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Phenotypic assessment of COPD using clinical, radiological, and functional parameters

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ABSTRACT

Aims: Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition with variable clinical presentation and disease progression. This study aimed to investigate the distribution of patients across defined COPD phenotypes and to compare their clinical, radiological, and functional characteristics.

Methods: This cross-sectional descriptive study included 96 patients diagnosed with COPD. Patients were classified into four phenotype groups: asthma-COPD overlap (ACO; previously termed ACOS), non-exacerbator (NE), frequent exacerbator with emphysema (FEE), and frequent exacerbator with chronic bronchitis (FECB). Demographic, clinical, and pulmonary function parameters were analyzed and compared among groups. Forced expiratory volume in one second (FEV1), body-mass index (BMI), COPD Assessment Test (CAT), diffusing capacity for carbon monoxide (DLCO), and inspiratory capacity/total lung capacity (IC/TLC) ratio were evaluated.

Results: Of the patients, 83 (86.5%) were male and 13 (13.5%) were female, with a mean age of 65.22±7.85 years. The distribution of phenotypes was as follows: ACO (9%), NE (53%), FEE (19%), and FECB (19%). The mean annual exacerbation rate was 1.27±1.2, and the mean FEV1 was 50.21±16.56%. The ACO phenotype was characterized by a higher proportion of female patients, younger age, history of asthma and atopy, better clinical status, and relatively preserved lung function. In contrast, the FEE phenotype demonstrated a higher exacerbation frequency, poorer quality of life, and more severe airflow limitation. Patients in the FEE group had lower FEV1 and BMI, higher CAT scores, increased lung volumes and airway resistance, lower DLCO and partial pressure of oxygen (pO_2), and an IC/TLC ratio below 25%.

Conclusion: Distinct COPD phenotypes, particularly ACO and FEE, exhibit significant differences in clinical and functional characteristics. Recognition of these phenotypes may help guide individualized management strategies, including pulmonary rehabilitation, nutritional support, and optimization of pharmacological and interventional treatments.

Keywords: Asthma-COPD overlap, chronic obstructive pulmonary disease, chronic bronchitis, emphysema, frequent exacerbation, phenotype

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a multifactorial and heterogeneous disorder characterized by persistent respiratory symptoms and airflow limitation that is not fully reversible, usually due to significant exposure to noxious particles or gases.[1] Despite being historically defined by spirometric parameters, especially the forced expiratory volume in one second (FEV_1), it has become increasingly clear that COPD encompasses a spectrum of clinical, functional, and radiological presentations that cannot be fully explained by airflow limitation alone.[2] Patients with similar degrees of obstruction may exhibit strikingly different symptom burdens, exacerbation risks, and prognoses.[3]

Recent GOLD 2024 reports emphasize that COPD should be viewed as a syndrome with multiple phenotypes and underlying endotypes, reflecting diverse pathobiological mechanisms such as chronic inflammation, tissue remodeling, and systemic effects.[4,5] Traditional classification based solely on spirometry fails to capture this complexity and provides limited insight into prognosis, comorbidities, and treatment response.[6] Accordingly, contemporary research has shifted toward phenotypic and endotypic characterization, integrating clinical features, biomarkers, and imaging-based parameters to achieve a more personalized management approach.[7,8]

Phenotyping allows identification of subgroups that share clinical or biological traits, such as frequent exacerbators, chronic bronchitic, emphysematous, or asthma-COPD overlap (ACO) phenotypes. This approach enables more precise therapeutic strategies, improved prediction of outcomes, and better design of clinical trials.[9,10] Beyond

clinical observation, recent advances in high-resolution computed tomography (HRCT) and quantitative imaging have provided objective markers for structural airway and parenchymal abnormalities, enhancing the ability to distinguish emphysema-predominant from airway-predominant disease.[11,12]

In parallel, studies employing multi-omics analyses-including genomics, transcriptomics, proteomics, and metabolomics-have identified molecular signatures associated with distinct COPD phenotypes and therapeutic responses.[13-15] For example, genetic studies have identified multiple susceptibility loci associated with COPD and COPD-related phenotypes, while distinct inflammatory profiles, including eosinophilic inflammation, have been linked to clinically relevant disease characteristics and exacerbation risk.[16-18] Similarly, inflammatory biomarkers, particularly blood eosinophil counts, may help identify clinically relevant treatable traits, while systemic inflammatory markers such as C-reactive protein and fibrinogen may provide additional information regarding disease activity and prognosis.[18,19]

Overall, phenotyping provides a framework to better understand the dynamic course of COPD-punctuated by exacerbations and variable clinical progression-and to identify targets for more effective, individualized interventions.[19]

Therefore, the present study aimed to evaluate the applicability of the phenotypic classification in COPD patients presenting to our clinic and to identify distinctive clinical, functional, radiological, and laboratory characteristics among these phenotype groups.

