

Cardiopulmonary phenotypes as markers of high risk in patients with COPD in primary care: the MASTER-EPOC study

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Abstract

Background

Chronic obstructive pulmonary disease (COPD) is managed primarily with respiratory-based algorithms, even though cardiovascular comorbidity is a major determinant of adverse outcomes. We aimed to identify and characterise cardiopulmonary phenotypes defined by exacerbator profile and cardiovascular risk (CVR) in patients with COPD managed in primary care.

Methods

Cross-sectional, multicentre, retrospective study of 1,307 patients with COPD across 52 primary care centres in six Spanish regions. Phenotypes cross-classified the exacerbator profile (GOLD) with cardiovascular burden (established cardiovascular disease [CVD] / high risk / low-to-moderate risk). We used mixed-effects logistic regression, intraclass correlation, ROC curves, collinearity analysis and a preliminary unsupervised clustering analysis (machine learning).

Results

Median age was 72.6 years; 65.7% were men, 58.8% had moderate airflow obstruction, 31.2% were exacerbators and 36.8% had established CVD. The most frequent phenotype was the non-exacerbator with high CVR (40.6%), whereas the exacerbator phenotype with established CVD carried the greatest burden of hospitalisations and disease severity. We identified a hidden-risk phenotype—non-exacerbators with CVD—with a higher risk of hospitalisation and poorer clinical control (adjusted OR 1.99; 95% CI 1.21–3.25; $p = 0.006$ vs non-exacerbator phenotypes; sensitivity analysis). Clustering confirmed the clinical findings.

Conclusions

In COPD, jointly considering exacerbations and cardiovascular burden defines clinically relevant phenotypes, including a hidden-risk group of non-exacerbators with CVD. These practical, readily available axes complement the eosinophil count and support an integrated cardiopulmonary assessment.

Highlights

Exacerbations plus cardiovascular burden define useful COPD phenotypes.

A hidden-risk group emerges non-exacerbators with established cardiovascular disease.

Established cardiovascular disease adds hospitalisations and poorer control without exacerbations.

Over half fall in the 100–300 cells/ μ L eosinophil grey zone.

Simple bedside axes complement eosinophils in COPD care.

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of mortality and imposes a substantial healthcare burden through exacerbations, hospitalisations, treatments and impaired quality of life [1–4]. Although respiratory complications take centre stage, cardiovascular mortality is more frequent than respiratory mortality in exacerbator patients with moderate-to-very-severe airflow limitation [5, 6], and heart failure is the most frequent cause of second and subsequent admissions [7]. In the Spanish COPD population, the risk of a major cardiovascular event is appreciable even during exacerbation-free periods (6.70 events per 100 patient-years) [8], indicating that cardiovascular burden accompanies the disease continuously and not only during exacerbations.

Risk assessment, clinical control and treatment of these patients are usually grounded in algorithms and protocols developed from respiratory variables [9–11]. The cardiovascular component, however, is not integrated into these therapeutic algorithms, even though COPD with established cardiovascular disease (CVD) is associated with higher mortality than COPD without CVD

[12, 13]. There is therefore a pressing need to incorporate the cardiopulmonary component, approaching COPD management from a multidisciplinary perspective and identifying the patient phenotypes at highest risk, so that they can receive personalised care and treatment strategies [14–17].

The multicentre MASTER-EPOC study (Mejorando el Abordaje Sanitario y Terapéutico con Evaluación en vida Real en la EPOC; Improving the Healthcare and Therapeutic Approach with Real-Life Evaluation in COPD) was designed to assess the management of patients with COPD in primary care across seven autonomous communities in Spain. The primary objective of this manuscript was to identify and clinically characterise risk-stratified cardiopulmonary phenotypes. Secondary objectives were to analyse the correlation of these cardiopulmonary phenotypes with clinical and quality-of-care variables, and to perform an exploratory unsupervised clustering analysis (machine learning) of the identified phenotypes.

Materials and methods

Design, setting and data collection

This was an observational, cross-sectional, descriptive study based on data from the multicentre MASTER-EPOC study. Anonymised data collection and entry took place between 15 March and 30 May 2026. Fifty-two primary care centres from seven autonomous communities took part (Aragón, Asturias, Castilla y León, Galicia, Madrid, Navarra and Comunitat Valenciana). The analysis was restricted to the six communities with sufficient patient contribution; Navarra was excluded because of its marginal contribution, yielding an analysis cohort of 1,307 patients (Fig. 1). At each centre the research team comprised one or more physician–nurse teams (one physician and one to two nurses). A dedicated database was set up centrally on the Research Electronic Data Capture (REDCap) platform of the Institute of Health Sciences of Castilla y León (ICSCYL), with internal consistency checks. Patients were registered anonymously. The database was closed on 31 May 2026 and, after review and validation, frozen on 12 June 2026. Data collection was organised through centre-specific access groups. The study adheres to the recommendations of the STROBE initiative [18].

Sampling and eligibility from patients coded as COPD to the analysis cohort (N = 1,307; six autonomous communities, Navarra excluded).

Population

We included patients with a diagnosis of COPD confirmed by spirometry (post-bronchodilator FEV1/FVC < 0.70) under routine follow-up in primary care. Each physician–nurse team selected patients by simple random sampling from the set of patients listed and coded as COPD, with a minimum target of 20 patients per team.

Inclusion criteria were: (a) age ≥ 40 years, either sex; (b) a prior diagnosis of COPD (ICD-10 code or explicit clinical note); (c) documented diagnostic criteria; (d) at least one consultation related to COPD or its complications in the previous 12 months; and (e) a documented record of the therapeutic management of COPD and cardiovascular comorbidities in the previous 12 months.

We excluded patients with a concomitant diagnosis of asthma or other incompatible lung diseases, institutionalised patients without access to the full medical record, or those not meeting any inclusion criterion.

