospitalized in internal medicine: a survey by FADOI. Ital J Med 2015;9:120-4.
21. Hawkins NM, Petrie MC, Jhund PS, et al. Heart failure and chronic obstructive pulmonary disease: diagnostic pitfalls and epidemiology. Eur J Heart Fail 2009;11:130-9.
22. Mentz RJ, Kelly JP, Von Lueder TG, et al. Noncardiac comorbidities in heart failure with reduced versus preserved ejection fraction. J Am Coll Cardiol 2014;64:2281-93.
23. Ather S, Chan W, Bozkurt B, et al. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. J Am Coll Cardiol 2012;59:998-1005.
24. Beghé B, Verduri A, Roca M, Fabbri LM. Exacerbation of respiratory symptoms in COPD patients may not be exacerbations of COPD. Eur Respir J 2013;41:993-5.
25. Aisanov Z, Khaltaev N. Management of cardiovascular comorbidities in chronic obstructive pulmonary disease patients. J Thorac Dis 2020;12:2791-802.
26. Redfield MM, Borlaug BA. Heart failure with preserved ejection fraction: a review. JAMA 2023;329:827-38.
27. Chirinos JA. Exercise training in heart failure with preserved ejection fraction: is the peripheral vasculature involved? JACC Heart Fail 2023;11:465-8.
28. Rucker D, Joseph J. Defining the phenotypes for heart failure with preserved ejection fraction. Curr Heart Fail Rep 2022;19:445-57.

29. Vaduganathan M, Docherty KF, Claggett BL, et al. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomized controlled trials. Lancet 2022;400:757-67.
30. Labaki WW, Xia M, Murray S, et al. NT-proBNP in stable COPD and future exacerbation risk: Analysis of the SPIROMICS cohort. Respir Med 2018;140:87-93.
31. Ozaki AF, Ko DT, Chong A, et al. Prescribing patterns and factors associated with sodium-glucose cotransporter-2 inhibitor prescribing in patients with diabetes mellitus and atherosclerotic cardiovascular disease. CMAJ Open 2023;11:E494-503.
32. Andrijevic I, Milutinov S, Lozanov Crvenkovic Z, et al. N-terminal prohormone of brain natriuretic peptide (NT-proBNP) as a diagnostic biomarker of left ventricular systolic dysfunction in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). Lung 2018;196:583-90.
33. Schneider A, Gantner L, Maag I, et al. Are ICD-10 codes appropriate for performance assessment in asthma and COPD in general practice? Results of a cross sectional observational study. BMC Health Serv Res 2005;5:11.
34. d'Avila Melo SM, de Oliveira LA, Wanderley JLF, Rocha RDA. Evaluating the extremely elderly at a pulmonary function clinic for the diagnosis of respiratory disease: frequency and technical quality of spirometry. J Bras Pneumol 2019;45:e20180232.
35. Chukowry PS, Spittle DA, Turner AM. Small airways disease, biomarkers and COPD: where are we? Int J Chron Obstruct Pulmon Dis 2021;16:351-65.
36. Rahman HH, Rashid MH, Miah NA, et al. Correlation study between COPD and heart failure in elderly patient. Mymensingh Med J 2022;31:498-505.
37. Hannink JD, van Helvoort HA, Dekhuijzen PN, Heijdra YF. Heart failure and COPD: partners in crime? Respirology 2010;15:895-901.
38. Ventrella F, Mastroianni F, Errico M. Chronic obstructive pulmonary disease pathways as a tool to improve appropriateness in internal medicine departments. Ital J Med 2015;9:96-108.
39. López-Pardo ME, Candal-Pedreira C, Valdés-Cuadrado L, et al. Factors related with hospital attendance and mortality in patients with COPD: a case-control study in a real-life setting. Int J Chron Obstruct Pulmon Dis 2022;17:809-19.
40. Pezzuto A, Ricci A, D'Ascanio M, et al. Short-term benefits of smoking cessation improve respiratory function and metabolism in smokers. Int J Chron Obstruct Pulmon Dis 2023;18:2861-5.