METHODS

Ethics

This study was conducted with the approval of the Ankara University Faculty of Medicine Ethics Committee (Date: 25.07.2014, Decision No: 38615). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Written informed consent was obtained from all individual participants prior to their inclusion in the study.

Patients and Study Design

This cross-sectional descriptive study included 96 stable COPD patients without recent exacerbations who attended the COPD outpatient clinic of Ankara University Faculty of Medicine, Department of Chest Diseases, between September 2014 and March 2016.

Patient Selection and Evaluation

Eligible patients were aged 40 years or older and had a confirmed diagnosis of COPD according to the 2015 GOLD criteria (post-bronchodilator $FEV_1/FVC<0.70$).[3] At the time of study design, the terminology ACOS was used in the prevailing GesEPOC and GOLD frameworks; however, the updated term ACO is used throughout this manuscript for consistency with current literature.

Demographic and clinical data-including symptoms, comorbidities, exacerbation frequency, atopy, occupational and family history, smoking exposure (pack-years), and body-mass index (BMI)-were recorded. Pulmonary function was assessed using spirometry, whole-body plethysmography, and single-breath carbon monoxide diffusion capacity (DLCO) measurement.

An early bronchodilator reversibility test was performed to support the diagnosis of asthma-COPD overlap syndrome (ACOS). A ≥15% and ≥400 ml increase in FEV_1 from baseline was accepted as a major criterion, while a ≥12% and ≥200 ml increase was considered a minor criterion (**Table 1**).

Table 1. Asthma-COPD overlap (ACO) phenotype diagnostic criteria

Major criteria
High positivity in the reversibility test:
->15% and >400 ml increase in FEV1
Sputum eosinophilia
Asthma history
Minor criteria
Elevated total IgE
History of atopy
Positivity in the reversibility test:
->12% and >200 ml increase in FEV1

COPD: Chronic obstructive pulmonary disease, ACO: Asthma-COPD overlap, FEV1: Forced expiratory volume in one second, IgE: Immunoglobulin E

Symptom burden and quality of life were evaluated using the six-minute walk test (6MWT), arterial blood gas analysis, the COPD Assessment Test (CAT), and the St. George's Respiratory Questionnaire (SGRQ). Serum total immunoglobulin E (IgE) levels and sputum eosinophil counts were obtained for ACO differentiation (**Table 1**).

Radiological evaluation included chest radiographs and thoracic computed tomography (CT) scans, which were reviewed for emphysema, bronchial wall thickening, bronchovascular branching, and bronchiectasis.

Thoracic CT scans were visually evaluated by two experienced radiologists who were blinded to the clinical phenotype classification. Assessments were based on qualitative radiological findings including emphysema, bronchial wall thickening, hyperlucency, bronchovascular branching, and bronchiectasis. Quantitative software-based CT analysis was not performed.

Phenotype Classification

Phenotypic categorization was based on the Spanish COPD Guidelines (GesEPOC), identifying four distinct clinical phenotypes (Figure 1):

- Non-exacerbator COPD (NE)
- Asthma-COPD overlap syndrome (ACOS)
- Frequent exacerbator with emphysema (FEE)
- Frequent exacerbator with chronic bronchitis (FECB)

Diagnostic criteria for ACO were determined according to the coexistence of major and minor criteria (**Table 1**).[4]

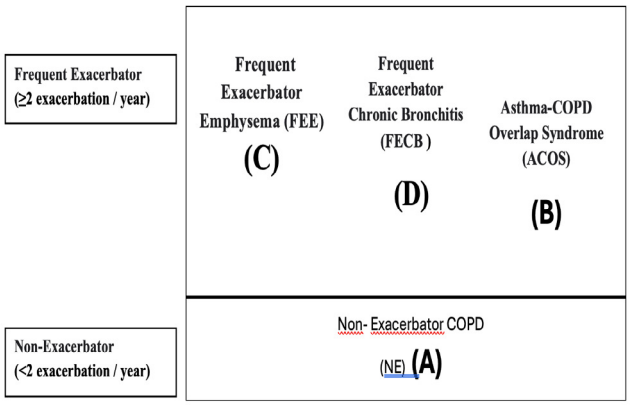

Figure 1. Phenotyping according to Spanish COPD guideline GesEPOC

FEE: Frequent exacerbator emphysema, FECB: Frequent exacerbator chronic bronchitis, COPD: Chronic obstructive pulmonary disease, ACOS: Asthma-COPD overlap syndrome, NE: Non-exacerbator, EPOC: Enfermedad pulmonar obstructiva crónica