Variables and operational definitions

We recorded demographic variables (age, sex, smoking status), functional and severity variables (FEV1 severity, GOLD stratification, dyspnoea by mMRC, clinical control scale), a 12-month history of exacerbations and hospitalisations by cause (respiratory, cardiovascular, other), comorbidities and their mainly cardiovascular treatments, vaccination, inhaled bronchodilator treatment and inhaler technique (six components) (Supplementary material, S1). Percentages were calculated over cases with valid data, with missing values declared. Poor control was defined as a score ≥ 4 out of 8 on the clinical control scale [19]; details of the scale and its components are provided in the Supplementary material (S2).

A. Exacerbations

A moderate exacerbation was defined as one requiring antibiotics and/or oral corticosteroids for a respiratory cause and/or emergency care lasting < 24 h, and a severe exacerbation as one requiring hospitalisation > 24 h for a respiratory cause. An exacerbator profile was defined as ≥ 2 moderate exacerbations or ≥ 1 severe exacerbation in the previous 12 months (GOLD 2025). One or no moderate exacerbation and no severe exacerbation defined the non-exacerbator profile.

B. Cardiovascular burden

Cardiovascular risk was stratified, adapted from the 2025 ESC guideline (20), into: very high (≥ 1 established cardiovascular disease [CVD]: ischaemic heart disease, heart failure, atrial fibrillation, stroke/TIA or peripheral arterial disease); high (> 2 cardiovascular risk factors [CVRF], or chronic kidney disease, or type 2 diabetes, or 2 CVRF with age ≥ 50 years); moderate (1–2 CVRF without diabetes or kidney disease and age < 50 years); and low (0 CVRF). Age was considered a non-modifiable CVRF and hypertension, dyslipidaemia, type 2 diabetes, active smoking and chronic kidney disease modifiable CVRF (Supplementary material, S2). For the phenotype analysis, low and moderate risk were combined, so that the cardiovascular axis comprised three levels: established CVD, high risk and low/moderate risk.

C. Eosinophils and phenotype scheme

The eosinophil count was expressed, after individual harmonisation, in cells/ μ L; unclassifiable records or those without a value were treated as missing, leaving 1,257 patients (96.2%) with a valid count (Supplementary material, S3).

The phenotype scheme was defined on two axes—the exacerbator profile and the cardiovascular burden—with the eosinophil count described as a third dimension within the groups rather than as a defining criterion. The intersection of the two axes defines the phenotypes, presented as a six-phenotype scheme.

The exacerbator axis (exposure) and the exacerbation component of the control index (outcome) share information, so there is partial overlap between the two. To bound this, we pre-specified a sensitivity analysis restricted to patients with no recorded exacerbations, in whom that component is null by construction (details of the scale in Supplementary material, S2).

Handling of missing values

In the 15 patients whose age was coded as missing, the age criterion could not be evaluated, and stratification was resolved by the algorithm's default clause, which assigns them to high risk. Missing values for exacerbations, for the five cardiovascular entities and for the CVRF were few (< 0.9%; Supplementary material, S3) and were imputed as zero (absence of the condition) before deriving the exacerbator profile and the risk stratification. The resulting prevalences are therefore conservative estimates. The robustness of this approach was checked by a complete-case sensitivity analysis.

Statistical analysis

Continuous variables are summarised as median and interquartile range and categorical variables as frequencies and percentages over valid cases, with 95% confidence intervals. Confidence intervals for centre-dependent variables (inhaler technique, spirometry, diagnosis, control and vaccination) were estimated with cluster-robust standard errors, and the remainder using the Wilson method. Comparisons of categorical variables between phenotypes were made with the χ^2 test. Poor clinical control was defined as a score ≥ 4 [19], and its association with phenotype was estimated using a mixed-effects logistic regression model with a random intercept per centre (complete-case analysis, $n = 1,180$), adjusted for age, sex and functional severity, taking the “non-exacerbator with high cardiovascular risk” phenotype as reference. Between-centre variability was quantified using the intraclass correlation coefficient (ICC = 0.12) and the median odds ratio (MOR = 1.87). Model discrimination was assessed with the area under the ROC curve (AUC = 0.86; 95% CI 0.83–0.88) and collinearity with the variance inflation factor (VIF < 1.1). As an exploratory analysis, unsupervised (data-driven) clustering was performed on a Gower distance matrix (mixed data), assessing structure with hierarchical clustering (Ward.D2) and PAM (k-medoids), with dimensionality reduction (MDS, UMAP) and bootstrap stability (500 replicates). Analyses were performed in R 4.5, with two-sided significance at $p < 0.05$.

Ethical considerations

The study was approved by the León–El Bierzo Research Ethics Committee (minutes of 29 June 2025, code 25208). It was conducted in accordance with the Declaration of Helsinki, with good clinical practice standards for non-interventional studies and with Spanish and European Union data protection regulations. Data were collected, recorded and analysed anonymously. Written consent was required only for face-to-face data collection. The study is reported in accordance with STROBE [18].

Results

General profile of the cohort

A total of 1,307 patients were analysed. The median age was 72.6 years (Q1–Q3 66.0–79.4), with 65.7% men. Active smokers accounted for 30.7% and ex-smokers for 60.8%. A documented COPD diagnosis was lacking in 11.6%. Dyspnoea was mostly mild (median mMRC 1) and 23.8% had poor clinical control. Vaccination characteristics and adherence to correct inhaler technique are shown in Table 1.

Table 1
General profile of the cohort

Variable	Value (95% CI)
N	1,307
Age, median (Q1–Q3)	72.6 (66.0–79.4)
Men, n (%)	857 (65.7%)
Current smoker, % (95% CI)	30.7 (28.1–33.3)
Ex-smoker, % (95% CI)	60.8 (58.1–63.5)
mMRC, median	1
Poor clinical control ($\geq 4/8$), % (95% CI)	23.8 (21.5–26.3)
Moderate obstruction, % (valid)	58.7
Severe/very severe, % (valid)	20.8
Established CVD, % (95% CI)	36.8 (34.2–39.5)
Heart failure, %	16.4
Exacerbator, % (95% CI)	31.2 (28.7–33.8)
Correct inhaler technique, % (assessed)	55.7 (n = 1,061)
Documented diagnosis, %	88.4
Influenza / COVID-19 / pneumococcal / zoster vaccination, %	83.8 / 85.8 / 75.0 / 32.3

95% CI: Wilson method (variables without centre dependence).