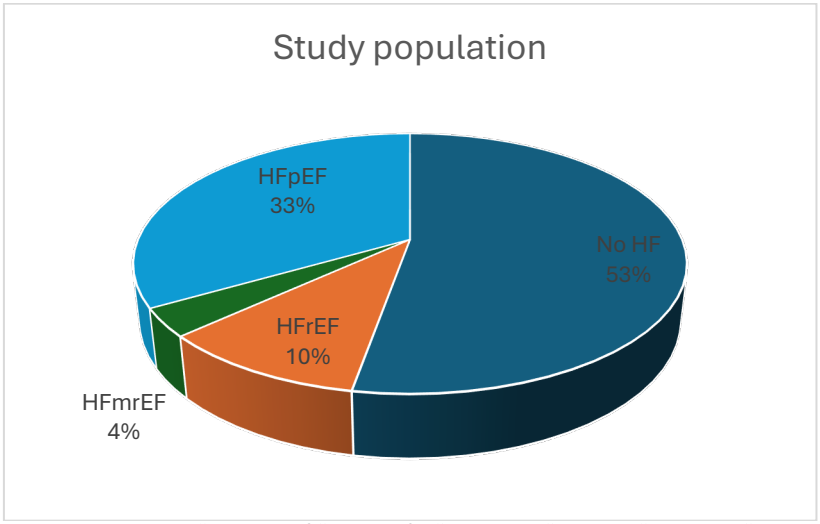

Figure 1. Incidence of heart failure in the study population and distribution among different categories. HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction.

Table 1. General clinical characteristics of the study population.

		COPD without HF (N=76) n (%)/mean (DS)	***COPD and HF (N=68) n (%)/mean (DS)***	***P***	***OR (IC 95%)***
Sex	*Female*	35 (46.1%)	32 (47.1%)	1.000	
	Male	41 (53.9%)	36 (52.9%)		
Age (years)		76.0 (9.1)	80.0 (9.0)	0.004	
BMI (kg/m^2)		24.0 (5.1)	26.5. (6.5)	0.011	
Barthel Index		63.4 (31.2.)	46.8 (27.6)	0.001	
Pack/year		42.8 (23.1)	38.9 (29.2)	0.390	
Daily Alcohol Units 2		23 (30.3%)	17 (25.0%)	0.577	
Spirometric diagnosis of COPD		52 (68.4%)	38 (55.9%)	0.126	
Frequent exacerbations		41 (53.9%)	37 (54.4%)	1.000	
Arterial hypertension		57 (75.0%)	59 (86.8%)	0.093	
Ischemic heart disease		13 (17.1%)	31 (45.6%)	<0.001	4.1 (1.9-8.7)
Dyslipidemia		37 (48.7%)	44 (64.7%)	0.065	
Moderate-severe valvulopathy		6 (7.9%)	20 (29.4%)	0.001	4.9 (1.8-12.0)
History of AF		13 (17.1%)	40 (58.8%)	<0.001	6.9 (3.2-14.9)
Diabetes mellitus		15 (19.7%)	23 (33.8%)	0.061	
Peripheral artery disease		7 (9.2%)	19 (27.9%)	0.005	3.8 (1.5.-9.8)
CKD		21 (27.6%)	39 (57.4%)	<0.001	3.5 (1.8-7.1)
Previous stroke		6 (7.9%)	8 (11.8%)	0,574	
>2 comorbidities		60 (78.9%)	64 (94.1%)	0.014	4.3 (1.3-13.5)
Charlson Index		5.7 (2.3)	7.6. (2.2)	<0.001	

COPD, chronic obstructive pulmonary disease; HF, heart failure; BMI, body mass index; pack/year, as expression of tobacco use in smokers' lifetime; CKD,chronic kidney disease.

Table 2. Home therapy, blood tests and echocardiographic data of the study population.