Statistical Analysis

Data distribution was tested using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Group comparisons for continuous variables were performed using one-way analysis of variance (ANOVA) with post hoc tests, while categorical variables were analyzed using the Chi-square or Fisher's exact test, as appropriate. Correlations between variables were evaluated using Pearson's correlation coefficient. Results are presented as mean±standard deviation (SD) for normally distributed variables, median (minimum-maximum) for nonparametric data, and as counts or percentages for categorical variables. Post hoc pairwise comparisons following ANOVA were performed using the Tukey HSD test. Statistical significance was defined as $p<0.05$. Analyses were conducted using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 96 patients were included in the study (**Table 2**). The distribution of phenotypes according to the GesEPOC criteria is shown in **Figure 2**. Of all patients, 83 (86.5%) were male and 13 (13.5%) were female. The proportion of females was significantly higher in the ACO group (55.6%) compared with the other phenotypes (p=0.007; **Figure 3**). Patients with ACO were younger and had fewer smoking pack-years, although the differences were not statistically significant. The ACO group had the highest mean BMI, whereas the FEE group had the lowest. Disease duration was significantly longer in ACO patients ($p<0.001$), while the FEE group had the highest number of hospitalizations (**Table 3**).

All patients with ACO (100%) reported a prior history of asthma, a finding that differed significantly from other groups ($p<0.001$). Likewise, atopy was more prevalent among ACO patients (66.7%) than in the NE, FEE, and FECB groups (p=0.003). Active smoking rates did not differ between groups (p=0.788). Cough and sputum production were significantly more frequent in the FECB group ($p<0.001$), whereas other symptoms showed no group differences.

Symptom severity and quality-of-life scores varied among phenotypes. mMRC dyspnea and CAT scores were highest in the FEE group, whereas SGRQ total, symptom, and impact scores were lowest in the NE group ($p<0.001$). Six-minute walk distance (6MWD) differed significantly among groups

Table 2. General characteristics of all patients (n: 96)

Parameters	Mean±SD	Median (min-max)
Age	65.22±7.85	65 (48-84)
Smoking (package-year)	49.84±29.58	40 (1-150)
Body-mass index (kg/m²)	26.67±5.18	25.65 (15.8-42.9)
Number of exacerbations per year	1.27±1.2	1 (0-6)
Number of hospitalizations per year	0.63±0.9	0 (0-6)
CAT score	11.9±7.1	10 (0-32)
St George total score	32.77±22.4	28.7 (1.05-82)
6-Minute Walk Test (m)	442±91	460 (220-640)
FEV1%	50.21±16.56	50 (17-84)
Reversibility ΔFEV1%	10.63±9.62	8 (-7-41)
Reversibility ΔFEV1 (ml)	142.83±134.82	120 (-50-670)
DLCO %	67.8±24.3	66 (21-116)

SD: Standard deviation, min: Minimum, max: Maximum, CAT: COPD Assessment Test, FEV1%: Forced expiratory volume in 1 second, percent predicted, DLCO%: Diffusing capacity of the lungs for carbon monoxide, percent predicted

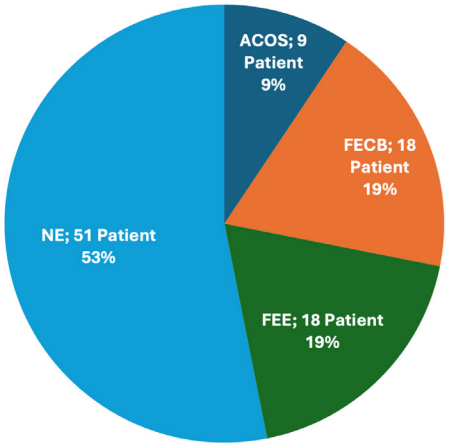

Figure 2. Distribution of patients across groups

ACOS: Asthma-COPD overlap syndrome, FECB: Frequent exacerbator chronic bronchitis, FEE: Frequent exacerbator emphysema, COPD: Chronic obstructive pulmonary disease, NE: Non-exacerbator