Among the 1,197 cases with valid functional stratification (91.6% of the sample), 58.8% had moderate obstruction and 20.8% severe or very severe obstruction. The prevalence of CVD was 36.8%, with heart failure the most frequent (16.4%). The prevalence of cardiovascular risk factors (CVRF) was high for hypertension and dyslipidaemia (64.9% and 66.4%) (Supplementary material, S4).

Distribution and clinical profile of the phenotypes

The most frequent phenotype (40.6%) was the non-exacerbator with high CVR, followed by the non-exacerbator with CVD (22.3%) (Fig. 2). Exacerbators accounted for 31.2% (95% CI 28.7–33.8) of patients, with a phenotype distribution of 14.9% for the exacerbator with high CVR and 14.5% for the exacerbator with CVD.

Phenotypes defined by the exacerbator profile and cardiovascular risk. Bars ordered by frequency; n (%) shown.

Analysis of the clinical characteristics of the phenotypes shows that exacerbators with established CVD are older, predominantly men, with greater dyspnoea and poorer control ($p < 0.001$ in all cases) (Table 2). Although moderate exacerbations were distributed homogeneously across the three exacerbator phenotypes, overall and respiratory-cause hospitalisations were more frequent in the exacerbator phenotype with established CVD. Cardiovascular-cause hospitalisations were concentrated in the exacerbator phenotype with established CVD (20%) and, to a lesser extent, in the non-exacerbator phenotype with established CVD (7%). Documented diagnosis did not differ between phenotypes (χ^2 , $p = 0.32$) (Supplementary material, S5).

Table 2
Clinical profile by phenotype (six groups)

Variable	Exacerbator· established CVD (n = 189)	Exacerbator· high CVR (n = 195)	Exacerbator· low/moderate CVR (n = 24)	Non- exacerbator· established CVD (n = 292)	Non- exacerbator· high CVR (n = 531)	Non- exacerbator· low/moderate CVR (n = 76)	p
Age, median (Q1–Q3)	77.9 (72.0–82.5)	72.2 (66.0–78.3)	64.3 (59.3–71.7)	76.8 (69.5–82.4)	70.0 (63.6–76.7)	66.4 (60.4–72.7)	< 0.001
Men, %	71.4%	60.0%	50.0%	74.0%	63.4%	55.4%	< 0.001
mMRC ≥ 2 , %	75.7%	62.1%	62.5%	47.1%	29.7%	27.8%	< 0.001
Poor clinical control, %	60.3%	44.1%	41.7%	15.8%	9.1%	7.0%	< 0.001
≥ 2 moderate exacerbations, %	57.1%	66.7%	66.7%	0.0%	0.0%	0.0%	< 0.001*
Respiratory hospitalisation, %	55.9%	41.0%	45.8%	4.5%	1.9%	1.4%	< 0.001
Cardiovascular hospitalisation, %	19.7%	2.6%	0.0%	6.5%	0.4%	0.0%	< 0.001
Triple therapy, %	68.8%	62.1%	66.7%	41.9%	31.4%	26.8%	< 0.001

Between-phenotype p : χ^2 (categorical) / Kruskal–Wallis (continuous). *The “ ≥ 2 moderate exacerbations” row is definitional of the exacerbator axis (0% in non-exacerbators by construction): its p is tautological. Exacerbation and CVD, which define the phenotype, are not tested. Hosp: hospitalisation within 12 months.

The descriptive analysis by cardiovascular risk level also showed a gradient of severity and burden of exacerbations/hospitalisations (Table 3). Respiratory hospitalisations doubled in very-high-risk patients, and cardiovascular hospitalisations were concentrated almost exclusively at this risk level.

Table 3
Profile by cardiovascular risk level

Variable	Established CVD (n = 481)	High CVR (n = 726)	Low/moderate CVR (n = 100)	p
Age, median (Q1–Q3)	77.1 (70.5–82.4)	70.7 (64.4–77.1)	65.5 (60.0–72.4)	< 0.001
Severe/very severe (FEV1), %	24.9%	17.7%	23.6%	0.012
Poor clinical control, %	33.3%	18.6%	15.8%	< 0.001
Exacerbator, %	39.3%	26.9%	24.0%	< 0.001
Respiratory hospitalisation, %	24.6%	12.5%	12.8%	< 0.001
Cardiovascular hospitalisation, %	11.7%	1.0%	0.0%	< 0.001
<i>Between-CV-risk-level p: χ^2 (categorical) / Kruskal–Wallis (continuous). “Exacerbator” is not definitional of the CV axis, so its p is informative. Hosp: hospitalisation within 12 months. Cardiovascular hospitalisations are concentrated at the established-disease level</i>				

Quality-of-care variables by phenotype

The most frequently prescribed inhaled treatment in the exacerbator phenotypes was triple therapy: 68.8% in the exacerbator with CVD, 62.1% in the high-risk phenotype and 66.7% in the low/moderate-risk phenotype (Fig. 3 and Supplementary material, S6). The LABA/LAMA combination was the most frequently prescribed among the non-exacerbator phenotypes (range 29–32%).

Distribution of inhaled treatment within each phenotype (% of phenotype). Triple therapy highest in exacerbator-established CVD, lowest in non-exacerbator-low/moderate risk.

Inhaler technique was assessed in 1,061 patients. Significant differences were observed between phenotypes, with a lower proportion of correct technique in the phenotypes with established CVD (χ^2 , $p < 0.001$) (Table 4).