	COPD without HF (N=76) N (%)/average (DS)	***COPD and HF (N=68) n (%)/average (DS)***	***p <0.005***	***OR (IC 95%)***
LTOT	21 (27.6%)	28 (41.2%)	0.113	
Inhalation therapy	48 (63.2%)	45 (66.2%)	0.730	
Triple inhalation therapy	27 (56.2%)	22 (48.8%)	0.727	
2 antihypertensive medications	28 (36.8%)	28 (41.2%)	0.612	
SGLT-2	3 (3.9%)	8 (11.8%)	0.115	
Beta-blocker	27 (35.5%)	46 (67.6%)	<0.001	3.8 (1.9-7.6)
Ongoing COPD exacerbation	52 (68.4%)	43 (63.2%)	0.598	
Respiratory failure at admission	53 (69.7%)	58 (85.3%)	0.030	2.5 (1.1-5.8)
Ongoing infection	45 (59.2%)	39 (57.4%)	0.866	
HB (g/dl)	12.5 (2.3)	11.6 (2.1)	0.019	
WBC ($x10^9$/l)	11.8 (7.4)	10.3 (5.9)	0.173	
Neutrophils ($x10^9$/l)	9.7 (6.6)	8.62 (5.7)	0.301	
Eosinophils ($x10^9$/l)	0.2 (0.5)	0.1 (0.1)	0.148	
Lymphocytes ($x10^9$/l)	1.1 (0.7)	0.9 (0.5)	0.033	
Creatinine (mg/dl)	1.3 (1.5)	1.6 (1.1)	0.168	
Urea (g/l)	0.8 (0.7)	1.0 (0.6)	0.142	
CRP (mg/l)	69.8 (79.5)	78.4 (88.2)	0.542	
NT-proBNP (pg/ml)	2886.0 (9050.3)	9790.9 (13864.5)	0.001	
Hs-TnT (pg/ml)	39.8 (51.9)	71.7 (40.7)	0.002	
Albumin (g/l)	32.8 (5.4)	32.5 (3.8)	0.850	
Hs-TnT at 24h (pg/ml)	46.2 (84.7)	83.9 (96.9)	0.095	
NT-proBNP at 72h (pg/ml)	2119.4 (5067.0)	8034.5 (13664.1)	0.007	
Left atrial enlargement	21 (31.3%)	47 (73.4%)	<0.001	6.1 (2.8-12.9)
Diastolic dysfunction	16 (23.5%)	31 (48.4%)	0.004	3.1 (1.5-6.4)
Ejection Fraction	59.5 (5.6)	51.7 (11.0)	<0.001	

COPD, chronic obstructive pulmonary disease; HF, heart failure; LTOT, long-term oxygen therapy; SGLT-2, sodium-glucose co-transporter-2 inhibitors; HB, hemoglobina; WBC, white blood cells.

Table 3. Secondary endpoints.

Secondary endpoints	**COPD without HF (N=76) n (%)/average (DS)**	**COPD and HF (N=68) n (%)/average (DS)**	***p <0.05***
In-hospital mortality	3 (3.9%)	4 (5.9%)	0.71
Need for transfer to UTI	5 (6.6%)	5 (7.4%)	1.00
Need for NIV during hospitalization	28 (36.8%)	34 (50.0%)	0.13
Length of hospital stay>14 days	25 (32.9%)	24 (35.3%)	0.86

COPD, chronic obstructive pulmonary disease; HF, heart failure.

Table 4. Follow-up at 30 days, 3 and 6 months.

		COPD without HF (N=76) n (%)/average (DS)	***COPD and HF (N=68) n (%)/average (DS)***	***P***	***OR (IC 95%)***
mMRC at 30 days	*0*	12 (16.0%)	8 (11.9%)	0.021	
	1	20 (26.0%)	11 (16.7%)		
	2	24 (32.0%)	18 (26.2%)		
	3	16 (20.0%)	23 (33.3%)		
	4	4 (6.0%)	8 (11.9%)		
Increased mMRC at 30 days		11 (22.0%)	14 (33.3%)	0.248	
Rehospitalization at 30 days		4 (7.7%)	5 (10.6%)	0.732	
Death at 30 days		3 (16.7%)	10 (29.4%)	0.502	
Rehospitalization at 3 and 6 months		11 (14.5%)	12 (17.6%)	0.653	
Death at 3 and 6 months		1 (1.3%)	8 (11.8%)	0.013	10.0 (1.2-82.2)

COPD, chronic obstructive pulmonary disease; HF, heart failure.