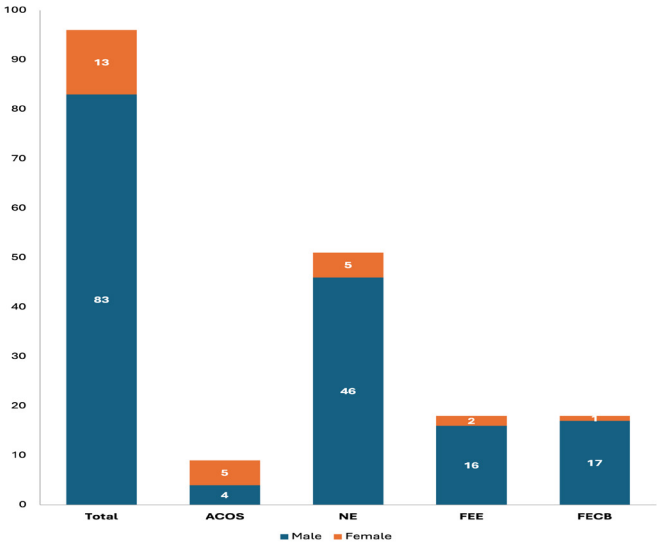

Figure 3. Gender distribution of patients across groups

ACOS: Asthma–COPD overlap syndrome, NE: Non-exacerbator, FEE: Frequent exacerbator emphysema, FECB: Frequent exacerbator chronic bronchitis

(p=0.010), although no significant difference was found between the two frequent-exacerbator phenotypes (p=0.297) (**Table 4**).

Table 3. General characteristics of phenotype groups

Parameters	ACO	NE	FEE	FECB	p-value
Age	57.88±7.76[a] 55 (48-68)	65.31±7.65[b] 64 (49-84)	66.11±8.05[b] 66 (49-78)	67.77±6.56[b] 68 (55-76)	0.016
Smoking (package-year)	35.50±39.98 17.50 (4-100)	50.04±28.95 40 (1-150)	53.11±29.30 50 (3-110)	51.05±29.11 45 (3-100)	0.656
Body-mass index kg/m^2	32.98±5.87 [a] 33.05 (25.2-42.9)	26.29±4.76 [bc] 25.5 (17-36)	23.07±4.25 [c] 22.6 (15.8-29.5)	27.05±3.13 [b] 25.75 (22.8-33.3)	<0.001
Duration of disease	23.44±8.45 [a] 21 (15-40)	9.62±5.73 [b] 10 (1-21)	10.44±6.02 [b] 10 (2-25)	13.5±6.51 [b] 13.5 (1-25)	<0.001
Number of exacerbations per year	1.0±0.70 [a] 1 (0-2)	0.43±0.50 [b] 0 (0-1)	2.61±1.14 [c] 2 (2-6)	2.52±1.06 [c] 2 (2-6)	<0.001
Number of hospitalizations per year	0.44±0.52 [a] 0 (0-1)	0.17±0.38 [a] 0 (0-1)	1.05±0.87 [b] 1 (0-6)	0.63±0.97 [c] 0 (0-6)	<0.001

ACO: Asthma-COPD overlap, NE: Non-exacerbator, FEE: Frequent exacerbator emphysema, FECB: Frequent exacerbator chronic bronchitis

Table 4. Quality of life scores, dyspnea scores, 6-Minute Walking Tests

Parameters	ACO	NE	FEE	FECB	p-value
mMRC	1.22±0.83 [a] 1 (0-3)	1.23±0.90 [a] 1 (0-4)	4.92±2.32 [b] 4 (1-8)	4.5±1.9 [ab] 4 (1-8)	0.001
CAT score	10.75±5.49 [ab] 10.5 (2-21)	9.16±5.41 [a] 8 (0-25)	17.73±8.58 [c] 18 (4-32)	14.6±6.74 [bc] 12 (8-29)	<0.001
6MWT m	464.44±81.25 [a] 480 (360-640)	466.29±82.28 [a] 468 (260-580)	401.8±90.77 [ab] 405 (220-520)	363.75±90.38 [b] 345 (220-520)	0.010
St George symptom score	52.42±21.77 [a] 53.4 (15.15-86.66)	32.76±21.67 [b] 28.18 (6.32-86.23)	58.78±21.82 [a] 65.01 (15.56-88.12)	58.89±16.15 [a] 63.25 (28.87-84.03)	<0.001
St George activity score	50.16±37.11 [a] 49 (0-92.51)	30.79±28.63 [ab] 29.49 (0-92.45)	66.01±27.9 [b] 72.44 (0-100)	56.2±28.93 [ab] 59.46 (5.96-92.51)	0.001
St George impact score	26.78±18.36 [a] 21.7 (3.62-57.07)	11.46±12.09 [b] 7.77 (0-61.09)	35.63±23.29 [a] 33.7 (8.92-77.31)	31.81±24.37 [a] 28.61 (0-81.09)	<0.001
St George total score	37.95±22.8 [a] 31.36 (7.40-67.20)	20.78±16.19 [b] 20.27 (1.05-65.88)	48.8±20.71 [a] 47.24 (7.14-82)	43.20±22.65 [a] 43.28 (10.98-80.99)	<0.001