Table 4
Inhaler technique and diagnosis by phenotype

Phenotype	N technique	Correct technique, %	Spirometry at the centre, %	Documented diagnosis, %
Exacerbator – established CVD	168	41.7	20.6	86.8
Exacerbator – high CVR	162	59.9	28.9	92.3
Exacerbator – low/moderate CVR	20	65.0	8.3	79.2
Non-exacerbator – established CVD	233	48.1	32.3	89.0
Non-exacerbator – high CVR	421	62.7	40.8	87.5
Non-exacerbator – low/moderate CVR	57	61.4	29.2	88.9

Correct technique = 0 errors among the assessed components. χ^2 technique $p < 0.001$; documented diagnosis $p = 0.321$ (n.s.).

Taking the non-exacerbator with high-risk phenotype as reference, all exacerbator phenotypes showed a significant odds ratio for poor control, greatest in the exacerbator with CVD (Fig. 4).

Mixed-effects logistic regression adjusted for age, sex and functional severity, with a random centre intercept. Reference: non-exacerbator · high cardiovascular risk (n = 1,180). OR (95% CI) on a log scale.

Particularly relevant was the excess of poor control in the non-exacerbator phenotype with CVD (adjusted OR 1.99; 95% CI 1.21–3.25; $p = 0.006$), estimated with a mixed-effects model with a random intercept per centre (ICC = 0.12; MOR = 1.87; conditional AUC = 0.86). On direct comparison of the non-exacerbator phenotype with established CVD with the low/moderate-risk exacerbator phenotype (“pure exacerbator”), no differences were found in the degree of clinical control (OR 0.51; 95% CI 0.18–1.46; $p = 0.211$) or in cardiovascular hospitalisations (6.5% vs 0%; $p = 0.379$), although there were differences in respiratory hospitalisations (4.5% vs 45.8%; $p < 0.001$).

Overall vaccination coverage was: influenza 83.8%, COVID-19 85.8%, pneumococcus 75.0% and herpes zoster 32.3%. Crude between-phenotype differences ceased to be significant after adjustment for age (influenza $p = 0.15$; pneumococcus $p = 0.05$; COVID-19 $p = 0.96$; zoster $p = 0.59$) (Supplementary material, S7).

Exploratory unsupervised clustering analysis

The unsupervised analysis ($n = 901$) did not identify discrete clusters: COPD in primary care behaved as a continuum of severity rather than as isolated groups (silhouette 0.19; Jaccard index 0.33–0.57) (Supplementary material, S8). This finding argues in favour of simple, pre-specified clinical axes, such as the one proposed here, over schemes based on emergent clustering. When four clusters were forced, exacerbation and cardiovascular burden emerged as the dominant axes (Fig. 5).

Heat map showing the prevalence (%) of six clinical and quality-of-care variables across the six cardiopulmonary phenotypes, defined by crossing the exacerbator profile with cardiovascular risk. Columns are ordered by increasing burden, from the non-exacerbator with low/moderate cardiovascular risk (left) to the exacerbator with established cardiovascular disease (right). Burden increases along this gradient: the exacerbator with established CVD concentrates the highest values for dyspnoea (mMRC ≥ 2 , 75.7%), poor clinical control (60.3%), respiratory hospitalisation (55.9%) and cardiovascular hospitalisation (19.7%), whereas the non-exacerbator with low/moderate risk shows the lowest. Cardiovascular hospitalisation tracks established cardiovascular disease rather than the exacerbator axis, being present in the non-exacerbator with established CVD (6.5%) and virtually absent in the low/moderate-risk groups (0–0.4%).

Discussion

This study describes how integrating the frequency of exacerbations and the presence of cardiovascular disease defines a clinical stratification scheme for the patient with COPD that adds information to an assessment based solely on respiratory parameters. Our findings help to characterise the emerging concept of cardiopulmonary risk as an axis of clinical severity in real-world practice, detecting phenotypes at maximum risk—such as exacerbators with established cardiovascular disease—and a hidden-risk phenotype: non-exacerbators with established cardiovascular disease. The internal coherence of these groups was supported by an exploratory unsupervised clustering analysis.

Our results should be interpreted in the setting of real-world primary care. The cohort reflects the usual complexity of COPD care, with an elderly population and a high proportion of active smokers, figures aligned with studies such as COPDGene, SPIROMICS and EPISCAN II [21–23]. The prevalence of cardiovascular comorbidity and established cardiovascular disease (36.8%) is consistent with other national and international real-world observational studies [24–26]. Likewise, the cohort's annual hospitalisation rate (26.3% of the total; 26.7% of cases with valid data) is like that reported in other real-world multicentre studies [27–29]. Although the study was conducted in primary care, we consider that the results may be generalisable to other populations and levels of care and contribute to articulating multidisciplinary continuity of care.

The exacerbator phenotype with CVD as the epicentre of high cardiopulmonary risk

One of the most relevant findings was the identification of the exacerbator phenotype with established CVD as the entity of maximum clinical vulnerability. This subgroup accumulated the greatest burden of hospitalisations (overall and of respiratory and cardiovascular cause), the poorest clinical control and the poorest functional status of the cohort. The coexistence of impaired lung function—arising from recurrent bronchial inflammation—and systemic, mainly atherosclerotic, arterial disease generates a high cardiopulmonary risk that has been described to increase during exacerbations [30–32]. Each exacerbation induces a state of systemic inflammation and endothelial dysfunction that acts as a vascular trigger, while the underlying heart

disease compromises haemodynamic reserve [33, 34]. In the Spanish COPD population, the risk of a major cardiovascular event remains high even during exacerbation-free periods [35], which underscores the crucial importance of recognising this phenotype to institute an intensive, multidisciplinary approach early.

The hidden risk of the non-exacerbator phenotype with CVD

An aspect of clinical importance is the behaviour of the non-exacerbator phenotype with CVD. Traditionally, the GOLD strategy [9] and other guidelines [10, 11] stratify patients without a history of exacerbations into a “low risk” category. Our results, however, show that, among non-exacerbator patients, the presence of established CVD was associated with greater dyspnoea and an excess of both respiratory and cardiovascular hospitalisations. Several studies support that COPD in the presence of established CVD is associated with greater functional impairment and a higher risk of cardiovascular events independently of previous exacerbations [36–38]. Furthermore, our results show that the degree of poor clinical control in the non-exacerbator phenotype with established CVD was comparable to that of the low/moderate risk exacerbator (“pure exacerbator”), while they differed in respiratory and cardiovascular hospitalisations, underscoring that both phenotypes share poor control but differ in their pattern of events. Apparent respiratory stability should therefore not create a false sense of security: active screening for cardiovascular disease and optimisation of cardioprotective treatment are priorities even in the absence of recent exacerbations.

Cardiovascular burden and exacerbations vs eosinophils: moving beyond the “grey zone”

Current guidelines position the eosinophil count as a biomarker to guide inhaled anti-inflammatory therapy [8, 10]. However, in our cohort 54.7% of patients fell within the intermediate “grey zone” (100–300 cells/ μ L), a range that entails uncertainty. In this context, our work offers a pragmatic reading: cardiovascular burden and exacerbation history are clinical axes directly observable in the clinic and were consistently associated with control and hospitalisation burden. Eosinophils are useful for predicting the response to targeted drugs [39, 40]; the two approaches are complementary, but cardiovascular comorbidity and exacerbations provide a clinical framework that is manageable and reproducible in the outpatient setting [41].

Coherence between the clinical classification and the unsupervised analysis

From a methodological standpoint, the structure of the proposed phenotypes was explored by unsupervised clustering (Gower distance and dimensionality reduction). The analysis showed that COPD in primary care behaves as a continuum of severity rather than as isolated categories. It should be noted that exacerbation and cardiovascular burden were among the clustering input variables; therefore, their emergence as dominant axes is a coherent consequence of the data structure and not an independent validation of the scheme. Interpreted as an exploratory analysis, this result supports the use of simple, pre-specified clinical axes over schemes based on emergent clustering, which are difficult to translate to the clinic.

Strengths and limitations

The sample size and multicentre nature confer a population representative of real-world clinical practice in primary care. Simple random sampling at each centre limits selection bias compared with cohorts recruited by treatment. Centralised, standardised data collection (REDCap), verification of variables against the raw data, rigorous characterisation of cardiovascular comorbidity and cross-validation using advanced machine-learning techniques add traceability and robustness to the results. The analysis explicitly distinguishes the descriptive from the circular, adjusts age-sensitive contrasts for age, and declares valid-case denominators, which reduces the risk of over-interpretation. The main finding rests on an outcome not contaminated by exacerbations, confirmed in the sensitivity analysis.

As the main limitation, the cross-sectional design does not allow causal or prognostic inference; the study includes no prospective follow-up, so mortality and incident events are not analysed. Hospitalisations and exacerbations are retrospective over 12 months and subject to possible recording bias. The variables that define the phenotype may generate tautological associations with related outcomes, which have been flagged as such and bounded by sensitivity analysis. Missing data for comorbidities and exacerbations, although few, were imputed as zero (“missing = absence”), which provides a conservative floor but may underestimate prevalences.

Conclusions

In a large cohort of COPD in primary care, jointly considering the exacerbator profile and the cardiovascular burden defines clinically relevant phenotypes. The exacerbator phenotype with established cardiovascular disease carried the greatest burden of hospitalisations and severity, and a hidden-risk phenotype emerged—the non-exacerbator with cardiovascular disease—with a higher risk of hospitalisation than the other non-exacerbator phenotypes, which questions its traditional classification as “low risk”. Considering both axes in the assessment of the patient with COPD offers a simple clinical framework, observable in the clinic, that supports an integrated cardiopulmonary assessment in COPD.

Declarations

Funding

This study received no funding from any private, public or not-for-profit entity or organisation.

Consent for publication

Not applicable. The manuscript does not contain identifiable data of any individual in any form.

Data availability

The datasets generated and analysed during the study are held in the custody of the investigators of the MASTER-EPOC project and may be requested from the corresponding author on reasonable, justified grounds, subject to the study's data-governance rules, ethics committee approval and European Union data protection regulations.

Declaration of generative AI use

During the preparation of this work the authors used a generative artificial intelligence assistant to support language editing, editorial auditing and analysis scaffolding. All content—including every citation, reference, numerical result and figure—was subsequently reviewed, verified against the original database and validated by the authors, who take full responsibility for the accuracy and integrity of the manuscript.

Author Contribution

CRedit authorship contribution statement Calderón-Montero A: Conceptualization, Project administration, Funding acquisition (ethics committee management), Methodology (variable and case-report-form design), Resources, Investigation, Writing – original draft, Writing – review & editing. Alonso-Avilés R: Methodology, Formal analysis, Data curation, Software, Visualization, Writing – original draft, Writing – review & editing. Pérez-Laorden A, Martínez-Tahoces SM, del Rey-Moya LM and Millares-López C: Conceptualization, Study design, Study management (ethics committee), Methodology. Sanz-García A: Methodology, Data curation, Formal analysis, Validation (statistical audit and reproduction of the multivariable models), Software. All authors critically reviewed the successive versions of the manuscript, contributing important concepts and improvements, approved the final version for publication and meet the four ICMJE authorship criteria.