ACO: Asthma–COPD overlap, NE: Non-exacerbator, FEE: Frequent exacerbator with emphysema, FECB: Frequent exacerbator with chronic bronchitis, mMRC: Modified medical research council, CAT: COPD assessment test, 6MWT: Six-Minute Walk Test

Spirometric and plethysmographic parameters also varied. The FEV_1/FVC ratio ranged from 35% to 69% across groups, with significantly lower FEV_1% predicted and absolute values in the FEE group ($p<0.001$). Reversibility was detected only in three ACO patients. Residual volume (RV) was elevated in all phenotypes but significantly higher in FEE, accompanied by increased functional residual capacity (FRC) and reduced inspiratory capacity to total lung capacity ratio (IC/TLC) ($p=0.008$), consistent with marked hyperinflation. Airway conductance (Gaw) was significantly lower in frequent exacerbator groups ($p=0.044$). The FEE group also demonstrated reduced diffusion capacity (DLCO) and lower pO_2 values, while hypercapnia was observed in all groups except ACO (**Table 5**).

Total serum IgE levels did not differ significantly among groups but were higher in the ACO group overall.

Radiological findings supported phenotypic differentiation. On chest radiography, hyperlucency was noted in 55.6% of ACO, 81.2% of NE, 88.9% of FEE, and 50% of FECB patients. On thoracic CT, hyperlucency was most frequent in the FEE phenotype (93%). Bronchial wall thickening was most common in FECB (68.7%), whereas bronchiectasis occurred in over half of the FEE (56%) and FECB (50%) groups, consistent with the higher frequency of exacerbations in these phenotypes.

DISCUSSION

COPD is increasingly recognized as a heterogeneous condition encompassing a spectrum of clinical, functional, and biological profiles rather than a single disease entity. Phenotyping aims to identify patient subgroups with shared pathophysiologic mechanisms, clinical presentations, and therapeutic responses. In the present study, COPD patients classified according to the GesEPOC framework demonstrated distinct demographic, functional, and radiological characteristics, particularly within the ACO and FEE phenotypes.

The ACO group was characterized by a higher proportion of females, younger age, longer disease duration, and higher BMI. These findings are consistent with previous reports indicating that ACO patients often exhibit eosinophilic inflammation, greater reversibility, and relatively preserved lung function compared with other COPD phenotypes.[9,18] The higher prevalence of atopy and prior asthma diagnosis further supports the concept that ACO represents a distinct inflammatory phenotype. Although serum IgE levels did not differ significantly between groups, they tended to be higher in ACO patients, in line with previous studies suggesting that eosinophilic and allergic markers may aid phenotype identification.[7,20]

In contrast, the FEE phenotype demonstrated the poorest clinical and functional status. Lower FEV_1%, reduced DLCO, increased lung volumes, and a lower IC/TLC ratio