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Figures

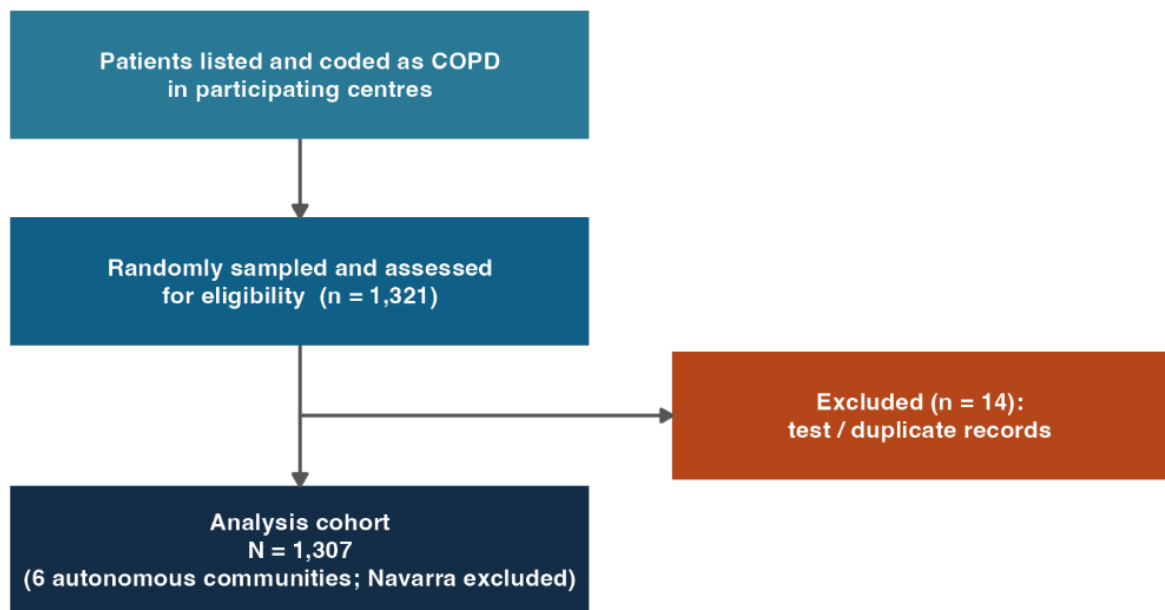


Figure 1

Cohort flow diagram.

Sampling and eligibility from patients coded as COPD to the analysis cohort (N=1,307; six autonomous communities, Navarra excluded).

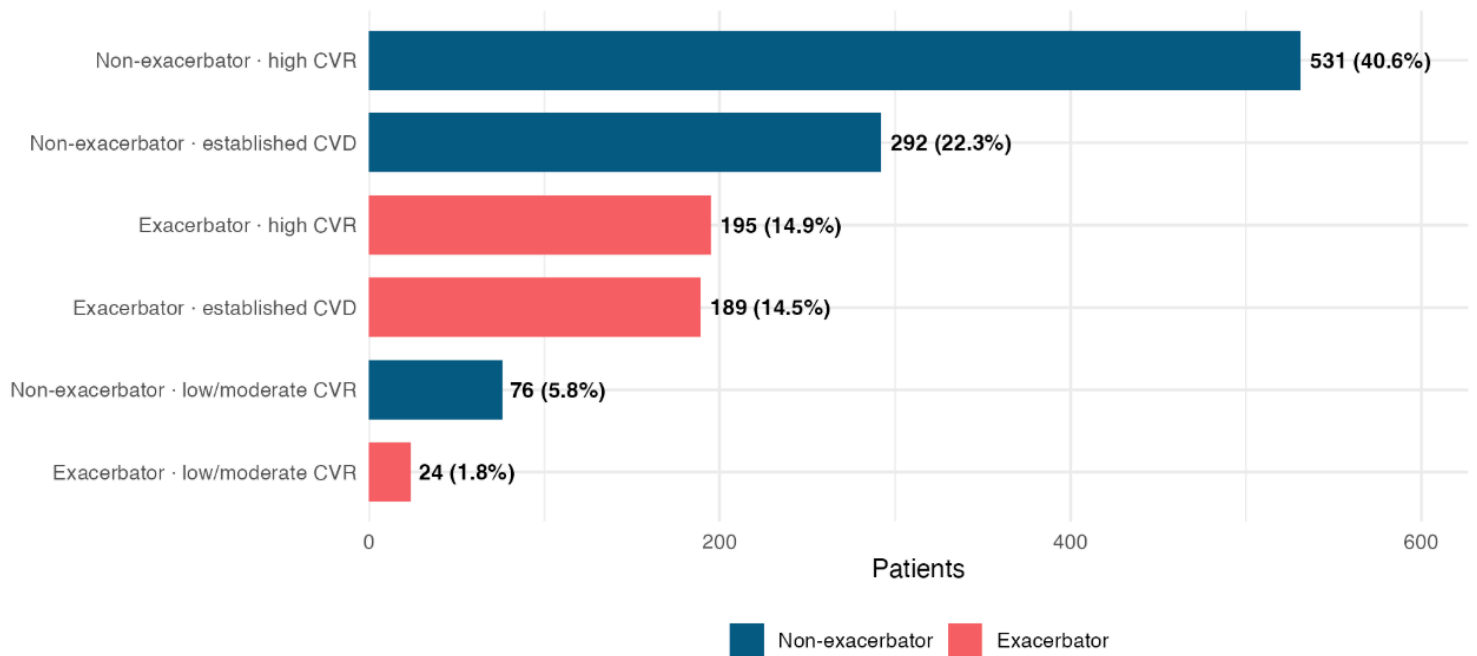


Figure 2

Distribution of the six phenotypes (N=1,307).

Phenotypes defined by the exacerbator profile and cardiovascular risk. Bars ordered by frequency; n (%) shown.

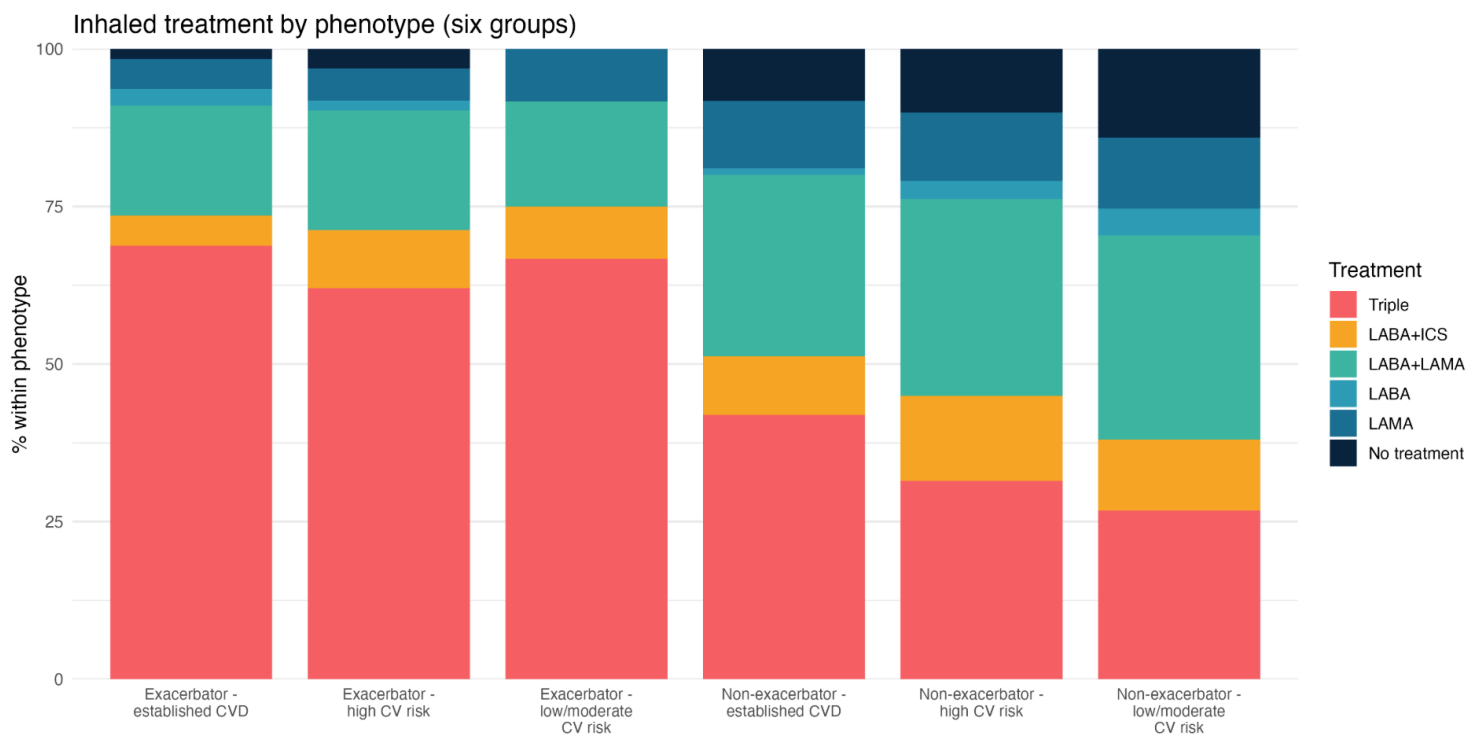


Figure 3

Inhaled treatment by phenotype.

Distribution of inhaled treatment within each phenotype (% of phenotype). Triple therapy highest in exacerbator-established CVD, lowest in non-exacerbator-low/moderate risk.