Table 5. Pulmonary function tests results of phenotype groups

Parameters	ACO	NE	FEE	FECB	p-value
FVC%	84.66±13.26 [a]	80.07±15.88 [a]	63.94±16.34 [b]	68.22±15.83 [b]	<0.001
FVC lt	2.66 ±0.9[ab]	2.89 ±0.7 [a]	2.23±0.4 [b]	2.40±0.4[ab]	0.006
FEV1%	57.55±14.29 [a]	55.66±14.52 [ab]	35.77±15.2 [c]	45.55±14.97 [bc]	<0.001
FEV1 lt	1.45±0.5 [a]	1.56±0.5 [a]	0.97±0.3 [b]	1.24±0.3[ab]	<0.001
FEV1/FVC%	56±12.12 [a]	54.18±9.11 [a]	42.63±8.19 [b]	51.51±9.62 [a]	<0.001
FEF 25-75%	21.44±7.6	22.8±11.08	16.5±10.47	18.66±8	0.122
FEF 25-75 lt	0.68±0.3 [a]	0.68±0.3 [a]	0.40±0.1 [b]	0.56±0.2 [ab]	0.003
Reversibility ΔFEV1%	14.12±8.95	10.57±9.34	6.2±10.43	12.5±9.98	0.320
Reversibility ΔFEV1 lt	0.177±0.116	0.163±0.148	0.058±0.096	0.131±0.106	0.149
TLC%	115.66±16.35	114.40±21.10	130.42±20.92	110.36±22.33	0.243
TLC lt	5.97±1.75	7.050±1.64	8.16±1.10	6.71±1.22	0.079
IC lt	2.86±1.62	2.94±1.06	2.03±4.61	2.67±1.08	0.274
RV%	166±31[a]	168±52 [a]	242±79 [b]	167±44 [a]	0.014
RV lt	3.20±0.80 [a]	3.96±1.22 [a]	5.61±1.58 [b]	3.96±0.95 [a]	0.004
FRC%	110.66±22.51 [a]	124.03±36.06[a]	181.14±38.86 [b]	122.9±35.11 [a]	0.001
FRC lt	3.10±0.68 [a]	4.16±1.14 [b]	6.12±1.21 [c]	4.03±0.80 [ab]	<0.001
VC%	92.25±9.17	77.9±14.3	70.2±25.51	78.33±17.10	0.281
VC lt	2.65±1.38	2.80±0.75	2.75±0.92	2.66±0.56	0.973
IC/TLC%	45.33±11.18 [a]	40.64±12.01 [a]	24.85±6.86 [b]	38.27±11.61 [a]	0.008
RV/TLC%	54.33±7.31	56.34±14.04	68±12.24	67.09±27.91	0.148
Raw%	128.5±33.8	147.77±96.81	238.66±150.07	194±78.14	0.125
sRaw%	331±135.69	399.84±424.1	841±568.21	471.81±231.39	0.075
Gaw%	55.28±18.47 [a]	49.5±18.06 [ab]	35.5±23.2 [b]	35.54±11.53 [b]	0.044
sGaw lt/s/cmH2O	0.77±0.31	0.68±0.025	0.041±0.038	0.055±0.025	0.087
DLCO%	83.80±20.06	70.10±25.90	48.37±18.44	68.87±16.10	0.052
DLCO ml/mmHg/min	18650±12010.41	17630±7002.27	11862.50±4778.8	16475±4565.63	0.207
DLCO/VA%	97.60±23.02	81.57±27	74±29.94	97±14.18	0.192
DLCO/VA ml/mmHg/min/lt	4582±1216.78 [a]	3238.45±1123.07 [b]	2853.75±1156.75 [b]	3738.75±625.03 [ab]	0.033

ACO: Asthma-COPD overlap, NE: Non-exacerbator, FEE: Frequent exacerbator emphysema, FECB: Frequent exacerbator chronic bronchitis, m: Meter, FVC: Forced vital capacity, FEV_1: Forced expiratory volume in one second, FEF: Forced expiratory flow, TLC: Total lung capacity, IC: Inspiratory capacity, RV: Residual volume, FRC: Functional residual capacity, VC: Vital capacity, IC/TLC: Inspiratory capacity/total lung capacity ratio, RV/TLC: Residual volume/total lung capacity ratio, Raw: Airway resistance, sRaw: Specific airway resistance, Gaw: Airway conductance, sGaw: Specific airway conductance, DLCO: Diffusing capacity of the lung for carbon monoxide, %: Percentage of predicted value, lt: Litre, lt/s/cmH_2O: Litre per second per centimetre of water

indicated marked hyperinflation and impaired gas exchange. Similar findings have previously been associated with increased mortality and hospital readmission risk.[21,22] These observations suggest that patients with the FEE phenotype may require closer clinical follow-up and more comprehensive management approaches.

The FECB phenotype exhibited a high symptom burden characterized by cough and sputum production, consistent with previous studies linking chronic bronchitis to increased exacerbation frequency and airway inflammation.[23,24] Although lung function impairment was less severe than in FEE patients, bronchial wall thickening and bronchiectasis were prominent CT findings, supporting the role of persistent airway inflammation in this phenotype.

Patients with the NE phenotype demonstrated the most stable clinical profile, with lower CAT and SGRQ scores and fewer exacerbations. These findings are compatible with previous studies indicating that NE patients generally have milder symptom burden and slower disease progression.[9]

The significantly higher mMRC scores and lower 6MWD observed particularly in the FEE and FECB phenotypes reflect the substantial symptomatic and functional burden associated with frequent exacerbations. Reduced exercise capacity in these phenotypes may be related to severe airflow limitation, dynamic hyperinflation, impaired gas exchange, and systemic deconditioning. Similar associations between dyspnea severity, exercise intolerance, and exacerbation frequency have been reported previously in COPD populations.