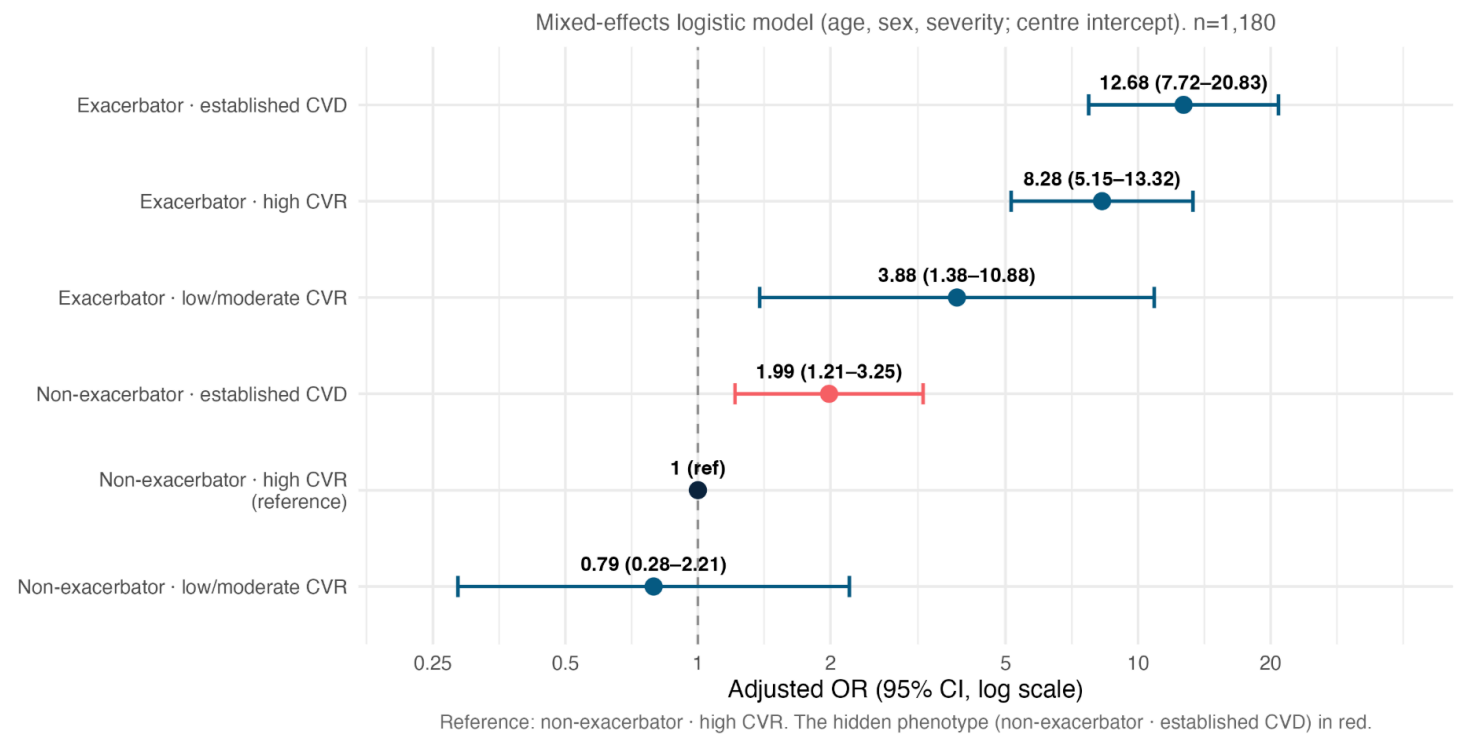


Figure 4

Forest Plot. Poor clinical control by phenotype: adjusted odds ratios.

Mixed-effects logistic regression adjusted for age, sex and functional severity, with a random centre intercept. Reference: non-exacerbator · high cardiovascular risk (n=1,180). OR (95% CI) on a log scale.

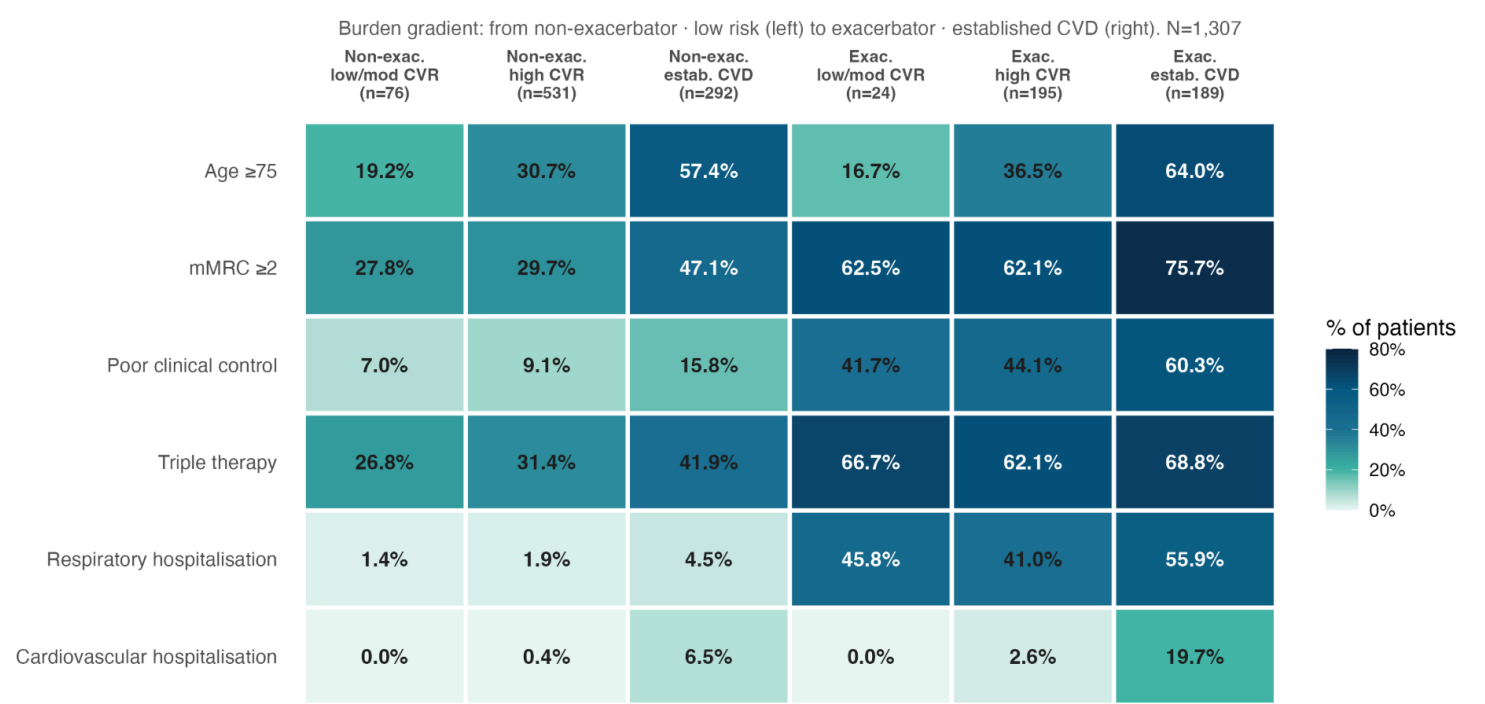


Figure 5

Outcomes and axes by phenotypic cluster (exploratory analysis).

Heat map showing the prevalence (%) of six clinical and quality-of-care variables across the six cardiopulmonary phenotypes, defined by crossing the exacerbator profile with cardiovascular risk. Columns are ordered by increasing burden, from the non-exacerbator with low/moderate cardiovascular risk (left) to the exacerbator with established cardiovascular disease (right). Burden increases along this gradient: the exacerbator with established CVD concentrates the highest values for dyspnoea (mMRC ≥2, 75.7%), poor clinical control (60.3%), respiratory hospitalisation (55.9%) and cardiovascular hospitalisation (19.7%), whereas the non-exacerbator with low/moderate risk shows the lowest. Cardiovascular hospitalisation tracks established cardiovascular disease rather than the exacerbator axis, being present in the non-exacerbator with established CVD (6.5%) and virtually absent in the low/moderate-risk groups (0–0.4%).

Supplementary Files

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