Recent advances in COPD research further support the concept that COPD represents a biologically heterogeneous syndrome rather than a uniform airflow-limitation disorder. Emerging evidence from genetic and multi-omics studies suggests that COPD encompasses biologically distinct molecular patterns that may contribute to clinically relevant phenotypic heterogeneity.[13-17] In particular, quantitative CT analysis and artificial intelligence-based imaging approaches may improve future identification of clinically meaningful COPD subgroups.[11,12,26] These developments are consistent with our findings demonstrating marked radiological and functional differences between ACO, FEE, FECB, and NE phenotypes.

The growing emphasis on inflammatory endotypes and "treatable traits" has also expanded the understanding of

COPD pathobiology. Recent studies have highlighted the clinical importance of eosinophilic inflammation, mucus plugging, and immune dysregulation in determining exacerbation risk and disease severity.[25,27,28] These concepts align with our observations regarding ACO and exacerbator phenotypes and support the transition toward multidimensional COPD assessment integrating clinical, radiological, and inflammatory parameters.

Our findings reinforce that phenotyping provides clinically meaningful insights into COPD heterogeneity and may contribute to more individualized management strategies. Identifying high-risk subgroups such as the FEE phenotype may be particularly valuable for optimizing follow-up and supportive interventions, whereas recognition of the ACO phenotype may support consideration of anti-inflammatory approaches in selected patients.

Limitations

Limitations of this study include its single-center, cross-sectional design and the relatively small sample size of some phenotypic subgroups, particularly ACO. Future multicenter and longitudinal studies integrating imaging, molecular, and clinical parameters are needed to validate these findings and explore their implications for prognosis and therapeutic response. Another limitation is that patient recruitment was performed between 2014 and 2016. Since COPD phenotyping concepts, imaging approaches, and GOLD recommendations have evolved substantially over the last decade, some phenotype definitions and therapeutic perspectives may differ from current clinical frameworks.

CONCLUSION

This study highlights the clinical importance of COPD phenotyping using the GesEPOC framework. Distinct differences among phenotypes-particularly the favorable clinical profile of the ACO group and the severe functional impairment observed in the FEE group-further emphasize the heterogeneity of COPD beyond spirometric classification alone. Integrating clinical, radiological, and functional parameters may provide a more comprehensive understanding of disease characteristics and contribute to more individualized patient management. Future multicenter and longitudinal studies are needed to further validate phenotype-specific findings and explore their prognostic and therapeutic implications.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was conducted with the approval of the Ankara University Faculty of Medicine Ethics Committee (Date: 25.07.2014, Decision No: 38615).

Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights-including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

Concept: DAK, SBS; Design: DAK, SBS; Control: SBS; Data Collection and/or Processing: DAK; Analysis and/or Interpretation: DAK, SBS; Literature Review: DAK; Article Writing: DAK; Critical Review: SBS. All Authors Read and Approved the Final Version of the Manuscript.

REFERENCES

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2024 report. Available from: https://goldcopd.org/
2. Agustí A, Hogg JC. Update on the pathogenesis of chronic obstructive pulmonary disease. *N Engl J Med*. 2019;381(13):1248-1256. doi:10.1056/NEJMra1900475
3. Han MK, Agusti A, Celli BR, et al. From GOLD 0 to pre-COPD. *Am J Respir Crit Care Med*. 2021;203(4):414-423. doi:10.1164/rccm.202008-3328PP
4. Agusti A, Vogelmeier CF. GOLD 2024: a brief overview of key changes. *J Bras Pneumol*. 2023;49(6):e20230369. doi:10.36416/1806-3756/e20230369
5. Agustí A, Celli B, Faner R. What does endotyping mean for treatment in chronic obstructive pulmonary disease? *Lancet*. 2017;390(10098):980-987. doi:10.1016/S0140-6736(17)32136-0
6. Celli BR, Wedzicha JA. Update on clinical aspects of chronic obstructive pulmonary disease. *N Engl J Med*. 2019;381(13):1257-1266. doi:10.1056/NEJMra1900500
7. Christenson SA. COPD phenotyping. *Respir Care*. 2023;68(7):871-880. doi:10.4187/respcare.11035
8. Han MK, Agusti A, Calverley PM, et al. Chronic obstructive pulmonary disease phenotypes: the future of COPD. *Am J Respir Crit Care Med*. 2010;182(5):598-604. doi:10.1164/rccm.200912-1843CC
9. Miravitlles M, Calle M, Soler-Cataluña JJ. Clinical phenotypes of COPD: identification, definition and implications for guidelines. *Arch Bronconeumol*. 2012;48(3):86-98. doi:10.1016/j.arbres.2011.10.007
10. Miravitlles M, Soler-Cataluña JJ, Calle M, Soriano JB. Treatment of COPD by clinical phenotypes: putting old evidence into clinical practice. *Eur Respir J*. 2013;41(6):1252-1256. doi:10.1183/09031936.00118912
11. Lynch DA, Al-Qaisi MA. Quantitative computed tomography in chronic obstructive pulmonary disease. *J Thorac Imaging*. 2013;28(5):284-290. doi:10.1097/RTI.0b013e318298733c
12. Raoof S, Shah M, Braman S, et al. Lung imaging in COPD part 2: emerging concepts. *Chest*. 2023;164(2):339-354. doi:10.1016/j.chest.2023.02.049
13. Gillenwater LA, Helmi S, Stene E, et al. Multi-omics subtyping pipeline for chronic obstructive pulmonary disease. *PLoS One*. 2021;16(8):e0255337. doi:10.1371/journal.pone.0255337
14. Tiew PY, Meldrum OW, Chotirmall SH. Applying next-generation sequencing and multi-omics in chronic obstructive pulmonary disease. *Int J Mol Sci*. 2023;24(3):2955. doi:10.3390/ijms24032955
15. Li CX, Wheelock CE, Sköld CM, Wheelock ÅM. Integration of multi-omics datasets enables molecular classification of COPD. *Eur Respir J*. 2018;51(5):1701930. doi:10.1183/13993003.01930-2017
16. Ragland MF, Benway CJ, Lutz SM, et al. Genetic advances in chronic obstructive pulmonary disease. Insights from COPDGene. *Am J Respir Crit Care Med*. 2019;200(6):677-690. doi:10.1164/rccm.201808-1455SO
17. Silverman EK. Genetics of COPD. *Annu Rev Physiol*. 2020;82:413-431. doi:10.1146/annurev-physiol-021317-121224
18. David B, Bafadhel M, Koenderman L, De Soyza A. Eosinophilic inflammation in COPD: from an inflammatory marker to a treatable trait. *Thorax*. 2021;76(2):188-195. doi:10.1136/thoraxjnl-2020-215167

19. Agustí A, Edwards LD, Rennard SI, et al. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. *PLoS One*. 2012;7(5):e37483. doi:10.1371/journal.pone.0037483
20. Barrecheguren M, Román-Rodríguez M, Miravitlles M. Is a previous diagnosis of asthma a reliable criterion for asthma-COPD overlap syndrome in a patient with COPD? *Int J Chron Obstruct Pulmon Dis*. 2015;10:1745-1752. doi:10.2147/COPD.S87025
21. Casanova C, Cote C, de Torres JP, et al. Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2005;171(6):591-597. doi:10.1164/rccm.200407-867OC
22. Tomioka R, Kawayama T, Suetomo M, et al. "Frequent exacerbator" is a phenotype of poor prognosis in Japanese patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2016; 11:207-216. doi:10.2147/COPD.S98205
23. Kim V, Davey A, Comellas AP, et al. Clinical and computed tomographic predictors of chronic bronchitis in COPD: a cross sectional analysis of the COPDGene study. *Respir Res*. 2014;15(1):52. doi:10.1186/1465-9921-15-52
24. de Oca MM, Halbert RJ, Lopez MV, et al. The chronic bronchitis phenotype in subjects with and without COPD: the PLATINO study. *Eur Respir J*. 2012;40(1):28-36. doi:10.1183/09031936.00141611
25. Massara L, Saber Cherif L, Ollivier A, et al. α5 nicotinic receptor polymorphism affects cigarette smoke-induced inflammation and COPD development. *Am J Respir Cell Mol Biol*. 2026. doi:10.1093/ajrcmb/aanag093
26. Namvar A, Shan B, Hoff B, et al. Feature-based parametric response mapping on thoracic computed tomography for robust disease classification in COPD. *medRxiv*. 2026. doi:10.64898/2026.04.24.26351675
27. Jaiswal D, Puri MM, Mullick S, Kumar V. Blood and sputum eosinophilia in chronic obstructive pulmonary disease patients and their association with exacerbations: a prospective observational study from a tertiary care center. *Monaldi Arch Chest Dis*. 2026. doi:10.4081/monaldi.2026.3619
28. Mari PV, Ricci A, Coppola A, et al. Mucus plugging as a treatable trait across the asthma-COPD spectrum: the role of type 2 cytokine blockade and quantitative imaging. *Biomedicines*. 2026;14(4):891. doi:10.3390/biomedicines14040891